Hoffmann | Rockstroh

HIV 2023/2024

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Preface 2023/2024

The goal of this book has not changed: To make a textbook that is easily readable and can be used in the daily practice of HIV treatment. A book that, despite (unrestricted) support from the pharmaceutical industry, remains independent and is freely available and accessible via a website.

As in previous years, all chapters of HIV 2023/24 have been thoroughly revised. A new book was urgently needed almost eight years after the last edition. A lot has happened. Not only have COVID-19 and monkeypox (Mpox) been added, but also many new drugs such as bictegravir, doravirine, lenacapavir, or fostemsavir, and long-acting and dual therapies. New chapters on parenteral and other routes of ART administration have been created, as well as chapters on prevention (PrEP!), HIV-2, rheumatology, psychiatry, and trans*medicine.

New editions are also planned for the future. As in the past, the editors and authors of this book may agree to remove the copyright on HIV 2023/2024 for all languages except English and German. Therefore, after an official inquiry, you may translate this book's content into any language and publish it without paying a license fee.

HIV 2023/2024 is also free and available online (www.hivbook.com). We firmly believe this is how medical textbooks should be handled in the 21st century. Research, knowledge, and expertise in the field of HIV should be shared and accessible to those dedicated to the treatment and care of people living with HIV.

Christian Hoffmann, Jürgen K. Rockstroh
Hamburg, Bonn – April 2023

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SECTION 4 Other Infections

Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
AIN	Anal Intraepithelial Neoplasia
ART	Antiretroviral Therapy
AUC	Area under the curve
BAL	Bronchoalevolar Lavage
BGA	Blood Gas Analysis
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CHD	Coronary Heart Disease
CMV	Cytomegalovirus
CNS	Central Nervous System
CROI	Conference on Retroviruses and Opportunistic Infections
CT	Computed Topography
CTL	Cytotoxic T Cells
CVC	Central Venous Catheter
DD	Differential diagnosis
DEXA	Dual Energy X-ray Absorptiometry
DNA	Deoxyribonucleic Acid
DOT	Directly Observed Therapy
EAP	Expanded Access Program
EBV	Epstein-Barr Virus
ED	Erectile Dysfunction
ELISA	Enzyme-Linked Immunosorbent Assay
ELISPOT	Enzyme-Linked Immunosorbent Spot Assay
EMEA	European Medicines Agency
FDA	US Food and Drug Administration
FDC	Follicular Dendritic Cells
G-CSF	Granulocyte Colony-Stimulating Factor
GFR	Glomerular Filtration Rate
HAART	Highly Active AntiRetroviral Therapy
HbsAG	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HDL	High-density Lipoprotein
HHV-8	Human Herpesvirus 8
HIV	Human Immunodeficiency Virus
HIVAN	HIV-Associated Nephropathy
HIVE	HIV-Encephalopathy
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HSR	Hypersensitivity Reaction
HSV	Herpes Simplex Virus
IC50	50% Inhibitory Concentration
INSTI	Integrase Strand Transfer Inhibitor

IRIS	Immune Reconstitution Inflammatory Syndrome
ITP	Idiopathic Thrombocytopenic Purpura
ITT Analysis	Intention-to-Treat Analysis
IU	International Unit
CHD	Coronary Heart Disease
KS	Kaposi's sarcoma
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LGV	Lymphogranuloma venereum
LIP	Lymphocytic Interstitial Pneumonia
LTNP	Long-Term Non-Progressor
MAC	Mycobacterium Avium Complex
MCD	Multicentric Castleman's Disease
MDR	Multi-Drug Resistant
MHC	Major Histocompatibility Complex
MRT	Magnet Resonance Tomography
MSM	Men who have sex with men
NASBA	Nucleic Acid Sequence Based Amplification
NHL	Non-Hodgkin's Lymphoma
NK-Cells	Natural Killer Cells
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
OHL	Oral Hairy Leukoplakia
OI	Opportunistic Infection
PBMC	Peripheral Mononuclear Cell
PCNSL	Primary Central Nervous System Lymphoma
PCP	Pneumocystis Pneumonia
PCR	Polymerase Chain Reaction
PEL	Primary Effusion Lymphoma
PEP	Post-Exposure Prophylaxis
PI	Protease Inhibitor
PML	Progressive Multifocal Leukoencephalopathy
PNP	Polyneuropathy
PrEP	Pre-Exposure Prophylaxis
RNA	Ribonucleic Acid
SD	Sexual Dysfunction
SIV	Simian Immunodeficiency Virus
STD	Sexually Transmitted Diseases
STI	Structured Treatment Interruption
TAM	Thymidine Analogue Mutation
TCR	T-cell Receptor
TDM	Therapeutic Drug Monitoring
TSH	Thyroid-stimulating Hormone
VL	Viral Load
VZV	Varicella Zoster Virus

For abbreviations of antiretroviral agents, see ART chapter.

SECTION 1

The Basics

1. Introduction

JÜRGEN KURT ROCKSTROH

Acquired immunodeficiency syndrome (AIDS) was first described as a clinical entity in 1981. The initial reports were based on an unusual clustering of previously rare conditions such as Kaposi sarcoma (KS) and Pneumocystis pneumonia (PCP). Although these syndromes occasionally occur in various populations (such as KS in older Mediterranean men or PCP in leukemia patients after intensive chemotherapy), the occurrence of these indicator diseases of immunodeficiency had never been observed in previously healthy young people. Given the initially affected patient group, men who have sex with men (MSM), the disease and those affected were strongly stigmatized. After the cause had initially been suspected to be specific lifestyles, the human immunodeficiency virus (HIV) was finally identified as the causative agent of AIDS in 1983.

The first antiretroviral agent, AZT (zidovudine, Retrovir®), was introduced in 1987. Although this – as monotherapy – inadequately suppressed HIV replication, it at least succeeded in improving symptoms of HIV infection in the short term and somewhat delaying the onset of AIDS. What followed remains unique in medicine: Within a decade of its discovery, an inevitably fatal disease became one that could be treated chronically and effectively. The rapid introduction of further classes of drugs and the so-called highly active antiretroviral therapy (HAART, a term that is replaced by **ART** in this book) succeeded and continues to this day in permanently suppressing viral replication and preventing progression of the disease – as long as the drugs are taken regularly and tolerated. Long-term toxicities and resistance necessitated searching for and identifying further promising substances with a different mechanism of action or a more favorable resistance profile. Incremental improvements have happened in the administration, use, and eventual tolerability of HIV drugs over the years. Today, in 2023, several HIV therapies are available via one tablet daily, a possibility via fixed-dose combinations, as well as once-monthly or bi-monthly injections of various agents.

However, all this should not hide the fact that lifelong drug treatment can cause considerable problems – in terms of both short-term and long-term toxicities and adherence to therapy (so far, limited long-term experience even after almost more than a quarter-century of effective use). Infection with HIV should continue to be avoided at all costs. Therefore, in addition to further improvement of ART and new concepts such as eradication, our efforts must focus on prevention to prevent further spread.

The HIV epidemic

In 1981, the first three clinical descriptions of AIDS appeared in the *Morbidity and Mortality Weekly Report* and later in the *New England Journal of Medicine*. They included an epidemic of community-acquired Pneumocystis pneumonia in previously healthy MSM and chronic ulcerative perianal herpes infections (Gottlieb 1981a, Gottlieb 1981b, Masur 1981, Siegal 1981).

A little later, in June 1982, a Centers for Disease Control (CDC) note was published on three cases of PCP in hemophiliacs (CDC 1982a). That same year, a clinical case of cryptosporidiosis in a Pennsylvania hemophiliac (Eyster 1982) and an AIDS case in a young child following a blood transfusion were also published (CDC 1982b). The occurrence of AIDS in hemophiliacs triggered a debate about whether AIDS might

be a virus-related disease (Marx 1982). In particular, the similarity of the risk populations for AIDS and hepatitis B suggested a viral genesis of AIDS.
Studies of AIDS cases from different patient collectives quickly revealed common features: for example, CD4-positive T lymphocytes were decreased in all of them compared with healthy control subjects. In contrast, there was a relative and absolute increase in CD8-positive T lymphocytes (Gottlieb 1981, Masur 1981, Siegal 1981, Mildvan 1982, Stahl 1982). It soon became apparent, however, that manifest disease was not a condition of immunodeficiency. A defect in cellular immunity associated with lymphadenopathy was described very early in otherwise asymptomatic MSM (Kornfeld 1982, Stahl 1982). In January 1983, a description of two hemophiliacs with lymphadenopathy syndrome appeared, both of whom had significant disturbances of cellular immunity (Ragni 1983). It suggested that the lymphadenopathy and cellular immunity disturbance were preliminary stages of AIDS and that transmission of the AIDS agent by blood products was likely. Subsequently, various papers reported alterations in cellular immunity in hemophiliacs. Only in individuals who were treated with small amounts of factor VIII or whose factor VIII consisted of small donor pools were regular lymphocyte subpopulations found (Luban 1983, Rasi 1984). The immunologic findings in hemophiliacs were initially controversial and were partly explained by a chronic antigen load due to factor VIII administration. Other groups considered this explanation unlikely since hemophiliacs had not shown an increased risk of infection than other populations (except for viral infections, especially hepatitis B and non-A non-B hepatitis via administration of blood products) until the arrival of AIDS. Overall, no reason was seen at this time that would question the concept of factor treatment in hemophiliacs (Anonymous 1983, Goldsmith 1983). Co-infection with human cytomegalovirus, drug use, inhalation of amyl nitrate (poppers), and exposure to foreign proteins (spermatozoa) were discussed as possible alternative explanations for AIDS within the MSM risk group (Essex 1997).
In 1983, several research groups suggested that the possible trigger of AIDS might be a variant of the T-lymphotropic retrovirus (HTLV-I) discovered by Gallo and colleagues in 1980 (Essex 1983, Gallo 1983). Several arguments supported this hypothesis. For example, at that time, HTLV-I was the only known human virus with the potential to infect CD4 T lymphocytes (Poiesz 1980). In addition, HTLV-I was transmitted via the same transmission routes as the possible causative agent of AIDS, namely via sexual contact, blood, and perinatally (Essex 1982).
Initial attempts to isolate a virus related to HTLV-I or -II were only partially successful. Although cross-reacting antibodies with HTLV-related genome sequences could be found in a few AIDS patients, the overall reactivity was weak, suggesting only HTLV co-infection. Instead, these observations suggested the etiological role of a more distant, weakly reactive virus. Indeed, a little later, the isolation of HTLV-III, later renamed human immunodeficiency virus type 1 (HIV-1), was identified as the causative agent of AIDS (Barré-Sinoussi 1983, Popovic 1984). In 2008, the French research group led by Luc Montagnier and Françoise Barré-Sinoussi was awarded the Nobel Prize in Medicine for this work.

Transmission routes

HIV is transmitted by
1. Unprotected sexual contact with an HIV-positive partner (who has a detectable HIV viral load).
2. Shared use of syringe paraphernalia, primarily for drug use.
3. In the context of transmission from an HIV-positive mother to the newborn (before birth, during birth or through breastfeeding).

There is still transmission in the context of transfusions of blood or blood products in countries where blood donations are not regularly tested for HIV. All other described types of infection transmission are very rare.
Absolute rarities are contact of infected blood with open wounds, mucous membranes, or HIV transmission via a bite wound (Bartholomew 2008). A few cases have also been published in which mothers infected their newborns, presumably through pre-chewed food (Gaur 2008). However, these are all rather casuistic communications. Extensive aggregate statistics, especially from the CDC, that have looked at other possible transmission routes clearly show that regular daily interaction, including using a shared toilet or drinking from the same glass, does not lead to transmission. Similarly, in health care settings, a composite statistic of saliva contacts, contacts with urine, or infectious blood in contact with skin failed to detect a single contagion (Henderson 1990). Below, the different transmission routes will be briefly presented and discussed about favorable factors and risks.

Sex

The most important route of infection for HIV remains sexual contact. The prerequisite for this is direct contact with infected body secretions or fluids. Here, the highest virus concentrations are found in blood and seminal fluid. It should be noted that it is impossible to calculate the transmission risk for individual risk exposure since this is also determined by many accompanying circumstances, such as sexual practices, other sexually transmitted diseases, skin lesions, circumcision, and mucosal injury. The average transmission risk for HIV transmission during unprotected sex with an HIV-positive partner not on antiretroviral therapy is summarized in Table 1.

Table 1: Risk probabilities of HIV transmission during unprotected sex (without condom, without PrEP) with an HIV-positive partner without antiretroviral therapy. It is calculated from seroincidence and cohort studies (Patel 2014).

Type of contact	Risk per 10,000 exposures	95% confidence interval
Receptive anal intercourse	138	102–186
Insertive anal intercourse	11	4–28
Receptive vaginal intercourse	8	6–11
Insertive vaginal intercourse	4	1–14
Oral sex	Individual cases described	

The dependence of transmission risk on the amount of virus present has important epidemiological consequences. Where body fluids such as blood and semen are exchanged with many people within days and weeks, there is a significantly increased risk of encountering people who have only been infected for a short time and are highly infectious. The probability of infecting other people within the few weeks between one's new infection and the appearance of antibodies is also increased. The stage when infection progresses without knowledge of the diagnosis and high viral loads are again observed shortly before the onset of AIDS is particularly infectious. STDs and inflammation open physiological skin and mucosal barriers, increasing the risk of HIV infection. This is especially true in endemic areas with a high prevalence of other STDs. For example, genital herpes infections, in particular, are a potential co-factor in the spread of HIV in endemic areas (Mahiane 2009).
The observation that the level of viral load is decisive for the infectivity of an infected person has triggered a discussion about the possibility of unprotected sexual contact. Thus, for the first time, the Swiss Federal Commission for AIDS Issues (EKAF) pro-

posed that HIV-positive persons whose viral load under ART is below the detection limit and who have been receiving antiretroviral treatment for at least six months, who consistently and reliably take medicine and regularly undergo medical check-ups, and who do not have any infections with other sexually transmitted pathogens, should be considered as persons who presumably do not pass on HIV via sexual contacts and, accordingly, may also safely have unprotected sex (Vernazza 2008). Additional data are now available from studies in discordant couples. They demonstrate no longer a relevant transmission risk in people with undetectable viral loads while on therapy (Cohen 2011). This was subsequently confirmed in discordant MSM couples and unprotected anal intercourse (Rodger 2019).

Syringe exchange

Sharing syringes and needles is the most critical transmission route among intravenous drug users. Due to the usually quite large amount of blood that is transferred, the risk is high. Aspiration to check needle position introduces blood into the syringe and thus provides the reservoir for transmission. Fortunately, with needle exchange programs, syringe vending machines, methadone substitution, and many other preventive and social measures, HIV transmission rates among intravenous drug users in Western Europe have dropped dramatically. In Eastern European countries, where drug use is prosecuted as a criminal act and clean injecting equipment is not provided, HIV transmissions continue to increase unabated. It is hoped that the successes in Western Europe will lead to more progressive handling and effective prevention programs in Eastern Europe.

Mother-to-child transmission

Without intervention, up to 40% of children born to HIV-1-positive mothers will become infected with HIV-1. The most critical risk factor is the viral load at birth. Since 1995, the mother-to-child transmission rate among pregnant women with known HIV-1 infection has been reduced to 1 to 2% in Germany. This has been achieved by a combination of antiretroviral treatment or prophylaxis for the pregnant woman, elective cesarian section before the onset of labor (now no longer necessary if the mother's viral load before birth is below the limit of detection), antiretroviral post-exposure prophylaxis (PEP) for the newborn, and abstinence from breastfeeding. For details, see chapter *HIV and Pregnancy*.

Blood

Transmission via blood and blood products remains a worldwide risk that has not been completely eliminated. In Germany, blood and blood products are considered safe. Since 1985, all blood donations have been tested for antibodies against HIV-1, and since 1989 also for HIV-2. For some years, PCR collection has been carried out to identify donors within the seroconversion period and for whom the HIV ELISA is still negative. Furthermore, people with so-called risk behavior, i.e., active drug users or "promiscuous" men and women (for example, people on oral PrEP must wait three months after stopping PrEP before donating blood, people on injectable PrEP must wait two years after stopping), and immigrants from endemic areas are excluded from blood donations.

Occupationally acquired HIV infection

The overall risk of becoming infected after an HIV-infected needle stick injury is 0.3%. However, it is significantly higher with a hollow needle – e.g., for blood collection – than with a surgical needle. For more information on transmission risks in different situations, see chapter *Post-exposure prophylaxis (PEP)* in this book.

Not suitable transmission routes: everyday contacts, insects

In general, HIV transmission through regular contact between family members is unlikely. It is essential to avoid blood-to-blood contact. Therefore, razor blades or toothbrushes should not be shared. If you use cannulas, used ones should go directly into the discard container and not be put back into the plastic syringe.
All studies that have investigated possible transmission of HIV by insects have concluded that this is not possible. This is also true for studies conducted in Africa with high AIDS prevalence and large insect populations, such as mosquitoes (Castro 1988).

The natural course of HIV infection

The natural course – i.e., without antiretroviral therapy – is shown in Figure 1. Shortly after the initial infection, a so-called acute retroviral syndrome is observed in some patients, which rarely lasts longer than four weeks. Leading symptoms are lymph node swelling, fever, a maculopapular exanthema, and myalgias (see also chapter *Acute HIV infection*). Symptoms are non-specific and variable, so an HIV diagnosis is rarely made without a specific suspicion. Several years follow, during which most patients are clinically asymptomatic.
After that, symptoms or diseases assigned to clinical category B may occur according to the CDC classification (see Table 2). In particular, oral thrush, oral hairy leukoplakia, and herpes zoster should be mentioned here, which should always lead to the differential diagnosis of HIV infection. Although these diseases are not AIDS-defining, they are causally related to HIV infection and indicate a disturbance of the cellular immune defense.
AIDS-defining diseases occur later – a median of 8 to 10 years after the initial infection. Without highly active antiretroviral therapy, they eventually lead to death after a period that varies from person to person.

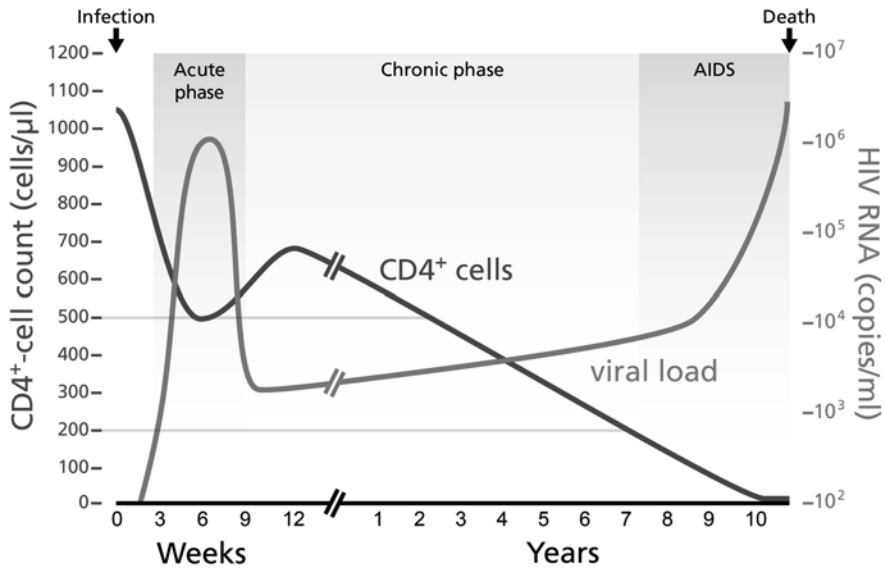

Figure 1: The "natural" course of HIV infection without ART, CD4 T-cells and viral load.

Table 2: Clinical categories of the CDC classification.

Category A
Asymptomatic HIV infection
- Acute, symptomatic (primary) HIV infection

Persistent generalized lymphadenopathy (LAS)

Category B
Symptoms of disease or illness that do not fall into category C but are causally attributable to HIV infection or indicate a disturbance in cellular immune defenses. These include:
- Bacillary angiomatosis
- Pelvic inflammatory disease, especially with complications of a tubal -or ovarian- abscess
- Herpes zoster in case of infestation of several dermatomes or after recurrences in one dermatome
- Idiopathic thrombocytopenic purpura
- Constitutional symptoms such as fever over 38.5 degrees or diarrhea existing for > 1 month
- Listeriosis
- Oral hairy leukoplakia (OHL)
- Oropharyngeal candidiasis
- Vulvovaginal candidiasis that is either chronic (> one month) or poorly treatable
- Cervical dysplasia or carcinoma in situ
- Peripheral neuropathy

Category C
AIDS-defining diseases
- Candidiasis of bronchial tubes, trachea or lungs
- Candidiasis, esophageal
- CMV infections (except liver, spleen, lymph nodes)
- CMV retinitis (with loss of visual acuity)
- Encephalopathy, HIV-related
- Herpes simplex infections: chronic ulcers (existing > 1 month); or bronchitis, pneumonia, esophagitis.
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic, intestinal, > one month existing
- Kaposi Sarcoma
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic, intestinal, > one month existing
- Lymphoma, Burkitt
- Lymphoma, immunoblastic
- Lymphoma, primary cerebral
- *Mycobacterium avium complex* or *M. kansasii* infection, disseminated or extrapulmonary
- Mycobacterium infection, other or unidentified species, disseminated or extrapulmonary
- Pneumocystis pneumonia
- Pneumonias, bacterial recurrent (> 2 within one year)
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Tuberculosis
- Toxoplasmosis, cerebral
- Wasting Syndrome
- Cervical carcinoma, invasive

The HIV viral load, which reaches extremely high values shortly after primary infection, usually drops to less than 1% of the initial value simultaneously as HIV antibodies appear and then initially remain relatively stable. This value is called the viral "setpoint". Its level decisively determines the speed of disease progression. While individuals with less than 1,000 HIV RNA copies/mL have virtually no AIDS even after 12 years, more than 80% of individuals with a viral load of more than 100,000 viral copies two years after seroconversion have already developed manifest AIDS (O'Brien 1996). The higher the viral "set point", the faster the drop in CD4 T-cells occurs. These usually drop significantly during acute infection, initially returning to above-average values after a few months, although rarely back to before infection. The average values vary depending on the laboratory and are usually about "absolute" 435–1,600/µl or "relative" 31–60% of lymphocytes for adults. For children, other standard values apply (see chapter *Antiretroviral therapy in children*).

In the further course of untreated HIV infection, there is a gradual decrease in CD4 T-cells. From a CD4 T-cell count below 200/µl, the occurrence of AIDS-defining diseases must be increasingly expected.

To estimate the degree of immunodeficiency, the relative proportion of CD4 T-cells should always be taken into account since, under certain circumstances (e.g., under myelosuppressive interferon therapy), low absolute CD4 T-cells are observed in the context of leukopenia and lymphopenia. However, an excellent immune status is still present in percentage terms. In this context, 200 CD4 T-cells/µl correspond to about 15% CD4-positive lymphocytes. Conversely, the absolute number may also suggest falsely high values, for example, after splenectomy. Depending on the rate of CD4 T-cell decline, a distinction is made (according to Stein 1997) between people at high risk of disease progression (decline above 100/µl within six months), moderate risk (decline 20–50/µl per year), and low risk (decline less than 20/µl per year).

While the overall AIDS risk increases significantly below 200 CD4 T-cells/µl, there are considerable differences between the individual AIDS-defining diseases (see also chapter *AIDS*). For example, opportunistic infections often occur at significantly lower CD4 T-cell counts than AIDS-associated malignancies (Schwartländer 1992). However, age is a significant risk factor in addition to CD4 T-cell count and viral load level. For example, a 55-year-old person with 50 CD4 T-cells/µl and an HIV RNA of 300,000 copies/mL has almost twice the risk of AIDS as a 25-year-old person.

In the "pre-HAART era," the time between the first AIDS complication and death was usually between two and four years. Without ART therapy, probably more than 90% of all people living with HIV (PLWH) die of AIDS. However, with the availability of ART today, the progression of the disease to the AIDS stage can be prevented. When maximum suppression of HIV RNA is achieved, CD4 T-cell counts usually recover, and life expectancy is almost normal. The level of viral load or viral "set point" is determined by several host-specific factors, such as chemokine receptor mutations, HLA types, and other factors, some of which have not yet been identified. In addition, there are also virus-specific factors that are likely to be decisive for progression. For more information, please refer to the chapter on *Basic Principles*. It is important to note that the measurable viral activity is a balance between viruses that emerge and viruses that are killed.

Staging of HIV infection

For staging, the CDC classification 1993 is still most broadly referenced, using the individual CD4 T-cell count and clinical manifestations as criteria (see Table 3). For both criteria, there are three stages each.

In 2014, a revised CDC version of staging was presented (Selik 2014). This now applies to all age groups, i.e., adults and adolescents over 13 years of age and children < 13 years of age. The goal of the revision was to provide a simplified staging for epidemiologic monitoring of all persons affected with HIV-1 and HIV-2 infection, which would also reflect improved diagnostics and treatment options. In addition to the three stages listed above, stage 0 was defined as early or recent HIV infection (with a negative HIV test within the last six months). The category "stage unknown" was introduced for patients without corresponding information. The basic rule is that a person is reclassified if the disease progresses, but no downgrading is possible. For example, a previously asymptomatic person with 530 CD4 T-cells/µl (category A1, new classification: stage 1) will receive category B2 (new: stage 2) if oral thrush occurs and CD4 T-cells drop to 320/µl. If the same person has a CD4 T-cell count of 550/µl again after successful thrush therapy and initiation of ART, they will remain in category B2 (new: stage 2).

Table 3: Classification of HIV infection according to the 1993 CDC classification.

CD4 T-cells	Asymptomatic or acute HIV disease	Symptomatic but not A or C	AIDS disease*
>500/µl	A1	B1	C1
200–499/µl	A2	B2	C2
<200/µl	A3	B3	C3

* See Table 2 for AIDS disease or clinic.

The CDC classification provides a first orientation to the (so far worst) condition of a person with HIV. It says nothing about the current situation. Unlike in Europe, where the term AIDS is only applied when an AIDS-defining illness has occurred, in the US, a drop in CD4 T-cells to below 200/µl is also considered AIDS. Old staging systems, such as those according to Walter-Reed or the Frankfurt classification, are no longer used.

Epidemiology

HIV probably originated in the 1920s-30s, when the Simian Immunodeficiency Virus (SIV) spread from chimpanzees to humans in West Africa (Worobey 2008). The oldest HIV-positive sample from a human was found in Kinshasa and dates back to 1959 (Zaire, Democratic Republic of Congo) (Zhu 1998). After the first description of AIDS in 1981, there is now no country that is not affected.

In most cases, people at increased risk of HIV transmission (IV drug users, sex workers, and MSM) contracted the disease first, with other groups of people subsequently becoming infected through unprotected sex. In most industrialized nations, gay anal sex is the most common mode of transmission; in the countries of the former Soviet Union, it is intravenous drug use (via sharing of needles). In sub-Saharan Africa, most people become infected through heterosexual intercourse. The prevalences in different countries and their impact on societies thus differ significantly. More of a marginal health problem in the industrialized countries of Western Europe, AIDS became the leading cause of death in sub-Saharan Africa. One in five deaths in Africa is now attributable to HIV/AIDS, and life expectancy in some countries has fallen by more than 20 years. Well over 10 million children have been orphaned. The economies of the affected countries have suffered and continue to suffer massive declines. According to UNAIDS, 37.7 million people worldwide were living with

HIV/AIDS at the end of 2020 (50% women). About 680,000 people died of AIDS in 2021 (see Table 4). There continues to be a significant decline in AIDS-associated deaths, indicating broader access to ART. It is also encouraging to note that globally, the number of new infections per year has declined from 2.1 million in 2010 to 1.5 million in 2020.

Table 4: The AIDS epidemic according to data from UNAIDS, 2021 (www.unaids.org).

	PLWH (adults and children)	New infections in 2020	Annual deaths from AIDS in 2020
East and South Africa	20,600,000	670,000	310,000
West and Central Africa	4,700,000	200,000	150,000
Middle East and North Africa	230,000	16,000	7,900
Asia and Pacific	5,800,000	240,000	130,000
Latin America	2,100,000	100,000	31,000
Caribbean	330,000	13,000	6,000
Western and Central Europe and North America	2,200,000	67,000	13,000
Eastern Europe and Central Asia	1,600,000	140,000	35,000
Total	37,700,000	1,500,000	680,000

The region most severely affected is sub-Saharan Africa, with approximately 25 million PLWH. The greatest rate of spread is currently seen in the countries of the former Soviet Union, especially Estonia, Latvia, Russia, and Ukraine, as well as in South and Southeast Asia.

Pre-exposure prophylaxis (PrEP, see chapter *Prevention of HIV infection*), available in Germany and other countries since 2017, is associated with the hope that new infections can also be prevented among key populations at increased risk of HIV transmission. In London, where PrEP has been given to HIV-negative MSM for some time, reductions in new infection rates of over 50% have already been reported.

Summary

The first serological evidence of HIV antibodies is found in old sera from Zaire in 1959, Uganda in 1972, and Malawi in 1974 – evidence that HIV was already circulating in Central Africa. The first AIDS cases were described in the United States in 1981. This was followed in 1983 by the discovery of HIV as the cause of AIDS. Since then, there has been a worldwide epidemic that is still spreading 41 years later, with 1.5 million new infections in 2020, a slower rate than in previous years but still significant. In particular, the unchanged high rates of new infections in Eastern Europe and Central Asia point to the multiple challenges in prevention that need to be overcome now and in the near future. Although the success of therapy to date leads us to believe that the life expectancy of PWLH is near normal, knowledge of the natural course of HIV infection remains essential to make the diagnosis before the onset of AIDS, even in the case of early symptoms. With 40–50% of all infected people in Europe unaware of their HIV infection, significant challenges remain. These are currently being addressed collectively in Europe (https://eurotest.org/) to provide patients with timely antiretroviral treatment and reduce the number of new infections.

Literature

Anonymous: Acquired immunodeficiency in hemophilia. Lancet 1983; 1: 745

Barre-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for AIDS. Science 1983, 220: 868-71.

Bartholomew CF, Jones AM. Human bites: a rare risk factor for HIV transmission. AIDS 2006, 20:631-2.

Castro KG, Lieb S, Jaffe HW, et al. Transmission of HIV in Belle Glade, Florida: lessons for other communities in the US. Science 1988, 239: 193-7.

Centers for Disease Control (a). Epidemiologic notes and reports persistent, generalized lymphadenopathy among homosexual males. MMWR Morb Mortal Wkly Rep 1982, 31: 249

Centers for Disease Control (b). Epidemiologic notes and reports update on Kaposi's sarcoma and opportunistic infections in previously healthy persons — the United States. MMWR 1982, 31: 294.

Centers for Disease Control. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and HIV infection and AIDS among children aged 18 months to <13 years – United States, 2008. MMWR Recomm Reports 2008;57:1-8

Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J 2011;365:493-505

Essex M. Adult T-cell leucemia/lymphoma: role of a human retrovirus. J Natl Cancer Inst 1982; 69: 981-985

Essex M, McLane MF, Lee TH, et al. Antibodies to cell membrane antigens associated with human T-cell leucemia virus in patients with AIDS. Science 1983; 22: 859-862

Essex ME. Origin of acquired immunodeficiency syndrome. In: VT DeVita jun, S Hellman, SA Rosenberg: AIDS: Biology, diagnosis, treatment and prevention. 4th edition, Lippincott-Raven Publ, 3-14; 1997

Eyster ME, Koch KL, Abt AB, et al. Cryptosporidiosis in a hemophiliac with acquired immunodeficiency. Blood 1982; 60 (Suppl 1): 211A (abstract)

Gallo RC, Sarin PS, Gelmann EP, et al. Isolation of human T-cell leucemia virus in acquired immunodeficiency syndrome. Science 1983; 220: 865-867

Gaur A, Dominguez K, Kalish M, Rivera-Hernandez D, Donohoe M, Mitchell C. Practice of offering a child pre-masticated food: an unrecognized possible risk factor for HIV transmission. Abstract 613b, 15th CROI 2008, Boston.

Goldsmith JC, Moseley PL, Monick M, et al. T-lymphocyte subpopulation abnormalities in apparently healthy patients with hemophilia. Ann Intern Med 1983; 98: 294-296

Gottlieb MS, Schanker HM, Fan PT, et al. Pneumocystis Pneumonia – Los Angeles. MMWR Weekly 1981, 30: 250-2s.

Gottlieb MS, Schroff R, Schanker HM, et al. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N Engl J Med 1981, 305:1425-31.

Henderson DK, Fahey BJ, Willy M, et al. Risk for occupational transmission of human immunodeficiency virus type 1 (HIV-1) associated with clinical exposures. A prospective evaluation. Ann Intern Med 1990, 113:740-6.

Kornfeld H, Vande-Stouwe RA, Lange M, et al. T-lymphocyte subpopulations in homosexual men. New Engl J Med 1982; 307: 729-731

Lifson AR, O'Malley PM, Hessol NA, et al. HIV seroconversion in two homosexual men after receptive oral intercourse with ejaculation: implications for counseling concerning safe sexual practices. Am J Public Health 1990; 80: 1509-1511

Luban NLC, Kelleher JF jr, Reaman GH. Altered distribution of T-lymphocyte subpopulations in children and adolescents with haemophilia. Lancet 1983; 1: 503-505

Mahiane SG, Legeai C, Taljaard D, et al. Transmission probabilities of HIV and herpes simplex virus type 2, effect of male circumcision and interaction: a longitudinal study in a township of South Africa. AIDS 2009; 23: 377-383

Marx JL. New disease battles a medical community. Science 1982; 217: 618-621

Masur H, Michelis MA, Greene JB, et al. An outbreak of community-acquired Pneumocystis carinii pneumonia: initial manifestation of cellular immune dysfunction. N Engl J Med 1981, 305:1431-8.

Mildvan D, Mathur U, Enlow RW, et al. Opportunistic infections and immune deficiency in homosexual men. Ann Intern Med 1982; 96: 700-704

O'Brien TR, Blattner, WA, Waters D, et al. Serum HIV-1 RNA-levels and time to development of AIDS in the Multicenter Hemophilia Cohort Study. JAMA 1996; 276: 105-110

Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J: Estimating per-act HIV transmission risk: a systematic review. Aids 2014, 28(10):1509-1519.

Poiesz PJ, Ruscetti FW, Gazdar AF, et al. Detection and isolation of type C retrovirus particles from fresh and culture lymphocytes of a patients with cutanous T-cell lymphoma. Proc Natl Acad Sci USA 1980; 77: 7415-7419

Popovic M, Sarngadharan MG, Read E, et al. Detection, isolation and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. Science 1984; 224: 497-500

Ragni MV, Lewis JH, Spero JA, et al. Acquired immunodeficiency-like syndrome in two haemophiliacs. Lancet 1983; 1: 213-214

Rasi VP, Koistinen JL, Lohman CM, et al. Normal T-cell subset ratios in patients with severe haemophilia A treated with cryoprecipitate. Lancet 1984; 1: 461.

Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. Lancet 2019, 393:2428-2438.

Schwartländer B, Horsburgh CR Jr, Hamouda O, et al. Changes in the spectrum of AIDS-defining conditions and decrease in CD4+ lymphocyte counts at AIDS manifestation in Germany from 1986 to 1991. AIDS 1992, 6:413-20.

Selik RM, Mokotoff ED, Branson B et al. Revised Surveillance Case Definition for HIV Infection — United States, 2014 Recommendations and Reports. MMWR 2014, 6: 31-10

Siegal FP, Lopez C, Hammer GS, et al. Severe acquired immunodeficiency in male homosexuals manifested by chronic perianal ulcerated herpes simplex lesions. N Engl J Med 1981; 305: 1439-1444

Stahl RE, Friedman-Kien A, Dubin R, et al. Immunologic abnormalities in homosexual men. Relationship to Kaposi's sarcoma. Am J Med 1982; 73: 171-8

Stein DS, Lyles RH, Graham NM, et al. Predicting clinical progression or death in subjects with early-stage HIV infection: a comparative analysis of quantification of HIV RNA, soluble tumor necrosis factor type II receptors, neopterin, and beta2-microglobulin. J Infect Dis 1997, 176:1161-7.

Vernazza P, Hirschel B, Bernasconi E, Flepp M. HIV-infizierte Menschen ohne andere STD sind unter wirksamer antiretroviraler Therapie sexuell nicht infektiös. Schweizerische Ärztezeitung 2008; 89:5, 165-169. www.aids.ch/d/hivpositiv/pdf/EKAF_d.pdf

Vittinghoff E, Douglas J, Judson F, et al. Per-contact risk of HIV transmission between male sexual partners. Am J Epidemiol 1999, 150:306-11.

Worobey M, Gemmel M, Teuwen DE, et al. Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960. Nature 2008, 455:661-4.

Zhu T, Korber BT, Nahmias AJ, Hooper E, Sharp PM, Ho DD. An African HIV-1 sequence from 1959 and implications for the origin of the epidemic. Nature 1998; 391:594-7.

2. HIV testing

CHRISTIAN NOAH

Rapid diagnosis of HIV infection enables access to antiretroviral therapy and helps prevent transmission. Despite widespread testing, many infections are still diagnosed at a late stage. In many European countries, there is already an advanced immune deficiency or even an AIDS-defining disease in about one-third of the cases. The number of undiagnosed HIV infections is high.
The indications and reasons for testing may vary. For example, every pregnant woman must be offered an HIV test. HIV diagnostics are also mandatory for blood and organ donation. HIV tests are also performed in cases of clinical suspicion of infection after exposure in a private or professional environment and to clarify the infection status in a partnership.

Diagnostics basics

Laboratory diagnosis is based on a screening test, the result of which must be verified with an alternative test format (confirmatory test) in the reactive case (stepwise diagnosis). Nowadays, a so-called 4th or 5th generation test is used as a screening test due to its comparatively high sensitivity. In addition to HIV-specific antibodies, these tests also detect a component of the virus, the p24 antigen. Because this antigen is detectable earlier than the antibodies, the diagnostic window is smaller than earlier test generations (Vallefuoco 2016). With a 5th generation test, in the case of a reactive result, it is possible to differentiate further whether the measurement signal results from detecting p24 antigen or HIV antibodies. Approved screening tests detect all known types (HIV-1 and -2), groups, and subtypes.
The principle of all commercially available screening test systems is based on antigen-antibody binding: the "prototype" is an ELISA (Enzyme-Linked Immunosorbent Assay). The central element is a plastic plate with 96 wells (microtiter plate) serving as reaction vessels (wells). On the surface of each well are coupled HIV antigens or HIV p24 antibodies. When serum or plasma containing HIV antibody or p24 antigen is added to a well, binding occurs. An enzyme-labeled second antibody is added that recognizes and binds human antibodies. Finally, a substrate is added, which is converted by the enzyme on the second antibody. This results in a color change, which is measured photometrically. The optical density correlates with the concentration of the antibodies or the p24 antigen. Modern test systems are mainly automated and standardized; they provide a test result in less than one hour. In these systems, the solid phase consists not of a plastic plate but microparticles to which viral antigens and antibodies are coupled. Accordingly, the method is called "Microparticle Enzyme Immunoassay" (MEIA).
The measured value is usually a dimension-free index calculated from the quotient of the measured value of the sample and the negative control (Sample/Control, S/Co). Values below one are judged to be negative, and values above are considered to be reactive. It should always be referred to as a "reactive" result rather than a positive result to document that this result must be confirmed using a second test format.
While maximum sensitivity is the top priority for the screening test (no infection should be overlooked), the confirmation test focuses on high specificity. A specificity of at least 99.5% is required for the screening tests approved in Germany. One in 200 HIV-negative samples may be falsely reactive on average. False-reactive results can be caused by, among other things, stimulation of the immune system (viral infections, pregnancy, vaccinations, autoimmune diseases). Pregnant women or dialysis

patients are more likely to have false-reactive screening tests. In our experience, at least one in five initial reactive screening test results is non-specific. The HIV prevalence plays a decisive role in the probability that a reactive screening test indicates an infection (positive predictive value): the lower the prevalence in a population group, the lower the significance of the reactive screening test result. In principle, an alternative test procedure must confirm every reactive result.

Immunoblot analysis (Western or line blot) is usually performed to confirm a reactive screening test. In the Western blot, viral proteins (antigens) are electrophoretically separated according to their molecular weight and transferred to a membrane, which is then used as a test strip. A further development is the so-called line blot, in which recombinant HIV antigens are sprayed onto a membrane. The test strip is incubated with patient serum or plasma. If HIV-specific antibodies are present, they bind to the antigen. The antigen-antibody complex is visualized analogous to ELISA (see above) using an enzyme-labeled antibody and a test strip substrate. A corresponding band spectrum appears on the test strip according to the antibody specificities present.

Ideally, the laboratory uses an immunoblot that also detects antibodies against HIV-2. If only a synthetic HIV-2 peptide is used for this purpose, any reaction must be confirmed by an additional HIV-2-specific immunoblot. Usually, the immunoblot discriminates between HIV-1 and HIV-2, but in some cases, cross-reactivities occur, i.e., antibody reactions against both virus types. In these cases, differentiation can be performed using a type-specific HIV PCR. The laboratory findings should always indicate whether an HIV-1 or HIV-2 infection is present, as this influences the selection of the therapy regimen.

HIV proteins are assigned to three functional groups. Here, "p" stands for protein, "gp" for glycoprotein. The following number denotes the molecular weight in each case (see Table 1). While antibodies against p24 and gp120 are detectable early, other antibodies (e.g. against p31) usually appear later (Fiebig 2003).

The interpretation criteria for a positive test result are defined by the manufacturers after appropriate validation and are binding as part of the approval of the test system. As a rule, an immunoblot is considered positive if at least two bands are visible. Further diagnostic clarification should be carried out if an antibody reaction is detected but does not meet the conditions for a positive result in terms of number and specificity. Since this constellation can occur in an acute infection, especially if "early" antibodies (for example, against p24) are detectable, it makes sense to perform an HIV PCR or at least a follow-up after 2–3 weeks.

Table 1: HIV proteins, three functional groups.

	Antigens		Function
	HIV-1	HIV-2	
Envelope proteins (env)	gp160	gp140	Precursor of the envelope proteins
	gp120	gp125	Outer layer protein
	gp41	gp36	Transmembrane protein
Polymerase proteins (pol)	p66	p68	Reverse transcriptase, RNase H
	p51	p53	Reverse transcriptase
	p32	p34	Endonuclease, integrase
Core proteins (gag)	p55	p56	Precursors of the nuclear proteins
	p24	p26	Inner core protein
	p17	p16	Outer core protein

In contrast to a 4th or 5th generation screening test, the p24 antigen is not detected by immunoblot. In the constellation "reactive screening test – negative immunoblot", an acute infection in which no HIV-specific antibodies have yet been formed but the p24 antigen is already detectable cannot be ruled out. At least such a result should be checked after 2–3 weeks. If an acute infection is suspected (acute retroviral syndrome, risk contact), HIV PCR is useful. PCR is also recommended without a risk history if the screening test is highly positive with a negative confirmatory test. For 5th-generation tests, detection of p24 antigen usually indicates acute infection. In contrast, a nonspecific reaction is more likely if only an antibody reaction is detectable. In case of doubt, the further procedure (PCR vs. follow-up) should be discussed with the laboratory.

To confirm a reactive screening test, HIV PCR can be used as an alternative to immunoblot (see below). This procedure is particularly useful if only a p24 antigen but no antibody response is detectable in the screening test. Other test formats (e.g., immunofluorescence tests) are less common.

A duplicate sample must confirm each positive initial result to exclude the possibility of sample mix-up, which is unlikely but possible. In particular, if HIV infection is suspected, the viral load (see chapter *Monitoring ART*) can also be determined for confirmation. A new serological test is then unnecessary. The earlier recommendation to inform patients about the test result only after this second blood sample has been taken is obsolete.

HIV PCR

In addition to serological test systems, molecular methods (nucleic acid amplification methods, NAT) are also available for detecting viral RNA. The most essential method is PCR; other methods (bDNA, NASBA) are less common. Quantitative detection of HIV RNA ("viral load determination") is an essential part of monitoring HIV infection (Wittek 2007, Thompson 2010). HIV PCR is also mandatory for blood donations. In contrast to individual serological testing, however, not every single donation is examined by PCR, but as a rule, so-called "pools" consisting of several individual samples. The maximum pool size depends on the sensitivity of the test method used. In a single sample, an HIV concentration of at least 10,000 international units/mL must be reliably detected. Although often not formally approved by the manufacturers for this indication, HIV PCR is nowadays also an integral part of primary HIV diagnostics beyond blood and organ donation. Indications include the exclusion of infection in newborns of HIV-positive mothers (see below), unclear serological constellations, and the suspicion of an acute HIV infection. HIV PCR can also be used – as an alternative to immunoblot – to confirm a reactive screening test. A reliable positive result in primary diagnostics can be assumed from a viral load of 1,000 copies/mL.

However, due to possible false-negative results, HIV PCR is of limited use for the exclusion of HIV transmission – it should only be used in addition to, and not instead of, serological testing procedures. Possible causes of false-negative results are:

1. Although HIV-2 is rare in most countries (the share of new diagnoses is 0.5% in Germany), it should be noted that routine PCR only detects HIV-1. For the molecular detection of HIV-2, an additional PCR is required.
2. HIV is characterized by high genetic diversity. In the case of new or previously unknown variants, sensitivity can be impaired by mutations affecting the primer and probe binding region. So-called "dual-target" PCR minimizes the risk of false-negative results (Chudy 2012; see also chapter *Monitoring ART*). Dual-target PCR has been mandatory in blood donation since 2015.

3. In the rare "elite controllers", no viral RNA is detectable in plasma by PCR despite serologically confirmed infection (Okulicz 2011).
4. A false-negative diagnosis would result if screening under successful ART was based on PCR alone.

HIV rapid and self-testing

Rapid tests correspond functionally to a screening test, i.e., an immunoblot must confirm a reactive result. They are simple and can be used as so-called "point-of-care" tests without equipment. Depending on the approval, whole or capillary blood (from fingertip or earlobe) is suitable as test material in addition to plasma and serum so that no centrifuge is required. For some tests, urine or oral fluid are also possible – however, sensitivity decreases when materials other than serum or plasma are used (Pavie 2010). The result is available in less than 30 minutes. The rapid test is usually based on immunochromatographic methods, but particle agglutination or immunofiltration are used less frequently (Branson 2003, Greenwald 2006).
Rapid tests that carry a CE mark and meet the requirements of the European Regulation for in vitro diagnostic medical devices are considered safe and show high sensitivity and specificity. 4th generation rapid tests that detect the p24 antigen component are superior to earlier tests (Chetty 2012, Fitzgerald 2017). However, sensitivity remains poor in acute HIV infection before seroconversion (Kilembe 2012, Brauer 2013, Lewis 2015, Tan 2016). Rapid tests should, therefore, only be used for initial guidance. They seem unsuitable for ruling out acute infection. The result should be confirmed in the routine laboratory with a conventional HIV test.
Rapid tests are helpful when the test result has an immediate consequence: in emergency surgery, needlestick injuries, or pregnancies with unknown HIV status at delivery. In such emergencies, the collaborating laboratory should be informed: even the result of a conventional HIV test may be available within only one hour of sample receipt. Rapid tests are also useful in countries lacking medical infrastructure and in the context of low-threshold testing services.
The first rapid HIV test for self-use (self-test) was already approved in the US in 2012. In Europe, self-tests have been available in pharmacies and drugstores since 2018. Given many undiagnosed infections and positive experiences from other countries, self-tests are a valuable addition to existing test offerings. Despite many concerns (lack of possibility of immediate confirmation or counseling and possible application errors with the risk of false-negative results), the willingness to test can be increased among people whose previous counseling and testing offers have not been reached.

The diagnostic window

The term "diagnostic window" refers to the period between the transmission of a pathogen and the first appearance of laboratory-measurable infection markers such as antibodies, antigens, or nucleic acids. In the case of HIV transmission, antibody production begins at the earliest after two weeks. After four weeks, specific antibodies are detectable in 60–65%, six weeks in 80%, eight weeks in 90% and twelve weeks in 95%. A "seronegative" HIV infection is a rarity (Spivak 2010). The p24 antigen can be detected about five days before seroconversion (the first appearance of specific antibodies). The earliest laboratory marker is HIV RNA, which can be detected about seven days before the p24 antigen and as early as two weeks after infection (Fiebig 2003). However, a negative PCR result at this time does not reliably exclude transmission.

A negative result in the screening test indicates the absence of HIV antibodies and p24 antigen at the time of testing. Accordingly, the person is considered HIV-negative. However, the certainty of this result depends in particular on the time interval to the possible transmission event. This has significant consequences:

1. An HIV test immediately after exposure is not meaningful since no antibodies have yet been formed. It is helpful in the 3rd week at the earliest unless it is to be proven, e.g., after a needlestick injury, that there was no HIV infection at the time of exposure.
2. According to guidelines (Gökengin 2014), HIV infection can be excluded with sufficient certainty six weeks after exposure, provided that tests of at least the 4th generation are used. In the case of post-exposure prophylaxis (PEP), the time window starts only from the end of PEP. In the case of immunodeficiencies or the presence of other sexually transmitted infections, a control test is recommended after 12 weeks. For 3rd generation HIV tests or rapid tests, the diagnostic window is always 12 weeks.
3. A negative test result is only sufficiently reliable if there was no re-exposure within the diagnostic window.

Diagnostics in pregnant women and newborns

Timely diagnosis and therapy can almost always prevent mother-to-child transmission (Gingelmaier 2005). According to current guidelines (2022), an HIV test is recommended for every pregnant woman as early as possible in pregnancy. Repeated testing is recommended in case of risk constellation (e.g., HIV-positive partner). A medical consultation should precede the HIV test. Only the performance of the test, but not the result, is documented in the maternity record.

In newborns of HIV-positive mothers, maternal antibodies may remain detectable up to the age of 18 months. They are transmitted transplacentally from the 32nd week of pregnancy but do not confer nest protection. A serological HIV test alone is not sufficient for the detection or exclusion of vertical HIV transmission since a positive result is to be expected in every case (Read 2007). According to the German-Austrian guidelines (2020), at least two negative PCR results are required to exclude transmission. The first HIV PCR should be performed after the first month of life (sensitivity 96%, specificity 99%) and the second after the third month of life because of the nearly one hundred percent sensitivity and specificity. However, laboratory diagnostics can only rule out vertical transmission if there has not been a renewed risk of infection through breastfeeding in the meantime. Even in the case of negative PCR results, the disappearance of maternal antibodies should be documented at least once. In the positive case, the result must be confirmed by examination of a second sample.

Diagnostics for occupational exposure

After needlestick injuries or other occupational exposure, hepatitis B and C and HIV infection should be ruled out in the index person (consent of the index person!). In the case of HIV infection, this is done using a screening test. Due to the possibly necessary post-exposure prophylaxis (PEP), every needlestick injury is an emergency: the earlier PEP is started, the higher the chances of success. According to the German-Austrian PEP guidelines (2022), PEP should be started within 24 hours, ideally within 2 hours. If a short-term result of a screening test or a rapid test is not available, PEP can also be started in case of doubt, which can be stopped at any time in case of a negative result.

If an index person does not exhibit symptoms compatible with an acute retroviral syndrome, a negative screening test excludes an infection with a high degree of certainty. HIV PCR is usually only considered if there is evidence of acute HIV infection in the index person. If, on the other hand, the index person has an HIV infection or if the status is unknown, an immediate screening test is advisable for the exposed person. It documents that no HIV infection was present at the time of the accident. Checks should be carried out after six weeks and three months. After six months, only HCV and (in the absence of immunity) HBV diagnostics should be performed (Stranzinger 2018).

Practical hints

• **Legal situation**: The HIV test retains a special status. Due to possible medical, social, and legal consequences, a test without explicit consent is considered an invasion of personal rights and can thus have legal implications for the ordering physician. Written consent is not required; however, it should be documented. For children or minors, parents or guardians must consent. In the US, CDC recommendations now include an "opt-out" screening concept to increase willingness to test. Although information is provided about a planned HIV test, it is always performed if the person concerned does not explicitly refuse it (Branson 2006).
• **Counseling:** HIV testing should be accompanied by prior counseling and education. This should include the test concept (step-by-step diagnostics) and its limitations, including the value of (frequently requested) HIV PCR as part of primary diagnostics (conditional suitability for rapid exclusion of HIV infection or transmission). The high cost of PCR is rarely a deterrent if the patient suffers from the disease. Attention should be drawn to the constellations of results, particularly the "diagnostic window." The desire for an HIV test can also be an occasion to discuss transmission risks and other relevant sexually transmitted infections (syphilis, gonorrhea, chlamydial infection).
• **Notification of findings:** If necessary, a negative test result can be communicated by telephone if the person concerned has been informed beforehand. Ideally, the diagnosis of "HIV" should be displayed in a personal conversation by a physician or healthcare professional. The affected person's reaction can only be poorly assessed on the phones. HIV centers and counseling services should be mentioned. Similarly, a negative confirmatory test with a reactive screening test should be discussed in person to discuss the possibility of acute infection. A reactive screening test without a confirmatory test should never be disclosed.

Literature

Branson BM. Point-of-Care Rapid Tests for HIV Antibodies. J Lab Med 2003; 27:288-295.

Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR 2006, 55:1-17.

Brauer M, De Villiers JC, Mayaphi SH. Evaluation of the Determine fourth generation HIV rapid assay. J Virol Methods 2013; 189: 180-183.

Chetty V, Moodley D, Chuturgoon A. Evaluation of a 4th generation rapid test for earlier and reliable detection of HIV infection in pregnancy. J Clin Virol 2012; 54: 180-184.

Chudy M, Weber-Schehl M, Pichl L. Blood screening nucleic acid amplification tests for human immunodeficiency virus Type 1 may require two different amplification targets. Transfusion 2012, 52: 431-439.

European Centre for Disease Prevention and Control. HIV/AIDS surveillance in Europe 2013. Stockholm: ECDPC 2014.

Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implication for diagnosis and staging o of primary infection. AIDS 2003, 17: 1871-1879.

Fitzgerald N, Cross M, O'Shea S, et al. Diagnosing acute HIV infection at the point of care: a retrospective analysis of the sensitivity and specificity of a fourth-generation point-of-care test for detecting HIV core protein p24. Sex Transm Infect 2017, 93: 100-101.

Gingelmaier A, Hollwitz B, Casteleyn et al. Schwangerschaftsverlauf und kindliches Outcome bei 599 HIV-exponierten Schwangerschaften an deutschen Schwerpunktzentren 1999-2003. Geburtshilfe und Frauenheilkunde 2005, 65:1058-1063.

Gökengin D, Geretti AM, Begovac J, et al. 2014 European Guideline on HIV testing. Int J STD AIDS 2014, DOI 10.1177/0956462414531244

Greenwald JL, Burstein GR, Pincus J, Branson B. A rapid review of rapid HIV antibody tests. Current Infectious Disease Reports 2006, 8:125–131.

Kilembe W, Keeling M, Karita E, et al. Failure of a novel, rapid antigen and antibody combination test to detect antigen-positive HIV infection in African adults with early HIV infection. PLoS ONE; 7: e7154.

Lewis JM, Macpherson P, Adams ER, et al. Field accuracy of fourth-generation rapid diagnostic tests for acute HIV-1: a systematic review. AIDS 2015; 29: 2465-2471.

Okulicz JF, Lambotte O. Epidemiology and clinical characteristics of elite controllers. Curr Opin HIV AIDS 2011, 6:163-168.

Pavie J, Rachline A, Loze B, et al. Sensitivity of five rapid HIV tests on oral fluid or finger-stick whole blood: a real-time comparison in a healthcare setting. PLoS ONE 2010; 5:e11581.

Read JS, Committee on Pediatric AIDS. Diagnosis of HIV-1 infection in children younger than 18 months in the US. Pediatrics 2007, 120: e1547-62

Spivak AM, Sydnor ER, Blankson JN, Gallant JE. Seronegative HIV-1 infection: a review of the literature. AIDS 2010; 1407-1414.

Stranzinger J, Wunderle W, Dulon M, et al. Konsenspapier zur Nachsorge von Stich- und Schnittverletzungen mit infektiösem Material. ASU Arbeitsmed Sozialmed Umweltmed 2018; 53; 249-255.

Tan WS, Chow EP, Fairley CK, et al. Sensitivity of HIV rapid tests compared with fourth-generation enzyme immunoassays or HIV RNA tests. AIDS 2016; 30: 1951-1960.

Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. JAMA 2010; 304: 321-333.

Vallefuoco L., Mazzarella P, Portella G. Fourth generation assays for HIV testing. Expert Rev Mol Diagn 2016. 16(7): 723-732.

WHO. AIDS: Proposed criteria for interpreting results from Western blot assays for HIV-1, HIV-2 and HTLV-I/HTLVII. Bull World Health Organ 1991; 69(1):127-129.

Wittek M, Stürmer M, Doerr HW, Berger A. Molecular assays for monitoring HIV infection and antiretroviral therapy. Exp Rev Mol Diagn 2007,7: 237–4.

3. Pathophysiology of HIV infection

HENNING GRUELL, PHILIPP SCHOMMERS, FLORIAN KLEIN

Structure and design

The human immunodeficiency viruses (HIV) are members of the lentivirus genus within the family of retroviruses. Two types of HIV (HIV-1 and HIV-2) need to be distinguished. These have a similar structure and a nucleic acid identity of about 50% but differ in the typically observed disease courses. HIV-2 (see chapter *HIV-2*) is endemic in West Africa but accounts for only a small proportion (<5%) of global HIV infections. Therefore, this chapter focuses on HIV-1.

Morphology

HIV-1 particles are about 100 nm in diameter and have a lipid surface membrane in which about 12–16 glycoprotein complexes (envelope, Env) are embedded. These are the only proteins of viral origin (Zhu 2006) expressed on the viral surface and form trimers composed of three heterodimers. These heterodimers are formed by two non-covalently linked glycoproteins (gp), named gp120 and gp41, according to their molecular mass (in kilodaltons). In addition to the Env protein, the lipid membrane of the virus contains human proteins that are incorporated during the budding of the virus from the virus-producing host cell. The inside of the viral membrane is lined by the matrix protein (p17), which houses the conically shaped capsid protein (p24) that encapsulates the viral genetic information and proteins. Within the capsid, the viral genome is present as two copies of single-stranded RNA bound in a protein-nucleic acid complex to nucleoprotein p7, reverse transcriptase (p66/p51), and integrase (p32). The viral protease, which plays an essential role in viral maturation after budding, is also found within the virion (Figure 1).

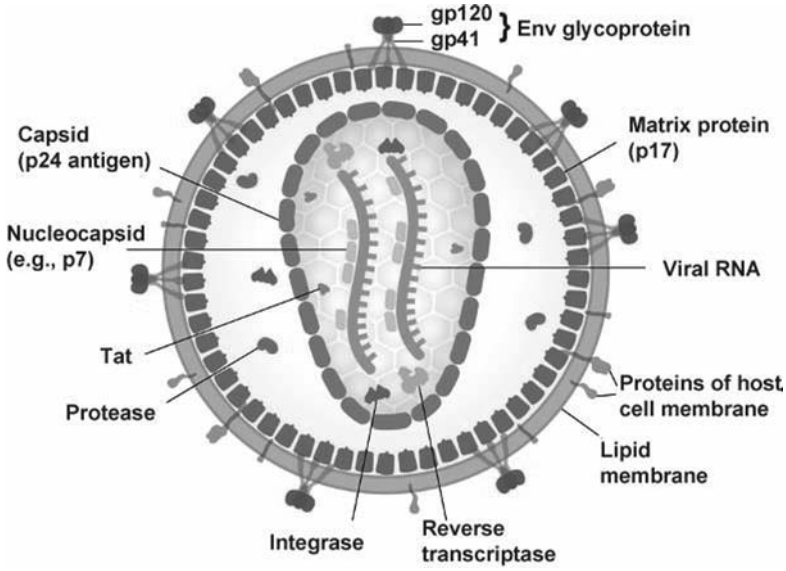

Figure 1: Structure of the HIV-1 virion.

Organization of the viral genome

Retroviruses have a similar genome structure characterized by partly overlapping open reading frames, allowing many different proteins to be encoded by a single nucleic acid strand (Figure 2). The three major components of the HIV-1 genome are the genes *gag* ("group-specific antigen"), *pol* ("polymerase"), and *env* ("envelope"). Each gene encodes different proteins that can be produced due to alternative splicing, ribosomal frameshifts, and cleavage of precursor peptides. The LTR regions ("long terminal repeats") located at both the 5' and 3' ends of the genome are involved in the regulation of transcription and integration into the host genome.

Viral proteins

While ***gag*** encodes for **structural proteins** (p24, p17, p7, and p6) and ***env*** encodes for **surface proteins** (gp120 and gp41), ***pol*** encodes for **enzymes** essential for viral replication (reverse transcriptase, protease, and integrase). These enzymes are targets of several antiretroviral drug classes and are discussed in more detail in the following section.

In addition, the HIV-1 genome has several genes encoding for proteins involved in **regulatory** processes (***tat***, ***rev***), as well as other so-called **accessory** genes (***nef, vif, vpr, vpu***) that contribute to viral replication:

Tat is involved in the initiation of viral transcription.

Rev binds to the genome's RRE (Rev Response Element) and is involved in the export of viral mRNA from the nucleus to the cytoplasm.

Nef induces downregulation of CD4, CD8, CD28, CD3, SERINC3/5, tetherin, and HLA class I antigens on the surface of HIV-1-infected cells. To this end, **Nef** interferes with intracellular transport mechanisms, including clathrin-coated vesicles containing cellular surface proteins. Lower expression of these surface markers reduces the antiviral immune response, increases the infectivity of HIV, and leads to higher viral replication rates (Buffalo 2019).

Vif inhibits the activity of APOBEC3G, a human enzyme that damages viral nucleic acid through mutations (Mariani 2003; see below).

Among other things, **Vpr** is involved in transporting the viral genome into the cell nucleus.

Vpu blocks the action of the antiviral tetherin protein that inhibits viral release from the cell surface. In addition, **Vpu** is involved in the degradation of CD4-gp120 complexes, increasing the levels of Env protein available for viral replication (Cullen 1998).

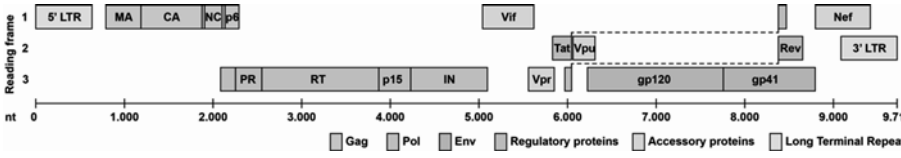

Figure 2: Gene map of HIV-1 showing encoded proteins. Individual gene regions overlap on the RNA strand of the virus and are transcribed from different reading frames. The gag, pol, and env genes encode different proteins: matrix protein (MA), capsid protein (CA), nucleocapsid (NC), protease (PR), reverse transcriptase (RT), integrase (IN), glycoprotein 120 (gp120), glycoprotein 41 (gp41), and other proteins such as p6 and p15. The regulatory proteins Tat and Rev are each composed of two exons (connected with dashed lines). Nucleotide numbering (nt) is based on reference virus strain HXB2.

The replication cycle of HIV-1

Entry of HIV-1 into the target cell

CD4 as primary HIV-1 receptor: In addition to the T cell receptor, the glycoprotein CD4 interacts with CD4 T-cells with the MHC class II complex on the surface of antigen-presenting cells. CD4 is, therefore, typically expressed on the surface of T helper cells but also found on monocytes, macrophages, dendritic cells, and CNS microglial cells. The viral Env surface protein binding to CD4 is the initial step of the viral replication cycle (Dalgleish 1984) and determines the spectrum of cell types infected by HIV-1 (Figure 3).

Chemokine receptors as HIV-1 co-receptors: While the binding of HIV-1 to CD4 is necessary, it is insufficient for cell infection. After the initial interaction of the virus with CD4, additional binding to a cellular coreceptor (the human chemokine receptor CCR5 or CXCR4) is required (Doranz 1996, Feng 1996). Different T cell populations differ in the expression of these chemokine receptors. For example, CCR5 is primarily found on the surface of memory T cells whereas CXCR4 is expressed on naive T cells. In addition, CCR5 can be detected on the surface of macrophages and dendritic cells.

HIV-1 variants differ in their requirements for the coreceptor (**tropism**), which is determined by sequences in the V3 loop of the envelope protein (Env). This results in the differentiation of viruses only using CCR5 as a coreceptor ("R5-tropic"), viruses that rely on CXCR4 ("X4-tropic"), and viruses that can use both coreceptors ("dual tropism").

Primary infection with HIV-1 is typically caused by R5-tropic variants that dominate in the initial phase of infection. However, a tropism switch to X4-tropic viruses associated with higher disease progression can occur in the course of infection.

The importance of the CCR5 coreceptor in the establishment of HIV-1 infection is evident from people with a defective CCR5 gene: A deletion of 32 base pairs in the CCR5 gene (CCR5 Δ32) leads to the formation of a non-functional CCR5 molecule. Homozygous carriers of this mutation (approx. 1% prevalence in the Caucasian pop-

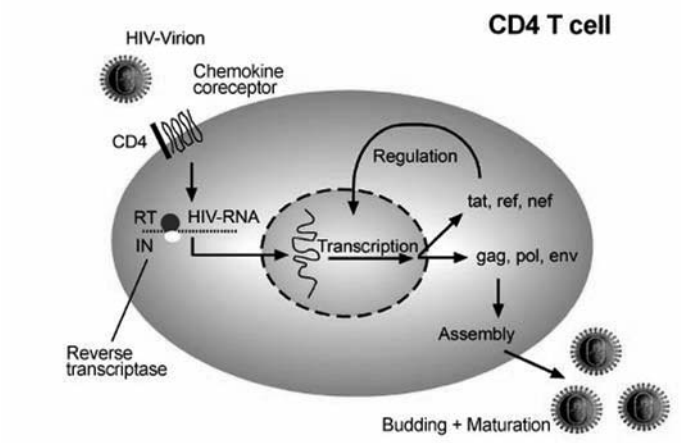

Figure 3: Life cycle of HIV. After binding to the surface receptors, the virus fuses with the cell membrane. After the release of the capsid into the cytoplasm, reverse transcription of viral RNA into DNA begins. DNA is transported into the cell nucleus (possibly still in the intact capsid) and incorporated into the human genome by the viral enzyme integrase. Regulatory genes and structural proteins are transcribed and translated from this so-called proviral DNA. New virus particles are assembled at the cell surface and only mature completely after budding.

ulation) are largely resistant to infection with HIV-1 and only occasional infections with X4-tropic viruses have been observed (Liu 1996, Naif 2002). CCR5 Δ32-mediated resistance also forms part of the therapeutic approach in the small number of HIV-1 patients reported cured to date (Hütter 2009, Gupta 2020, Hsu 2022, Jensen 2023). Due to severe hematologic disease, these individuals were dependent on allogeneic stem cell transplantation for which stem cell donors with a homozygous CCR5 Δ32 mutation could be identified. After discontinuation of antiretroviral therapy, no evidence of persistent viral replication was found in these patients. Heterozygous carriers of CCR5 Δ32 (approximately 10% in Europe) show reduced CCR5 expression associated with reduced susceptibility to HIV-1 infection, lower viral load, and slower disease progression (Dean 1996).

Fusion of HIV-1 with the cell membrane: CD4-binding of the gp120 unit induces a change in the structural conformation of Env and enables additional binding to the respective coreceptor. Through an incompletely understood mechanism mediated by gp41, subsequent fusion occurs between the viral and cellular membranes (Shaik 2019).

Processes after the virus entry

After membrane fusion, the viral capsid enters the cytosol and is transported along microtubules towards the nucleus. After entering the cytosol and starting from the LTR regions of the viral genome, the viral RNA is converted into double-stranded DNA by the enzyme **reverse transcriptase** (RT). This highly error-prone process introduces sequence mutations and often leads to defects in the viral genome, precluding the formation of new viral particles. However, the high mutation rate (approximately five to ten errors per HIV-1 genome per round of replication) also explains the large sequence variability of HIV-1. It leads to the development of closely related but differing viral variants **("quasispecies")** within an infected individual (Preston 1988). Most critically, the incorporation of mutations during viral replication can also result in the development of resistance to antiviral drugs or the host immune response.

During uncoating, the capsid disintegrates and releases the viral genetic information in the form of the pre-integration complex that supports the integration of the viral DNA into the human genome. While earlier studies suggested uncoating to be initiated shortly after viral entry into the cytosol, more recent data indicate that it occurs only upon reaching the nucleus or even within the nucleus (Zila 2021). This may be necessary to prevent viral nucleic acid recognition by cellular "pattern recognition receptors" (PRRs). In addition, the binding of cyclophilin a to the viral capsid shortly after entry into the cell also serves this purpose (Campbell 2015).

Within the nucleus, the viral enzyme **integrase** mediates the stable integration of the viral genetic information as double-stranded DNA into the human genome. This integration does not appear to occur in specific chromosomal regions but is clustered in regions of actively transcribed genes (Schröder 2002). After integration into the human chromosome, the viral genome is also referred to as **provirus.** From the proviral DNA, transcription of viral genes occurs by exploiting cellular replication mechanisms that can be enhanced by cell activation (e.g., NF-κB-mediated in the context of inflammatory immune responses).

Transcription of regulatory genes (***tat***, ***rev***, ***nef***) occurs early after infection, whereas ***gag***, ***pol,*** and ***env*** are transcribed at later stages of infection. The generation of structural proteins takes place in the cytoplasm using ribosomal translation, while the Env precursor protein gp160 is formed in the rough endoplasmic reticulum, cleaved into the gp120 and gp41 subunits by cellular proteases, and transported to the cell surface via the Golgi apparatus.

The interaction of ***gag***-encoded structural precursor proteins, the cell membrane, and cell membrane-integrated Env proteins results in the generation of new virus particles ("**assembly**") at the cell surface, which also includes the packaging of intermediately generated complete HIV-1 genomes in single-stranded RNA form. After **budding** from the cell surface, necessary maturation processes in the secreted virus particles include **protease**-mediated cleavage of structural precursor proteins.

HIV-1 latency

Even after years of continuous suppression of viremia, discontinuation of antiretroviral therapy almost inevitably leads to a "viral rebound" and detectable viral plasma RNA within a few weeks. As with other retroviruses, HIV-1 infection leads to stable integration of viral genetic information into the human genome. Transcription of proviral DNA and subsequent production of viral particles usually results in the rapid death of infected cells. However, in a fashion somewhat similar to other viruses (e.g., herpes viruses), latent infection also develops. In this form of virologic quiescence, no production of viral particles occurs, and the infected cell is unaffected by the viral DNA. In addition, these cells are poorly recognized by the immune system because they do not present viral antigens.

Since HIV-1 also infects very long-lived cells (e.g., memory T cells), a reservoir of latently infected cells persists and can be the source of viral production (e.g., following cellular activation in the context of inflammatory reactions). Based on the observed half-life of the reservoir of latently infected cells circulating in the blood in ART-treated patients (44 months, Finzi 1999), it was calculated that continuous and complete suppression of viral replication over several decades (about 50–60 years) would be necessary to achieve (a highly speculative) elimination of this reservoir. Thus, the reservoir of latently infected cells represents the critical hurdle for HIV-1 cure.

HIV-1 and the immune system

The human immune system plays a unique role in the context of HIV-1 infection. The main clinical manifestations of HIV-1 infection result from direct and/or indirect damage to the immune system, resulting in opportunistic infections and HIV-associated diseases. While the number of CD4 T helper cells has high prognostic and clinical relevance as a surrogate parameter for HIV-mediated immunodeficiency, HIV also damages other immune system components. Although the immune response fails to eliminate the virus once HIV-1 infection is established, immunologic antiviral activity can significantly influence the course of the disease. In particular, spontaneous control of viral load in the blood is related to the immune response. For example, **Long-Term Non-Progressors** (LTNPs, frequency approx. 10%) and **Elite Controllers** (<1%) can be distinguished from other individuals. While LTNPs have a detectable but low viral load of <2,000 HIV-1 RNA copies/mL without therapy, elite controllers often have negative HIV-1 plasma RNA in the absence of antiretroviral therapy.

Due to the high relevance of the immune system in HIV-1 infection, individual components will be discussed in more detail below.

Innate immune system

While relatively non-specific, the innate immune system provides a first and very rapidly active line of defense against pathogens. Although innate immunity does not specifically adapt to a pathogen, it interacts with parts of the adaptive immune system.

Dendritic cells

Dendritic cells (DCs) are a heterogeneous group of myeloid or lymphoid cells whose essential function is HLA class II-mediated presentation of antigens to other immune cells such as T helper cells (Wu 2006). Although DCs are relatively poorly infected by HIV-1, they may play a role in transmission across DC-rich mucosae as part of the processes establishing HIV-1 infection. They can transport HIV in vesicles without becoming infected themselves. Migration into T-cell-rich lymphoid tissues and shedding of the vesicles can subsequently infect CD4 T-cells ("trans-infection") (Wu 2006). It is also possible that DCs themselves become infected and produce viral particles. Plasmacytoid DCs, a rare form of dendritic cells in the blood, can be strongly activated by contact with HIV-1 and contribute to damaging immune activation via the production of pro-inflammatory Interferon-α (Fonteneau 2004).

Follicular dendritic cells (FDCs) represent a cell type that can be distinguished from other dendritic cells. Unlike other dendritic cells, FDCs are not derived from hematopoietic stem cells and do not have HLA class II molecules. They accumulate in lymphoid follicles and interact with B cells in the germinal centers. Importantly, FDCs are considered to trap intact HIV-1 particles on their surface for long periods, allowing subsequent infection or stimulation of other target cells (Smith 2001).

Restriction factors

In recent years, intracellular host mechanisms that serve to defend against HIV-1 have become increasingly known. These restriction factors are located on the cell membrane, in vesicles, or the cytosol and can initiate antiviral mechanisms. However, the accessory proteins of HIV have evolved to enable effective replication despite many of the following restriction factors:

APOBEC3G ("Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G") leads to unspecific degradation of viral nucleic acid by deaminating cytosine to uracil. This results in increased G-to-A mutations with stop codons. However, DNA degradation often occurs beforehand, as uracil is modified by uracil DNA glycosidase, and the viral genome then becomes a target of specific endonucleases (Sauter 2018).

CARD8 ("Caspase recruitment domain-containing protein 8") can recognize the activity of the HIV protease and subsequently induce cell death in infected cells. However, since the HIV protease is usually inactive in the cytosol of infected cells and only takes up its activity in the virion, HIV can bypass this recognition mechanism. Targeted intracellular activation of the HIV protease could make it possible to exploit the effect of CARD8 therapeutically to eliminate infected cells (Wang 2021).

BST-2 ("bone marrow stromal antigen 2", also called tetherin or CD137) is expressed on the cell surface in response to interferon. It prevents the budding of newly produced immature virus particles. In addition, BST-2 can internalize newly formed virions and deliver them to endosomes/lysosomes, which can destroy the viruses. **BST-2** itself acts as a PRR and can initiate cytokine release.

IFI16 ("Interferon-Gamma Induced Protein 16") and **cGAS** ("Cyclic GMP-AMP synthase") recognize the DNA products of reverse transcriptase in the cytosol. cGAS then forms cGAMP, which activates the cell's interferon production via STING ("stimulator of interferon genes") and thus increases the formation of other interferon-stimulated proteins (Altfeld 2015).

MX2 ("MX Dynamin Like GTPase 2") interacts with the HIV capsid directly or via CypA, preventing its uncoating or the correct import of viral DNA into the nucleus. In addition, MX2 appears to be essential for SAMHD1 activity. However, the exact interaction of both factors is still largely unclear (Kane 2013).

RIG-I ("retinoic acid-inducible gene I") is located in the cytosol and can recognize viral RNA of the invading HI virus and newly produced viral mRNA. However, HIV can escape this recognition through protease-mediated degradation of RIG-I (Bergantz 2019).

SAMHD1 ("SAM domain and HD domain-containing protein 1") inhibits HIV-1 replication, probably by depleting the intracellular pool of deoxynucleoside triphosphates. However, *Vpx* (present only in HIV-2) appears to reverse this effect by promoting proteosomal degradation of SAMHD1 (Lahouassa 2012).

SERINC3 and **SERINC5** ("serine incorporator 3/5") are cell surface proteins that become part of the membrane of newly emerging viruses and prevent the reinfection of further cells. However, the incorporation of SERINC3/5 into the viral membrane is prevented by HIV through Nef, which guides the SERINC3/5 proteins to the lysosomes. This resistance mechanism is thought to be one of the most critical functions of Nef (Usami 2015).

TPIM5α ("tripartite motif-containing protein 5 α") recognizes the HIV capsid and leads to faster "uncoating", allowing PRRs to recognize the viral RNA/DNA better. Another recently discovered restriction factor that recognizes the capsid (especially of HIV-2) is NONO (Lahaye 2018).

ZAP ("zinc finger antiviral protein") recognizes newly formed viral mRNA in the cytosol and destroys it (Zhu 2011).

Natural killer cells (NK cells)

NK cells are of lymphoid origin but do not use antigen-specific receptors to recognize pathogens and are classified as components of innate immunity. They express various activating receptors through which they can recognize, for example, cellular stress signals. In addition, they exhibit inhibitory receptors such as KIRs (killer cell immunoglobulin-like receptors) that interact with HLA class I molecules. The association of favorable disease outcomes with HLA alleles (see below) that act as NK cell ligands underscores the importance of NK cells in HIV infection (Flores-Villanueva 2001).

Activated NK cells can lead to the elimination of HIV-1-infected cells via various mechanisms. For example, the release of perforin and granzyme leads to apoptosis of the targeted cell. This cytotoxic NK cell activity can also be mediated by antibodies that label HIV-1-infected cells and interact with the activating Fc receptor on the surface of NK cells via their Fc domains (see also section *Humoral Immune Response*). In addition, NK cells can, among other things, modulate the antiviral immune response by secreting cytokines such as Interferon-γ and inhibit the binding of HIV-1 to co-receptors via the secretion of chemokines such as MIP-1β.

Adaptive immune response

Adaptive (or "acquired") immunity enables an immune response that specifically adapts to the pathogen. The enormous diversity of antigen receptors required for this is made possible by the rearrangement of various gene segments and somatic hypermutation.

The HLA system

The human leukocyte antigen (HLA, also known as MHC, major histocompatibility complex) system comprises a group of surface receptors that present antigens to T cell receptors and are encoded on chromosome 6. HLA classes I and II differ structurally and functionally (Klein 2000). HLA class I molecules are found on almost all

nucleated cells and are essential for presenting antigens to cytotoxic T cells. Specific HLA class I alleles, such as B*27 and B*57, are associated with enhanced control of HIV-1 infection. In contrast, other alleles (e.g., B*07 and B*35) are typically associated with more rapid progression of HIV infection (O'Brien 2001, Pereyra 2010). HLA class II molecules are found on specialized antigen-presenting cells (e.g., B cells, macrophages, dendritic cells) and present antigens to CD4 T helper cells.

CD8 T-cells

CD8 T-cells recognize specific antigens (such as HIV-1 peptides) presented via HLA class I molecules through their T cell receptors. Following HLA-mediated activation, CD8 T-cells can secrete perforins and granzymes that can induce apoptosis and eliminate virally infected cells. CD8 T-cells are, therefore, also referred to as cytotoxic T cells. In addition, they can secrete several other pro-inflammatory substances, including, for example, MIP-1β, interferon-γ, TNF-α, and IL-2.

In the context of HIV-1 infection, a robust immune response by CD8 T-cells against various epitopes is almost invariably induced (Addo 2003). However, viral variants carrying resistance mutations against the CD8 T-cell response are subsequently selected (Allen 2005). High CD8 T-cell activity can often still be detected in the late stages of the disease. However, a lack of induction of novel escape mutations suggests that this activity is not necessarily associated with substantial antiviral effects (Draenert 2004).

The development of an HIV-1-specific CD8 T-cell response is associated with the control of viral replication during the acute phase of HIV-1 infection and the development of the so-called viral setpoint, i.e., the relatively stable early viral load after acute infection (Streeck 2009, Collins 2020). Therefore, the CD8 T-cell-mediated immune response plays a significant role in the extent of spontaneous HIV-1 control and, thus, disease progression. As mentioned above, specific alleles of HLA class I molecules interacting with the T cell receptor on CD8 T-cells are associated with favorable or adverse disease outcomes. Compared with CD8 T-cells from individuals with typical disease courses, CD8 T-cells from long-term non-progressors often have a higher proliferative capacity (Migueles 2002). A possible cause for the lower activity of CD8 T-cells in typical progressive disease might be PD1-mediated immune exhaustion (Day 2006).

CD4 T-cells ("Helper T-cells")

Different types of CD4 helper T-cells can be phenotypically distinguished. These include Th1 (type 1), Th2 (type 2), Th17 (type 17), and (follicular) Tfh cells. The CD4 surface protein plays a role as a co-receptor in the interaction of the T cell receptor with HLA class II molecules. By secreting cytokines, helper T-cells can regulate the immune response against pathogens. For example, Th1 cells activate macrophages and CD8 T-cells in particular via Interferon-γ, whereas Th2 cells stimulate B cells via interleukin-4. Th17 cells play an essential role in neutrophil granulocyte activation through the secretion of interleukin-17. In addition, Th17 cells are responsible for maintaining intestinal barrier function, which is often disrupted due to cell loss during HIV infection (Brenchley 2008). Follicular T helper cells play an essential role in B-cell activation in the germinal centers of lymphoid follicles (Crotty 2019). A type of CD4 T-cell to be considered separately from classical CD4 T helper cells is represented by regulatory T-cells (Tregs) associated with immune system suppression. HIV-1 can also infect these cells, although the significance of infection and possible depletion of these cells for HIV-1 pathogenesis is the subject of ongoing research.

CD4 helper T cells are probably the most crucial target cells of HIV-1; the loss of these cells is an expression of the increasing immunodeficiency. The CD4 T-cell count is considered the most important surrogate parameter for the extent of HIV-mediated immune damage in routine clinical care. The **depletion of CD4 T-cells** that typically occurs in peripheral blood during HIV-1 infection can occur for a variety of reasons:

- **Apoptosis/pyroptosis** as a form of programmed cell death (e.g., as a result of virus-induced cytotoxic effects, cytotoxic activity of CD8 T lymphocytes, or the release of proinflammatory cytokines by other infected CD4 T-cells in the environment).
- Medium- to long-term damage to CD4 T-cell regenerative capacity due to **lymphocyte turnover** resulting from **immune activation.**
- **Reduced production** due to HIV-induced damage to the thymus and the bone marrow.
- **Redistribution** of CD4 T-cells from peripheral blood to lymphoid tissues.

Humoral immune response

Antibody-mediated immunity is an essential component of the adaptive humoral immune system. Antibodies are produced by plasma cells that develop in lymphoid follicles from activated B cells. Antibodies can specifically bind to a target structure (epitope) via highly variable regions. In addition, antibodies have constant regions in which the so-called Fc region (fragment crystallizable) is located.

This composition explains the potential dual functionality of antibodies in the context of the immune response. By binding to HIV-1 Env, antibodies can prevent the virus from interacting with its target cell receptors (**neutralizing function** of antibodies), interfering with infection and interrupting viral replication. Moreover, through their **Fc region**, antibodies can interact with other immune system components (Parsons 2018). In addition to possible activation of the complement system, binding of the Fc region to Fc receptors on immune cells can mediate a cellular immune response. These cell-mediated mechanisms include **ADCC** (antibody-dependent cellular cytotoxicity), which can lead to the elimination of HIV-1-infected cells via NK cells. Similarly, antibodies can promote phagocytosis by macrophages or dendritic cells (**ADCP**, antibody-dependent cellular phagocytosis).

The fact that virtually all people living with HIV form antibodies against various virus components within a few weeks is exploited by serological tests that diagnose HIV infection. Many of these antibodies do not immediately affect circulating viruses because they are directed against viral proteins found intracellularly or because their binding to the viral envelope protein Env fails to prevent cellular infection (**non-neutralizing antibodies**). While **neutralizing antibodies** are also produced, their activity is usually relatively specific to the viruses circulating in the individual. It is offset by the development of viral escape mutations resulting in resistance to the autologous antibody response (Overbaugh 2012).

During the course of infection, a small proportion of people living with HIV-1 (approx. 20%) develops antibodies that exhibit activity against many different HIV-1 strains (**broadly neutralizing antibodies**) and are, in rare cases (in so-called elite neutralizers; frequency approx. 1%), extraordinarily potent. These antibodies are characterized by targeting relatively conserved regions of the Env surface protein and the capacity to neutralize many existing HIV-1 variants at very low concentrations (Gruell 2022). In the few individuals that produce potent and broadly neutralizing antibodies, these antibodies typically do not result in viral control due to the selection of viral resistance. However, recombinantly produced broadly neutralizing antibodies represent a promising option for the prevention and therapy of HIV-1 infection that is currently investigated in numerous clinical trials (see chapter 5.3., section on *Broadly Neutralizing Antibodies*).

HIV-1-induced immune dysfunction

During the course of HIV-1 infection, functional impairments can be demonstrated for virtually all cellular components of the immune system. In addition, structural damage to critical lymphoid tissues, such as lymphoid follicles, is often seen (Pantaleo 1993). These changes contribute to the increasing degree of immunodeficiency characteristic of progressive HIV-1 infection. However, a large proportion of HIV-1-induced damage to the immune system is probably due to a persistently elevated level of immune activation during infection. The high immune system stimulation also likely underlies the increased HIV-associated risk of various other diseases, such as cardiovascular or hepatic conditions (Tenorio 2014).

An important reason for this immune system stimulation is the depletion of CD4 T-cells in the lymphoid tissue of the gastrointestinal tract (GALT, gut-associated lymphoid tissue) during acute infection. The damage to the immunological integrity of the mucosal barrier caused by T-cell depletion can lead to increased transmission of pro-inflammatory microbial products (e.g., LPS) (Brenchley 2006). The prolonged stimulation of immune cells can lead to a kind of "immune exhaustion", characterized by a decrease in proliferative capacity and effector functions. In addition, an increased expression of anti-inflammatory proteins (e.g., PD-1) or cytokines (e.g., IL-10) can typically be observed (Fenwick 2019).

Literature

Addo MM, Yu XG, Rathod A, et al. Comprehensive epitope analysis of human immunodeficiency virus type 1 (HIV-1)-specific T-cell responses directed against the entire expressed HIV-1 genome demonstrate broadly directed responses, but no correlation to viral load. J Virol 2003, 77: 2081-2092.

Allen TM, Altfeld M, Geer SC, et al. Selective escape from CD8+ T-cell responses represents a major driving force of human immunodeficiency virus type 1 (HIV-1) sequence diversity and reveals constraints on HIV-1 evolution. J Virol 2005, 79: 13239-13249.

Altfeld M, Gale M. Innate immunity against HIV-1 infection. Nat Immunol 2015, 16: 554-562

Bergantz L, Subra F, Deprez E, et al. Interplay between Intrinsic and Innate Immunity during HIV Infection. Cells 2019, 17:8.

Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 2006, 12:1365-1371.

Brenchley JM, Paiardini M, Knox KS, et al. Differential Th17 CD4 T-cell depletion in pathogenic and nonpathogenic lentiviral infections. Blood 2008, 112:2826-2835

Buffalo CZ, Iwamoto Y, Hurley JH, et al. How HIV Nef Proteins Hijack Membrane Traffic To Promote Infection. J Virol 2019, 26:93.

Campbell EM, Hope TJ. HIV-1 Capsid: The Multifaceted Key Player in HIV-1 infection. Nat Rev Microbiol 2015, 13: 471-483.

Collins DR, Gaiha GD, Walker BD. CD8+ T cells in HIV control, cure and prevention. Nat Rev Immunol 2020, 20: 471-482.

Crotty S. T Follicular Helper Cell Biology: A Decade of Discovery and Diseases. Immunity 2019, 50: 1132-1148.

Cullen BR. HIV-1 auxiliary proteins: making connections in a dying cell. Cell 1998, 93: 685-692.

Dalgleish AG, Beverley PC, Clapham PR, et al. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature 1984, 312: 763-767.

Day CL, Kaufmann DE, Kiepiela P, et al. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. Nature 2006, 443: 350-354.

Dean M, Carrington M, Winkler C, et al. Genetic restrictions of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Science 1996, 273: 1856-1862.

Doranz BJ, Rucker J, Yi Y, et al. A dual-tropic primary HIV-1 isolate that uses fusin and the β-chemokine receptors CKR-5, CKR-3, and CKR-2b as fusion cofactors. Cell 1996, 85: 1149-1158.

Draenert R, Verrill CL, Tang Y, et al. Persistent recognition of autologous virus by high-avidity CD8 T cells in chronic, progressive human immunodeficiency virus type 1 infection. J Virol 2004, 78: 630-641.

Feng Y, Broder CC, Kennedy PE, Berger EA. HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. Science 1996, 272: 872-877.

Fenwick C, Joo V, Jacquier P, et al. T-cell exhaustion in HIV infection. Immunol Rev 2019, 292: 149-163.

Finzi, D, Blankson, J., Siliciano, J. et al. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. Nat Med 1999, 5: 512–517.

Flores-Villanueva PO, Yunis EJ, Delgado JC, et al. Control of HIV-1 viremia and protection from AIDS are associated with HLA-Bw4 homozygosity. Proc Natl Acad Sci U S A 2001, 98: 5140-5145.

Fonteneau JF, Larsson M, Beignon AS, et al. Human immunodeficiency virus type 1 activates plasmacytoid dendritic cells and concomitantly induces the bystander maturation of myeloid dendritic cells. J Virol 2004, 78: 5223-5232.

Gruell H, Schommers P. Broadly neutralizing antibodies against HIV-1 and concepts for application. 54: 101211.

Gupta RK, Peppa D, Hill AL, et al. Evidence for HIV-1 cure after CCR5Δ32/Δ32 allogeneic haemopoietic stem-cell transplantation 30 months post analytical treatment interruption: a case report. Lancet HIV 2020, 7: E340-E347.

Hütter G, Nowak D, Mossner M, et al. Long-term control of HIV by CCR5 delta32/delta32 stem-cell transplantation. NEJM 2009, 360: 692-698.

Hsu J, van Besien K, Glesby MJ, et al. HIV-1 remission with CCR5D32D32 haplo-cord transplant in a U.S woman: IMPAACT P1107. Conference on Retroviruses and Opportunistic Infections, abstract 65LB, 2022.

Jensen BO, Knops E, Cords L, et al. In-depth virological and immunological characterization of HIV-1 cure after CCR5Δ32/Δ32 allogeneic hematopoietic stem cell transplantation. Nat Med 2023, 29:583-587.

Kane M, Yadav SS, Bitzegeio J, et al. MX2 is an interferon-induced inhibitor of HIV-1 infection. Nature 2013, 502: 563–566.

Klein J, Sato A. The HLA system. First of two parts. N Engl J Med 2000, 343: 702-709.

Lahouassa H, Daddacha W, Hofmann H, et al. SAMHD1 restricts the replication of human immunodeficiency virus type 1 by depleting the intracellular pool of deoxynucleoside triphosphates. Nat Immunol 2012, 13:223-228.

Lahaye X, Gentili M, Silvin A., et al. NONO Detects the Nuclear HIV Capsid to Promote cGAS-Mediated Innate Immune Activation. Cell 2018, 175: 488-501.

Liu R, Paxton WA, Choe S, et al. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. Cell 1996, 86: 367-377.

Mariani R, Chen D, Schröfelbauer B, et al. Species-specific exclusion of APOBEC3G from HIV-1 virions by vif. Cell 2003; 114: 21-31.

Migueles SA, Alisha C, Laborico W, et al. HIV-specific CD8+ T cell proliferation is coupled to perforin expression and is maintained in nonprogressors. Nat Immunol 2002, 3: 1061–1068.

Naif H, Cunningham A, Alali M, et al. A human immunodeficiency virus type 1 isolate from an infected person homozygous for CCR5D32 exhibits dual tropism by infecting macrophages and MT2 cells via CXCR4. J Virol 2002, 76: 3114 – 24.

O'Brien SJ, Gao X, Carrington M. HLA and AIDS: a cautionary tale. Trends Mol Med 2001, 7: 379-381.

Overbaugh J, Morris L. The Antibody Response against HIV-1. Cold Spring Harb Perspect Med 2012, 2: a007039.

Pantaleo G, Graziosi C, Demarest JF, et al. HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. Nature 1993, 362: 355-359.

Parsons MS, Chung AW, Kent SJ. Importance of Fc-mediated functions of anti-HIV-1 broadly neutralizing antibodies. Retrovirology 2018, 15: 58.

Pereyra F, Jia X, McLaren PJ, et al. The major genetic determinants of HIV-1 control affect HLA class I peptide presentation. Science 2010, 330: 1551-1557.

Preston BD, Poiesz BJ, Loeb LA. Fidelity of HIV-1 Reverse Transcriptase. Science 1988; 242: 1168-1171.

Sauter D, Kirchhoff F. Multilayered and versatile inhibition of cellular antiviral factors by HIV and SIV accessory proteins. Cytokine Growth Factor Rev 2018, 40: 3-12.

Schröder AR, Shinn P, Chen H, et al. HIV-1 integration in the human genome favors active genes and local hotspots. Cell 2002, 110: 521–529.

Shaik MM, Peng H, Jianming L, et al. Structural basis of coreceptor recognition by HIV-1 envelope spike. Nature 2019, 565: 318-323.

Smith BA, Gartner S, Liu Y, et al. Persistence of Infectious HIV on Follicular Dendritic Cells. J Immunol 2001, 166: 690-696.

Streeck H, Jolin JS, Ying Q, et al. Human Immunodeficiency Virus Type 1-Specific CD8+ T-Cell Responses during Primary Infection Are Major Determinants of the Viral Set Point and Loss of CD4+ T Cells. J Virol 2009, 83: 7641-7648.

Tenorio AR, Zheng Y, Bosch RJ, et al. Soluble markers of inflammation and coagulation but not T-cell activation predict non-AIDS-defining morbid events during suppressive antiretroviral treatment. J Infect Dis 2014, 210: 1248-1259.

Usami Y, WU Y, Göttlinger HG. SERINC3 and SERINC5 restrict HIV1 infectivity and are counteracted by Nef. Nature 2015, 526: 218-223.

Wang Q, Gao H, Clark KM, et al. CARD8 is an inflammasome sensor for HIV-1 protease activity. Science 2021, 371, eabe1707.

Wu L, KewalRamani VN. Dendritic-cell interactions with HIV: infection and viral dissemination. Nat Rev Immunol 2006, 6: 859-868.

Zila V, Margiotta E, Turonová B, et al. Cone-shaped HIV-1 capsids are transported through intact nuclear pores, Cell 2021, 184, 1032–1046.

Zhu P, Liu J, Bess Jr J, et al. Distribution and three-dimensional structure of AIDS virus envelope spikes. Nature 2006, 441: 847-52.

Zhu Y, Chen G, Lv F, et al. Zinc-finger antiviral protein inhibits HIV-1 infection by selectively targeting multiply spliced viral mRNAs for degradation. Proc Natl Acad Sci U S A 2011, 108: 15834-15839.

4. Acute HIV infection

HENDRIK STREECK

Acute HIV-1 infection (see also chapter *HIV-2*) is uniquely positioned in diagnosis and treatment while generating significant scientific interest in vaccine and cure research. Approximately two weeks after infection, around 70–80% of individuals experience transient symptoms frequently mistaken for other viral diseases, such as flu or mononucleosis, as HIV-1-specific antibodies are often not detectable at this early stage. Early diagnosis is significant for several reasons: for example, about 50% of all new infections are caused by newly infected individuals (Brenner 2007); early ART has long-term immunologic and virologic benefits (see below). Acute HIV infection can manifest differently when individuals are taking pre-exposure prophylaxis (PrEP). An accurate diagnosis is essential to prevent PreP-related resistance (see chapter *ART and Prevention*).

Definition and classification

Acute HIV-1 infection (AHI) is defined by either a high HIV-1 viral load in the absence of a positive anti-HIV ELISA or a positive HIV test when the Western blot is positive in fewer than three bands.

It is essential to differentiate between "acute" HIV infection and "early" HIV-1 infection (EHI), which refers to infection within the past six months. This is independent of seroconversion status, but a negative HIV-1 test must have been documented in the last six months. AHI and EHI are combined under the term "primary HIV-1 infection" (PHI). To objectively compare early changes in the HIV reservoir and immune system, a classification was introduced (Fiebig 2009) that subdivides the AHI according to immunopathological features (Figure 1). Here, simply put, stages I-III correspond to acute and stages IV-VI to early HIV-1 infection. The system is

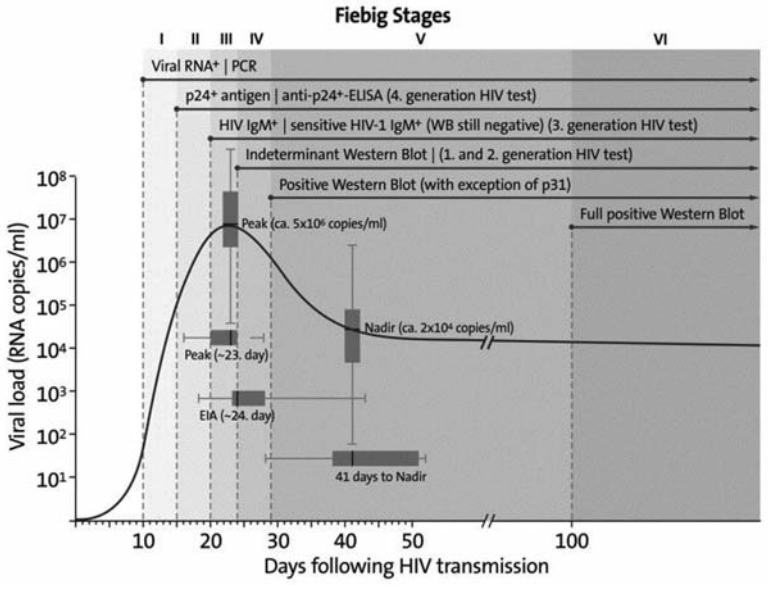

Figure 1: Schematic progression of acute HIV infection, Fiebig stages. Dashes, gray-shaded bars: median and interquartile ranges according to Robb 2016.

based on a distinction between p24 antigen and anti-p24 antibody (second-generation HIV test). Since fourth-generation tests detect p24 antigen and IgG/IgM antibodies simultaneously, a different classification system incorporating the fourth-generation test has been proposed (Ananworanich 2013). It distinguishes three stages: HIV RNA+/4th EIA-/3rd EIA- (stage 1); HIV RNA+/4th EIA+/3rd EIA- (stage 2); HIV RNA+/4th EIA+/3rd EIA+ (stage 3). Another classification system includes the Signal-to-Cutoff ratio (Crowell 2021). The classifications of the different stages of acute HIV infection primarily serve scientific questions, while this distinction is less crucial for diagnosis and/or therapy.

Clinic

AHI occurs approximately 14 days after infection (Robb 2016) and is associated with a rapid increase in plasma viremia. Just before and during the viral load peak, the AHI usually manifests with characteristic clinical symptoms that disappear after hours to a few days (Hecht 2002). Symptoms (e.g., lymph node swelling, tachycardia) are noted in up to 94%, even when the acute phase is subjectively asymptomatic (Robb 2016). Fever between 38° and 40°C persists for approximately 1–8 days.

Table 1: Leading symptoms of acute HIV-1 infection, frequency in % (n.a. = not specified).

Symptom	San Francisco Pike 2002	East Africa Robb 2016	Thailand Crowell 2018	San Diego (US) Hoenigl 2016	Mean value
Fever	80	55	77	77	72
Lymph node swelling	n.a.	9	14	n.a.	12
Skin rash	51	n.a.	32	19	34
Oral ulcers	37	n.a.	23	n.a.	30
Arthralgia	54	n.a.	23	20	32
Pharyngitis	44	18	53	49	41
Loss of appetite	54	n.a.	n.a.	n.a.	54
Weight loss > 2.5 kg	32	n.a.	34	22	29
Fatigue	68	42	63	70	61
Headache	54	52	35	n.a.	47
Myalgia	49	n.a.	45	70	55
Cough	n.a.	30	53	n.a.	42
Tachycardia	n.a.	33	29	n.a.	31

The clinical symptoms of AHI resemble those of mononucleosis (Cooper 1985) but appear slightly different depending on region, HIV subtype, and in men vs. women (Robb 2016). Also, the viral load level during AHI determines the severity of symptomatology (Crowell 2018). Individuals with severe and prolonged persistent symptomatology rapidly progress to AIDS (Keet 1993).

A maculopapular rash occurs in about one-third of people about 48–72 hours after the onset of fever and occurs mainly on the trunk, neck region, and face. Furthermore, painful oral ulcerations, lymphadenopathy, arthralgias, pharyngitis, lassitude, weight loss, aseptic meningitis, and myalgias (Kahn 1998) have been described; myocarditis, pancreatitis, or renal failure may also occur in rare cases. In one study, fever (80%) and fatigue (68%) showed the highest sensitivity for clinical diagnosis, whereas weight loss (86%) and oral ulcerations (85%) showed the highest specificity (Hecht 2002). However, the frequency of the symptoms described depends on why acute HIV infection was tested for in the first place. In the case of an incidental

finding during routine testing, the course is often asymptomatic (Sullivan 2012). Co-infection with other sexually transmitted diseases, such as Mpox or gonorrhea, can mask acute HIV infection. The initial viral load maximum has reached a median of 14 days after infection (Robb 2016), typically exceeding 1 million HIV RNA copies/mL. The maximum predicts subsequent viral load progression and is a critical factor in long-term prognosis. The early viral load setpoint is reached at a median of 31 days (18–42 days), marking the onset of early chronic HIV infection.

Diagnostics

Although most of those affected develop symptoms at least briefly, these are often mild, so diagnosis is often not considered. In addition, the symptoms can be masked by PrEP (especially when needed). Initial suspicion is thus based on a combination of history and symptoms, with only a nucleic acid test able to detect AHI at this stage. The HIV-1 antibody test (3rd generation) is positive on average only after approximately 14 days post-infection, and thus often only when the viral load drops again (Robb 2016). In PrEP users, seroconversion may not occur at all.

All tested detection methods for HIV-1 RNA (branched chain DNA, PCR, and Gen-Probe) show a sensitivity of 100% but yielded false positive results in 2–5% (Hecht 2002). These are primarily below 2,000 HIV-1 RNA copies/mL, well below the high levels that generally occur during AHI (in our studies, an average of 13 x 10^6 HIV-1 RNA copies/mL, with a range of 0.25–95.5 x 10^6). Repeated determination of HIV-1 RNA from the same specimen using the same assay resulted in a negative test result in all false positive cases. In contrast, detection of p24 antigen has a sensitivity of only 79%, with a specificity of 99.5–99.96%. The diagnosis of AHI must then be confirmed with a positive antibody test within the following weeks.

Four different HIV tests are on the market, which can diagnose HIV-1 infection early with varying degrees of success (see chapter *HIV Testing*). The first- and second-generation EIA tests detect only IgG antibodies; they are hardly ever used anymore. The time window between infection and positive test result is estimated to be 25–35 days (Branson 2012). Third-generation EIAs are somewhat more sensitive

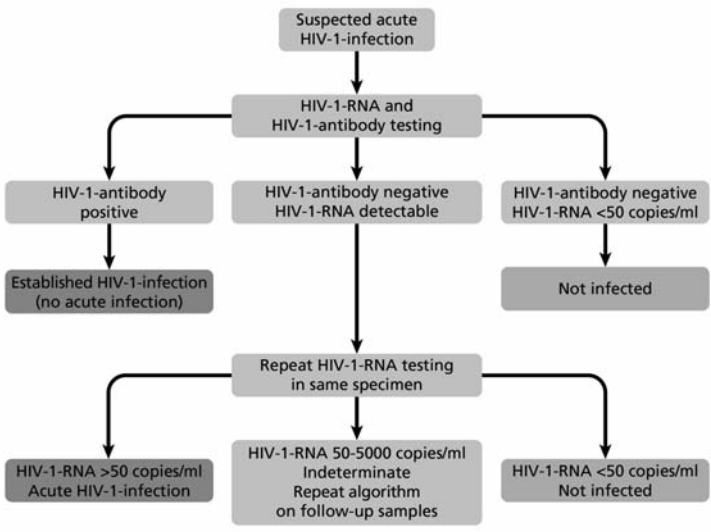

Figure 2: Testing algorithm for current HIV-1 infection.

because they can detect IgM antibodies; they appear to identify about three-quarters of AHI (Hecht 2002). Fourth-generation EIAs combine an antibody EIA with a p24 antigen EIA. These identify even those individuals who have not yet produced antibodies. The time between infection and earliest possible diagnosis is shortened to 15–20 days (Branson 2012). Still, a second diagnostic window opens when antibody and antigen neutralize each other for a short time (Ly 2007).

During the AHI, there is often a marked decrease in CD4 T-cells and B cells. Occasionally, such low CD4 T-cell counts are observed that opportunistic infections are already possible at this time (Gupta 1993). Although CD4 T-cell counts rise again after primary infection, they rarely return to baseline levels without ART. In contrast, CD8 T-cell counts increase significantly, which can result in a CD4/CD8 ratio of less than 1.

In summary, the most crucial task in diagnosing AHI is to consider it a differential diagnosis in the first place and consider the window of time when it cannot yet be detected. Clinical suspicion then requires HIV-1 testing and possibly repeat determination of HIV-1 viral load, as shown in Figure 2.

Immunological and virological events

During AHI, robust viral replication occurs, and the viral load often reaches more than 100 million HIV-1 RNA copies/mL. The initial interaction between HIV and the host is believed to play a crucial role in subsequent disease progression. Thus, the initial viral load's magnitude is associated with the viral load rebound rate after treatment interruption (Colby 2022). (Colby 2022). Furthermore, the initial phase provides a unique opportunity to study determinants of HIV transmission, the evolution and emergence of immune responses, and the emergence of the viral reservoir.

Unlike hepatitis B or C, AHI is associated with a dramatic cytokine cascade. This proceeds in waves, activating different arms of the immune responses (Teigler 2018). At as early as seven days, there is a rapid increase in cytokines of the innate pro-inflammatory immune response, followed by TNF-alpha and INF-gamma signaling pathways, with some very closely associated with increasing viral load (e.g., IP10). These cytokines, although serving in part to control infection, are likely to contribute mainly to immunopathogenesis (Stacey 2009). Furthermore, cytotoxic NK (natural killer) cells are activated (Alter 2007), expand, and can exert antibody-dependent cell-mediated cytotoxicity (Chung 2011). Neutralizing antibodies directed against HIV are usually not found during this phase. Several factors may influence HIV-1 replication in the acute phase and, thus, the early viral setpoint. These include the virus's replication capacity (viral fitness) (Troyer 2009), genetic factors, and the various arms of the immune response.

The HIV-1-specific cellular immune response occupies a key position in the control of HIV replication; thus, the initial drop in viremia is closely temporally related to the appearance of HIV-1-specific CD8 T-cells (Koup 1994). These can eliminate HIV-1-infected cells directly by MHC class I-restricted cytolysis or indirectly by limiting the production of cytokines, chemokines, or other soluble factors (Yang 1997). Another indication of the antiviral activity of HIV-1-specific cytotoxic T lymphocytes (CTL) during AHI is the rapid selection of viral species with mutations of CTL epitopes. These species, which arise under selection pressure, can be detected in humans as early as a few weeks after HIV-1 infection and can influence viral fitness (Price 1997). In particular, the initial CD8 T-cell responses during AHI appear to play a role; thus, individuals with a strong CTL response during AHI have a significantly lower early viral setpoint (Streeck 2009). In contrast, no relationship between the

breadth or strength of CD8 T-cell responses and viral load was found during chronic HIV infection (Frahm 2004). Many of these early CTL responses are restricted by HLA class I alleles that are beneficial to the further course of infection, such as HLA-B57 or HLA-B27 (Altfeld 2006). These immunodominant protective immune responses are directed against epitopes that are not widely scattered across the HIV-1 genome but occur in clusters in a defined region of p24 *gag* (Streeck 2007), a region that appears to be essential for the stability of the HIV capsid (Schneidewind 2007). The effectiveness of early CD8 T-cell responses in controlling HIV replication may be attributed to the presence and assistance provided by antigen-specific CD4 T-cells (Schieffer 2014). However, it is worth noting that these CD4 T-cells are also preferentially targeted and infected by HIV (Douek 2002). HIV-specific CD4 T-cell responses with cytotoxic features also expand during the acute phase of HIV infection. They can directly affect viral replication (Soghoian 2012). Little is known about the role of these cytolytic CD4 T-cells; they may control HIV infection in macrophages, whereas CD8 T-cells inhibit HIV in CD4 T-cells. Moreover, CD4 T-cells influence the efficacy of the HIV-specific CD8 T-cell response via antigen-specific IL-21 secretion (Chevalier 2010). Furthermore, studies from the LCMV mouse model show that the development and maintenance of long-lived memory CD8 T-cell response requires the presence of CD4 T helper cells even during the first hours of generation of new CD8 T-cell responses (Janssen 2003). However, it is not known precisely which CD4 T-cell signals are necessary to maintain HIV-specific CD8 T-cells. The declining functionality and effectiveness of CD8 T-cells over time correlate directly with the level of viral load. The gradual loss of function could be indirectly correlated with the expression of inhibitory receptors, such as programmed death-1 (PD-1) (Day 2006), which is upregulated on HIV-specific CD8 T-cells. The importance of identifying such receptors may lie in the exploration of potential immunotherapies that, for example, reactivate the body's immune system against HIV by blocking these receptors.

In addition to the host immune response, genetic factors also play a crucial role in determining susceptibility and resistance to HIV-1 infection and influencing the rate of disease progression. The most significant of these factors is a deletion at the gene of the major coreceptor for HIV-1 entry into the CD4 T-cell, the CCR5 chemokine receptor (see *Basics* and, in *ART*, the section on *coreceptor antagonists*).

In addition to mutations at chemokine receptor genes, several HLA class I alleles have been associated with lower viral setpoints and slower disease progression, such as HLA-B27 and -B57 (O'Brien 1997, Kaslow 1996). In contrast, individuals expressing a specific isoform of HLA-B35 (HLA-B35px or HLA-B3502/HLA-B3503) show significantly faster disease progression. The cause of this has not yet been clarified. Furthermore, it has been shown that certain killer immunoglobulin-like receptors (KIR), expressed primarily on NK cells but also on T cells, also have a significantly slower progression course in combination with a group of HLA-B alleles (HLA-Bw4-80I) (Martin 2007), which may indicate a role of NK cells in HIV immunopathogenesis. Indeed, NK cells can recognize HIV-infected cells, exert selection pressure, and thereby critically influence viral replication (Alter 2011). This suggests that host genetic factors influence the clinical manifestation of AHI. Host factors are thus important determinants of subsequent viral setpoint and the rate of disease progression.

Therapy

The results of the START and TEMPRANO trials demonstrated the benefits of ART. Although neither study collected specific information on individuals with early infection, they suggest that ART should generally be started as early as possible. As with

chronic infection, patients must be willing and able to undergo treatment. If ART initiation is delayed, close monitoring is essential. There are several reasons for starting ART immediately: First, early ART leads to shortening and alleviating the symptomatic phase. Second, it lowers HIV transmission risk, reduces the number of infected cells, maintains HIV-1-specific immune responses, and potentially reduces the viral setpoint in the long term. Smaller studies have shown that ART during AHI increases HIV-specific immune responses and allows long-term viral suppression.
In addition, early ART can achieve temporary control of viral replication (Grijsen 2012) and significantly increase the CD4 T-cell count in the long term (Hecht 2006). However, there is usually a viral load rebound later (Streeck 2006). In rare cases, control of HIV infection can be observed even if ART is discontinued later. However, these so-called post-treatment controllers (PTC) are rare (Hocqueloux 2010) and cannot be explained by genetic or immunological characteristics (Saez-Cirion 2013). Other benefits of early therapy include limiting viral diversification (Delwart 2002) and improved innate and adaptive immune system functions (Oxenius 2000, Alter 2005, Moir 2010). However, the extent to which early antiviral therapy effectively limits the viral reservoir remains unclear. While some studies have demonstrated an effect (Ananworanich 2013), paradoxically, other studies have shown a larger reservoir when therapy is initiated earlier. With the early initiation of treatment, the reservoir primarily resides in the T cell zone rather than the B cell follicles, suggesting that the lack of immune responses may not have sufficiently eliminated the infected cells (Kroon 2022). Intensification of early therapy (mega-HAART) has not affected immunologically or reservoir size (Ananworanich 2015).
Treatment of acute HIV infection should follow consensus guidelines. When considering the treatment of PrEP users, check that resistance to TDF or FTC has not developed. Due to high viral replication, an agent with a high resistance barrier should be used in addition to NRTIs. Before initiating ART, a genotypic resistance test is mandatory, but its result does not necessarily need to delay the initiation of ART – treatment can be modified later if needed.
CD4 T-cell count and viral load should initially be monitored closely every 2 to 8 weeks after initiation of treatment and every 3 to 4 months after sufficient viral suppression below the detection limit. ART should be continued indefinitely as per the guidelines for chronic infection.

Literature

Alter G, Teigen N, Davis BT, et al. Sequential deregulation of NK cell subset distribution and function starting in acute HIV-1 infection. Blood 2005, 106:3366-9.

Alter G, Martin MP, Teigen T, et al. Differential natural killer cell-mediated inhibition of HIV-1 replication based on distinct KIR/HLA subtypes. J Exp Med 2007, 204:3027-3036.

Alter G, Heckerman D, Schneidewind A, et al. HIV-1 adaptation to NK-cell-mediated immune pressure. Nature 2011, 476:96-100.

Altfeld M, Kalife ET, Qi Y, et al. HLA alleles associated with delayed progression to AIDS contribute strongly to the initial CD8(+) T cell response against HIV-1. PLoS Med 2006, 3:e403.

Ananworanich J, Vandergeeten C, Chomche N, et al. Early ART Intervention Restricts the Seeding of the HIV Reservoir in Long-lived Central Memory CD4 T Cells. Abstract 47, 20th CROI, Atlanta 2013.

Ananworanich J, Fletcher JL, Pinyakorn S, et al. A novel acute HIV infection staging system based on 4th generation immunoassay. Retrovirology. 2013

Ananworanich J, Chomont N, Fletcher JL, Markers of HIV reservoir size and immune activation after treatment in acute HIV infection with and without raltegravir and maraviroc intensification. J Virus Erad. 2015, 1:116-122.

Branson BM, Stekler JD. Detection of acute HIV infection: we can't close the window. J Infect Dis 2012, 205:521-4

Brenner BG, Roger M, Routy JP, et al. High rates of forward transmission events after acute/early HIV-1 infection. J Infect Dis 2007, 195:951-959.

Chung AW, Navis M, Isitman G, et al. Activation of NK Cells by ADCC Responses During Early HIV Infection. Viral Immunol 2011, 24:171-5.

Chevalier MF, Jülg B, Pyo A, et al. HIV-1-specific interleukin-21+ CD4+ T cell responses contribute to durable viral control through the modulation of HIV-specific CD8+ T cell function. J Virol 2011, 85:733-41.

Crowell TA, Ritz J, Coombs RW et al. Novel Criteria for Diagnosing Acute and Early Human Immunodeficiency Virus Infection in a Multinational Study of Early Antiretroviral Therapy Initiation. Clin Infect Dis 2021, 73:e643-e651.

Cooper DA, Gold J, Maclean P, et al. Acute AIDS retrovirus infection. Definition of a clinical illness associated with seroconversion. Lancet 1985,1:537.

Day CL, Kaufmann DE, Kiepiela P, et al. PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. Nature 2006, 443:350-354.

Delwart E, Magierowska M, Royz M, et al. Homogeneous quasispecies in 16 out of 17 individuals during very early HIV-1 primary infection. AIDS 2002, 16:189-95.

Crowell TA, Colby DJ, RV254/SEARCH010 Study Group, et al. Acute Retroviral Syndrome Is Associated With High Viral Burden, CD4 Depletion, and Immune Activation in Systemic and Tissue Compartments. Clin Infect Dis 2018, 66:1540-1549.

Douek DC, Brenchley JM, Betts MR, et al. HIV preferentially infects HIV-specific CD4+ T cells. Nature 2002, 417:95-98.

Fiebig EW, Wright DJ, Rawal BD, et al. Dynamics of HIV viremia and antibody seroconversion in plasma donors: implications for diagnosis and staging of primary HIV infection. AIDS 2003; 17:1871-9.

Frahm N, Korber BT, Adams CM, et al. Consistent cytotoxic-T-lymphocyte targeting of immunodominant regions in human immunodeficiency virus across multiple ethnicities. J Virol 2004, 78:2187-2200.

Gray C, Mlotshwa M, Riou C, et al. Human immunodeficiency virus-specific gamma interferon enzyme–linked immunospot assay responses targeting specific regions of the proteome during primary subtype c infection are poor predictors of the course of viremia and set point. J Virol 2009, 83:470-478.

Gupta KK. Acute immunosuppression with HIV seroconversion. N Engl J Med 1993, 328:288-289.

Grijsen ML, Steingrover R, Wit FW, et al. No treatment versus 24 or 60 weeks of antiretroviral treatment during primary HIV infection: the randomized Primo-SHM trial. PLoS Med 2012, 9:e1001196.

Hecht FM, Busch MP, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. AIDS 2002,16:1119-1129.

Hecht FM, Wang L, Collier A, et al. A multicenter observational study of the potential benefits of initiating combination antiretroviral therapy during acute HIV infection. J Inf Dis 2006, 194:725-33.

Hocqueloux L, Prazuck T, Avettand-Fenoel V, et al. Long-term immunovirologic control following antiretroviral therapy interruption in patients treated at the time of primary HIV-1 infection. AIDS 2010, 24:1598-601.

Hoenigl M, Green N, Camacho M, et al. Signs or Symptoms of Acute HIV Infection in a Cohort Undergoing Community-Based Screening. Emerg Infect Dis 2016, 22:532-4.

Janssen EM, Lemmens EE, Wolfe T, et al. CD4+ T cells are required for secondary expansion and memory in CD8+ T lymphocytes. Nature 2003, 421:852-856.

Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. New England Journal of Medicine 1998, 339:33-39.

Kaslow RA, Carrington M, Apple R, et al. Influence of combinations of human major histocompatibility complex genes on the course of HIV-1 infection. Nat Med 1996, 2:405-411.

Keet IP, Krijnen P, Koot M, et al. Predictors of rapid progression to AIDS in HIV-1 seroconverters. AIDS 1993,7:51-57.

Koup RA, Safrit JT, Cao Y, et al. Temporal association of cellular immune responses with the initial control of viremia in primary human immunodeficiency virus type 1 syndrome. J Virol 1994,68:4650-4655.

Kroon E, Chottanapund S, Buranapraditkun S, et al. Paradoxically Greater Persistence of HIV RNA-Positive Cells in Lymphoid Tissue When ART Is Initiated in the Earliest Stage of Infection. J Infect Dis 2022, 225:2167-2175.

Ly TD, Ebel A, Faucher V, Fihman V, Laperche S. Could the new HIV combined p24 antigen and antibody assays replace p24 antigen specific assays? J Virol Methods 2007, 143:86-94.

Martin MP, Qi Y, Gao X, et al. Innate partnership of HLA-B and KIR3DL1 subtypes against HIV-1. Nat Genet 2007, 39:733-740.

Mdluli T, Li Y, Pinyakorn S et al. Acute HIV-1 infection viremia associate with rebound upon treatment interruption. Med (NY) 2022, S2666-6340

Mellors JW, Kingsley LA, Rinaldo CR, et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. Ann Int Med 1995,122:573-9.

Moir S, Buckner CM, Ho J, et al. B cells in early and chronic HIV infection: evidence for preservation of immune function associated with early initiation of antiretroviral therapy. Blood 2010, 116:5571-9.

Ngo-Giang-Huong N, Deveau C, Da Silva I, et al. Proviral HIV-1 DNA in subjects followed since primary HIV-1 infection who suppress plasma viral load after one year of highly active antiretroviral therapy. AIDS 2001, 15:665-73.

O'Brien SJ, Gao X, Carrington M. HLA and AIDS: a cautionary tale. Trends Mol Med 2001,7:379-381.

Oxenius A, Price DA, Easterbrook PJ, et al. Early highly active antiretroviral therapy for acute HIV-1 infection preserves immune function of CD8+ and CD4+ T lymphocytes. Proc Natl Acad Sci U S A 2000, 97:3382-7.

Price DA, Goulder PJ, Klenerman P, et al. Positive selection of HIV-1 cytotoxic T lymphocyte escape variants during primary infection. Proc Natl Acad Sci U S A 1997, 94:1890-1895.

Robb ML, Eller LA, Kibuuka H, et al. A prospective analysis of acute HIV-1 infection in high-risk adults in Africa and Thailand. NEJM 2016, 374:2120-30.

Sáez-Cirión A, Bacchus C, Hocqueloux L, et al. Post-treatment HIV-1 controllers with a long-term virological remission after the interruption of early initiated antiretroviral therapy ANRS VISCONTI Study. PLoS Pathog 2013, 9:e1003211.

Schneidewind A, Brockman MA, Yang R, et al. Escape from the dominant HLA-B27-restricted cytotoxic T-lymphocyte response in Gag is associated with a dramatic reduction in HIV type 1 replication. J Virol 2007, 81:12382-12393.

Schieffer M, Jessen HK, Oster AF, et al. Induction of Gag-specific CD4 T cell responses during acute HIV infection is associated with improved viral control. J Virol 2014, 88:7357-66

Stacey AR, Norris PJ, Qin L, et al. Induction of a striking systemic cytokine cascade prior to peak viremia in acute human immunodeficiency virus type 1 infection, in contrast to more modest and delayed responses in acute hepatitis B and C virus infections. J Virol 2009, 83:3719-33.

Streeck H, Jessen J, Alter G, et al. Immunological and virological impact of HAART initiated during acute HIV-1 infection. J Inf Dis 2006, 194:734-739.

Streeck H, Lichterfeld M, Alter G, et al. Recognition of a defined region within p24 gag by CD8+ T cells during primary HIV type 1 infection in individuals expressing protective HLA class I alleles. J Virol 2007, 81:7725-7731.

Streeck H, Jolin JS, Qi Y, et al. Human immunodeficiency virus type 1-specific CD8+ T-cell responses during primary infection are major determinants of the viral set point and loss of CD4+ T cells. J Virol 2009, 83:7641-8.

Soghoian DZ, Jessen H, Flanders M, et al. HIV-Specific Cytolytic CD4 T Cell Responses During Acute HIV Infection Predict Disease Outcome. Sci Transl Med 2012, 4:123ra25.

Sullivan PS, Fideli U, Wall KM, et al. Prevalence of seroconversion symptoms and relationship to set-point viral load: findings from a subtype C epidemic, 1995-2009. AIDS 2012;26:175–84.

Teigler JE, Leyre L, RV254/RV217 study groups et al. Distinct biomarker signatures in HIV acute infection associate with viral dynamics and reservoir size. JCI Insight 2018, 3(10).

Troyer RM, McNevin J, Liu Y, et al. Variable fitness impact of HIV-1 escape mutations to cytotoxic T lymphocyte (CTL) response. PLoS Pathog 2009, 5:e1000365.

Wherry EJ, Ahmed R. Memory CD8 T-cell differentiation during viral infection. J Virol 2004, 78:5535-5545.

Yang OO, Kalams SA, Trocha A, et al. Suppression of human immunodeficiency virus type 1 replication by CD8+ cells: evidence for HLA class I-restricted triggering of cytolytic and noncytolytic mechanisms. J Virol 1997, 71:3120-8.

Yerly S, Vora S, Rizzardi P, et al. Acute HIV infection: impact on the spread of HIV and transmission of drug resistance. AIDS 2001, 15:2287-92.

SECTION 2

Antiretroviral Therapy (ART)

5. ART 2023

5.1. Perspective

CHRISTIAN HOFFMANN

Hardly any other field of medicine has experienced such a dramatic evolution as antiretroviral therapy. After the early days, the cautious hopes with AZT, the first approved drug, in March 1987 (Volberding 1990, Fischl 1990), the Concorde study in 1994 plunged all involved into a sink of depression for several years. AZT was largely ineffective. Some participants still talk about the somber, still mood at the Berlin World AIDS Conference in June 1993. Infected people suffered and died. Hospices were set up, and AIDS care services were established. AIDS and death were dealt with. Sure, there was progress – cotrimoxazole, ganciclovir, and fluconazole saved lives in the short term, but hopelessness still dominated. Between 1989 and 1994, very little improved.

This did not change until September 1995, when two large trials, DELTA from Europe and ACTG 175 from the US (Delta 1996, Hammer 1996), attracted attention. It became apparent that two nucleoside analogs were more effective than one, including clinical endpoints. On top of that, the first trials of protease inhibitors (PIs), a new class of drugs developed thanks to knowledge of the molecular structure of HIV and protease, had been going on for months – preliminary data and many rumors were circulating. The race between the three companies, Abbott, Roche, and MSD, culminated in the fall of 1995. The amount of work involved in the pivotal studies of ritonavir, saquinavir, and indinavir was enormous. Study monitors "lived" for weeks in the trial centers, and thousands of queries had to be answered until late at night – between December 1995 and March 1996, all three PIs were approved in fast-track procedures.

However, many people (including this author) were unaware of what happened during these months. Although the AIDS rates in many centers had dropped by half between 1992 and 1996 (Brodt 1997), AIDS remained ever-present, and many were still dying. Doubts remained. Hopes had already been raised too many times in the previous years by supposed miracles. No one dared proclaim a breakthrough. In February 1996, during the 3rd CROI in Washington, when Bill Cameron reported the first data of the ABT-247 study during the late-breaker session, many held their breath. The auditorium was absolutely silent. Riveted, those in the audience heard that adding ritonavir oral solution decreased the frequency of death and AIDS from 38% to 22% (Cameron 1998). These results were sensational compared to anything else that had ever been published!

The World AIDS Conference in Vancouver a few months later, in June 1996, where the great potential of PIs came to light, developed into a celebration. Even regular news channels reported in great depth on the new "AIDS cocktails." The strangely unscientific expression "highly active antiretroviral therapy" (HAART) began to spread irreversibly.

By this time, David Ho, Time magazine's "Man of the Year" in 1996, had shed light on the hitherto completely misunderstood kinetics of HIV with his groundbreaking studies (Ho 1995, Perelson 1996). A year earlier, Ho had coined the slogan "hit early and hard," and almost all clinicians were now taking him at his word. With the new knowledge of the incredibly high turnover of the virus, there was no longer a latency period – and no life without antiretroviral therapy. Within only three years, 1994–1997, the proportion of untreated patients in Europe decreased from 37% to 9%, while the proportion on "HAART" rose from 2% to 64% (Kirk 1998).

Things were looking good. By June 1996, a third drug class was introduced when the first non-nucleoside reverse transcriptase inhibitor (NNRTI), nevirapine, was licensed. One now had a great selection of medications at hand. Most patients seemed to tolerate the pills. Twenty pills a day? We could live with that, if that's what it took. And how it helped! The number of AIDS cases was drastically reduced. Within only four years, between 1994 and 1998, the incidence of AIDS in Europe dropped from 30.7 to 2.5/100 patient-years (Mocroft 2000). Many ubiquitous opportunistic infections just seemed to disappear. Large OI trials, planned only a few months before, faltered due to a lack of patients. Hospices, just up and running on donations, shut down or had to change their focus. The first patients began to leave the hospices and went back to work. AIDS wards were occupied by other patients.

Sure, in early 1997, some began to complain about a fat belly. But what was that compared to AIDS? In June 1997, the FDA issued its first warning about diabetes mellitus with PIs. At the 5th CROI in Chicago in February 1998, old medical wisdom proved true: No drug that works is without side effects – one poster after another, whole walls of pictures showed fat abdomens, buffalo necks, thin legs, and faces. A new term was born: lipodystrophy. A setback, also psychological. Guidelines were modified; "Hit hard but only when necessary" was the imperative (Harrington 2000). Lactic acidosis, nephrolithiasis, polyneuropathies, allergies, and the hardly controllable diarrhea with many PIs, especially ritonavir, did the rest – clinicians became more defensive, and 200 CD4 T-cells were considered the new time point for starting therapy. Could treatment interruptions help to reduce side effects? At the beginning of the noughties, ART, although life-saving, did not have an excellent reputation.

But fortunately, times have changed again. Modern therapies have become much better. Integrase inhibitors, in particular – the first, raltegravir, came on the market in 2007 – have greatly enriched ART. Side effects are less and less of an issue; particularly, lipodystrophy has become rare. SMART (2006), HTPN052 (Cohen 2011), and START (2015) have impressively shown that every person with HIV infection should start ART and stay on it. Even with good immune status, there is less AIDS with ART, fewer health problems, and a better quality of life. And, of course, there are fewer transmissions. ART is still the best prevention. TasP, Treatment as Prevention, has become a generally accepted concept.

The development of therapy remains dynamic. Many drugs that were indispensable for a long time will now disappear; many already have done so. Pharmacokinetics are being further optimized, and single-tablet regimens have become the rule. The first injectable treatments are in use, and antibodies are becoming visible on the horizon. These new options may once again revolutionize HIV therapy. On the other hand, patents will expire over the next few years, as will prices and incentives. Patents for the first-generation INSTIs will expire in the next few years. New drugs will have a hard time being better than the existing ones (although that has been said before!).

What seemed utopian a few years ago has become a reality: a normal life expectancy with HIV infection. However, this also means that people with HIV must remain on treatment forever – a challenge. The comfortable situation today should not be a reason to relax. A "Plan B" is needed if there is no cure. New drugs are needed. What about the heart, kidneys, bones, and other organs in an aging population? New strategies are also needed. Where can exposure be reduced? The resistance barrier of some new agents is so high that the dogma of triple therapy has fallen. On the other hand, especially when facing decades of therapy, any resistance should be avoided. Careful studies are necessary to determine in whom de-escalation is possible (and whom it helps).

And what about "Plan A", the cure? We still cannot correctly measure or "wash out" the latent reservoirs in which this tricky virus hibernates. This will not change with

gene therapy, promoted by basic researchers (with careless media statements), that has been raising hopes again and again since around 2016. Gene therapy will probably not be the solution. Nor will stem cell transplants, a hazardous procedure that has received much media attention. On the other hand, if you don't have vision, you will never reach your goal. At least functional cures in selected cases do not seem impossible – the *HIV Cure* chapter will continue to expand. In the meantime, we will continue to pursue Plan B: keep HIV at bay in the long term. HIV remains a dangerous opponent. Patients and clinicians will tackle it together. The following sub-chapters describe how this might be done.

Literature

Brodt HR, Kamps BS, Gute P, et al. Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. AIDS 1997, 11:1731-8.

Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomized placebo-controlled trial of ritonavir in advanced HIV-1 disease. Lancet 1998, 351:543-9.

Cohen MS, Ying QC, McCauley M, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. N Engl J Med 2011; 365:493-505.

Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. Lancet 1994, 343:871-81.

Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. Lancet 1996, 348: 283-91.

Fischl MA, Parker CB, Pettinelli C, et al. A randomized controlled trial of a reduced daily dose of zidovudine in patients with the acquired immunodeficiency syndrome. N Engl J Med 1990; 323:1009-14.

Hammer SM, Katzenstein DA, Hughes MD, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. N Engl J Med 1996, 335:1081-90.

Harrington M, Carpenter CC. Hit HIV-1 hard, but only when necessary. Lancet 2000, 355:2147-52.

Ho DD. Time to hit HIV, early and hard. N Engl J Med 1995, 333:450-1.

Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 1995, 373:123-6.

INSIGHT START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med 2015; 373:795-807.

Kirk O, Mocroft A, Katzenstein TL, et al. Changes in use of antiretroviral therapy in regions of Europe over time. AIDS 1998, 12: 2031-9.

Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994-98: the EuroSIDA study. Lancet 2000, 356:291-6.

Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. Science 1996, 271:1582-6.

The SMART Study Group. CD4+ Count–Guided Interruption of Antiretroviral Treatment. N Engl J Med 2006; 355:2283-2296.

Volberding PA, Lagakos SW, Koch MA, et al. Zidovudine in asymptomatic HIV infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. N Engl J Med 1990, 322:941-9.

5.2. Overview – Classes of antiretrovirals and specific drugs

CHRISTIAN HOFFMANN

Currently (June 2023), more than 30 preparations are approved for the treatment of HIV infection. These come from six different drug classes:
1. Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs).
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs).
3. Protease inhibitors (PIs)
4. Entry inhibitors (coreceptor antagonists, attachment and fusion inhibitors).
5. Integrase strand transfer inhibitors (INSTIs)
6. Capsid inhibitors

There are also many fixed-dose combinations in which different drugs from different classes are combined, generally 1–2 NRTIs with an NNRTI, PI, or INSTI. Since NRTIs and NNRTIs each target reverse transcriptase, there are currently four main points of attack in the HIV replication cycle (Figure 2.1): HIV entry into the target cell, which is further subdivided into at least three sub-steps, and the three enzymes reverse transcriptase, integrase, and protease.

Here, the individual agents classified by drug class are discussed with their specific advantages and problems. First-line therapies, switching, salvage therapies, and experimental agents are discussed in separate chapters. The following table provides an initial overview of antiretroviral drugs.

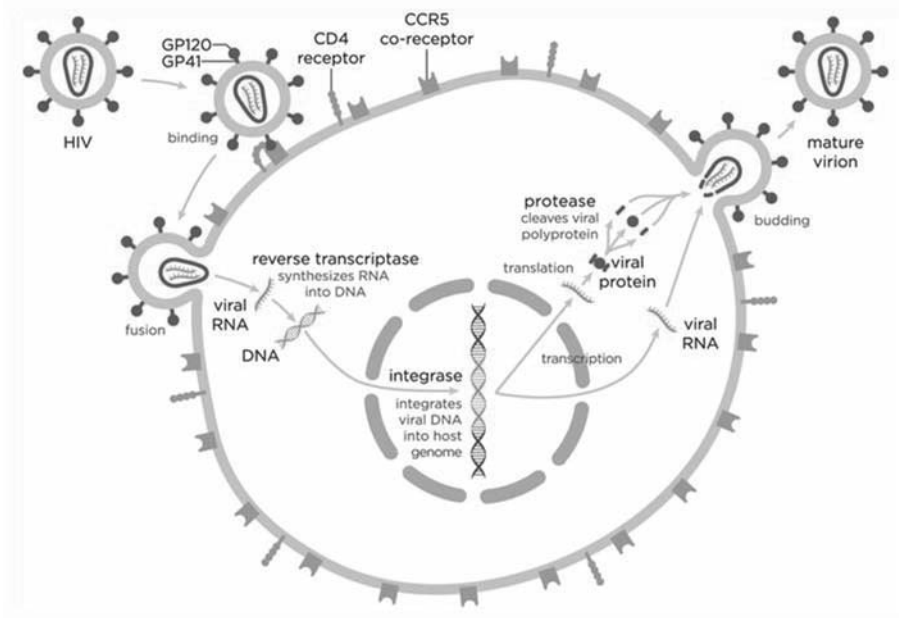

Figure 2.1: Targets in the replication cycle of HIV: entry, reverse transcriptase, integrase, and protease (capsid inhibitors are not yet considered).

Table 2.1: Antiretroviral drugs (brand names outside Germany in parentheses).

Trade name	Abbr.	Agent Name	Orig. manufacturer	Note
Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTIs)				
Emtriva®	FTC	Emtricitabine	Gilead Sciences	Generics
Epivir®	3TC	Lamivudine	ViiV Healthcare	Generics
Retrovir®	AZT	Zidovudine	ViiV Healthcare	Generics
Viread®	TDF	Tenofovir	Gilead Sciences	Generics
Ziagen®	ABC	Abacavir	ViiV Healthcare	Generics
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)				
Edurant®	RPV	Rilpivirine	Janssen-Cilag	
Intelence®	ETV	Etravirine	Janssen-Cilag	
Pifeltro®	DOR	Doravirine	MSD	
Sustiva® (Stocrin®)	EFV	Efavirenz	BMS/MSD	Generics
Viramune®	NVP	Nevirapine	Boehringer	Generics
Protease inhibitors (Pis)				
Aptivus®	TPV	Tipranavir	Boehringer	Generics
Invirase®	SQV	Saquinavir	Roche	Generics
Kaletra®	LPV	Lopinavir/Ritonavir	AbbVie	Generics
Prezista®	DRV	Darunavir	Janssen-Cilag	Generics
Reyataz®	ATV	Atazanavir	Bristol-Myers Squibb	Generics
Entry inhibitors				
Celsentri® (Selzentry®)	MVC	Maraviroc	ViiV Healthcare	
Fuzeon®	T-20	Enfuvirtide	Roche	
Rukobia®	FOS	Fostemsavir	ViiV Healthcare	
Trogarzo®	IBA	Ibalizumab	Theratech	only US
Capsid inhibitors				
Sunlenca®	LEN	Lenacapavir	Gilead Sciences	
Integrase inhibitors (elvitegravir, bictegravir only in the context of combination preparations)				
Isentress®	RAL	Raltegravir	MSD	
Tivicay®	DTG	Dolutegravir	ViiV Healthcare	
Vocabria®+Recambys®	CAB	Cabotegravir+RPV	ViiV Healthcare (+Janssen)	
NRTI combination drugs				
Combivir®	CBV	AZT+3TC	ViiV Healthcare	Generics
Descovy®	DVY	TAF+FTC	Gilead Sciences	
Kivexa® (Epzicom®)	KVX	ABC+3TC	ViiV Healthcare	Generics
Truvada®	TVD	TDF+FTC	Gilead Sciences	Generics
STR combinations (single-tablet regimen)				
Atripla®	ATP	TDF+FTC+EFV	Gilead+BMS+MSD	Generics
Biktarvy®	BIC	TAF+FTC+BIC	Gilead Sciences	
Delstrigo®		TDF+3TC+DOR	MSD	
Dovato®		3TC+DTG	ViiV Healthcare	
Eviplera® (Complera®)	EVP	TDF+FTC+RPV	Gilead (+Janssen)	
Genvoya®		TAF+FTC+EVG+COB	Gilead Sciences	
Juluca®		DTG+RPV	ViiV (+Janssen)	
Odefsey®		TAF+FTC+RPV	Gilead (+Janssen)	
Stribild®	STB	TDF+FTC+EVG+COB	Gilead Sciences	
Symtuza®		TAF+FTC+DRV+COB	Janssen (+Gilead)	
Triumeq®	TMQ	ABC+3TC+DTG	ViiV Healthcare	
Pharmacoenhancers (boosters)				
Norvir®	RTV	Ritonavir	AbbVie	Generics
Tybost®	COB	Cobicistat	Gilead Sciences	

As can be seen from the table, there are various single-tablet regimens that contain a complete ART combination. Some agents are missing because they are not marketed in all European countries. These include Evotaz® (atazanavir/c), Rezolsta® (darunavir/c, also Prezcobix®), Viracept® (nelfinavir), Rescriptor® (delavirdine), and Vitekta® (elvitegravir). In 2022, Trogarzo® (ibalizumab) was withdrawn from the European market, although it can still be obtained for selected patients through international pharmacies.

Many other compounds have already disappeared from the market, including the previously widely used D-drugs HIVID® (ddC), Videx® (ddI), and Zerit® (d4T). At the end of 2019, sales of the PIs Crixivan® (indinavir) and Reyataz® (atazanavir) were discontinued, and in 2021, this was seen for Viramune® (nevirapine) and Aptivus® (tipranavir). However, generics are still available for some of these compounds. Withdrawal of Trizivir® (AZT/3TC/abacavir) and Telzir® (fosamprenavir) is expected in 2023, as many other PIs.

In the summer of 2022, the first capsid inhibitor, lenacapavir, was approved, but the indication is restricted to individuals with limited options. The exact mechanism of action of capsid inhibitors is still unclear; different steps in the replication cycle are probably inhibited to different degrees. Although lenacapavir is currently only a niche drug, a start has been made.

Brand names, generics

Unfortunately, the US FDA and the European EMA sometimes disagree on the assignment of brand names – as a result, brand names sometimes differ from country to country. In some cases, the manufacturer's rights do not apply worldwide. For example, the NNRTI efavirenz is marketed in Germany by the company BMS under the trade name Sustiva® and in Austria by MSD as Stocrin®. Generics are now available for nearly all NRTIs and PIs (INSTIs soon expected). Even the first STR Atripla® is available generically as Padviram®. Although generics may often represent an appropriate alternative to branded products, this may not always be true. Mandatory generic switching may lead to confusion and unintended consequences. Specifically, several studies suggested switching may negatively impact medication adherence (Straka 2017). However, plausible reasons for staying with the original and expensive preparation do not exist, but any switch needs communication with the person. Patients can become anxious when pharmacies (obliged to do so in many countries) issue unfamiliar drug packages without prior explanation and information.

In 2022, due to Russia's invasion of Ukraine, HIV clinicians in many European countries have faced a new problem. Ukraine, home to about 250,000 PLWH, has nearly ten times as many PLWH as neighboring countries. Most Ukrainian refugees living with HIV take 'TLD', a fixed-dose combination (FDC) of TDF, 3TC, and dolutegravir produced by generic manufacturers. TLD has become the most widely used HIV regimen in the world but is still unavailable in the European Union. This means that if people want to stay on dolutegravir, they must be switched to two-pill combinations. The information that their STR is not available in Western Europe is often met with incomprehension. Given the language barrier, the fact that they are not to be deprived of anything but that other patent regulations apply here can often not be conveyed to the people concerned. Mistrust can develop.

Indication restrictions

Definitions for indication areas vary widely. Some agents are not licensed for first-line therapy: Maraviroc, T-20, tipranavir, etravirine, but also the combination preparation Atripla® or the combination of dolutegravir and rilpivirine (Juluca®). Also, the two sustained-release drugs cabotegravir (Vocabria®) and rilpivirine-LA (Rekambys®)

are reserved for adults who are "virally suppressed under their stable current antiretroviral therapy regimen" and who do not have resistance. The entry inhibitors ibalizumab and fostemsavir are indicated only for multidrug-resistant cases where "no other suppressive regimen can be assembled." The NNRTI rilpivirine should generally not be prescribed in patients with high viremia, and nevirapine should not be prescribed for high CD4 T-cell counts. HLA or tropism testing is required for abacavir or maraviroc. Further restrictions apply to pregnant women, adolescents, and children; see the relevant chapters for details. Different dosages (Descovy®, but also Prezista® or Isentress®) must also be considered, whether this is due to interactions, the resistance situation, or renal insufficiency (see chapter *Drugs* at the end of this book). Given cost pressures, clinicians are well advised to adhere to the specific indication areas. Fortunately, this is usually possible due to a wide range of options.

Costs

Antiretroviral drugs have been expensive in many Western countries. However, there has been a lot of movement in the market in recent years. With the fall of the patent of tenofovir-DF (TDF) or TDF/FTC (Truvada®) in July 2017, a price war of generic companies has broken out. Fueled by PrEP approval (many self-paying PrEP users, public pressure), this competition led to unprecedented price erosion. TDF/FTC, which was very expensive a few years ago at over 800 euros per monthly pack in Germany, is now available for around 40 euros. A triple combination of TDF/FTC plus nevirapine or efavirenz is now available for less than 250 euros/month, a fraction of the old price – at least when TDF/FTC and, for example, efavirenz are given separately. In addition to the NRTIs, the old NNRTIs nevirapine, and efavirenz, almost all PIs are available as generics and have fallen considerably in price. More than half of all antiretroviral agents are thus generic. For the INSTIs, it will take a little longer; the raltegravir patent is still valid during 2023, and that for dolutegravir until 2026/27.

Drug patents have been disregarded in some African countries, such as India or Thailand. Generics are now produced there for almost all drugs. The most prescribed drug in Ukraine is TLD (see above). In Western countries, however, these preparations play no role.

It remains to be seen what impact the end of the patents will have on ART in the near future. Will the development of new agents be worth the cost? New agents must offer advantages to achieve those higher and higher prices. In many countries, new agents without significant advantages over preexisting drugs ("me-too drugs") will be downgraded to the generic level. The companies know that. A good example is GSK's decision not to progress their new maturation inhibitor into late-stage trials when it became clear that "the candidate was not differentiated enough in the daily oral HIV market". In other words, in the era of Bikarvy® and Dovato®, it has become almost impossible to noticeably improve single-tablet regimens to charge a higher price.

But will drugs be withdrawn from the market because they are no longer profitable? The example of Trogarzo® in 2022 will not be the last – Theratechnologies could not arrive at key pricing and reimbursement conditions in Europe and now only sells ibalizumab in North America. There is no doubt that antiretroviral therapy is in for a restructuring.

Sometimes, more than 20,000 euros is the annual price for a therapy for a multiresistant virus. The pricing policies of the industry, however, remain difficult to understand. Discount agreements with health insurers remain obscure. Why some directly competing preparations cost almost the same to the penny and other agents in the same class of active ingredients, differ so much cannot be explained by devel-

opment costs alone. There is no question that much money is still being made with ART. In 2019, market leader Gilead Sciences made 15 of 22 billion dollars in global sales with HIV drugs. The market remains competitive, and the existing monopolies will be exploited as long as possible. Innovations are needed to continue generating such sales. This is one of the reasons why such intensive research is being conducted into new options, such as long-acting agents or antibodies – they will indeed be needed for new profit paradigms when the major INSTI patents expire by the end of this decade.

However, two aspects should not be forgotten in this debate. First, the enormous development costs of new drugs, which are estimated by manufacturers at over a billion dollars in some cases (which is admittedly also disputed). Without the prospect of profit, not a single agent would be developed. Most of them never make it to market. An approved compound like T-20 will never recoup the development costs, which reportedly swallowed up $600 million in development. Second, there is hardly a more effective therapy than antiretroviral therapy. Estimates in the US range from $13,000 to $23,000 per QALY (quality-adjusted year of life) year gained (Freedberg 2001). This is comparatively cheap. Treatments for advanced HIV (AIDS) hospital and nursing costs can be saved by ART. In the Hanover cohort, total annual costs per case were reduced from 35,865 to 24,482 euros between 1997 and 2001 (Stoll 2002). In the PROPHET study, treatment costs were still around 20,000 euros between 2014 and 2017, with a downward trend (Valbert 2020). Patients remain fit for work, so costs are reduced economically (Sendi 1999).

The bottom line, however, is that ART is expensive. Patients can use supplies and packs if they switch for strategic reasons (pill reduction or concern about long-term toxicities). Only monthly packs should be prescribed at the beginning and during a switch. Only when the ART is well-tolerated and has a constant effect can one resort to the three-month packs most companies offer. They are usually cheaper than monthly packs. Larger quantities than for three months should not be prescribed.

Nucleoside analogs (NRTIs)

Mode of action

The target of nucleoside analogs ("nukes") or nucleoside reverse transcriptase inhibitors (NRTIs) is the HIV enzyme reverse transcriptase. Acting as alternative substrates, they compete with physiological nucleosides, differing from them only by a minor modification to the ribose molecule. Their incorporation of nucleoside analogs induces DNA chain termination because durable phosphodiester bridges can no longer be built to stabilize the double strand. NRTIs are pro-drugs; they are converted to the active metabolite only after endocytosis, whereby they are phosphorylated to the effective triphosphate derivatives. AZT and d4T are thymidine analogs, FTC, and 3TC cytidine analogs. A combination of FTC plus 3TC makes no sense because both compete for the same bases. Abacavir a guanosine analog. TDF and TAF are precursors of tenofovir, a nucleotide analog structurally related to adenosine monophosphate, which is phosphorylated intracellularly to the active tenofovir diphosphate and competes with the natural substrate deoxyadenosine triphosphate in nucleic acid synthesis.

Nukes were the first HIV drugs on the market – AZT was approved in 1987. Tolerability is fair. However, frequent complaints in the first few weeks are fatigue, headaches, and gastrointestinal problems, which vary widely from a mild feeling of fullness to vomiting and diarrhea (see *Side Effects* below). Older NRTIs, in particular, caused a broad spectrum of long-term side effects, ranging from myelotoxicity, lactic acidosis, polyneuropathy, and pancreatitis. Metabolic disorders and lipoatrophy have also been associated with NRTIs. Much can probably be explained by mitochondrial toxicity (Brinkman 1999). Mitochondrial function requires nucleosides: the metabolism of these essential organelles is disrupted by the incorporation of false nucleosides (the drugs), leading to mitochondrial degeneration.

With the NRTIs used today, however, such side effects are rare. TDF, TAF, 3TC, and FTC still play an essential role, as does abacavir in some cases. On the other hand, the notorious three toxic "D drugs" (d4T, ddI, ddC) have disappeared completely. AZT will do so soon.

However, another mechanism may also play a role: *in vitro,* inhibition of telomerase by NRTIs has been shown (Hukezali 2012, Leeansyah 2013). Telomerase, a reverse transcriptase, restores telomeres, those ends of chromosomes consisting of repetitive DNA and proteins that become shorter with each cell division (aging process). Thus, NRTIs could promote premature aging of cells. However, clinical data are conflicting (Solomon 2014, Montejano 2018, Stella-Ascariz 2018).

Nucleoside analogs are predominantly renally eliminated and do not interact with drugs metabolized by hepatic enzyme systems. Therefore, the potential for interaction is low; however, dose adjustments must be considered with TAF. Doses of some NRTIs also need to be adjusted in cases of renal failure. There is a high degree of cross-resistance (see chapter on *Resistance*).

Individual agents

Abacavir (**Ziagen®**, also in **Kivexa®** or **Epzicom®**, **Trizivir®**, **Triumeq®**, generics available, abbreviation ABC) is a guanosine analog that is phosphorylated intracellularly to carbovir triphosphate. As monotherapy, abacavir reduces viral load by approximately 1.4 logs after four weeks (Harrigan 2000). After initial approval in July 1999, abacavir was also approved for single daily administration in October 2004. It is almost exclusively combined with 3TC (available as Kivexa®, as well as generics), forming a backbone (see below). In a meta-analysis, abacavir was very effective, even at high viral loads (Cruciani 2014). Since late 2014, it has also been a component of the single-table regimen Triumeq®, a combination with 3TC and dolutegravir. The single agent Ziagen® or the combination with AZT and 3TC, Trizivir®, hardly plays a role anymore.

Abacavir is tolerated relatively well, but nausea occurs slightly more frequently than with TAF (Gallant 2017). Regarding mitochondrial toxicity, abacavir is more favorable than, for example, d4T (Hoy 2004). One significant drawback is the hypersensitivity reaction (HSR) seen with abacavir in 5–8% of Caucasians (in other ethnicities, incidence is somewhat lower). This allergic reaction is often accompanied by fever and feeling sick, usually occurring in the first six weeks. HSR can be life-threatening, especially in cases of re-exposure. In these cases, rapid action within minutes is required. Severe HSR after a single tablet (De la Rosa 2004) or a break in therapy when previously tolerated have been described (El-Sahly 2004).

There is a genetic predisposition for this hypersensitivity. People with the HLA allele B*57:01 may develop HSR up to 80% with ABC (Mallal 2002, Hetherington 2002). Cases without this HLA type are sporadic (Tangamornsuksan 2015). Abacavir likely binds to a specific site on the HLA-B*57:01 molecule, altering its specificity and resulting in alloreactive T-cell activation. The PREDICT study demonstrated the predictive value of HLA testing in nearly 2000 patients (Mallal 2008). HLA testing is mandatory before starting any ABC-containing ART and should be initiated once in everyone with HIV. Because it is a genetic test, prior written consent is required. HLA-B57 status should be prominently noted in the medical record. Since the institution of broad HLA testing, HSR is rarely observed today (Roen 2018).

Once the problem with HSR was resolved, abacavir came under pressure again in 2008. Since then, numerous cohort studies have consistently reported a nearly twofold increased risk of myocardial infarction, especially with newly initiated abacavir therapy. Although this effect was not seen in meta-analyses of clinical trials (Nan 2018), it remained evident in more recent cohorts (Dorjee 2018). The prothrombogenic pathomechanisms can now be plausibly explained, involving both aggregation and activation of platelets (Mallon 2018, O'Halloran 2018, Taylor 2019). We have replaced abacavir with other options in most patients, especially those at high risk for cardiovascular events. The higher the risk, the faster and more active the switch. In times of dual therapies, abacavir has mainly become dispensable.

AZT (**zidovudine**, **Retrovir®**, also in **Combivir®** and **Trizivir®**, generics available) was the first antiretroviral drug ever on the market in 1987. In the 1990s, AZT was among the most widely used drugs; it now plays little role. Compared with newer NRTIs, AZT is less well tolerated, especially with regard to gastrointestinal complaints. Myelotoxicity, which should not be underestimated even at current lower dosages of 500–600 mg/day, is sometimes manifested by marked anemia (blood count checks!), and MCV (mean corpuscular volume of erythrocytes) is almost always elevated with long-term use. Countless studies have shown that lipoatrophy improves when switching from AZT to other therapies (see chapter 5.7. *Management of side effects*). In addition to poor tolerability, another disadvantage is twice daily

dosing. Thus, its use today is reserved in cases of resistance. In the case of the tenofovir mutation K65R, AZT can be used due to its viral hypersensitivity, and lower doses may be sufficient for this purpose. Also, because of its good CSF penetration, it is still occasionally used in HAND or PML to reduce viral load in the CNS as effectively as possible.

ddC (**zalcitabine, Hivid®**) was the third NRTI in 1992. Weak efficacy and problems with pharmacokinetics and side effects led to ddC being withdrawn from the market in 2006 – the first withdrawal in HIV medicine.

ddI (**didanosine, Videx®**) was the second NRTI in 1991. Its effectiveness is comparable to that of AZT. Due to its toxicity (gastrointestinal symptoms, polyneuropathies, pancreatitis, lipoatrophy), distribution in Europe was discontinued in 2020.

d4T (**stavudine, Zerit®**) was the second thymidine analog and as effective as AZT. Its higher long-term toxicity compared with other NRTIs manifested as polyneuropathies and lipoatrophy, but also as lactic acidosis. In Europe, it was discontinued in 2019. Why is it still mentioned? There are still people suffering from d4T-induced polyneuropathies.

3TC (**lamivudine, Epivir®**, also part of **Combivir®**, **Delstrigo®**, **Kivexa®** or **Epzicom®**, **Trizivir®**, **Triumeq®**) was licensed in August 1996 as the fifth NRTI in Europe. 3TC (the colloquial abbreviation describes the chemical formula 2′-deoxy-3′-thiacytidine) is a very well-tolerated cytidine analog. Its primary disadvantage is the rapid development of resistance: the point mutation M184V, likely to develop after only a few weeks on monotherapy, is sufficient for resistance against 3TC (Eron 1995). Therefore, the full effect of 3TC only emerges in combination with other drugs (which admittedly is true for most). In extensive clinical studies such as NUCB 3002 or CAESAR, 3TC significantly improved disease progression and survival (Staszewski 1997). The M184V mutation, which is also most likely to be found in the virological failure of modern ART regimens, not only has disadvantages but may also increase AZT-resistant viruses' susceptibility (Miller 2002). More importantly, M184V reduces viral fitness and flexibility (see *Salvage Therapy*). It may be prudent to remain on 3TC to conserve the M184V mutation through selection pressure and reduce the replicative capacity of HIV. Further viral resistance mutations may be prevented (Stirrup 2020).

Although the half-life is not quite as long, the antiviral potency of 3TC is equivalent to that of its main competitor, FTC (see below). A meta-analysis including three studies that directly compared the two compounds (with identical backbones) found no relevant clinical differences (Ford 2017). Thus, 3TC and FTC are interchangeable, both with excellent tolerability. Because of this, the choice between 3TC and FTC is usually made by adjunctive therapy, as both agents are available in different combination preparations. The most common use of 3TC in classical triple therapies today is in the STRs Triumeq® (with dolutegravir and abacavir) and Delstrigo® (doravirine, TDF). However, 3TC is also used in dual therapies. Within the GEMINI and TANGO trials, it was as effective in fixed combination with dolutegravir (Dovato®) as a classic triple therapy in both treatment-naïve and pretreated individuals without resistance (Cahn 2019, van Wyk 2020). Dovato® was approved in the summer of 2019 and is now among the most frequently prescribed STRs. Also, with boosted PIs such as darunavir or lopinavir, 3TC seems sufficient as the only NRTI, although there are no fixed combinations in Western Europe.

It is important to note that 3TC dosage must be reduced in renal insufficiency. It is often forgotten that fixed combinations (usually 300 mg 3TC) must be discontinued with a creatine clearance of < 50 mL/min. Another effect of 3TC is its efficacy against HBV, which can be used in co-infections. However, given the rapid devel-

opment of HBV resistance, 3TC should be combined with another HBV-active NRTI, most likely tenofovir. The combination of ABC+3TC is, therefore, not recommended in HBV co-infection.

FTC (emtricitabine, Emtriva®, also in **Truvada®**, **Descovy®**, **Atripla®**, **Biktarvy®**, **Eviplera®** or **Complera®**, **Genvoya®**, **Odefsey®**, **Stribild®**, and **Symtuza®**) is another well-tolerated cytidine analog that was approved in October 2003. FTC is biochemically very similar to 3TC but has a longer half-life. Clinically, however, there are no relevant differences. According to a comprehensive meta-analysis, the two compounds are interchangeable, and potential differences are negligible (Ford 2017). As with 3TC, efficacy is abrogated by the M184V mutation. There is also a moderate efficacy against HBV. Tolerability is good, and interaction potential is low (Frampton 2005). FTC has a comparatively low affinity for mitochondrial polymerase, so the risk of mitochondrial toxicity is probably relatively low. It is important to note that with a creatinine clearance of less than 30 mL/min, the dose of FTC must be adjusted. FTC is probably the most widely used substance in HIV therapy today, given the many fixed combinations available (NNRTIs, PIs, INSTIs, mostly with TDF or TAF). In contrast, the single substance as Emtriva® plays practically no role, and the concomitant therapy almost always decides for or against FTC. In recent years, FTC has also been evaluated in the context of dual therapies. Still, the data situation is much less conclusive than for 3TC – manufacturer Gilead continues to rely entirely on triple therapy. FTC is also used extensively in PrEP; most large PrEP studies were conducted with FTC (and not with 3TC).

TAF (tenofovir alafenamide fumarate, included in **Descovy®**, **Biktarvy®**, **Odefsey®**, **Genvoya®**, **Symtuza®**, as single agent **Vemlidy®** only for hepatitis B) is a pro-drug of tenofovir. Tenofovir has a phosphoric acid residue in addition to pentose and nucleic base and is, therefore, referred to as a nucleotide analog. In contrast to TDF (see below), TAF is first converted to tenofovir intracellularly and not already in plasma, resulting in higher tenofovir concentrations in peripheral blood cells. With TAF, plasma tenofovir levels in the blood are 90% lower, while intracellular levels are about five-fold higher. So, with the same efficacy, the adverse effects on the kidney and bones of TDF are reduced (Review: Wang 2016). Since 2016, TAF has been part of various combination preparations; as a single agent, it is only approved for hepatitis B.

The overall effect is comparable to that of TDF (Sax 2015, Gallant 2016), and the renal tolerability is probably better. In two large Phase III trials in treatment-naïve patients (with FTC and elvitegravir/c), TAF had less impact than TDF on bone mineral density and renal biomarkers (Sax 2015). In ART-experienced patients, proteinuria and bone density improved with switching from TDF to TAF, both in the presence and the absence of moderate renal damage – see Table 2.2 (Mills 2016, Pozniak 2016). A meta-analysis found a benefit in renal events and bone markers only with boosted regimens; overall differences were small (Hill 2018). In at least two studies, an approximately 5% increased rate of headache was observed compared to TDF (Gallant 2016, Mills 2016). In one double-blind study, switching from abacavir to TAF did not affect renal or bone biomarkers (Winston 2018). TAF is not a substrate of renal tubule transport systems. Thus, no accumulation is expected. The drug can be dosed normally, even in moderate renal insufficiency (clearance up to 30 mL/min). Renal monitoring is less stringent than under TDF (see below). On the other hand, TAF has recently been associated with weight gain (Venter 2019, DeJesus 2019, Sax 2019).

TAF levels are influenced by concomitant therapy. Therefore, unlike TDF, two different TAF doses are available (10 and 25 mg). In combination with boosted PIs or elvitegravir/c, 10 mg TAF is sufficient. The combination drugs Genvoya® (with

elvitegravir/c) and Symtuza® (with darunavir/c) each contain 10 mg, whereas Biktarvy® (with bictegravir) and Odefsey® (with rilpivirine) contain 25 mg TAF. The dose also needs to be adjusted for some other drugs. Drugs such as rifampicin, rifabutin, and even St. John's wort, all of which induce P-glycoprotein (P-gp), can significantly decrease the plasma concentration of TAF. They should not be given together; in these cases, TDF is recommended.

Since 2016, some TDF-containing combinations have been replaced by TAF-containing ones, i.e., Truvada® by Descovy®, Eviplera® by Odefsey® and Stribild® by Genvoya®. Many countries nevertheless did not consider any of these preparations to have proven additional benefits, neither for patients who were naïve to therapy nor for pre-treated patients. This is particularly relevant given the price decline of the generically available Truvada® (TDF/FTC). In 2021, Gilead has withdrawn its application for TAF/FTC as PrEP in the EU. This is likely due to the differences compared to generic TDF/FTC that would not be acceptable to European health systems.

TDF (tenofovir disoproxil fumarate, Viread®, also in **Truvada®**, **Atripla®**, **Delstrigo®**, **Eviplera®** or **Complera®**, **Stribild®**) is, like TAF, a precursor of tenofovir. Since 2017, many generics have existed, some very cheap, especially for the combination of TDF/FTC. Of note, some generic manufacturers do not use the fumarate as the water-soluble salt but rather as a succinate or maleate, so that the abbreviation TDF is, strictly speaking, incorrect (but will remain here for the sake of simplicity). As a phosphonate, TDF is first freed from the phosphonate moiety by a serum esterase and activated intracellularly by two phosphorylation steps.

TDF is well tolerated, and its affinity for mitochondrial polymerases is low (Suo 1998). In extensive studies, TDF was superior to older NRTIs like AZT, mainly due to better tolerability (Review: Dadi 2017). Switching to TDF may help improve lipoatrophy and dyslipidemia (see below, section 5.7). Another advantage is its sustained efficacy against HBV, which led to its approval for hepatitis B in 2008. Other potential indications include mother-to-child prevention and, more recently, PrEP (see relevant chapters). Since its approval in 2001, TDF has been one of the most widely used agents in HIV medicine.

However, with widespread use, problems also have come to light. The most important is the potential nephrotoxicity of TDF (see *HIV and Nephrology*). Though renal dysfunction is mostly mild and often reversible (Review: Hall 2011), detailed renal monitoring instructions are available for all TDF-containing preparations. Before initiation, creatinine clearance should be calculated, and renal function (creatinine clearance and serum phosphate) should be monitored at 2–4 weeks, 3 months, and every 3 to 6 months after that – or more frequently if abnormalities and/or renal risk are evident. However, severe renal abnormalities are rare. In a meta-analysis of 11 randomized trials, discontinuation rates due to renal events were 0.6% (17/2,689) with TDF versus 0.1% (2/3,771) with TAF (Hill 2018). Moreover, an increased risk of renal events was found only with boosted regimens. In the Swiss cohort, 46 of 2,592 individuals (1.6%) had to discontinue TDF due to renal toxicity after an average of 442 days (Fux 2007). Renal failure on TDF is also observed in the setting of Fanconi syndrome, a defect of proximal tubule transport. Patients with renal damage should not receive TDF. This applies also to elderly individuals and those who weigh less, as well as those with boosted PIs (Young 2012) and with potentially nephrotoxic co-medication. For example, a worryingly high incidence of acute renal failure has been observed with co-administration of diclofenac (Bickel 2013). TDF has also long been associated with changes in bone biomarkers and bone damage (see S*ide Effects*). So far, many healthcare systems do not see any additional benefit for TAF compared to TDF. Think twice about switching for no reason! An argument in favor of staying with TDF is the fact that the dose of the co-medication does not have to be adjusted.

Moreover, the data and experience regarding long-term use are greater for TDF (as well as on PrEP) than for TAF. A newer finding is that, unlike TAF, TDF does not seem to cause any (or less) weight gain. In meta-analyses, patients on TDF gained significantly less weight (Sax 2019, DeJesus 2019). Whether this is caused by a toxic, "catabolic" effect of TDF or a direct effect of TAF is still unclear.

The choice of the NRTI backbone

Classical ART regimens have contained a "nuke backbone", i.e., usually two nucleoside/nucleotide analogs. This is mainly a historical artifact: NRTIs were the first HIV drugs, and by the time PIs or NNRTIs came on the market, the administration of two NRTIs was established as the standard. With the current knowledge of the toxicity of some NRTIs, this concept is increasingly being questioned. With Juluca® or Dovato®, regimens are now available that contain only one or even no NRTI (see *De-escalation*). They are mainly used in treatment-experienced patients.

In treatment-naïve individuals, a classic backbone of two NRTIs remains the standard. By far, the most important backbones are TAF or TDF plus FTC or 3TC and, with declining popularity, ABC/3TC. 3TC alone can also be considered (see below). No other NRTI backbones play a significant role and are no longer recommended; they are discussed at the end of this section.

Thus, when choosing the backbone of two NRTIs, there are only two questions: TAF or TDF? Is there a case for abacavir? In the following section, the data on this topic is briefly summarized.

TDF/FTC, TAF/FTC or TDF/3TC?

There are convincing data for combining one of the two tenofovir prodrugs, TDF or TAF plus FTC; these are currently the most widely used NRTI backbones. Both tenofovir prodrugs are used exclusively with FTC, again for historical (as well as) patent reasons. Since the introduction of Delstrigo® in 2019, TDF+3TC has also become a frequently used backbone in Europe. Worldwide, TLD (TDF/3TC/dolutegravir) is the most widely used HIV regimen.

Incompatibilities or intolerability for FTC or 3TC practically never occur; both agents are interchangeable (Ford 2017). Direct comparisons with older, previously widely used backbones such as AZT/3TC do not exist for TAF/FTC, but only for TDF/FTC. In the Gilead 934 study (Gallant 2006), TDF+FTC and AZT+3TC (plus efavirenz in each case) were compared in 509 therapy-naive individuals. After 48 weeks, a viral load below 50 copies/mL was achieved more frequently with TDF+FTC (80% versus 70%), mainly due to better tolerability. After 144 weeks, lipoatrophic side effects were less frequent with TDF+FTC than with AZT+3TC (Arribas 2008).

Numerous studies have been devoted primarily to comparing TDF+FTC and TAF+FTC, each combined with different third agents (see Table 2.2). Most studies were conducted by the manufacturer, Gilead Sciences. All showed comparable virological efficacy of both backbones, with differences in tolerability.

To conclude, there is a moderate improvement in renal function with TAF compared to TDF after 48 weeks. The difference in GFR is 4–5 mL/min (a lower decrease in therapy-naive patients or an increase in experienced patients switching to TAF). Some renal markers (tubular proteinuria) are also somewhat more favorably affected. Positive effects are also observed with regard to bone density. Total cholesterol, on the other hand, is somewhat more favorably affected by TDF. Still, the cholesterol/HDL ratio or the rate of individuals requiring a lipid-lowering drug remains the same. At least two studies found a slightly higher rate of headache with TAF. Regarding clinical endpoints (renal failure, fractures, cardiovascular events, mortality), no study has shown differences between TAF and TDF; these events were too rare.

Table 2.2: Randomized Phase II/III trials of TDF+FTC versus TAF+FTC (comparable virologic efficacy in all studies).

Study	Setting	Significant outcomes for TAF versus TDF in terms of kidneys, bone, lipids
ART-naive patients		
GS-292-102 (Sax 2014)	n=170 plus EVG/c	RF better (GFR drop –6 vs. –11 mL/min), BM better, cholesterol worse, slightly more nausea with TAF
GS-292-104/111 (Sax 2015)	n=1,733 plus EVG/c	RF better (GFR drop –6 vs. –11 mL/min), BM better, cholesterol slightly worse, AEs overall same
GS-299-102 (Mills 2015)	n=153 plus DRV/c	RF better (GFR drop –3 vs. –11 mL/min), BM better, cholesterol slightly worse, AEs overall same
AMBER (Eron 2018)	n=725 plus DRV/c	RF better (approx. 3 mL/min difference), BM better, cholesterol slightly worse (lipid-lowering drugs rarely necessary), AEs same
ADVANCE (Venter 2019)	n=702 plus DTG	RF almost the same, BM better, AEs same, but more weight gain with TAF
ART-experienced patients with < 50 HIV RNA copies/mL, switch to TAF		
GS-1089 (Gallant 2016, Post 2017)	n=668 plus various (DRV/r > NVP > RAL)	RF better (GFR increase +8 vs. +3 mL/min), BM better, cholesterol slightly worse, AEs overall same, results independent of the third agent
GS-366-1216 (Orkin 2017)	n=630 plus RPV	RF better (GFR increase +5 vs. +1 mL/min), BM better, fewer AEs overall.
EMERALD (Orkin 2017)	n=1,141 plus various PIs	RF better, BM better, limitations*
GS-292-109 (Mills 2016)	n=1,436 plus various (EVG/r, EFV, ATV/r)	RF slightly better, also BM, lipids slightly worse, study open-label, with limitations in terms of TAF/TDF*

* In these studies, only one subgroup replaced TDF exclusively with TAF; in the other patients, the third substance was also replaced with DRV/c or EVG/c. GFR = glomerular filtration rate, RF = renal function, BM = bone markers, AEs = adverse events.

In a meta-analysis of 11 randomized trials, discontinuation rates due to renal events were 0.6% (17/2,689) with TDF versus 0.1% (2/3,771) with TAF (Hill 2018). However, an increased risk of TDF was found only with boosted regimens; this was also true for bone events. Thus, at least in unboosted regimens, TAF+FTC and TDF+FTC/3TC can be considered equivalent.

Another controversial issue is weight gain with TAF, which was more pronounced than TDF in several meta-analyses (Sax 2019, DeJesus 2019). Some data point to TAF, and other data attribute a "catabolic", weight-reducing, effect to TDF. Or, to put it another way, when TAF is used, weight gain is particularly measurable if TDF was previously used (see *Side Effects*).

The data available to date were insufficient for many European health authorities to assign even a small additional benefit to TAF compared with TDF. According to the updated EACS guidelines of October 2021, TAF should be preferred to TDF if cardiovascular disease, osteoporosis, progressive osteopenia, or a high risk for these is present. TAF should also be given preference in the presence of concomitant medication with nephrotoxic drugs or previous TDF toxicity.

Given the massive price reduction of generic TDF since 2017, clinicians should rethink switching to TAF without justification and/or without the risk factors defined by EACS, laid out above. This is especially true for the NRTI fixed combination TAF/FTC (Descovy®). However, the costs are often identical for patented STRs that differ only in TAF and TDF (Eviplera and Odefsey®, STRIBILD® and Genvoya®).

TAF or TDF/FTC or ABC/3TC?

The backbone ABC/3TC, available as Kivexa® or Epzicom® in a fixed combination (numerous generics now exist), is also used. In the double-blind randomized trial, CNA30024, ABC+3TC were as effective as AZT+3TC (DeJesus 2004). ABC/3TC has also been compared with TDF/FTC in several randomized trials in treatment-naive and -experienced patients. A recent study compared ABC+3TC with TAF+FTC in pre-treated patients (see Table 2.3).

Table 2.3: Randomized trials TDF/FTC or TAF/FTC versus ABC/3TC.

Study	Setting	Main results
ART-naive patients		
HEAT (Smith 2009)	Double-blind (n=688) plus LPV/r	Non-inferiority of ABC/3TC vs. TDF/FTC shown, AEs same in both arms
ACTG 5202 (Sax 2011)	Double-blind (n=1858) plus EFV or ATV/r	TDF/FTC better at high VL, also more AEs with ABC/3TC
ASSERT (Stellbrink 2010)	Open-label (n=385) plus EFV	TDF/FTC virologically better. Under ABC/3TC, more AEs overall but fewer renal, bone AEs
ART-experienced patients		
GS 1717 (Winston 2018)	Double-blind (n=556) plus various	TAF/FTC virologically non-inferior, no differences in lipid profile, renal and bone biomarkers
STEAL (Martin 2009)	Open-label (n=357) VL <50	Effectiveness equal, but more AEs with ABC/3TC than with TDF/FTC (including cardiovascular, but smaller decrease in bone density)
BICOMBO (Martinez 2009)	Open-label (n=333) VL <200 >6 mo	Non-inferiority of ABC/3TC versus TDF/FTC *not* shown, more AEs

VL = viral load in copies/mL, AE = adverse events.

As can be seen, the data are mixed. In HEAT and STEAL, ABC/3TC and TDF/FTC were largely equivalent, but in ACTG 5202, ASSERT, and BICOMBO, ABC/3TC were somewhat inferior, especially at high baseline viral load (Sax 2011). However, careful analyses suggested this was probably not due to antiviral potency (Grant 2013). Severe adverse events are somewhat more frequent with ABC/3TC. However, in some studies, such as BICOMBO or ACTG 5202, HLA testing was not performed, which significantly reduces the risk of abacavir HSR and is now standard.

Despite different settings, the overall differences between TDF/FTC and ABC/3TC were insignificant. With regard to lipodystrophy, there are also unlikely to be relevant differences (McComsey 2011, Curran 2012). However, in randomized trials, lipids improved significantly when switching from ABC/3TC to TDF/FTC, combined with PIs (Campo 2013) or efavirenz (Moyle 2015). Whether this also translates into fewer cardiovascular events remains unclear. On the other hand, more adverse effects on bone density were seen with TDF/FTC use in different settings (Haskelberg 2012, Rasmussen 2012, Tebas 2015). Renal function is also less negatively affected by ABC/3TC (Stellbrink 2010, Wyatt 2015). In summary, the advantages of ABC/3TC

over TDF/FTC are fewer renal and bone events, whereas the disadvantages are a worse lipid profile and possibly more cardiovascular events.
But what about TAF/FTC? In GS 1717, a double-blind study of virologically successfully treated patients switching from ABC/3TC to TAF/FTC showed no apparent effect on renal and bone biomarkers (Winston 2018). Lipid profiles were also comparable. Given the considerable price difference of TAF compared with abacavir, this study suggested no clear rationale for switching from abacavir to TAF.
Table 2.4. lists the advantages and disadvantages of the three common backbones that could affect treatment decisions. Not so much potency as the risk profile and co-morbidities usually determine the direction. Avoid TDF for kidney problems and osteoporosis; for cardiovascular risks and hepatitis B, avoid abacavir. According to some experts, abacavir is still a preferred agent, especially in children and adolescents (Jesson 2022).

Table 2.4: Overview of the most important backbones.

Backbone	Preparations (STR = single-tablet regimen), main pros and cons
TAF+FTC	**Descovy®,** in STRs **Biktarvy®** (with bictegravir), **Odefsey®** (with rilpivirine), **Genvoya®** (with elvitegravir/c), **Symtuza®** (with darunavir/c) Pros: No or minor nephrotoxicity or bone density reduction, flexibility (used in various STRs), good efficacy against HBV Cons: High cost, little long-term data, interactions (different TAF doses to consider), no beneficial effects on lipids, probably more weight gain with TAF than with TDF
TDF+FTC	Generics available, **Truvada®**, in STRs **Eviplera®** (with rilpivirine), **Atripla®** (with efavirenz), **Stribild®** (with elvitegravir/c) Pros: Flexibility (various STRs), positive effect on lipids, good long-term data, good efficacy against HBV, lower weight gain than with TAF Cons: Potential nephrotoxicity, bone density reduction
TDF+3TC	Generic available in the STR **Delstrigo®** (with doravirine). Outside the EU and the US, also in "TLD" (with dolutegravir) Pros: Positive effect on lipids, good long-term data, effective against HBV Cons: Potential nephrotoxicity, bone density reduction
ABC+3TC	Generic available, **Kivexa®**, in the STR **Triumeq®** (with dolutegravir) Pros: Low cost of ABC generics, no nephrotoxicity/bone density reduction, good long-term data Cons: HSR (HLA-B57 test mandatory), possible increased cardiovascular risk, somewhat low efficacy in highly viremic individuals, only one STR available, 3TC not sufficient for HBV co-infection

Backbones not recommended

It should be emphasized that most of the above studies refer to first-line therapy. Other backbones may be necessary in pre-treated patients due to resistance and/or intolerance. However, this is the case only very rarely.
AZT/3TC (Combivir®) was the standard backbone of first-line therapy for many years. It is no longer recommended, given its poorer tolerability compared to TDF and ABC (Gallant 2006, Pozniak 2006). In addition, once-daily administration is not feasible. Its use is usually only considered in particular (scarce) resistance situations. With the fall of patents, several generic preparations have been available since 2013.
For **AZT+FTC**, there are no data and no aspects that justify its use. **TDF+ABC**, as a combination, is likely to be problematic due to the rapid development of resistance.

FTC+3TC and, of course, a combination of **TDF+TAF** are antagonistic and should not be implemented. **ABC+FTC** or **TAF+3TC** makes no sense. They might be useful in exceptional cases, for example, if there is intolerance for one of the two cytidine analogs, FTC or 3TC. In clinical routine, however, this rarely occurs. All therapies with d-drugs (**d4T**, **ddI, ddC**) are also explicitly not recommended.

Literature on nucleoside and nucleotide analogs

Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis. J AIDS 2008, ;47:74-8.

Bickel M, Khaykin P, Stephan C, et al. Acute kidney injury caused by tenofovir disoproxil fumarate and diclofenac co-administration. HIV Med 2013, 14:633-8.

Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of ART-related lipodystrophy. Lancet 1999, 354:1112-5.

Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet 2019, 393:143-155.

Campo R, Dejesus E, Bredeek UF, et al. SWIFT: Prospective 48-Week Study to Evaluate Efficacy and Safety of Switching to Emtricitibine/Tenofovir From Lamivudine/Abacavir in Virologically Suppressed HIV-1 Infected Patients on a Boosted Protease Inhibitor Containing Antiretroviral Regimen. Clin Infect Dis 2013 Mar 28.

Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. Lancet 1994, 343:871-81.

Cruciani M, Mengoli C, Malena M, et al. Virological efficacy of abacavir: systematic review and meta-analysis. J Antimicrob Chemo 2014, 69:3169-80.

Curran A, Martinez E, Podzamczer D, et al. Changes in body composition and mitochondrial DNA in HIV-1-infected patients switching to fixed-dose abacavir/lamivudine or tenofovir/emtricitabine: a substudy of the BICOMBO Trial. Antivir Ther. 2012 Feb 28. [Epub ahead of print].

Dadi TL, Kefale AT, Mega TA, et al. Efficacy and Tolerability of Tenofovir Disoproxil Fumarate Based Regimen as Compared to Zidovudine Based Regimens: A Systematic Review and Meta-Analysis. AIDS Res Treat. 2017: 5792925.

De la Rosa R, Harris M, Uyeda L, et al. Life-threatening reaction after first ever dose of abacavir in an HIV-1-infected patient. AIDS 2004, 18:578-9.

DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. Clin Infect Dis 2004, 39:1038-46.

DeJesus E, Villanueva JF, Arribas JR. Tenofovir Alafenamide (TAF) Versus Tenofovir Disoproxil Fumarate (TDF) in Hispanic/Latinx and Black Participants: Efficacy, Bone and Renal Safety Results from a Pooled Analysis of 7 Clinical Trials. Abstract 318, ID Week 2019, Washington.

Dorjee K, Choden T, Baxi SM, et al. Risk of cardiovascular disease associated with exposure to abacavir among individuals with HIV: A systematic review and meta-analyses of results from 17 epidemiologic studies. Int J Antimicrob Agents 2018, 52:541-553.

El-Sahly HM. Development of abacavir hypersensitivity reaction after rechallenge in a previously asymptomatic patient. AIDS 2004,18:359-60.

Eron JJ, Benoit SL, Jemsek J, et al. Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. New Eng J Med 1995, 333:1662.

Eron JJ, Orkin C, Gallant J, et al. A week-48 randomized phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients. AIDS 2018, 32:1431-1442.

Fischl MA, Richman DD, Hansen N, et al. The safety and efficacy of zidovudine (AZT) in the treatment of subjects with mildly symptomatic HIV infection. A double-blind, placebo-controlled trial. Ann Intern Med 1990; 112:727-37.

Ford N, Vitoria M, Doherty M, Gray A. Candidates for inclusion in a universal antiretroviral regimen: are lamivudine and emtricitabine interchangeable? Curr Opin HIV AIDS 2017, 12:334-338.

Frampton JE, Perry CM. Emtricitabine: a review of its use in the management of HIV infection. Drugs 2005, 65:1427-48.

Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. NEJM 2001;344:824-31.

Fux CA, Rauch A, Simcock M, et al. Tenofovir use is associated with an increase in serum alkaline phosphatase in the Swiss HIV Cohort Study. Antivir Ther 2008, 13:1077-82.

Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet 2017, 390:2063-2072.

Gallant JE, Daar ES, Raffi F, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. Lancet HIV 2016; 3:e158–165.

Galli M, Ridolfo AL, Adorni F, et al. Body habitus changes and metabolic alterations in protease inhibitor-naive HIV-1-infected patients treated with two nucleoside reverse transcriptase inhibitors. JAIDS 2002, 29: 21-31.

Grant PM, Tierney C, Budhathoki C, et al. Early virologic response to abacavir/lamivudine and tenofovir/emtricitabine during ACTG A5202. HIV Clin Trials 2013, 14:284-91.

Hall AM, Hendry BM, Nitsch D, Connolly JO. Tenofovir-associated kidney toxicity in HIV-infected patients: A review of the evidence. Am J Kidney Dis 2011, 57:773-80.

Harrigan PR Stone C, Griffin P, et al. Resistance profile of the HIV type 1 reverse transcriptase inhibitor abacavir (1592U89) after monotherapy and combination therapy. JID 2000, 181:912-920.

Haskelberg H, Hoy JF, Amin J, STEAL Study Group. Changes in bone turnover and bone loss in HIV-infected patients changing treatment to tenofovir-emtricitabine or abacavir-lamivudine. PLoS One. 2012;7:e38377.

Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet 2002, 359:1121-2.

Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide versus tenofovir disoproxil fumarate: Is there a true difference in efficacy and safety? J Virus Erad 2018, 4:72-79.

Hoy JF, Gahan ME, Carr A, et al. Changes in mitochondrial DNA in peripheral blood mononuclear cells from HIV-infected patients with lipoatrophy randomized to receive abacavir. J Infect Dis 2004, 190:688-92.

Hukezalie KR, Thumati NR, Côté HC, Wong JM. In vitro and ex vivo inhibition of human telomerase by anti-HIV nucleoside reverse transcriptase inhibitors (NRTIs) but not by non-NRTIs. PLoS One 2012;7:e47505.

Jesson J, Saint-Lary L, Revegue MHDT, et al. Safety and efficacy of abacavir for treating infants, children, and adolescents living with HIV: a systematic review and meta-analysis. Lancet Child Adolesc Health 2022, 6:692-704.

Leeansyah E, Cameron PU, Solomon A, et al. Inhibition of telomerase activity by human immunodeficiency virus (HIV) nucleos(t)ide reverse transcriptase inhibitors: a potential factor contributing to HIV-associated accelerated aging. J Infect Dis 2013, 207:1157-65.

Llibre JM, Hill A. Abacavir and cardiovascular disease: A critical look at the data. Antiviral Res. 2016 Aug;132:116-21.

Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet 2002, 359:727-32.

Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008, 358:568-79.

Mallon PW, Maughan RT, Garcia AA, et al. Change in soluble glycoprotein VI (SGPVI) when switching from ABC/3TC to TAF/FTC. Abstract 677LB, 25th CROI 2018, Boston.

Martin A, Bloch M, Amin J, et al. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine: a randomized, 96-week trial. Clin Infect Dis 2009, 49:1591-601.

Martinez E, Arranz JA, Podzamczer D, et al. A simplification trial switching from nucleoside reverse transcriptase inhibitors to once-daily fixed-dose abacavir/lamivudine or tenofovir/emtricitabine in HIV-1-infected patients with virological suppression. J AIDS 2009;51:290-297.

Martinez E, Arranz JA, Podzamczer D, et al. Efficacy and safety of NRTIs switch to tenofovir plus emtricitabine (vs. abacavir plus lamivudine (Kivexa) in patients with virologic suppression receiving a lamivudine containing HAART: the BICOMBO study. Abstract WESS102, 4th IAS 2007, Sydney.

Martinez E, Milinkovic A, de Lazzari E, et al. Pancreatic toxic effects associated with co-administration of didanosine and tenofovir in HIV-infected adults. Lancet 2004, 364:65-7.

Mathias AA, Hinkle J, Menning M, Hui J, Kaul S, Kearney BP. Bioequivalence of efavirenz/emtricitabine/tenofovir disoproxil fumarate single-tablet regimen. J Acquir Immune Defic Syndr 2007;46:167-73.

McComsey GA, Kitch D, Sax PE, et al. Peripheral and central fat changes in subjects randomized to abacavir-lamivudine or tenofovir-emtricitabine with atazanavir-ritonavir or efavirenz: ACTG Study A5224s. Clin Infect Dis 2011, 53:185-96.

Miller V, Stark T, Loeliger AE, Lange JM. The impact of the M184V substitution in HIV-1 reverse transcriptase on treatment response. HIV Med 2002, 3:135-45.

Mills A, Arribas JR, Andrade-Villanueva J, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. Lancet Infect Dis 2016; 16:43–52.

Mills A, Crofoot G, Jr, McDonald C, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate in the first protease inhibitor-based single-tablet regimen for initial HIV-1 therapy: a randomized phase 2 study. J Acquir Immune Defic Syndr 2015; 69:439–445.

Montejano R, Stella-Ascariz N, Monge S, et al. Impact of Nucleos(t)ide Reverse Transcriptase Inhibitors on Blood Telomere Length Changes in a Prospective Cohort of Aviremic HIV-Infected Adults. J Infect Dis 2018, 218:1531-1540.

Moyle GJ, Orkin C, Fisher M, Dhar J, et al. A randomized comparative trial of continued abacavir/lamivudine plus efavirenz or replacement with efavirenz/emtricitabine/tenofovir DF in hypercholesterolemic HIV-1 infected individuals. PLoS One 2015, 10:e0116297.

Nan C, Shaefer M, Urbaityte R, et al. Abacavir Use and Risk for Myocardial Infarction and Cardiovascular Events: Pooled Analysis of Data From Clinical Trials. Open Forum Infect Dis 2018, 5:ofy086.

O'Halloran JA, Dunne E, Tinago W, et al. Switching from abacavir to tenofovir disoproxil fumarate is associated with rises in soluble glycoprotein VI, suggesting changes in platelet-collagen interactions. AIDS 2018, 32:861-866.

Orkin C, DeJesus E, Ramgopal M, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, non-inferiority study. Lancet HIV 2017; 4:e195-e204.

Post FA, Yazdanpanah Y, Schembri G3, et al. Efficacy and safety of emtricitabine/tenofovir alafenamide (FTC/TAF) vs. emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) as a backbone for treatment of HIV-1 infection in virologically suppressed adults: subgroup analysis by third agent of a randomized, double-blind, active-controlled phase 3 trial. HIV Clin Trials 2017, 18:135-140.

Pozniak A, Arribas JR, Gathe J, et al. Switching to Tenofovir Alafenamide, Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, in HIV-Infected Patients With Renal Impairment: 48-Week Results From a Single-Arm, Multicenter, Open-Label Phase 3 Study. J Acquir Immune Defic Syndr 2016, 71:530-7.

Pozniak AL, Gallant JE, DeJesus E, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes—a 96-week analysis. J AIDS 2006; 43: 535-40.

Rasmussen TA, Jensen D, Tolstrup M, et al. Comparison of bone and renal effects in HIV-infected adults switching to abacavir or tenofovir based therapy in a randomized trial. PLoS One 2012 ; 7:e32445.

Roen A, Laut K, Pelchen-Matthews A, et al. Abacavir usage patterns and hypersensitivity reactions in the EuroSIDA cohort. HIV Med 2018, 19:252-260.

Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet 2008, 371:1417-1426.

Sax PE, Erlandson KM, Lake JE, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. Clin Infect Dis. 2019 Oct 14. pii: ciz999.

Sax PE, Tierney C, Collier AC, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. NEJM 2009, 361:2230-40.

Sax PE, Tierney C, Collier AC, et al. Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. JID 2011, 204:1191-201.

Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet 2015; 385:2606–2615.

Sax PE, Zolopa A, Brar I, et al. Tenofovir alafenamide vs. tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study. J Acquir Immune Defic Syndr 2014; 67:52–58.

Sendi PP, Bucher HC, Harr T, et al. Cost effectiveness of HAART in HIV-infected patients. Swiss HIV Cohort Study. AIDS 1999, 13:1115-22.

SMART. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. AIDS 2008, 22:F17-F24.

Smith KY, Patel P, Fine D, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. AIDS 2009, 23:1547-56.

Solomon A, Tennakoon S, Leeansyah E. No difference in the rate of change in telomere length or telomerase activity in HIV-infected patients after three years of darunavir/ritonavir with and without nucleoside analogues in the MONET trial. PLoS One 2014, 9:e109718.

Staszewski S, Hill AM, Bartlett J, et al. Reductions in HIV-1 disease progression for zidovudine/lamivudine relative to control treatments: a meta-analysis of controlled trials. AIDS 1997, 11:477-483.

Stella-Ascariz N, Montejano R, Rodriguez-Centeno J, et al. Blood Telomere Length Changes After Ritonavir-Boosted Darunavir Combined With Raltegravir or Tenofovir-Emtricitabine in Antiretroviral-Naive Adults Infected With HIV-1. J Infect Dis 2018, 218:1523-1530.

Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. Clin Infect Dis 2010, 51:963-72.

Stirrup OT, Asboe D, Pozniak A, et al. Continuation of emtricitabine/lamivudine within combination antiretroviral therapy following detection of the M184V/I HIV-1 resistance mutation. HIV Med. 2020 Jan 11.

Stoll M, Claes C, Schulte E, et al. Direct costs for the treatment of HIV-infection in a German cohort after the introduction of HAART. Eur J Med Res 2002, 7:463-471

Suo Z, Johnson KA. Selective inhibition of HIV-1 reverse transcriptase by an antiviral inhibitor, (R)-9-(2-Phosphonylmethoxypropyl)adenine. J Biol Chem 1998, 273:27250-8.

Tangamornsuksan W1, Lohitnavy O, Kongkaew C, et al. Association of HLA-B*5701 genotypes and abacavir-induced hypersensitivity reaction: a systematic review and meta-analysis. J Pharm Pharm Sci 2015, 18:68-76.

Taylor KA, Smyth E, Rauzi F, et al. Pharmacological impact of antiretroviral therapy on platelet function to investigate human immunodeficiency virus-associated cardiovascular risk. Br J Pharmacol 2019, 176:879-889.

Tebas P, Kumar P, Hicks C, et al. Greater change in bone turnover markers for efavirenz/emtricitabine/tenofovir disoproxil fumarate versus dolutegravir + abacavir/lamivudine in antiretroviral therapy-naive adults over 144 weeks. AIDS 2015, 29:2459-64.

Valbert F, Wolf E, Schewe K, et al. Cost of Human Immunodeficiency Virus (HIV) and Determinants of Healthcare Costs in HIV-Infected Treatment-Naive Patients Initiated on Antiretroviral Therapy in Germany: Experiences of the PROPHET Study. Value Health 2020, 23:1324-1331.

Van Wyk J, Ajana F, Bisshop F, et al. Efficacy and Safety of Switching to Dolutegravir/Lamivudine Fixed-Dose Two-Drug Regimen Versus Continuing a Tenofovir Alafenamide-Based Three- or Four-Drug Regimen for Maintenance of Virologic Suppression in Adults With HIV-1: Phase 3, Randomized, Non-inferiority TANGO Study. Clin Infect Dis. 2020 Jan 6.

Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med 2019, 381:803-815.

Wang H, Lu X, Yang X, Xu N. The efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate in antiretroviral regimens for HIV-1 therapy: Meta-analysis. Medicine (Baltimore). 2016, 95:e5146.

Winston A, Post FA, DeJesus E, et al. Tenofovir alafenamide plus emtricitabine versus abacavir plus lamivudine for treatment of virologically suppressed HIV-1-infected adults: a randomised, double-blind, active-controlled, non-inferiority phase 3 trial. Lancet HIV 2018, 5:e162-e171.

Wohl DA, Bhatti L, Small CB, et al. The ASSURE study: HIV-1 suppression is maintained with bone and renal biomarker improvement 48 weeks after ritonavir discontinuation and randomized switch to abacavir/lamivudine + atazanavir. HIV Med 2016, 17:106-17.

Wyatt CM, Kitch D, Gupta SK, et al. Changes in proteinuria and albuminuria with initiation of antiretroviral therapy: data from a randomized trial comparing tenofovir disoproxil fumarate/emtricitabine versus abacavir/lamivudine. J AIDS 2014, 67:36-44.

Young J, Schäfer J, Fux CA, et al. Renal function in patients with HIV starting therapy with tenofovir and either efavirenz, lopinavir or atazanavir. AIDS 2012, 26:567-575.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Mode of action

The NNRTIs were first described in 1990. As with NRTIs, the target enzyme is reverse transcriptase (RT). However, NNRTIs bind directly and non-competitively to the RT at a position near to but distinct from the substrate binding site for nucleosides. The resulting complex blocks the catalyst-activated binding site of the reverse transcriptase. This, in turn, can bind fewer nucleosides, slowing down polymerization significantly. In contrast to NRTIs, NNRTIs do not require activation within the cell. The first-generation NNRTIs nevirapine, delavirdine, and efavirenz entered the market in 1996–1999. Although studies such as ACTG 241 or INCAS showed early efficacy (D'Aquila 1996), the start was rather hesitant. This was due to the early observation that functional monotherapy, adding an NNRTI to a failing regimen, had practically (and unsurprisingly) no effect. Moreover, resistance develops frequently and rapidly – if an NNRTI-based regimen shows insufficient viral suppression, cross-resistance to other NNRTIs can quickly develop. Mothers who had taken nevirapine only once as part of transmission prophylaxis showed resistance rates as high as 65% (Cunningham 2002, Jourdain 2004, Johnson 2005). This may affect the success of subsequent NNRTIs (Lockman 2010).

In a large meta-analysis, NNRTIs were as effective as PIs (Borges 2016). However, virologic failure is more common, especially in the context of resistance. Facing resistance rates as high as 2–6% in treatment-naïve patients, significantly higher than PIs or INSTIs, some guidelines have now completely removed NNRTIs from first-line therapy. In some countries like Germany, only rilpivirine was recommended until 2019 – limited to patients with viremia below 100,000 copies/mL. In early 2019, a new agent was added to the market, doravirine, which was non-inferior to the PI darunavir in a head-to-head comparison. Resistance was rarely seen with this NNRTI – doravirine has the potential to revitalize this drug class, displaying a higher resistance barrier than rilpivirine, and has no food restrictions.

In the event of virological failure, any NNRTI should be rapidly discontinued to avoid further resistance mutations; the replicative capacity of HIV is not affected by NNRTI mutations, unlike some PI or NRTI mutations (Piketty 2004). In Europe, the rate of transmitted NNRTI resistance is relatively stable at about 5% (Miranda 2022), so resistance testing results should be available before starting therapy. As "maintenance" therapy, however, NNRTIs are very effective, and if virologic suppression is good, switching to an NNRTI-containing regimen can be a good option (see chapter 5.7. and 5.8.). Doravirine and rilpivirine are preferred. Efavirenz and nevirapine are no longer recommended for which generics are available (for efavirenz, in STRs). Delavirdine has never played a significant role, and etravirine is only considered in certain resistance situations.

All NNRTIs are metabolized by the cytochrome P450 system (Usach 2013). Although not as strong as PIs, some interactions are to be expected.

Individual agents

Delavirdine (Rescriptor®) was 1997 the second NNRTI to be licensed by the FDA. In Europe, an application for licensure was rejected because of insufficient efficacy data. In any case, it is no longer prescribed because of the high number of pills.

Doravirine (MK-1439, **Pifeltro®**, also in **Delstrigo®**) is an NNRTI launched by MSD in early 2019. It is effective against wild-type viruses and some NNRTI-resistant mutations (K103N, Y181C, G190A, and E138K) but not against Y188L. It likely has a higher resistance barrier than rilpivirine or efavirenz (Feng 2016). Doravirine appears effective against some rilpivirine-resistant viruses, and *vice versa*; the resistance pro-

files are not entirely overlapping (Smith 2016). Doravirine resistance is uncommon among NNRTI-experienced patients, confirming a distinguishing resistance pattern within NNRTIs. However, previous efavirenz and etravirine experience poses a higher risk of doravirine resistance (Sterrantino 2019). Doravirine has a reasonably long half-life; once-daily administration is feasible, and unlike rilpivirine, absorption is independent of food intake (Wilby 2018).

In a pilot study, viral load decreased by 1.3–1.4 logs after 7 days of monotherapy (Schürmann 2016). However, a Phase II study testing different doses from 25 to 200 mg doravirine vs. efavirenz found no clear dose-response relationship. Tolerability was better than with efavirenz, and efficacy was comparable. For further development, the decision was made to use 100 mg (Gatell 2019). In two double-blind, randomized Phase III trials, doravirine showed good efficacy as a first-line therapy. In DRIVE-FORWARD, it performed well compared with darunavir/r (each combined with 2 NRTIs), surprising not only with an excellent response even in highly viremic patients but also with a low resistance rate. Tolerability was good, and the lipid profile was more favorable than with darunavir/r (Molina 2018). In DRIVE-AHEAD, the fixed combination of TDF/3TC/doravirine was non-inferior to and better tolerated than Atripla®, while the lipid profile was more favorable (Orkin 2019). Again, few cases of resistance occurred in this study, with a combined rate of 9/747 (1.2%) in first-line therapy in both studies (FORWARD and AHEAD), indicating a relatively high resistance barrier. In DRIVE-Shift, patients on different therapies (first or second line of therapy, no known resistance mutations) switched to doravirine. Virologic suppression remained sustained (Johnson 2019) for years (Kumar 2021).

Doravirine can be dosed normally in renal impairment. A small PK study showed no relevant difference in levels with a GFR of less than 30 mL/min (Ankrom 2018). The interaction potential is not particularly pronounced. Concomitant administration of rifampicin and other strong CYP3A inducers will likely decrease doravirine levels. There are no interactions with dolutegravir or atorvastatin (Wilby 2018). Also, no QT prolongations were found with high doses (as with rilpivirine).

At the end of 2018, doravirine was approved by EMA, both in the fixed combination with TDF/3TC (Delstrigo®) and as a single agent (Pifeltro®). The latter is likely to play only a minor role given the many STRs available and is reserved for special situations (resistance or intolerance). Taken together, doravirine seems to have overcome some of the weaknesses of older NNRTIs (low resistance barrier, food restrictions) and has gained an important role in HIV therapy as an STR.

Efavirenz (**Sustiva®**, also in **Atripla®** as well as in numerous generics) was 1999 the third NNRTI to be approved. At that time, the 006 study showed superiority to indinavir (Staszewski 1999). Efavirenz also still performed well in comparison to lopinavir (Riddler 2008). However, comparisons against modern agents such as rilpivirine, doravirine, or various INSTIs showed partial inferiority, primarily due to tolerability. To reduce the frequent CNS side effects, it is recommended to be taken in the evening before sleep. Dizziness and lightheadedness are very common, as are vivid dreams or nightmares. In one study, after four weeks, 66% reported dizziness, 48% reported abnormal dreams, 37% reported drowsiness, and 35% reported insomnia (Fumaz 2002). Efavirenz appears to disrupt the sleep architecture (Gallego 2004). Potentially hazardous tasks such as driving or operating machinery are not advised. The side effects correlate with high plasma levels (Marzolini 2001), and there appears to be a genetic predisposition, especially in people of African descent (Haas 2004). The mechanism of CNS toxicity is unclear; toxic metabolites may contribute to neurotoxicity (Tovar-y-Romo 2013). Other problems are sometimes painful gynecomastia (Rahim 2004) and adverse lipids effects compared to other NNRTIs (Behrens 2014). Potential teratogenicity (Ford 2011) has not been clinically demonstrated.

Efavirenz should be replaced unless the patient requests explicitly continuation. It is no longer recommended in first-line therapy. A dose reduction to 400 mg, which improved tolerability in a randomized trial (ENCORE 2015), has not gained acceptance.

Etravirine (**Intelence®**, formerly **TMC-125**) is a diaryl pyrimidine (DAPY) analog developed by Janssen-Cilag. In 2008, it was the first second-generation NNRTI. Approval is limited to experienced individuals on boosted PI regimens. Etravirine works well against classic NNRTI resistance mutations such as K103N (Andries 2004). It may remain effective in nevirapine failure rather than after efavirenz (Cozzi-Lepri 2012). The resistance barrier is higher than for other NNRTIs because etravirine can bind more flexibly to reverse transcriptase through conformational changes (Vingerhoets 2005). Mutations at the enzyme's binding site are thus less likely to affect binding.

In Phase I/II studies, etravirine reduced viral load by as much as 0.89 logs in individuals with NNRTI mutations (Gazzard 2003). However, a Phase II trial of benefit after NNRTI failure was terminated because etravirine remained significantly inferior to individually selected PIs (Ruxrungtham 2008). Two Phase III trials (DUET-1 and -2) led to the approval of etravirine. In these, 1,203 individuals with treatment failure, NNRTI resistance, and at least three primary PI resistances received either etravirine or placebo, each combined with darunavir/r (Lazzarin 2007, Madruga 2007). In addition, at least two individually selected NRTIs and, optionally, T-20 were given. After 96 weeks, 57% achieved a viral load below 50 copies/mL with etravirine, compared to 36% with a placebo (Katlama 2010). However, the effect was markedly lower with an increasing number of existing NNRTI mutations.

The tolerability of etravirine is pretty good, and in the DUET studies, it was comparable to placebo. Only the typical NNRTI rash (primarily mild) was observed more frequently, with 19% versus 11% (Katlama 2010). In October 2009, the company issued a warning letter following sporadic cases of severe allergy (toxic epidermal necrolysis, DRESS syndrome). Switching from efavirenz to etravirine may help reduce CNS side effects of efavirenz and improve lipids (Fätkenheuer 2012).

The recommended dosage is one tablet of 200 mg twice daily, which should be taken with a meal to increase absorption. The tablets can be dissolved. Single-dose administration seems possible (Fätkenheuer 2012) but has not been approved. Since Janssen-Cilag also manufactures the competitor drug rilpivirine, there is no huge interest in further development.

In the case of NNRTI resistance, etravirine needs other active agents to avoid being rapidly burned up. According to the product information, it should be combined with a boosted PI (preferably darunavir, not tipranavir). Darunavir should be combined with ritonavir rather than cobicistat, as darunavir/c levels drop with etravirine (Moltó 2017). However, the drug is sometimes given without PIs in clinical routine care.

Nevirapine (**Viramune®**, generics available) was the first NNRTI approved in 1997, and the combination with AZT+ddI is the first published triple combination (D'Aquila 1996). In 2NN, nevirapine was as effective as efavirenz (van Leth 2004), in ARTEN as effective as atazanavir/r – however, more resistance mutations were observed in the setting of virological failure (Soriano 2011). The resistance barrier is so low that nevirapine should no longer be used in first-line therapy.

Marked GGT elevations are very common and may subject patients to false appearances of excess alcohol consumption.

Nevirapine causes elevation of liver enzymes in up to 20% of people, which occasionally can be severe. It should always be dosed gradually, and transaminases should be checked every two weeks for the first eight weeks. Exanthema (rash) occurs in

15–20%, requires discontinuation in up to 7%, and cannot be prevented by antihistamines or steroids (Launay 2004). Treatment can often be continued if an isolated rash or transaminase elevation (up to 5 times normal) occurs. But caution is needed if both co-occur! In the case of rash, discontinuation is recommended even with mildly elevated transaminases (> 2-fold norm). The first 18 weeks are critical, though liver toxicity may occur later. People with chronic hepatitis are at risk, as are women with low body weight (Usach 2013). There is an increased risk, especially with good immune status. For women with CD4 T-cells above 250/µl, the risk is increased 12-fold (11% vs. 1%); for men, the risk increases above 400 CD4 T-cells/µl (6% vs. 1%). Nevirapine should not be started above these levels. In contrast, the risk does not appear to be increased in pre-treated individuals. Genetic predisposition is likely, but no test can reliably predict intolerance. In 2011, an extended-release formulation was approved that allows single daily dosing. However, dose reduction during the first 14 days is still required. It is important to note that the matrix may be excreted undigested and visible in the stool. Generics have been available since 2013. Although ong-gone from first-line therapy, some patients have been successfully treated with nevirapine for over two decades (there are better options today).

Rilpivirine (**Edurant®**, also available in **Eviplera®** or **Complera®**, in **Odefsey®** and **Juluca®**, or as a long-acting injection **Rekambys®**) was licensed in November 2011. Like etravirine, the compound is a DAPY NNRTI effective against isolated NNRTI resistance such as K103N or G190A and has a longer half-life of 40 hours. In a Phase IIa study, viral load dropped by 1.2 log levels after 7 days of monotherapy without a dose-dependent effect (Goebel 2005). At 25 mg, the lowest dose was chosen, which is not only significantly lower than all other NNRTIs but may be too low in some cases (Aguri 2016).

Two double-blind, randomized Phase III trials (ECHO and THRIVE) in 1368 treatment-naïve patients showed comparable efficacy to efavirenz, with better tolerability after 96 weeks (Cohen 2011, Molina 2011, Behrens 2014). Lipids were also less adversely affected (Tebas 2014). In a third large open-label study (STaR) in 786 treatment-naïve patients, non-inferiority was shown for Eviplera® compared to Atripla®. After 48 weeks, viral load was undetectable in 89%, compared to 82% with Atripla®, which was less tolerated due to efavirenz' CNS side effects (Cohen 2014). However, resistance mutations and virologic failure were observed more frequently with rilpivirine than with efavirenz: 9% versus 5% in ECHO/THRIVE and 4% versus 1% in STaR (Cohen 2012+2014). Resistance mutations affected NNRTIs and NRTIs (Rimsky 2012), especially when viremia was high. Therefore, in most guidelines, approval in treatment-naïve individuals was restricted to those presenting with viral loads below 100,000 copies/mL.

In late 2013, approval was extended to pre-treated patients. In the SPIRIT trial, 476 patients with good viral suppression either switched to rilpivirine or remained on their boosted PI regimen (maximum of two prior therapies allowed). The switch was successful, and lipids improved (Palella 2012). Viral suppression persisted in 18/19 individuals with a historical K103N, i.e., an NNRTI mutation (Porter 2016). However, in experienced patients with viral suppression, pre-existing resistance mutations must be considered before switching to a rilpivirine-containing STR. The presence of resistance mutations to both NRTIs and NNRTIs is associated with an increased risk of virological rebound, highlighting the need for an accurate selection of patients before simplification (Armenia 2017).

Overall, rilpivirine is well-tolerated. Mild CNS symptoms may occur but are significantly less pronounced than with efavirenz. The QT prolongation observed with high doses does not appear relevant with the current dosage, and the risk of teratogenicity is low.

The most commonly used preparation is Odefsey®, the fixed combination of TAF+FTC and rilpivirine. In patients with adequate viral suppression, it was virologically non-inferior in two large double-blind randomized trials (GS-1216 and 1160) compared to the continuation of Eviplera® (TDF/FTC/rilpivirine) and Atripla® (TDF/FTC/efavirenz). Switching to Odefsey® had positively affected bone density (Orkin 2017, DeJesus 2017).

Another drug is Juluca®, the fixed combination of dolutegravir and rilpivirine. Juluca® was licensed 2018 as the first dual therapy (2DR) in pre-treated patients. Two large Phase III trials (SWORD I+II) tested Juluca® against the continuation of successful ART. Virologic failure was rare, and INSTI resistance did not occur (Aboud 2019). However, CNS side effects were more likely to lead to discontinuation (7% overall at 100 weeks), and mild side effects were also more common under this 2DR regimen. Ultimately, it has remained unclear for whom Juluca® is useful.

Rilpivirine has become an important agent, especially with Odefsey®. The disadvantage in everyday life is that food intake is necessary to ensure sufficient absorption. A high-calorie drink or protein snack is not enough; it must be a meal with 500 kcal (Crauwels 2013). This can cause problems with irregular lifestyles or diets. Rilpivirine is, therefore, unsuitable for adherence problems. A new field of development for rilpivirine is long-acting, which is used as a depot injection (Rekambys®, see below).

Literature on NNRTIs

Aboud M, Orkin C, Podzamczer D, et al. Efficacy and safety of dolutegravir-rilpivirine for maintenance of virological suppression in adults with HIV-1: 100-week data from the randomised, open-label, phase 3 SWORD-1 and SWORD-2 studies. Lancet HIV. 2019 Jul 12.

Andries K, Azijn H, Thielemans T, et al. TMC125, a novel next-generation nonnucleoside reverse transcriptase inhibitor active against nonnucleoside reverse transcriptase inhibitor-resistant human immunodeficiency virus type 1. Antimicrob Agents Chemother 2004; 48:4680-6.

Ankrom W, Yee KL, Sanchez RI. Severe Renal Impairment Has Minimal Impact on Doravirine Pharmacokinetics. Antimicrob Agents Chemother 2018, 62(8). pii: e00326-18.

Aouri M, Barcelo C, Guidi M, et al. Population Pharmacokinetics and Pharmacogenetics Analysis of Rilpivirine in HIV-1-Infected Individuals. Antimicrob Agents Chemother 2016 Dec 27;61.

Armenia D, Di Carlo D, Calcagno A, et a. Pre-existent NRTI and NNRTI resistance impacts on maintenance of virological suppression in HIV-1-infected patients who switch to a tenofovir/emtricitabine/rilpivirine single-tablet regimen. J Antimicrob Chemother 2017;72:855-865.

Behrens G, Rijnders B, Nelson M, et al. Rilpivirine versus efavirenz with emtricitabine/tenofovir disoproxil fumarate in treatment-naïve HIV-1-infected patients with HIV-1 RNA ≤100,000 copies/mL: week 96 pooled ECHO/THRIVE subanalysis. AIDS Patient Care STDS 2014, 28:168-75.

Borges ÁH, Lundh A, Tendal B, et al. Nonnucleoside Reverse-transcriptase Inhibitor- vs Ritonavir-boosted Protease Inhibitor-based Regimens for Initial Treatment of HIV Infection: A Systematic Review and Meta-analysis of Randomized Trials. Clin Infect Dis 2016;63:268-80.

Cohen C, Molina J, Cahn P, et al. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naïve, HIV-1-infected patients: Pooled results from the phase 3 double-blind, randomized ECHO and THRIVE trials. JAIDS. 2012 Feb 16. [Epub ahead of print].

Cohen C, Wohl D, Arribas JR, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs. efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV-1-infected adults. AIDS 2014, 28:989-97.

Cohen CJ, Andrade-Villanueva J, Clotet B, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. Lancet 2011, 378:229-37.

Cozzi-Lepri A, Paredes, Phillips AN, et al. The rate of accumulation of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance in patients kept on a virologically failing regimen containing an NNRTI. HIV Med 2012, 13:62-72.

Crauwels HM, van Heeswijk RP, Buelens A, Stevens M, Boven K, Hoetelmans RM. Impact of Food and Different Meal Types on the Pharmacokinetics of Rilpivirine. J Clin Pharmacol 2013 May 30.

Cunningham CK, Chaix ML, Rekacewicz C, et al. Development of resistance mutations in women receiving standard antiretroviral therapy who received intrapartum nevirapine to prevent perinatal HIV type 1 transmission: A substudy of pediatric ACTG 316. JID 2002, 186:181-8.

D'Aquila RT, Hughes MD, Johnson VA, et al. Nevirapine, zidovudine, and didanosine compared with zidovudine and didanosine in patients with HIV-1 infection. Ann Intern Med 1996, 124:1019-30.

DeJesus E, Ramgopal M, Crofoot G, et al. Switching from efavirenz, emtricitabine, and tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, non-inferiority study. Lancet HIV 2017, 4:e205-e213.

ENCORE1 Study Group, et al. Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study. Lancet Infect Dis 2015, 15:793-802.

Fätkenheuer G, Duvivier C, Rieger A, et al. Lipid profiles for etravirine versus efavirenz in treatment-naive patients in the randomized, double-blind SENSE trial. J Antimicrob Chemother 2012, 67:685-690.

Feng M, Sachs NA, Xu M, et al. Doravirine Suppresses Common Nonnucleoside Reverse Transcriptase Inhibitor-Associated Mutants at Clinically Relevant Concentrations. Antimicrob Agents Chemother 2016, 60:2241-7.

Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. AIDS 2011, 25:2301-4.

Fumaz CR, Tuldra A, Ferrer MJ, et al. Quality of life, emotional status, and adherence of HIV-1-infected patients treated with efavirenz versus PI-containing regimens. J AIDS 2002, 29:244-53.

Gallego L, Barreiro P, del Rio R, et al. Analyzing sleep abnormalities in HIV-infected patients treated with Efavirenz. Clin Infect Dis 2004, 38:430-2.

Gatell JM, Morales-Ramirez JO, Hagins DP, et al. Doravirine dose selection and 96-week safety and efficacy versus efavirenz in antiretroviral therapy-naive adults with HIV-1 infection in a Phase IIb trial. Antivir Ther 2019, 24:425-435.

Gazzard BG, Pozniak AL, Rosenbaum W, et al. An open-label assessment of TMC 125 – new, next-generation NNRTI, for 7 days in HIV-1 infected individuals with NNRTI resistance. AIDS 2003;17:F49-54.

Goebel F, Yakovlev A, Pozniak A, et al. TMC278: Potent anti-HIV activity in ART-naive patients. Abstract 160, 12th CROI 2005, Boston.

Johnson JA, Li JF, Morris L, et al. Emergence of drug-resistant hiv-1 after intrapartum administration of single-dose nevirapine is substantially underestimated. J Infect Dis 2005, 192:16-23.

Johnson M, Kumar P, Molina JM, et al. Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial. J Acquir Immune Defic Syndr 2019, 81:463-472.

Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. N Engl J Med 2004, 351:229-40.

Katlama C, Clotet B, Mills A, et al. Efficacy and safety of etravirine at week 96 in treatment-experienced HIV type-1-infected patients in the DUET-1 and DUET-2 trials. Antivir Ther 2010, 15:1045-52.

Kumar P, Johnson M, Molina JM, et al. Brief Report: Switching to DOR/3TC/TDF Maintains HIV-1 Virologic Suppression Through Week 144 in the DRIVE-SHIFT Trial. J Acquir Immune Defic Syndr 2021, 87:801-805.

Launay O, Roudiere L, Boukli N, et al. Assessment of cetirizine, an antihistamine, to prevent cutaneous reactions to nevirapine therapy: results of the viramune-zyrtec double-blind, placebo-controlled trial. Clin Infect Dis 2004, 38:e66-72.

Lazzarin A, Campbell T, Clotet B, et al. DUET-2 study group. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet 2007; 370:39-48.

Lochet P, Peyriere H, Lotthe A, et al. Long-term assessment of neuropsychiatric adverse reactions associated with efavirenz. HIV Med 2003, 4:62-6.

Lockman S, Hughes MD, McIntyre J, et al. Antiretroviral therapies in women after single-dose nevirapine exposure. NEJM 2010, 363:1499-509.

Madruga JV, Cahn P, Grinsztejn B, et al. DUET-1 study group. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet 2007; 370:29-38.

Martinez E, Arnaiz JA, Podzamczer D, et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with HIV infection. N Eng J Med 2003; 349:1036-46.

Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS 2001, 15: 71-5.

Miranda MNS, Pingarilho M, Pimentel V, et al. Trends of Transmitted and Acquired Drug Resistance in Europe From 1981 to 2019: A Comparison Between the Populations of Late Presenters and Non-late Presenters. Front Microbiol. 2022 Apr 13;13:846943.

Molina JM, Cahn P, Grinsztejn B, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised, double-blind active-controlled trial. Lancet 2011, 378:238-46.

Molina JM, Squires K, Sax PE. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV 2018, 5:e211-e220.

Moltó J, Curran A, Miranda C, et al. Pharmacokinetics of darunavir/cobicistat and etravirine alone and co-administered in HIV-infected patients. J Antimicrob Chemother. 2017 Dec 11.

Orkin C, DeJesus E, Ramgopal M, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, non-inferiority study. Lancet HIV 2017; 4:e195-e204.

Orkin C, Squires KE, Molina JM, et al. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-naive Adults With Human Immunodeficiency Virus-1 Infection: Week 48 Results of the DRIVE-AHEAD Trial. Clin Infect Dis 2019, 68:535-544.

Palella FJ Jr1, Fisher M, Tebas P, et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. AIDS 2014, 28:335-44.

Piketty C, Gerard L, Chazallon C, et al. Virological and immunological impact of non-nucleoside reverse transcriptase inhibitor withdrawal in HIV-infected patients with multiple treatment failures. AIDS 2004, 18:1469-71.

Porter DP, Toma J, Tan Y, et al. Clinical Outcomes of Virologically-Suppressed Patients with Pre-existing HIV-1 Drug Resistance Mutations Switching to Rilpivirine/Emtricitabine/Tenofovir Disoproxil Fumarate in the SPIRIT Study. HIV Clin Trials 2016, 17:29-37.

Rahim S, Ortiz O, Maslow M, et al. A case-control study of gynecomastia in HIV-1-infected patients receiving HAART. AIDS Read 2004, 14:23-4.

Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med 2008, 358:2095-106.

Rimsky L, Vingerhoets J, Van Eygen V, et al. Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients on rilpivirine therapy experiencing virologic failure in the phase 3 ECHO and THRIVE studies: 48-week analysis. J AIDS 2012, 59:39-46.

Ruxrungtham K, Pedro RJ, Latiff GH, et al. Impact of reverse transcriptase resistance on the efficacy of TMC125 (etravirine) with two nucleoside reverse transcriptase inhibitors in protease inhibitor-naïve, NNRTI-experienced patients: study TMC125-C227. HIV Med 2008, 9:883-96.

Schürmann D, Sobotha C, Gilmartin J, et al. A randomized, double-blind, placebo-controlled, short-term monotherapy study of doravirine in treatment-naive HIV-infected individuals. AIDS 2016, 30:57-63.

Smith SJ, Pauly GT, Akram A, et al. Rilpivirine and Doravirine Have Complementary Efficacies Against NNRTI-Resistant HIV-1 Mutants. J AIDS 2016, 72:485-91.

Soriano V, Arastéh K, Migrone H, et al. Nevirapine versus atazanavir/ritonavir, each combined with tenofovir disoproxil fumarate/emtricitabine, in antiretroviral-naive HIV-1 patients: the ARTEN Trial. Antivir Ther 2011, 16:339-48.

Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. NEJM 1999, 341:1865-73.

Sterrantino G, Borghi V, Callegaro AP, et al. Prevalence of predicted resistance to doravirine in HIV-1-positive patients after exposure to non-nucleoside reverse transcriptase inhibitors. Int J Antimicrob Agents 2019, 53:515-519.

Tebas P, Sension M, Arribas J, et al. Lipid Levels and Changes in Body Fat Distribution in Treatment-Naive, HIV-1-Infected Adults Treated With Rilpivirine or Efavirenz for 96 Weeks in the ECHO and THRIVE Trials. Clin Infect Dis 2014, 59:425-34.

Tovar-y-Romo LB, Bumpus NN, Pomerantz D, et al. Dendritic spine injury induced by the 8-hydroxy metabolite of efavirenz. J Pharmacol Exp Ther 2012, 343:696-703.

Usach I, Melis V, Peris JE. Non-nucleoside reverse transcriptase inhibitors: a review on pharmacokinetics, pharmacodynamics, safety and tolerability. J Int AIDS Soc 2013; 16: 18567.

Van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. Lancet 2004, 363:1253-63.

Vingerhoets J, Azijn H, Fransen E, et al. TMC125 displays a high genetic barrier to the development of resistance: evidence from in vitro selection experiments. J Virol 2005;79:12773-82.

Wilby KJ, Eissa NA. Clinical Pharmacokinetics and Drug Interactions of Doravirine. Eur J Drug Metab Pharmacokinet 2018, 43:637-644.

Winston A, Pozniak A, Smith N, et al. Dose escalation or immediate full dose when switching from efavirenz to nevirapine-based highly active antiretroviral therapy in HIV-1-infected individuals? AIDS 2004, 18:572-4.

Protease inhibitors (PIs)

Mode of action

The HIV protease cuts the viral gag-pol polyprotein into functional subunits. If the protease is inhibited and proteolytic splicing is prevented, non-infectious virus particles will result. With the knowledge of the molecular structure of the protease encoded by the virus, the first protease inhibitors were designed in the early nineties; these agents were modified to fit precisely into the active site of the HIV protease (review: Youle 2007).

Protease inhibitors (recognizable by the suffix "-navir") revolutionized HIV therapy in the mid-1990s. At least three studies with clinical endpoints demonstrated the efficacy of indinavir, ritonavir, and saquinavir (Hammer 1997, Cameron 1998, Stellbrink 2000). Although PIs were initially criticized for their high pill burden and side effects (see below), they remain an essential component of antiretroviral therapies. The most widely used PI is darunavir, for which Symtuza®, the first fixed combination with 2 NRTIs, has been available since 2017. Atazanavir and lopinavir are also still used occasionally, tipranavir only in rare resistance situations. The other PIs are only mentioned here because some patients remain on these regimens.

Besides gastrointestinal side effects, all PIs used in long-term therapy show tolerability problems – to a greater or lesser extent, all are associated with lipodystrophy and dyslipidemia (Review: Nolan 2003). Cardiovascular disease (Lundgren 2017) and sexual dysfunction have also been attributed to PIs (Schrooten 2001), although the data does not remain unchallenged (Lallemand 2002, Bavinger 2013).

PIs are less susceptible to resistance compared to NNRTIs and INSTIs. Among boosted PIs, resistance is rarely observed in first-line therapy, and the genetic barrier is very high. This is true not only for lopinavir/r (Hammer 2006) but also for atazanavir/r (Malan 2008) and darunavir/r (Ortiz 2008). Boosted PIs are used mainly in cases of high viral load and adherence problems. With first-generation PIs, cross-resistance was often quite pronounced. However, with darunavir (and tipranavir), second-generation PIs, they work well in the presence of most PI resistances (see below). Except for atazanavir, all PIs must be boosted to achieve sufficient drug levels with ritonavir or cobicistat (see below). As a consequence, many interactions need to be considered not only for antiretroviral combinations but also for concomitant medication (see *Interactions*).

Boosting PIs with ritonavir or cobicistat – why and how?

Ritonavir is a potent inhibitor of isoenzyme 3A4, a cytochrome P450 enzyme system subunit. By inhibiting these gastrointestinal and hepatic enzyme systems, the key pharmacokinetic parameters of almost all PIs can be significantly increased (hereinafter "boosted") to achieve a maximum concentration, trough level, and half-life (Kempf 1997). The interaction between ritonavir and the other PIs allows pill reduction, reduces the necessary frequency of intake, and makes absorption partially independent of food intake. The daily dosing regimen is simplified. For some PIs, this has made single-dose administration possible. Ritonavir is also used in COVID-19 therapy to boost the SARS-CoV-2 PI nirmatrelvir (Paxlovid®).

In 2014, a second PI booster, cobicistat, was licensed. It was originally developed as a booster for the integrase inhibitor elvitegravir within the fixed combination Stribild® and was launched as such in 2013. However, 150 mg of cobicistat induced similar levels of atazanavir and darunavir compared to ritonavir (Elion 2011, Kakuda 2014). In a double-blind, randomized trial of 692 treatment-naïve patients starting with TDF+FTC+atazanavir that was boosted with either cobicistat or ritonavir, the efficacy and tolerability of both boosters were comparable (Gallant 2013). Based on

these data, cobicistat is also available as a stand-alone product (Tybost®). Approval remains limited to atazanavir and darunavir. Cobicistat is more soluble and appears to be suitable for additional STRs. Thus, it is no longer found only in Stribild® and Genvoya®, but since 2017, also in the fixed combination Symtuza® with darunavir. The moderate creatinine increases seen under cobicistat reflect a reduced tubular secretion and not an impaired renal function (German 2013). Usually, boosting with 100–400 mg of ritonavir or 150 mg of cobicistat is indicated by an "/r" or "/c" following the agent's name.

Table 2.5: Common protease inhibitor doses with boosters.

	Doses (mg)	Pills*/day	Comment
Atazanavir/r or /c	1 x 300/100**	1 x 2	No limitation
Darunavir/r	2 x 600/100	2 x 2	No limitation
Darunavir/r or /c	1 x 800/100**	1 x 1-2	Only with limited mutations
Fosamprenavir/r	2 x 700/100	2 x 2	Hardly ever used
Fosamprenavir/r	1 x 1400/200	1 x 4	Only approved in the USA (PI-naïve)
Lopinavir/r	2 x 400/100	2 x 2	Only fixed booster combination
Lopinavir/r	1 x 800/200	1 x 4	Only with a few PI mutations
Saquinavir/r	2 x 1,000/100	2 x 3	Hardly ever used
Tipranavir/r	2 x 500/200	2 x 4	Only approved in pre-treated patients

* Pill numbers, including boosters. ** Instead of 100 mg ritonavir, 150 mg cobicistat is possible (one tablet each). For darunavir/c, there is a STR fixed combination with TAF+FTC.

Boosting is also associated with risks. There is a high degree of variability in plasma levels among individuals. Trough levels and peak levels are elevated, which may lead to more side effects. If in doubt (lack of efficacy, side effects), plasma levels should be measured in cases of boosting, especially in patients with severe hepatic disease, because the extent of the interaction cannot be predetermined in individual cases. Nowadays, switching from a PI to other options is usually much more accessible than fiddling around with the PI dose. This question only arises in rare, complex cases and definitely needs an expert opinion.

Individual agents

Atazanavir (formerly **Reyataz®**, generics) was the first once-daily PI in 2004. In the CASTLE study in 883 treatment-naïve patients, atazanavir/r was virologically equivalent to lopinavir/r, with better lipid profiles and gastrointestinal tolerability (Molina 2010). In ACTG 5237, it was also mainly equivalent to darunavir/r, although weaker and less well-tolerated than raltegravir (Lennox 2014). In GS-236-103, atazanavir/r was comparable to elvitegravir/c (DeJesus 2012), but in the two large studies, WAVE and ARIA, it performed worse than elvitegravir/c and dolutegravir in treatment-naïve women (Squires 2016, Orrell 2017).

Atazanavir is the only PI for which boosting is not mandatory. According to a meta-analysis, unboosted atazanavir (400 mg instead of 300/100 mg) is no worse than boosted PIs (Baril 2014). Still, approval in Europe is limited to patients with no previous virologic failure or resistance mutations; otherwise, it is, after all, somewhat worse than lopinavir/r (Cohen 2005). The high resistance barrier is probably lower if atazanavir is not boosted.

A meal is required for adequate absorption; PPIs and tenofovir are not recommended with unboosted atazanavir (Fournier 2013). A significant problem is bilirubin elevations, which reach grades 3–4 in about 30% and are even more frequent with boosters (Squires 2004). Quite a few patients develop icterus. The mechanism is

similar to the conjugation disorder in Meulengracht disease, and an otherwise harmless genetic defect has been identified (Rotger 2005). Although hyperbilirubinemia is rarely severe (Eholie 2004), atazanavir should be discontinued in the presence of icterus and marked bilirubin elevation (> 5–6 x above normal). In Thai patients, in whom exposure is higher than in Caucasians, the atazanavir dose was successfully reduced in a large study. Hyperbilirubinemia decreased, and virologic control persisted (Bunupuradah 2016). Atazanavir has favorable effects on the lipid profile compared to older PIs. There is no difference compared to darunavir or raltegravir (Lennox 2014). One study in PI/r-treated subjects showed no effect on abdominal fat from switching to atazanavir/r (Moyle 2012), and another, compared with efavirenz, even showed an increase in visceral fat (McComsey 2011).
The resistance profile of atazanavir is similar to that of other PIs (Schnell 2003). Primary resistance is at I50L, a mutation that does not affect the sensitivity of other PIs (Colonno 2003). Overall, atazanavir is rarely used today, primarily because of hyperbilirubinemia and moderate performance compared with INSTIs. Due to a lack of demand, BMS discontinued the originator drug Reyataz® at the end of 2019. Some generics are still circulating.

Darunavir (**Prezista®**, generics, also in **Rezolsta®**, **Symtuza®**) is a PI developed by Janssen-Cilag. It is now the only PI of significance. Darunavir has impressive activity against PI-resistant viruses (Koh 2003). In February 2007, two Phase IIb trials in nearly 600 patients led to accelerated approval in Europe, initially for pre-treated patients (Clotet 2007). Despite numerous resistance mutations, the viral load in the 600 mg group (600/100 BID) remained below 50 copies/mL in 46% of the participants at 48 weeks – a significantly better result than the control PI (10%). The substance also performed well in the DUET studies, in which darunavir was combined with etravirine. In the TITAN study of 595 individuals pre-treated predominantly with PIs (but lopinavir-naive), 71% had a viral load below 50 copies/mL after 48 weeks, compared with 60% on lopinavir (Madruga 2007). Virologic failure and resistance to concomitant agents were significantly less frequent under darunavir. Interestingly, PI mutations did not compromise efficacy (De Meyer 2008+2009). New resistance mutations during therapy are sporadic (El Bouzidi 2016).
In 2008, darunavir's license was expanded to treatment-naïve individuals. In ARTEMIS, darunavir was at least as effective as lopinavir when given once daily (Mills 2009). Once-daily dosing is also feasible in ART-experienced patients, provided no darunavir resistance exists (Cahn 2011, Lathouwers 2013). In first-line therapy, darunavir has been tested primarily against integrase inhibitors. In FLAMINGO and ACTG 5237, almost no resistance mutations were observed, confirming its high resistance barrier. However, in both studies, darunavir performed slightly worse than dolutegravir and raltegravir (Clotet 2014, Lennox 2014).
Darunavir is well-tolerated. The typical PI gastrointestinal side effects tend to be moderate; diarrhea is usually milder than with other PIs (Clotet 2007, Madruga 2007). Dyslipidemias and liver elevations seem to play a minor role. On the other hand, the rash develops in 5–15%. Cohort studies suggest a slightly increased cardiovascular risk (Lundgren 2017). However, a large case-control study found no increased CV risk when adjusting for other factors such as ART history (Costagliola 2019). Unlike for abacavir, there is no (well) explained pathomechanism so far. Bias would thus be conceivable – darunavir is preferentially used in late presenters.
Boosting is also possible with cobicistat. The combination (Rezolsta®) without any NRTI backbone is approved in Europe but is not marketed in most countries. A fixed drug combination (FDC) of TAF/FTC/darunavir/c, Symtuza®, has been available since 2017. Two large Phase III trials led to the approval of this FDC. In AMBER, Symtuza®

was as effective as single agents in first-line therapy (Orkin 2019), and in EMERALD, switching from PI/r regimens in patients with virological suppression was also successful (Eron 2019), regardless of pre-existing resistance (Lathouwers 2020). Symtuza® should be taken with food, which improves bioavailability (Crauwels 2019). The potency of darunavir is, of course, not unlimited. With more than three resistance mutations at codons 32, 47, 50, and 87 (De Meyer 2006), efficacy is reduced significantly (Pozniak 2008). In treatment-experienced patients with darunavir-associated mutations, twice-daily dosing (600/100 mg BID) is recommended based on an analysis of subjects with triple-class experience with one or more primary PI resistance mutations (Clotet 2007).

Again, darunavir is now the only PI of significance, primarily due to Symtuza®, the only PI-containing STR to date. Various generics are available for the single agent. The resistance barrier is among the highest among antiretroviral therapies, making it particularly suitable in cases of adherence problems or any risk of treatment failure. In the salvage setting and in the presence of pre-existing resistance, darunavir is almost indispensable. Increasingly, it is also being investigated in the context of dual therapies, either with 3TC or with INSTIs.

Lopinavir/r (**Kaletra®**, generics available) was the only PI with a fixed booster dose of ritonavir when approved in April 2001. Worldwide, it is still a commonly prescribed PI. Since October 2009, it has been approved for single-dose use, but only in the absence of or limited PI mutations (Flexner 2010). In treatment-naïve patients, randomized trials such as ARTEMIS or CASTLE showed no advantage over other boosted PIs such as darunavir (Mills 2009) or atazanavir (Molina 2008). In ACTG 5142, lopinavir/r was even inferior to or less well-tolerated than the NNRTI efavirenz (Riddler 2008). It was slightly weaker in pre-treated individuals compared to darunavir/r (Madruga 2007, De Meyer 2009).

Resistance in first-line therapy is rare (Conradie 2004, Friend 2004). The resistance barrier is high, and probably 6–8 cumulative PI resistances are necessary for treatment failure (Kempf 2002). Major problems are gastrointestinal side effects (diarrhea). In addition, patients frequently develop notable dyslipidemias with lopinavir, which are more pronounced than with atazanavir (Molina 2008, Mallolas 2009) and darunavir (Mills 2009). There are also numerous interactions to consider (see *Interactions*). In recent years, lopinavir has hardly been used due to high pill counts and gastrointestinal problems.

Ritonavir (Norvir®) was the first PI whose efficacy was demonstrated with clinical endpoints (Cameron 1998). However, as a sole PI, ritonavir is obsolete because tolerability is poor. As gastrointestinal complaints and perioral paresthesias can be very disturbing, ritonavir is now only given to boost other PIs. The "baby dose" (1–2 x 100 mg) commonly used for this purpose is better tolerated. Due to the strong enzyme induction, many interactions and contraindications exist (see *Interactions*). Metabolic disturbances are also more common than with other PIs. Caution is advised in the presence of hepatic dysfunction. Ritonavir recently experienced a renaissance in COVID-19 therapy – to boost the SARS-CoV-2 PI nirmatrelvir (Paxlovid®).

Obsolete – these PIs should (or can) no longer be prescribed

Amprenavir (Agenerase®) was the fifth PI in Europe in June 2000. It was replaced by fosamprenavir (see below) in 2004 and withdrawn from the market.

Fosamprenavir (Telzir®, US: **Lexiva®**) is more absorbable than amprenavir. It was approved in 2004 at a dose of 2 x 700 mg plus 2 x 100 mg ritonavir daily (2 x 2 pills). Unboosted or once-daily dosing was not licensed in Europe. Fosamprenavir/r is slightly weaker than lopinavir/r in pre-treated patients. Fosamprenavir no longer

plays a role: there is no advantage over other PIs. According to the manufacturer, it will be withdrawn from the market at the end of 2023.

Indinavir (Crixivan®) is one of the oldest, initially widely used PIs. Due to its skin and kidney problems (nephrolithiasis!), its need for 3 liters of water per day, and twice-daily administration, it was discontinued in 2019.

Nelfinavir (Viracept®) was the fourth PI in 1998. Due to high pill counts, diarrhea, and lower antiviral potency, the agent was not very used. Roche let the approval expire in January 2013.

Saquinavir (Invirase 500®, formerly **Invirase®, Fortovase®**) was the first PI to be licensed in 1995 and is still one of the few agents whose efficacy has been demonstrated based on clinical endpoints (Stellbrink 2000). The hard-gel (Invirase®) and soft-gel (Fortovase®) capsules were replaced in 2005 by Invirase 500® tablets, which reduced the daily pill count to six (2 x 2 tablets with 500 mg plus 2 x 100 mg ritonavir). In GEMINI, Invirase 500® was as effective as lopinavir/r (Walmsley 2009). In 2014, a warning about QT prolongation was published. The dose should be increased during the first week with ECG monitoring – hardly practical in everyday life. There is no advantage over other PIs. Saquinavir should no longer be used.

Tipranavir (Aptivus®) was the first non-peptide PI approved in Europe in July 2005 for heavily pre-treated patients. Its moderate oral bioavailability requires boosting with ritonavir; 2 x 200 mg (2 x 2 pills!) of ritonavir should be used (McCallister 2004), each with a meal. Tipranavir is effective against PI-resistant viruses, even with multiple mutations (Larder 2000). Two Phase III studies (RESIST) in 1483 intensively pre-treated patients with at least one primary PI mutation led to approval, in which tipranavir was superior to a comparator PI (Hicks 2006).
Major side effects are dyslipidemias, which are more pronounced than with comparator PIs, and in some cases, significant increases in transaminases. In first-line therapy, tipranavir also performed worse than lopinavir/r for this reason (Cooper 2016). The indication, therefore, remains limited to "heavily pre-treated adults with viruses resistant to multiple PIs." It should be discontinued or avoided if transaminases are elevated. In addition, there are unfavorable interactions (see *Interactions*): Abacavir or etravirine levels decrease, and the combinations should be avoided. Tipranavir is practically no longer needed in salvage therapy today, thanks to new options.

Literature on protease inhibitors

Ananworanich J, Hirschel B, Sirivichayakul S, et al. Absence of resistance mutations in antiretroviral-naive patients treated with ritonavir-boosted saquinavir. Antivir Ther 2006;11:631-635.
Baril J, Conway B, Giguère P, et al. A meta-analysis of the efficacy and safety of unboosted atazanavir compared with ritonavir-boosted protease inhibitor maintenance therapy in HIV-infected adults with established virological suppression after induction. HIV Med 2014, 15:301-10.
Bavinger C, Bendavid E, Niehaus K, et al. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. PLoS One 2013;8:e59551.
Cahn P, Fourie J, Grinsztejn B, et al. Week 48 analysis of once-daily vs. twice-daily darunavir/ritonavir in treatment-experienced HIV-1-infected patients. AIDS 2011, 25:929-939.
Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. Lancet 1998, 351:543-9.
Clotet B, Bellos N, Molina JM, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2. Lancet 2007, 369:1169-78.
Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet 2014, 383:2222-31.
Cohen C, Nieto-Cisneros L, Zala C, et al. Comparison of atazanavir with lopinavir/ritonavir in patients with prior protease inhibitor failure: a randomized multinational trial. Curr Med Res Opin 2005, 21:1683-92.
Colonno RJ, Thiry A, Limoli K, Parkin N. Activities of atazanavir (BMS-232632) against a large panel of HIV type 1 clinical isolates resistant to one or more approved protease inhibitors. Antimicrob Agents Chemother 2003, 47:1324-33.

Conradie F, Sanne I, Venter W, et al. Failure of lopinavir-ritonavir (Kaletra)-containing regimen in an antiretroviral-naive patient. AIDS 2004, 18:1084-5.

Cooper DA, Cordery DV, Zajdenverg R, et al. Tipranavir/Ritonavir (500/200 mg and 500/100 mg) Was Virologically Non-Inferior to Lopinavir/Ritonavir (400/100 mg) at Week 48 in Treatment-Naïve HIV-1-Infected Patients: A Randomized, Multinational, Multicenter Trial. PLoS One 2016, 11:e0144917.

Costagliola D, Potard V, Lang S, et al. Is the Risk of Myocardial Infarction in People With Human Immunodeficiency Virus (HIV) Associated With Atazanavir or Darunavir? A Nested Case-Control Study Within the French Hospital Database on HIV. J Infect Dis 2019 Dec 11.

Crauwels HM, Baugh B, Van Landuyt E, et al. Bioequivalence of the Once-Daily Single-Tablet Regimen of Darunavir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide Compared to Combined Intake of the Separate Agents and the Effect of Food on Bioavailability. Clin Pharmacol Drug Dev 2019, 8:480-491.

Daar ES, Tierney C, Fischl MA, et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1: A randomized trial. Ann Intern Med 2011, 154:445-456.

De Meyer S, Hill A, Picchio G, DeMasi R, De Paepe E, de Béthune MP. Influence of baseline protease inhibitor resistance on the efficacy of darunavir/ritonavir or lopinavir/ritonavir in the TITAN trial. J AIDS 2008, 49:563-4.

De Meyer S, Lathouwers E, Dierynck I, et al. Characterization of virologic failure patients on darunavir/ritonavir in treatment-experienced patients. AIDS 2009, 23:1829-40.

DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet 2012, 379:2429-38.

Eholie SP, Lacombe K, Serfaty L, et al. Acute hepatic cytolysis in an HIV-infected patient taking atazanavir. AIDS 2004, 18:1610-1.

El Bouzidi K, White E, Mbisa JL, et al. HIV-1 drug resistance mutations emerging on darunavir therapy in PI-naive and -experienced patients in the UK. J Antimicrob Chemother 2016, 71:3487-3494.

Elion R, Cohen C, Gathe J, et al. Phase 2 study of cobicistat versus ritonavir each with once-daily atazanavir and fixed-dose emtricitabine/tenofovir df in the initial treatment of HIV infection. AIDS 2011, 25:1881-6.

Eron JJ, Orkin C, Cunningham D, et al. Week 96 efficacy and safety results of the phase 3, randomized EMERALD trial to evaluate switching from boosted-protease inhibitors plus emtricitabine/tenofovir disoproxil fumarate regimens to the once daily, single-tablet regimen of darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) in treatment-experienced, virologically-suppressed adults living with HIV-1. Antiviral Res 2019, 170:104543.

Flexner C, Tierney C, Gross R, et al. Comparison of once-daily versus twice-daily combination antiretroviral therapy in treatment-naive patients: results of AIDS clinical trials group (ACTG) A5073, a 48-week randomized controlled trial. Clin Infect Dis 2010, 50:1041-52.

Focà E, Ripamonti D, Motta D, Torti C. Unboosted atazanavir for treatment of HIV infection: rationale and recommendations for use. Drugs 2012, 72:1161-73.

Fournier C, Higgins N, Thomas R, et al. Negligible effect of tenofovir on atazanavir trough concentrations and genotypic inhibitory quotients in the presence and absence of ritonavir. Ther Drug Monit 2013, 35:264-9.

Friend J, Parkin N, Liegler T, et al. Isolated lopinavir resistance after virological rebound of a rit/lopinavir-based regimen. AIDS 2004, 18:1965-6.

Gallant JE, Koenig E, Andrade-Villanueva J, et al. Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV type 1-infected patients: week 48 results. J Infect Dis 2013, 208:32-9.

German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. J AIDS 2012, 61:32-40.

Ghosn J, Carosi G, Moreno S, et al. Unboosted atazanavir-based therapy maintains control of HIV type-1 replication as effectively as a ritonavir-boosted regimen. Antivir Ther 2010, 15:993-1002.

Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. JAMA 2006, 296:827-843.

Hammer SM, Vaida F, Bennett KK, et al. Dual vs single protease inhibitor therapy following antiretroviral treatment failure: a randomized trial. JAMA 2002, 288:169-80.

Hicks CB, Cahn P, Cooper DA, et al. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the RESIST studies: an analysis of combined data from two randomised open-label trials. Lancet 2006, 368:466-475.

Kempf DJ, Isaacson JD, King MS, et al. Analysis of the virological response with respect to baseline viral phenotype and genotype in PI-experienced HIV-1-infected patients receiving lopinavir/ritonavir therapy. Antiviral Therapy 2002, 7:165-174.

Kempf DJ, Marsh KC, Kumar G, et al. Pharmacokinetic enhancement of inhibitors of the HIV protease by coadministration with ritonavir. Antimicrob Agents Chemother 1997, 41:654-60.

Koh Y, Nakata H, Maeda K, et al. Novel bis-tetrahydrofuranylurethane-containing nonpeptidic protease inhibitor UIC-94017 (TMC114) with potent activity against multi-PI-resistant HIV in vitro. Antimic Ag Chemo 2003; 47: 3123-3129.

Kozal MJ, Lupo S, DeJesus E, et al. A nucleoside- and ritonavir-sparing regimen containing atazanavir plus raltegravir in antiretroviral treatment-naïve HIV-infected patients: SPARTAN study results. HIV Clin Trials 2012, 13:119-30.

Lallemand F, Salhi Y, Linard F, Giami A, Rozenbaum W. Sexual dysfunction in 156 ambulatory HIV-infected men receiving HAART combinations with and without protease inhibitors. J AIDS 2002, 30: 187-90.

Larder BA, Hertogs K, Bloor S, et al. Tipranavir inhibits broadly protease inhibitor-resistant HIV-1 clinical samples. AIDS 2000, 14:1943-8.

Lathouwers E, De La Rosa G, Van de Casteele T, et al. Virological analysis of once-daily and twice-daily darunavir/ritonavir in the ODIN trial of treatment-experienced patients. Antivir Ther. 2013 Apr 4.

Lathouwers E, Wong EY, Brown K, et al. Week 48 Resistance Analyses of the Once-Daily, Single-Tablet Regimen Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) in Adults Living with HIV-1 from the Phase III Randomized AMBER and EMERALD Trials. AIDS Res Hum Retroviruses 2020, 36:48-57.

Lennox JL, Landovitz RJ, Ribaudo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. Ann Intern Med 2014, 161:461-71.

Lundgren J, Mocroft A, Ryom L. Contemporary protease inhibitors and cardiovascular risk. Curr Opin Infect Dis. 2017 Dec 9.

Madruga JV, Berger D, McMurchie M, et al. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. Lancet 2007, 370:49-58.

Malan DR, Krantz E, David N, et al. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naive patients. J AIDS 2008, 47:161-7.

Malan DR, Krantz E, David N, Wirtz V, Hammond J, McGrath D. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naive patients. J AIDS 2008; 47:161-167.

McCallister S, Valdez H, Curry K, et al. A 14-day dose-response study of the efficacy, safety, and pharmacokinetics of the nonpeptidic protease inhibitor tipranavir in treatment-naive HIV-1-infected patients. J AIDS 2004, 35:376-82.

McComsey GA, Kitch D, Sax PE, et al. Peripheral and central fat changes in subjects randomized to abacavir-lamivudine or tenofovir-emtricitabine with atazanavir-ritonavir or efavirenz: ACTG Study A5224s. Clin Infect Dis 2011, 53:185-96.

Mills AM, Nelson M, Jayaweera D, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. 30. AIDS 2009, 23:1679-88.

Molina JM, Andrade-Villanueva J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. J AIDS 2010, 53:323-32.

Moltó J, Curran A, Miranda C, et al. Pharmacokinetics of darunavir/cobicistat and etravirine alone and co-administered in HIV-infected patients. J Antimicrob Chemother. 2017 Dec 11.

Moyle GJ, Andrade-Villanueva J, Girard PM, et al. A randomized comparative 96-week trial of boosted atazanavir versus continued boosted protease inhibitor in HIV-1 patients with abdominal adiposity. Antivir Ther 2012, 17:689-700.

Nolan D. Metabolic complications associated with HIV protease inhibitor therapy. Drugs 2003, 63:2555-74.

Noor MA, Parker RA, O'mara E, et al. The effects of HIV protease inhibitors atazanavir and lopinavir/ritonavir on insulin sensitivity in HIV-seronegative healthy adults. AIDS 2004, 18:2137-2144.

Orkin C, Eron JJ, Rockstroh J, et al. Week 96 results of a phase 3 trial of darunavir/cobicistat/ emtricitabine/tenofovir alafenamide in treatment-naïve HIV-1 patients. AIDS 2019 Dec 10.

Pulido F, Ribera E, Lagarde M, et al. Dual Therapy With Darunavir and Ritonavir Plus Lamivudine vs Triple Therapy With Darunavir and Ritonavir Plus Tenofovir Disoproxil Fumarate and Emtricitabine or Abacavir and Lamivudine for Maintenance of Human Immunodeficiency Virus Type 1 Viral Suppression: Randomized, Open-Label, Noninferiority DUAL-GESIDA 8014-RIS-EST45 Trial. Clin Infect Dis 2017; 65:2112-18.

Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med 2008, 358:2095-2106.

Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. N Engl J Med 2003, 349: 2293-303.

Rodriguez-French A, Boghossian J, Gray GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in ART-naive HIV-1-infected patients. JAIDS 2004, 35:22-32.

Rotger M, Taffe P, Bleiber G, et al. Gilbert syndrome and the development of antiretroviral therapy-associated hyperbilirubinemia. JID 2005, 192:1381-6.

Schrooten W, Colebunders R, Youle M, et al. Sexual dysfunction associated with protease inhibitor containing HAART. AIDS 2001, 15: 1019-23.

Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. N Engl J Med 2003, 349: 2304-15.

Soriano V, Arastéh K, Migrone H, et al. Nevirapine versus atazanavir/ritonavir, each combined with tenofovir disoproxil fumarate/emtricitabine, in antiretroviral-naive HIV-1 patients: the ARTEN Trial. Antivir Ther 2011, 16:339-48.

Squires KE, Young B, DeJesus E, et al. ARIES 144 week results: durable virologic suppression in HIV-infected patients simplified to unboosted atazanavir/abacavir/lamivudine. HIV Clin Trials 2012, 13:233-44.

Squires KE, Young B, DeJesus E, et al. Safety and efficacy of a 36-week induction regimen of abacavir/lamivudine and ritonavir-boosted atazanavir in HIV-infected patients. HIV Clin Trials 2010, 11:69-79.

Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. N Engl J Med 1999, 341:1865-73.

Stellbrink HJ, Hawkins DA, Clumeck N, et al. Randomised, multicentre phase III study of saquinavir plus zidovudine plus zalcitabine in previously untreated or minimally pretreated HIV-infected patients. Clin Drug Invest 2000, 20:295-307.

Walmsley S, Avihingsanon A, Slim J, et al. Gemini: A noninferiority study of saquinavir/ritonavir versus lopinavir/ritonavir as initial HIV-1 therapy in adults. J Acquir Immune Defic Syndr 2009, 50:367-74.

Wasmuth JC, Lambertz I, Voigt E, et al. Maintenance of indinavir by dose adjustment in HIV-1-infected patients with indinavir-related toxicity. Eur J Clin Pharmacol 2007;63:901-8.

Youle M. Overview of boosted protease inhibitors in treatment-experienced HIV-infected patients. J Antimicrob Chemother 2007;60:1195-205.

Integrase inhibitors

Mode of action

Integrase, along with reverse transcriptase and protease, is one of the three key enzymes in the HIV-1 replication cycle. This enzyme consists of 288 amino acids, is encoded by the HIV *pol* gene, and is involved in integrating viral DNA into host DNA in the cell nucleus (Nair 2002). In human cells, there is probably no enzyme comparable to integrase. At least four steps lead to viral DNA integration (Review: Engelman 2018). Different integrase inhibitors may theoretically inhibit all these steps. Briefly, these steps are:

1. **Binding** the integrase enzyme in the cytoplasm to the viral DNA. This results in a relatively stable so-called pre-integration complex (pre-integration complex, PIC) → this step can be inhibited by binding inhibitors such as pyrano-dipyrimides.
2. **3′-processing**: In the first catalytic step, the integrase removes a dinucleotide at each end of the viral DNA, producing new 3′-hydroxyl ends within the PIC → so-called processing inhibitors are styryl quinolones or diketo acids.
3. **Strand transfer**: After the transport of the PIC from the cytoplasm through a nuclear pore into the cell's nucleus, integrase binds to the host chromosomal DNA. By doing this, integrase mediates irreversible binding of viral and cellular DNA → this step is inhibited by the approved integrase inhibitors, so-called strand transfer inhibitors (INSTIs, ending in "-gravir").
4. **Gap repair**: The combination of viral and host cell DNA is an intermediate product with gaps repaired by host cell repair enzymes. This probably no longer requires integrase → but repair can be inhibited by, for example, methylxanthines.

After the principle of strand transfer inhibition was elucidated (Hazuda 2000), raltegravir became the first INSTI to be licensed in December 2007. Since then, four others have become available: elvitegravir, dolutegravir, bictegravir, and cabotegravir. As with all new drug classes, some questions remain. While efficacy and tolerability appear good in the short and medium term, nothing is known about long-term toxicities. Mainly, mild neuropsychiatric events occur (Hoffmann 2019), as does substantial weight gain sometimes, especially in combination with TAF (Hill 2019, Sax 2019). Pathways or mechanisms remain largely unclear. Another issue is the relatively low resistance barrier with first-generation INSTIs, raltegravir and elvitegravir. This is especially evident with pre-existing resistance (Eron 2009). Cross-class resistance is possible.

There are also problems with measuring plasma levels, where the large inter- and individual variability does not allow reliable statements to be made (Cattaneo 2012). Once resistance is present, INSTIs, like NNRTIs, should be discontinued, as replication capacity is unlikely to be affected and further mutations prevented (Wirden 2009). Despite these problems, it is hard to imagine HIV therapy without INSTIs. Given their high potency and good tolerability, many are already talking about the INSTI era. The individual agents are discussed below.

Individual agents

Bictegravir (formerly GS-9883, a component of **Biktarvy®**) was developed by Gilead Sciences. Since its approval in June 2018, bictegravir has been available exclusively as Biktarvy®, a fixed-dose combination with TAF+FTC. Unlike elvitegravir, bictegravir does not require boosting; moreover, its half-life of 18 hours allows for daily once-daily dosing. The antiviral efficacy of bictegravir in monotherapy was over 2 logs (Gallant 2017). It has efficacy against some INSTI-resistant isolates. However, the resistance profile broadly matches that of dolutegravir (Tsiang 2016, Saladini 2019).

As first-line therapy, TAF/FTC/bictegravir was tested in large Phase III trials, mainly against dolutegravir. In GS-1489, it was compared to ABC/3TC/dolutegravir (Triumeq®,) and in GS-1490 against dolutegravir plus TAF/FTC. In both studies, Biktarvy® was virologically non-inferior to the comparator at 96 weeks and tolerated well. There were few discontinuations, infrequent virologic failure, and not a single case of resistance (Wohl 2019, Stellbrink 2019).
There are also good data for pre-treated patients. In GS-1878, pre-therapy consisted of boosted PIs such as darunavir/r and atazanavir/r (Daar 2018); in GS-1844, it was Triumeq® (Molina 2018); and in GS-1961, a women-only study, it was almost exclusively elvitegravir (Kityo 2018). In all studies, virologic suppression persisted. In addition to women, other chronically under-represented groups have been studied in randomized trials, including Black Americans (Hagins 2021) and people over 65 years of age (Maggiolo 2022).
Tolerability was good, even slightly better than dolutegravir (Wohl 2019). In GS-1878, more patients mainly reported mild headache (12% versus 4%). The double-blind, randomized GS-4030 trial explicitly allowed resistance to NRTIs, NNRTIs, and PIs to determine the potential of Biktarvy® in pre-existing resistance (Sax 2021). Subjects were enrolled on dolutegravir-containing regimens, randomized to either Biktarvy® or dolutegravir plus TAF+FTC. Efficacy remained good despite significant resistance in some cases, particularly in the NRTI backbone – bictegravir and dolutegravir appear to have similar salvage potential.
The tolerability of the combination is good, but Biktarvy® is also associated with weight gain, which is likely to be similar to that of dolutegravir (Sax 2019). Neuropsychiatric side effects have also been seen in the first few months, as with dolutegravir, with about 3% discontinuing therapy because of this (Hoffmann 2020). There is a small potential for interaction. Bictegravir is not eliminated renally.
Overall, bictegravir is a highly effective INSTI that does not require a booster and has displaced elvitegravir and other agents in our daily practice. However, a significant advantage over dolutegravir has not been identified, except that bictegravir is available in a TAF-based STR. Unlike dolutegravir, however, flexible use is impossible; only one fixed combination exists.

Cabotegravir (**GSK744**, **Vocabria®** or **Cabenuva®**, as PrEP also **Apretude®**) is an INSTI that is very similar to dolutegravir. It is used exclusively as a long-acting injection in combination with the NNRTI rilpivirine (Rekambys®, cabotegravir plus rilpivirine long-acting, "CARLA"). CARLA requires two intramuscular injections each, every 1–2 months. PK studies found a half-life of 21–50 days after intramuscular injection. Levels are still detectable in plasma for many months after discontinuation (Stellbrink 2018).

Strong cross-resistance exists with the second-generation INSTIs dolutegravir and bictegravir. Especially against INSTI mutations occurring among first-generation INSTIs raltegravir and elvitegravir, cabotegravir appears to have somewhat lower potency (Saladini 2019, Smith 2019).
As monotherapy, single injections decreased viral load by 2.2–2.3 logs (Spreen 2013). In the LATTE pilot study, 243 treatment-naïve individuals received two NRTIs and various oral doses of cabotegravir or efavirenz. Subsequently, patients switched to CARLA or remained on efavirenz plus 2 NRTIs. After 48 weeks, 82% achieved a viral load below the detection limit, compared with 71% on the standard efavirenz regimen (Margolis 2015). In LATTE-2, a Phase IIb trial, 309 individuals received either CARLA every 4 or 8 weeks or oral ART with cabotegravir plus ABC+3TC after induction. The rates of undetectable viral load at 96 weeks were even higher in the injection arms (87% and 94%, respectively) than with oral ART (84%). However, injection site reactions were observed in nearly all participants and were still

"moderate" in 15% (Margolis 2017). Nevertheless, treatment satisfaction among the participants was high, even after five years (Smith 2022).
Two large Phase III trials in 2019 ultimately led to approval. In ATLAS, 705 people had been successfully pre-treated with different ART regimens for a mean of four years (Swindells 2020); in FLAIR, 629 treatment-naïve people had initially received several months of induction therapy with Triumeq®, and 566 were randomized (Orkin 2020+2021). Half remained on the old ART in each trial, and the other half switched to quad-weekly injections. Both ATLAS and FLAIR showed non-inferiority of CARLA. The rate of undetectable viral loads at week 48 was comparable (93–96%). Still, there were a few overall virologic failures in the LA arm in both trials, some of which even showed a combination of NNRTI and INSTI resistance. Even if these were primarily Russian patients with HIV subtype A – CARLA received its first minor dents here. Plasma levels during treatment failure were relatively low but not too low to explain the failure. In November 2017, ATLAS was expanded to include ATLAS-2M. This trial compared four- versus eight-week injections of CARLA and demonstrated non-inferiority of the 8-week arm at 96 weeks (Hunter 2021). Consequently, the approval of cabotegravir covers 4- and 8-week administration.
Sufficient levels are also achieved in the CNS (Letendre 2019). Administration is safe even in severe renal insufficiency (Parasrampuria 2019). Concomitant administration of rifabutin is possible, and levels remain adequate (Ford 2019). In contrast, this is probably not true with rifampicin (Rajoli 2019).
Cabotegravir is also being developed as PrEP. It was superior to conventional PrEP in large Phase III trials and has been approved in the US since 2022 under the trade name Apretude® (Landovitz 2022, see *PrEP*).

Dolutegravir (**Tivicay®**, part of **Dovato®**, **Juluca®**, **Triumeq®**) is a second-generation INSTI developed by ViiV Healthcare and the first to enable once-daily, unboosted INSTI administration in 2014. In a Phase IIa study, during ten days of monotherapy, the viral load dropped by up to 2.5 logs (Min 2011).
Treatment-naïve patients: In SPRING-2, a double-blind, randomized trial against raltegravir BID, 81% versus 76% were below detection at 96 weeks, with equal tolerability. Less resistance was observed in the case of treatment failure (Raffi 2013). In SINGLE, the fixed combination of ABC/3TC/dolutegravir (Triumeq®) was slightly better than TDF/FTC/efavirenz in 833 treatment-naive individuals (Walmsley 2013). In FLAMINGO, dolutegravir was virologically superior to darunavir/r (Clotet 2014), and in the women-only ARIA trial, it was superior to atazanavir (Orrell 2017). In two other Phase III trials, dolutegravir-containing regimens were as effective as bictegravir (Wohl 2019, Stellbrink 2019). In the GEMINI trials, a two-drug combination with dolutegravir/3TC was also sufficient in many patients, even those with high viral loads (Cahn 2019, Eron 2020).
Pre-treated patients: In the double-blind, randomized SAILING trial of 715 PLWH with plasma viremia of at least 400 copies/mL on ART (half with triple-class resistance), dolutegravir was virologically superior to raltegravir (Cahn 2013). Even in the case of INSTI resistance, there is still efficacy – the VIKING trials showed that in patients with raltegravir and elvitegravir resistance, higher doses of dolutegravir can help overcome resistance (Eron 2013, Castagna 2014). With 100 mg of dolutegravir, a substantial proportion still achieved a viral load below the detection limit.
On the other hand, dual combinations (see below) with rilpivirine (Aboud 2019) or 3TC (van Wyk 2020) have proven effective in the context of de-escalation approaches.
Dolutegravir is well-tolerated, even at higher doses (Castagna 2014). Mild creatinine elevations are due to inhibition of a renal transporter system. Relatively typical side effects are neuropsychiatric events and (usually mild) sleep disturbances, in our experience, occurring mainly in women and the elderly (Hoffmann 2017). Relatively

high rates of (mild) side effects were also reported in STRIIVING and SWORD (Trottier 2017, Aboud 2019). However, switching from boosted PIs improves lipids (Gatell 2017). Significant weight gain was observed with TAF (Venter 2019, Sax 2019), but the cause is still unclear. In contrast, a higher risk of neural tube defects in newborns reported in Botswana has not been further seen (Zash 2019).
The resistance barrier is higher than for other INSTIs (Hightower 2011). The effect persists with some INSTI resistance but decreases with raltegravir-type mutations at codon 148 (Castagna 2014+2017, Anstett 2017). Relevant interactions with boosted PIs do not exist, but the NNRTI etravirine significantly reduces levels (Song 2011). For rifampicin, a dose increase is necessary (Dooley 2013). Absorption remains unaffected by food intake (Song 2012).
Dolutegravir is undoubtedly one of the most important and frequently prescribed antiretroviral agents. Since 2018, WHO HIV treatment guidelines have recommended the combination of TDF, 3TC, and dolutegravir ("TLD", not available in Western Europe) as the preferred first-line regimen for initiating ART among adults and adolescents. Advantages of dolutegravir are the high resistance barrier and the dispensable booster, as well as its flexibility: with Juluca® (plus rilpivirine) and Dovato® (plus 3TC), two dual therapies are available (see below) – whether STR, 2DR or single agent, dolutegravir allows for an individualized therapy.

Elvitegravir (a component of **Stribild®** and **Genvoya®**) is an INSTI developed by Gilead Sciences. The compound is chemically similar to quinolone antibiotics (Sato 2006) and must be boosted, allowing daily single-dose administration. To be independent of the monopoly booster ritonavir, elvitegravir was developed together with the new pharmacoenhancer cobicistat. In an initial study, viral load decreased by about 2 logs after ten days of monotherapy (DeJesus 2006). It showed an excellent effect in pre-treated patients compared to a boosted PI (Zolopa 2010).
In two Phase III trials in *ART-naïve* patients, the "QUAD" pill (Stribild®), a fixed combination of the four Gilead compounds elvitegravir, cobicistat, TDF, and FTC, was as effective as TDF/FTC plus efavirenz (Sax 2012) or atazanavir (DeJesus 2012). Stribild® was approved in June 2013. In two other large Phase III trials, there were significantly fewer renal and osseous side effects on the new "$QUAD_{TAF}$" pill Genvoya®, in which TAF replaces TDF. Genvoya® was approved in early 2016 and primarily replaced Stribild® (Sax 2015).
In *pre-treated* patients, elvitegravir achieved comparable effects to raltegravir in a double-blind, randomized Phase III trial in over 700 individuals with resistance (Elion 2013). Switching from virologically effective PI and NNRTI therapy is also possible, as shown in two large studies (Arribas 2014, Pozniak 2014). However, in these studies, participants were on first- or second-line therapy, and pre-existing resistance was allowed only in a minimal manner. This was also true in another trial, in which the participants were switched from different regimens from other trials to Genvoya® (Mills 2016). Thus, caution is warranted in patients with intensive pre-treatment and/or resistance. In pre-treated patients with renal damage, proteinuria and bone mineral density improved when switching from TDF to TAF, supporting safety in this population (Pozniak 2016).
Elvitegravir is well tolerated, with no specific side effects that can be attributed to the agent alone. Patients who switched from NNRTI therapy to elvitegravir reported more headaches and nausea (Pozniak 2014), but this was not the case when switching from a PI (Arribas 2014). Slightly more diarrhea is likely to occur than with other INSTIs.
Regarding resistance mutations, there are at least two resistance pathways via T66I or E92Q (Shimura 2008). For the most part, the resistance profiles of elvitegravir and raltegravir overlap, and cross-resistance is likely (DeJesus 2007, Garrido 2012). The resistance barrier is likely lower than among second-generation INSTIs. Relevant

interactions with elvitegravir hardly exist; the interactions are almost exclusively caused by the booster cobicistat. Many agents that CYP3A metabolizes are contraindicated or should be avoided (Nguyen 2016).
With the approval of Biktarvy®, elvitegravir has lost ground since 2018. The main disadvantages are the lower resistance barrier, the rigidly fixed combination, and, most importantly, the interaction risk due to the booster. There are hardly any reasons left that currently speak in favor of elvitegravir. The single agent elvitegravir (**Vitekta®**) is not marketed in many countries, although it is approved in Europe.

Raltegravir (Isentress®) was the first INSTI licensed in December 2007. It has broad activity against R5- and X4-tropic HIV-1 strains and against HIV-2. Ten days of monotherapy decreased viral load by approximately 2 logs (Markowitz 2006). Two identically designed trials, BENCHMRK-1 and -2, initially led to approval in *pre-treated* patients (Cooper 2008, Steigbigel 2008). A total of 699 individuals with triple-class resistance received either 2 x 400 mg raltegravir or placebo for optimized therapy. After 16 weeks, 79% versus 43% achieved a viral load below 400 copies/mL. Without a single active agent, the rate was still 57% (versus 10%). Even after five years, the effects were visible (Eron 2013). However, raltegravir was inferior to dolutegravir in the SAILING study in intensively pre-treated patients (see above).
Raltegravir was also successful in *ART-naïve* patients. In STARTMRK, raltegravir was superior to efavirenz, both virologically and in terms of tolerability. The effects persisted for more than five years (Rockstroh 2013). Raltegravir has also been approved for first-line therapy since September 2009. In SPRING-2, it was slightly weaker than dolutegravir (see above). In the three-arm ARDENT trial, it performed superior to atazanavir/r and darunavir/r (Lennox 2014). Because viral load declines more rapidly with raltegravir than with PIs and NNRTIs (Siliciano 2009), it has also been studied in eradication approaches (see section on *Cure* in 5.4).
Tolerability of raltegravir is excellent and possibly even better than other INSTIs, including neuropsychiatric events and sleep disturbances; in BENCHMARK, it was comparable to placebo. Anecdotal evidence exists for rhabdomyolysis or hepatitis (Dori 2010, Tsukada 2010). Renal insufficiency does not require dose adjustment.
There appear to be three resistance pathways at codons N155, Q148, and Y143, which are localized in the catalytic core of the integrase. Resistance emerges quickly compared to second-generation INSTIs, with broad cross-resistance with elvitegravir (Anstett 2017). With pre-treatment and especially in the case of NRTI resistance, the ice is thin: in SWITCHMRK (Eron 2010), viral breakthroughs occurred in 6% after switching from lopinavir/r to raltegravir. Although the smaller SPIRAL study could not replicate these findings (Martinez 2010), this argues against an overly naïve switch from boosted PIs to raltegravir.
The recommended dose is one tablet of 400 mg twice daily, regardless of food intake. The once-daily 800 mg dose was slightly weaker in QDMRK (Eron 2011), but a reformulated dose (1 x 2 tablets of 600 mg) showed non-inferiority in the double-blind randomized ONCEMRK trial in 802 patients (Cahn 2017). As a consequence, once-daily dosing was approved in 2017.
Raltegravir is neither an inducer nor an inhibitor of the cytochrome 450 enzyme system. Relevant interactions are unlikely (Rizk 2014). Thus, raltegravir remains an option for interaction-prone co-medication, such as tuberculosis (Grinsztejn 2014) or chemotherapies. Combination with rifampicin seems possible (Wenning 2009). However, raltegravir levels increase 3–4-fold when PPIs such as omeprazole are given concomitantly – but the clinical relevance is unclear (Iwamoto 2009).
Raltegravir is an excellently tolerated drug with good efficacy and low interaction potential. A disadvantage is that it is not available in fixed combinations. In addition, the resistance barrier is lower than for second-generation INSTIs.

Literature on integrase inhibitors

Aboud M, Orkin C, Podzamczer D, et al. Efficacy and safety of dolutegravir-rilpivirine for maintenance of virological suppression in adults with HIV-1: 100-week data from the randomised, open-label, phase 3 SWORD-1 and SWORD-2 studies. Lancet HIV 2019, 6:e576-e587.

Anderson MS, Kakuda TN, Hanley W, et al. Minimal pharmacokinetic interaction between the human immunodeficiency virus nonnucleoside reverse transcriptase inhibitor etravirine and the integrase inhibitor raltegravir in healthy subjects. Antimicrob Agents Chemother 2008, 52:4228-32.

Anstett K, Brenner B, Mesplede T, Wainberg MA. HIV drug resistance against strand transfer integrase inhibitors. Retrovirology 2017, 14:36.

Arribas JR, Pialoux G, Gathe J, et al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. Lancet Infect Dis 2014, 14:581-9.

Cahn P, Kaplan R, Sax PE, et al. Raltegravir 1200 mg once daily versus raltegravir 400 mg twice daily, with tenofovir disoproxil fumarate and emtricitabine, for previously untreated HIV-1 infection: a randomised, double-blind, parallel-group, phase 3, non-inferiority trial. Lancet HIV 2017, 4:e486-e494.

Cahn P, Madero JS, Arribas JR, et al. Durable Efficacy of Dolutegravir Plus Lamivudine in Antiretroviral Treatment-Naive Adults With HIV-1 Infection: 96-Week Results From the GEMINI-1 and GEMINI-2 Randomized Clinical Trials. J AIDS 2019 Dec 10.

Cahn P, Pozniak AL, Mingrone H, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet 2013, 382:700-8.

Castagna A, Ferrara M, Galli L, et al. Long-term efficacy of dolutegravir in treatment-experienced subjects failing therapy with HIV-1 integrase strand inhibitor-resistant virus. J Antimicrob Chemother. 2017 Oct 24.

Castagna A, Maggiolo F, Penco G, et al. VIKING-3 Study Group. Dolutegravir in Antiretroviral-Experienced Patients With Raltegravir- and/or Elvitegravir-Resistant HIV-1: 24-Week Results of the Phase III VIKING-3 Study. J Infect Dis 2014, 210:354-62.

Cattaneo D, Gervasoni C, Meraviglia P. Inter- and intra-patient variability of raltegravir pharmacokinetics in HIV-1-infected subjects. J Antimicrob Chemother 2012, 67:460-4.

Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet 2014, 383:2222-31.

Cooper DA, Steigbigel RT, Gatell JM, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. NEJM 2008, 359:355-65.

Daar ES, DeJesus E, Ruane P, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1. Lancet HIV 2018;5:e347-e356.

De Boer MG, van den Berk GE, van Holten N, Oryszcyn JE, Dorama W, Moha DA, Brinkman K. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. AIDS 2016, 30:2831-2834.

DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection. Lancet 2012, 379:2429-38.

Delelis O, Thierry S, Subra F, et al. Impact of Y143 HIV-1 integrase mutations on resistance to raltegravir in vitro and in vivo. Antimicrob Agents Chemother 2010, 54:491-501.

Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J AIDS 2013, 62:21-7.

Dori L, Buonomini AR, Viscione M, Sarmati L, Andreoni M. A case of rhabdomyolysis associated with raltegravir use. AIDS 2010, 24:473-5.

Elion R, Molina JM, et al; Study 145 Team. A randomized phase 3 study comparing once-daily elvitegravir with twice-daily raltegravir in treatment-experienced subjects with HIV-1 infection: 96-week results. J AIDS 2013, 63:494-7.

Engelman AN, Singh PK. Cellular and molecular mechanisms of HIV-1 integration targeting. Cell Mol Life Sci 2018, 75:2491-2507.

Eron J, Hung CC, Baril JG, et al. Virologic Response by Baseline Viral Load With Dolutegravir Plus Lamivudine vs Dolutegravir Plus Tenofovir Disoproxil Fumarate/Emtricitabine: Pooled Analysis. J Acquir Immune Defic Syndr. 2020 Jan.

Eron JJ Jr, Rockstroh JK, Reynes J, et al. Raltegravir once daily or twice daily in previously untreated patients with HIV-1: a randomised, active-controlled, phase 3 non-inferiority trial. Lancet Infect Dis 2011, 11:907-15.

Eron JJ, Clotet B, Durant J, et al. Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. J Infect Dis 2013, 207:740-8.

Eron JJ, Cooper DA, Steigbigel RT, et al. Efficacy and safety of raltegravir for treatment of HIV for 5 years in the BENCHMRK studies: final results of two randomised, placebo-controlled trials. Lancet Infect Dis 2013, 13:587-96.

Eron JJ, Young B, Cooper DA, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1+2): two multicentre, double-blind, randomised controlled trials. Lancet 2010, 375:396-407.

Ford SL, Lou Y, Lewis N, et al. Effect of rifabutin on the pharmacokinetics of oral cabotegravir in healthy subjects. Antivir Ther 2019, 24:301-308.

Gallant JE, Thompson M, DeJesus E, et al. Antiviral Activity, Safety, and Pharmacokinetics of Bictegravir as 10-Day Monotherapy in HIV-1-Infected Adults. JAIDS 2017, 75:61-66.

Gatell JM, Assoumou L, Moyle G, et al. Switching from a ritonavir-boosted protease inhibitor to a dolutegravir-based regimen for maintenance of HIV viral suppression in patients with high cardiovascular risk. AIDS 2017, 31:2503-2514.

Grinsztejn B, De Castro N, Arnold V, et al. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial. Lancet Infect Dis 2014, 14:459-67.

Hagins D, Kumar P, Saag M, et al. Switching to Bictegravir/Emtricitabine/Tenofovir Alafenamide in Black Americans With HIV-1: A Randomized Phase 3b, Multicenter, Open-Label Study. J Acquir Immune Defic Syndr 2021, 88:86-95.

Harris M, Larsen G, Montaner JS. Outcomes of multidrug-resistant patients switched from enfuvirtide to raltegravir within a virologically suppressive regimen. AIDS 2008, 22:1224-1226.

Hazuda DJ, Felock P, Witmer M, et al. Inhibitors of strand transfer that prevent integration and inhibit HIV-1 replication in cells. Science 2000, 287:646-50.

Hightower KE, Wang R, Deanda F, et al. Dolutegravir (S/GSK1349572) exhibits significantly slower dissociation than raltegravir and elvitegravir from wild-type and integrase inhibitor-resistant HIV-1 integrase-DNA complexes. Antimicrob Agents Chemother 2011, 55:4552-9.

Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? J Virus Erad 2019, 5:41-43.

Hoffmann C, Llibre JM. Neuropsychiatric Adverse Events with Dolutegravir and Other Integrase Strand Transfer Inhibitors. AIDS Rev 2019;21:4-10.

Hoffmann C, Schewe K, Fenske S, et al. Short-term neuropsychiatric tolerability of bictegravir combined with emtricitabine/tenofovir alafenamide in clinical practice. Antivir Ther 2020, 25:83-90.

Hoffmann C, Welz T, Sabranski M, Kolb M, Wolf E, Stellbrink HJ, Wyen C. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Medicine 2017, 18:56-63.

Iwamoto M, Wenning LA, Nguyen BY, et al. Effects of omeprazole on plasma levels of raltegravir. Clin Infect Dis 2009, 48: 489-492.

Jaeger H, Overton ET, Richmond G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 96-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. Lancet HIV. 2021, 8:e679-e689.

Kityo C, Hagins D, Koenig E, et al. Switching to Fixed-Dose Bictegravir, Emtricitabine, and Tenofovir Alafenamide (B/F/TAF) in Virologically Suppressed HIV-1 Infected Women: A Randomized, Open-Label, Multicenter, Active-Controlled, Phase 3, Noninferiority Trial. J AIDS 2019, 82:321-328.

Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. NEJM 2021, 385:595-608.

Lennox JL, Landovitz RJ, Ribaudo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. Ann Intern Med 2014, 161:461-71.

Maggiolo F, Rizzardini G, Molina JM, et al. Bictegravir/emtricitabine/tenofovir alafenamide in older individuals with HIV: Results of a 96-week, phase 3b, open-label, switch trial in virologically suppressed people ≥65 years of age. HIV Med 2022 May 8.

Margolis DA, Brinson CC, Smith GH, et al. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. Lancet Inf Dis 2015, 15:1145-55.

Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet 2017, 390:1499.

Martínez E, Larrousse M, Llibre JM, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. AIDS 2010, 24:1697-707.

Miller M, Barnard R, Witmer M, et al. Short-term raltegravir monotherapy does not predispose patients to develop RAL resistance during subsequent combination therapy: analysis of samples from protocol 004. Abstract 557, 17th CROI 2010, San Francisco.

Mills A, Arribas JR, Andrade-Villanueva J, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection. Lancet Infect Dis 2016; 16:43–52.

Min S, Sloan L, DeJesus E, Hawkins T, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults. AIDS 2011, 25:1737-45.

Molina JM, Ward D, Brar I, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1. Lancet HIV 2018;5:e357-e365.

Nair V. HIV integrase as a target for antiviral chemotherapy. Rev Med Virol 2002, 12:179-93.

Nguyen T, McNicholl I, Custodio JM, et al. Drug Interactions with Cobicistat- or Ritonavir-Boosted Elvitegravir. AIDS Rev 2016, 18:101-111.

Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-Acting Cabotegravir and Rilpivirine after Oral Induction for HIV-1 Infection. N Engl J Med 2020, 382:1124-1135.

Orkin C, Oka S, Philibert P, et al. Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study. Lancet HIV 2021, 8:e185-e196.

Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA). Lancet HIV 2017;4:e536-e546.

Parasrampuria R, Ford SL, Lou Y, et al. A Phase I Study to Evaluate the Pharmacokinetics and Safety of Cabotegravir in Adults With Severe Renal Impairment and Healthy Matched Control Participants. Clin Pharmacol Drug Dev 2019, 8:674-681.-1510.

Pozniak A, Arribas JR, Gathe J, et al. Switching to Tenofovir Alafenamide, Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, in HIV-Infected Patients With Renal Impairment: 48-Week Results From a Single-Arm, Multicenter, Open-Label Phase 3 Study. J AIDS 2016, 71:530-7.

Pozniak A, Markowitz M, Mills A, et al. Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority trial. Lancet Infect Dis 2014, 14:590-9.

Raffi F, Jaeger H, Quiros-Roldan E, et al; extended SPRING-2 Study Group. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naïve adults with HIV-1 infection (SPRING-2 study): 96-week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis 2013, 13:927-35.

Rajoli RK, Curley P, Chiong J, et al. Predicting Drug-Drug Interactions Between Rifampicin and Long-Acting Cabotegravir and Rilpivirine Using Physiologically Based Pharmacokinetic Modeling. J Infect Dis 2019, 219:1735-42.

Rizk ML, Houle R, Chan GH, Hafey M, Rhee EG, Chu X. Raltegravir has a low propensity to cause clinical drug interactions through inhibition of major drug transporters: an in vitro evaluation. Antimicrob Agents Chemother 2014, 58:1294-301.

Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. J AIDS 2013, 63:77-85.

Saladini F, Giannini A, Boccuto A, et al. Comparable In Vitro Activities of Second-Generation HIV-1 Integrase Strand Transfer Inhibitors (INSTIs) on HIV-1 Clinical Isolates with INSTI Resistance Mutations. Antimicrob Agents Chemother. 2019 Dec 20;64(1).

Sato M, Motomura T, Aramaki H, et al. Novel HIV-1 integrase inhibitors derived from quinolone antibiotics. J Med Chem 2006, 49:1506-8.

Sax PE, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet 2012, 379:2439-48.

Sax PE, Erlandson KM, Lake JE, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. Clin Infect Dis 2019 Oct 14. pii: ciz999.

Sax PE, Rockstroh JK, Luetkemeyer AF, et al. Switching to Bictegravir, Emtricitabine, and Tenofovir Alafenamide in Virologically Suppressed Adults With Human Immunodeficiency Virus. Clin Infect Dis 2021, 73:e485-e493.

Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet 2015, 385:2606-15.

Shimura K, Kodama E, Sakagami Y, et al. Broad antiretroviral activity and resistance profile of the novel human immunodeficiency virus integrase inhibitor elvitegravir (JTK-303/GS-9137). J Virol 2008;82:764-74.

Siliciano R. New approaches for understanding and evaluating the efficacy of ARVs. Abstract 16, 16th CROI 2009 Montréal.

Smith GHR, Henry WK, Podzamczer D, et al. Efficacy, Safety, and Durability of Long-Acting Cabotegravir and Rilpivirine in Adults With Human Immunodeficiency Virus Type 1 Infection: 5-Year Results From the LATTE-2 Study. Open Forum Infect Dis. 2021, 8:ofab439.

Smith SJ, Zhao XZ, Burke TR Jr, et al. Efficacies of Cabotegravir and Bictegravir against drug-resistant HIV-1 integrase mutants. Retrovirology 2018, 15:37.

Song I, Borland J, Chen S, et al. Effect of Atazanavir and Atazanavir/Ritonavir on the Pharmacokinetics of the Next-Generation HIV Integrase Inhibitor, S/GSK1349572. Br J Clin Pharmacol 2011, 72:103-8.

Song I, Borland J, Chen S, et al. Effect of food on the pharmacokinetics of the integrase inhibitor dolutegravir. Antimicrob Agents Chemother 2012, 56:1627-9.

Song I, Borland J, Min S, et al. The effect of etravirine alone and with ritonavir-boosted protease inhibitors on the pharmacokinetics of dolutegravir. Antimicrob Agents Chemother 2011, 55:3517-21.

Spreen W, Min S, Ford SL, et al. Pharmacokinetics, safety, and monotherapy antiviral activity of GSK1265744, an HIV integrase strand transfer inhibitor. HIV Clin Trials 2013, 14:192-203.

Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. NEJM 2008, 359:339-354.

Stellbrink HJ, Arribas JR, Stephens JL, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection. Lancet HIV 2019;6:e364-e372.

Stellbrink HJ, Hoffmann C. Cabotegravir: its potential for antiretroviral therapy and preexposure prophylaxis. Curr Opin HIV AIDS 2018, 13:334-340.

Stellbrink HJ, Reynes J, Lazzarin A, et al. Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. AIDS 2013, 27:1771-8.

Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression. N Engl J Med 2020, 382:1112-1123.

Trottier B, Lake JE, Logue K, et al. Dolutegravir/abacavir/lamivudine versus current ART in virally suppressed patients (STRIIVING): a 48-week, randomized, non-inferiority, open-label, Phase IIIb study. Antivir Ther 2017, 22:295-305.

Tsiang M, Jones GS, Goldsmith J, et al. Antiviral activity of bictegravir (GS-9883), a novel potent integrase strand transfer inhibitor with an improved resistance profile. Antimicrob Agents Chemother 2016, 60:7086-7097.

Tsukada K, Teruya K, Tasato D, et al. Raltegravir-associated perihepatitis and peritonitis: a single case report. AIDS 2010, 24:160-1.

Van Wyk J, Ajana F, Bisshop F, et al. Efficacy and Safety of Switching to Dolutegravir/Lamivudine Fixed-Dose Two-Drug Regimen Versus Continuing a Tenofovir Alafenamide-Based Three- or Four-Drug Regimen for Maintenance of Virologic Suppression in Adults With HIV-1: Phase 3, Randomized, Non-inferiority TANGO Study. Clin Infect Dis. 2020 Jan 6.

Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med 2019, 381:803-815.

Walmsley SL, Antela A, Clumeck N, et al; SINGLE Investigators. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med 2013, 369:1807-18.

Wenning LA, Hanley WD, Brainard DM, et al. Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. Antimicrob Agents Chemother 2009, 53:2852-6.

Wirden M, Simon A, Schneider L, et al. Raltegravir has no residual antiviral activity in vivo against HIV-1 with resistance-associated mutations to this drug. J Antimicrob Chemother. 2009, 64:1087-90.

Wohl D, Clarke A, Maggiolo F, et al. Patient-Reported Symptoms Over 48 Weeks Among Participants in Randomized, Double-Blind, Phase III Non-inferiority Trials of Adults with HIV on Co-formulated Bictegravir, Emtricitabine, and Tenofovir Alafenamide versus Co-formulated Abacavir, Dolutegravir, and Lamivudine. Patient 2018, 11:561-573.

Wohl DA, Yazdanpanah Y, Baumgarten A, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet HIV 2019;6:e355-e363.

Zash R, Holmes L, Diseko M, et al. Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. N Engl J Med 2019, 381:827-840.

Zolopa AR, Berger DS, Lampiris H, et al. Activity of elvitegravir, a once-daily integrase inhibitor, against resistant HIV Type 1: results of a phase 2, randomized, controlled, dose-ranging clinical trial. J Infect Dis 2010, 201:814-22.

Entry inhibitors

Mode of action

There are three key sites in the entry of HIV into the CD4 T-cell:
1. Binding via the envelope protein gp120 to the CD4 receptor ("attachment").
2. Binding to co-receptors,
3. The fusion of virus and cell

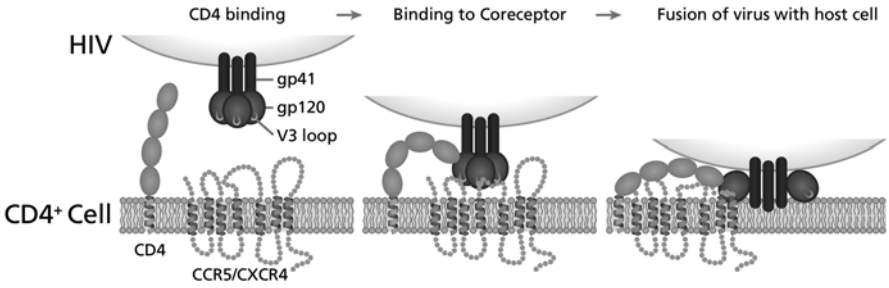

Figure 1: HIV entry into the CD4 host cell showing the three crucial steps.

All three entry steps can be inhibited. Step 1 is inhibited by attachment inhibitors, step 2 by co-receptor antagonists, and step 3 by fusion inhibitors. All three drug classes are called entry inhibitors. Entry inhibitors were the fourth drug class in antiretroviral therapy after NRTIs, NNRTIs, and PIs. Unlike the other classes, they do not act intracellularly but instead start earlier in the replication cycle of HIV – a circumstance that hopefully improves tolerability. With maraviroc, T-20, ibalizumab, and fostemsavir, four fundamentally different agents are now on the market, discussed here. For further entry inhibitors, especially the exciting field of broadly neutralizing antibodies, please refer to the coming ART chapter, 2024/2025.

Attachment Inhibitors

The docking of the HIV glycoprotein gp120 to the CD4 receptor is the first step in HIV entry. Theoretically, the docking (attachment) or interaction of gp120 and CD4 can be inhibited in various ways – for example, both the CD4 receptor and the binding site of gp120 can be blocked. Consequently, the attachment inhibitors are heterogeneous, and it is impossible to speak of a single substance class. In the early 1990s, experiments were conducted with soluble molecules that prevent the docking of HIV to CD4 T-cells (Daar 1990, Schooley 1990). Unfortunately, what initially looked good in the laboratory did not work in humans, probably due to the short half-life of soluble CD4 (a few minutes). Polymorphisms in the gp120 gene can cause natural resistance in some viruses (Charpentier 2012).

Individual agents

Fostemsavir (Rukobia®, GSK3684934, formerly **BMS-663068)** is a prodrug of BMS's attachment inhibitor **temsavir** (BMS-6265209). It is a successor to BMS-488043, which was stopped in 2004. As a "small molecule" it binds reversibly to gp120 of HIV and prevents a conformational change of this molecule, which is necessary for docking to the CD4 T-cell. Thus, it does not bind to the CD4 receptor-like ibalizumab (see below), but to the virus. The effect extends across R5 and X4-tropic viruses. Viral load in monotherapy decreases between 1.2 and 1.8 logs (Nettles 2012). Unfortunately, significant interindividual variations were seen. In a Phase IIb trial, 251 pre-treated individuals with at least 1,000 copies/mL viremia received TDF,

raltegravir, and various doses of fostemsavir (600–1,200 mg) or atazanavir/r. In the experimental arms, approximately 70% achieved viral suppression comparable to the control arm (Thompson 2017).

Since fostemsavir inhibits various transporter proteins (including those for statins), interactions are to be expected, and dose adjustments are necessary (Landry 2016). Another problem could be the rapid development of resistance; the binding site of gp120 is one of the most variable sites. Resistance was found in some individuals who had never been treated with attachment inhibitors due to natural polymorphisms in the gp120 gene (Charpentier 2012). The resistances have been characterized in more detail (Zhou 2013) and probably involve HIV subtype O (Alessandri-Gradt 2018). No cross-resistance appears to exist to other entry inhibitors. However, in the above Phase II study, resistance occurred more frequently in the fostemsavir arm (predominantly affecting raltegravir) than with atazanavir (Lataillade 2017).

In the meantime, the substance was acquired by ViiV Healthcare. The trend is sharply toward salvage therapy: in the Phase III BRIGHTE trial, 371 pre-treated individuals with treatment failure (> 400 copies/mL) and three-class failure were treated with fostemsavir and optimized background ART. All were intensively treatment-experienced, with less than half still having more than one active agent available. After 96 weeks (Lataillade 2020), 60% achieved a viral load below 40 copies/mL, compared with 37% in the subgroup with no option. The response rates were not only dependent on the number of active agents in the optimized adjuvant ART but also on viral load and CD4 T-cells. The higher the viremia, the lower the CD4 T-cells the lower the rates (Ackerman 2021).

Overall, tolerability of fostemsavir is good, with rare side effects beyond grade 1 and predominantly gastrointestinal and headache.

In early 2021, the EMA granted approval for "adults with multidrug-resistant HIV-1 infection for whom no other suppressive antiretroviral treatment regimen is available." This has made fostemsavir a potentially important salvage option. Given the sharply limited indication and the twice-daily administration, fostemsavir has led to a niche existence. The full potential of this compound may never be realized.

Ibalizumab (formerly **TNX-355**, **Trogarzo®**) is a monoclonal antibody that binds directly to the CD4 receptor, preventing HIV entry. It must be infused, in the case of ibalizumab, at two-week intervals for 30–60 minutes each. Unlike other attachment inhibitors, ibalizumab does not appear to prevent the binding of gp120 to CD4 but rather the subsequent conformational change and, thus, the binding of gp120 to CCR5 and CXCR4. Thus, it is more of a post-attachment inhibitor. One question is whether the functionality of CD4 T-cells is affected. Reportedly, the binding site of ibalizumab to CD4 is also localized differently from the binding sites of the natural CD4 ligands, the HLA class II molecules. Thus, CD4 T-cells should be able to perform their normal functions. Developed first by Biogen starting in 1997, then by Tanox, TaiMed Biologics, and most recently Theratechnologies, ibalizumab is the antibody with the most clinical experience.

In a placebo-controlled Phase II study (Norris 2006), intensively pre-treated patients received an infusion of two different doses (10 or 15 mg/kg) or placebo every two weeks in addition to optimized ART. After 48 weeks, there was a sustained viral load decline of approximately one log level in both active arms. In a Phase IIb study, ibalizumab was given every 2 or 4 weeks in 113 intensively pre-treated patients. At week 24, 59% and 31% achieved viral loads below 50 copies/mL (Khanlou 2011). In another study, 43% of 40 intensively pre-treated individuals achieved a viral load below 50 copies/mL after 24 weeks – with bi-weekly infusions. Virologic success mainly persisted for 48 weeks (Emu 2018). Tolerability was good. Subcutaneous administration

is also being studied but may be somewhat weaker (Lin 2017). Likely, bolus administration is also possible instead of infusions (DeJesus 2022).
Trogarzo® was approved in the EU in September 2019 for the treatment of people with "multidrug-resistant HIV for whom no other suppressive regimen can be composed". However, given the low numbers of these cases, the annual therapy costs of more than 100,000 euros, and the required biweekly infusions, very few patients received the infusions in Europe.
Unfortunately, Theratech decided to withdraw the drug from the market and focus on North America because "the pricing and reimbursement conditions in key European countries were not satisfactory". For the few cases in which ibalizumab is still necessary, an import on a named patient basis is possible. In this case, it is essential to clarify the coverage of costs by the health insurance company beforehand. With the introduction of fostemsavir and lenacapavir, two new options have become available, probably making ibalizumab less important.

Co-receptor antagonists

In addition to the CD4 receptor, HIV needs so-called co-receptors to enter the target cell. The two most essential co-receptors are CCR5 and CXCR4, discovered in the mid-1990s (Alkhatib 1996, Deng 1996, Doranz 1996). They were named after the natural chemokines that generally bind to them. Their nomenclature is derived from the amino acid sequence. For CCR5 receptors, it is the "CC chemokines" MIP and RANTES; for CXCR4 receptors, it is the "CXC chemokine" SDF-1. HIV variants use either CCR5 or CXCR4 receptors for entry into the target cell and are referred to as R5 or X4 viruses, respectively. R5 viruses predominantly infect macrophages (formerly "M-tropic" viruses), while X4 viruses predominantly infect T cells (formerly "T-tropic" viruses). "Dual-tropic" viruses can use both receptors; there are mixed populations of R5 and X4 viruses. In most people with HIV infection, R5 viruses are found in the early stages; X4 viruses, which can probably also infect a broader range of cells, appear later. They are also found almost exclusively in X4/R5 mixed populations. The R5 to X4 tropism change is often accompanied by disease progression (Connor 1997, Scarlatti 1997).
In some individuals, there is congenital reduced expression of the CCR5 receptor. This is due to a 32-base pair deletion in the CCR5 gene (Δ32 mutation). People with such a gene defect are less likely to become infected with HIV, and if infected, progression to AIDS is slower (Dean 1996, Liu 1996, Samson 1996). The absence of the CCR5 receptor due to this gene defect remains largely without disease significance. Drug-induced CCR5 receptor blockade by CCR5 (co-receptor) antagonists is an attractive therapeutic target. In 2008, the case of an HIV patient with acute myeloid leukemia and allogeneic stem cell transplantation whose healthy stem cell donor was homozygous for the Δ32 mutation was published. After transplantation, the viral load remained below the detection limit for more than ten years without ART (Hütter 2009, Allers 2011).
In therapy-naive people, R5 populations are present in about 80–90%; in pre-treated patients, it is about 50% (Hoffmann 2007). Receptor tropism correlates with the stage of infection. The higher the CD4 T-cells and the lower the viral load, the more likely R5 viruses are present. In contrast, pure X4 populations are almost only present in advanced disease stages. Above 500 CD4 T-cells/µl, they are found in only 6%, but at less than 25 CD4 T-cells/µl, they are found in over 50% (Brumme 2005), which is why CCR5 antagonists should be used rather early in the disease course. They are often unsuitable as a salvage strategy for advanced infection (and X4 viruses).

Tropism testing

Although CCR5 antagonists seem not to have adverse effects in X4/R5 mixed populations (see below), for cost reasons, testing before therapy is necessary to clarify whether the use of a CCR5 antagonist makes sense (see *Resistance*).

Commercial assays are available for *phenotypic* tropism determination, but they are laborious, succeed only with a minimum of 500–1,000 virus copies/mL, and take several weeks. The technically simpler and more cost-effective *genotypic* tropism determination has been validated and largely replaced phenotypic testing in routine testing. Since 2013, it has been a health insurance benefit. It focuses on the V3 loop of the envelope protein gp120, as HIV binds to the co-receptor with this region. However, tropism does not appear to be determined solely by the sequence of the V3 loop – viruses with identical V3 loops can differ in tropism (Low 2007). A significant advantage of genotypic testing is that it is also possible and valid from proviral DNA and thus in the presence of viral suppression. Measurement from proviral DNA examines the genetic material of HIV integrated into the genome of infected cells (Soulié 2010, Poveda 2017).

Tropism shift and other consequences

Under CCR5 antagonists, a selection-related shift toward X4 viruses is observed in patients with virologically unsuccessful therapy. These X4-tropic viruses are likely selected from pre-existing pools (Westby 2006). In a pilot study in which infected individuals with X4/R5 mixed populations received maraviroc, CD4 T-cells increased compared with placebo (Saag 2009) – so HIV progression while on CCR5 antagonists caused by the X4 shift seems rather unlikely.

Although people with the congenital Δ32 gene defect are generally healthy, there are fears that blocking the co-receptor with drugs will have negative consequences. After all, this chemokine receptor must be good for something. People with the Δ32 deletion have been investigated in countless studies to determine whether certain diseases are more frequent (or less frequent) in them. There is no clear association – the most intense discussion has been of an increased incidence of West Nile virus infections (Glass 2006). A meta-analysis found no adverse effects of maraviroc on immune function (Ayoub 2007). Because the Δ32 deletion appears protective for rheumatoid arthritis (Prahalad 2006), maraviroc has been tested in rheumatoid arthritis, but without success.

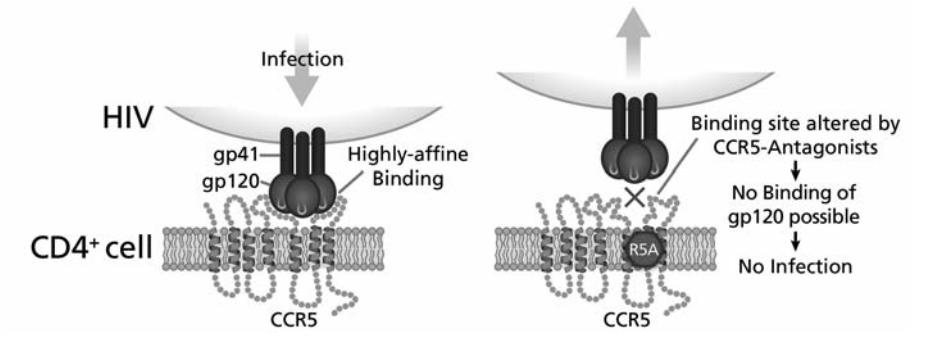

Figure 2: Effect of the allosteric CCR5 antagonist maraviroc. Binding into a transmembrane pocket spatially alters the receptor molecule, making it impossible for the viral protein gp120 to bind to the receptor. Thus, the receptor is not simply occupied. R5A = CCR5 antagonist.

Early observations of excellent CD4 T-cell increases under maraviroc led to the hypothesis that CCR5 antagonists might serve as immune modulators. However, a meta-analysis found no evidence of improved immune reconstitution (Pichenot 2012). In ANRS 146 (OPTIMAL), additional administration in 409 late presenters with AIDS or low helper cells resulted in no immunologic, virologic, or clinical benefits (Lelievre 2017).

Individual agents

Maraviroc (Celsentri®, US: Selzentry®) was the first and only CCR5 antagonist approved for the treatment of HIV infection in September 2007. Maraviroc binds allosterically to the receptor (Figure 2). With maraviroc monotherapy, the viral load fell by approximately 1.6 log levels after 10–15 days (Fätkenheuer 2005). Maraviroc is ineffective against non-R5 viruses; however, CD4 T-cells surprisingly increased in one study (Saag 2009). Two almost identical Phase III trials, MOTIVATE-1 and -2, led to the approval of maraviroc. These enrolled 1,049 patients with R5 viruses and at least 5,000 copies/mL who were either pre-treated with three classes and/or had viral resistance to three classes (Gulick 2008, Fätkenheuer 2008). Maraviroc was administered either 300 mg once daily, 150 mg twice daily, or placebo to an optimized therapy – in which, however, agents such as darunavir or raltegravir were not allowed. After 48 weeks, the proportions with a viral load below 50 copies/mL were significantly higher in the maraviroc arms than on placebo (46% and 43% vs. 17%, respectively). The effect was also seen in high viral load and multiple resistance (Fätkenheuer 2008) and remained stable over 96 weeks (Hardy 2010). Tolerability did not differ from placebo. Moreover, the selection-induced shift to X4 viruses, observed in half without virological therapeutic success, had no adverse consequences.

Maraviroc has also been tested in treatment-naïve patients (Cooper 2010, Sierra-Madero 2010). In the MERIT trial, 721 subjects received either efavirenz or maraviroc 300 mg twice daily in addition to AZT+3TC (a once-daily arm was stopped early due to poor efficacy). Virologic failure was observed more frequently (12% versus 4%). Although CD4 T-cells increased more significantly, non-inferiority to efavirenz was not achieved. Surprisingly, the difference in efficacy was observed only in Southern Hemisphere countries. The retrospective analysis also showed that nearly 4% had shown a shift from R5- to dual-tropic virus in the weeks between screening and baseline. Among these people, the response was particularly poor. According to retrospective studies, the difference between maraviroc and efavirenz would not have been relevant with better tropism testing (Cooper 2010). The FDA approved Maraviroc in November 2009, including treatment-naïve patients. In Europe, EMA did not consider this data sufficient, and approval remained restricted to pre-treated patients. Consequently, ViiV has tried tirelessly to find new ways to establish maraviroc for broader patient groups. In 2014, the MODERN trial, an attempt to use the drug in a nuke-sparing strategy with maraviroc+darunavir/r as first-line therapy, had to be terminated prematurely. The effect was somewhat weaker than standard therapy (Stellbrink 2016). The approach of PI/r and maraviroc also proved inferior to standard therapy in pre-treated patients (Rossetti 2017, Pett 2018).

Maraviroc is well tolerated, even with long-term use (Gulick 2014). In MERIT, discontinuation rates due to adverse events were only 4% vs. 14% with efavirenz. Lipid profiles were also more favorable (MacInnes 2011).

Data on resistance are limited. Mutations in the genes responsible for the V3 loop of the envelope protein gp120 provide complete resistance, and the viruses can remain R5-tropic – so a shift to X4 is unnecessary. The mutations are primarily localized at the tip of the loop. They could help the virus either bind to the CCR5 recep-

tor spatially altered by maraviroc or increase the affinity of the viruses for unbound CCR5 receptors (Westby 2007). Overall, the resistance barrier appears relatively high (Jubb 2009). Importantly, for practice, the recommended maraviroc dose is based on the concomitant therapy. For boosted PIs (except tipranavir), the usual dose of 2 x 300 mg is halved, whereas for efavirenz (or other enzyme inducers such as rifampicin or carbamazepine), it must be doubled. No dose adjustments are necessary with INSTIs. Given the need for tropism testing, the limited approval (in Europe), and the not entirely straightforward dosing, the use of maraviroc in HIV therapy remains limited despite its excellent tolerability.

Fusion Inhibitors

Fusion inhibitors prevent the final step of HIV's entry into the target cell. This fusion of virus and cell is complex. After binding to the CD4 and co-receptor, a conformational change is triggered in the viral transmembrane protein gp41. This gp41 protein then impales a hairpin-like junction into the cell membrane, its two "arms" – the C-terminal region anchored in the virus, the N-terminal region hooked to the cell membrane – folding together to pull the virus envelope and cell membrane toward each other. Just before folding, gp41 is in an intermediate position: the two arms are unfolded for a moment – forming targets for fusion inhibitors (Root 2001).

Individual agents

T-20 (enfuvirtide, Fuzeon®) is the prototype among FIs and has been approved in Europe since May 2003 in antiretroviral pre-treated adults. As a relatively large peptide, it must be injected subcutaneously daily. T-20 binds to the intermediate structure of the HIV protein gp41, which is formed when HIV fuses with the target cell. In early studies of intravenous monotherapy, the viral load fell by 1.6–2 logs in a dose-dependent manner (Kilby 1998+2002).

Two Phase III trials in 995 intensively pre-treated patients with mostly multidrug-resistant viruses led to the approval of subcutaneous administration (Lalezari 2003, Lazzarin 2003). In TORO-1, the viral load decreased by 0.94 log levels after 48 weeks, and in TORO-2 by 0.78 log (Nelson 2005). In other studies, T-20 showed a virological benefit (see *Salvage Therapy*) with tipranavir, darunavir, maraviroc, or raltegravir.

An unexpected finding in the TORO trials was the accumulation of lymphadenopathies and bacterial pneumonia (Trottier 2005). The binding of T-20 to granulocytes is suspected as the cause. Major side effects are the obligatory (98% in TORO), often painful skin reactions at the injection sites. Many patients refuse to continue with T-20 at some point (see *Side Effects* section). The development of a bioinjection system in which T-20 is pressed into the skin has been discontinued. Injecting the double dose only once daily is not recommended: trough levels are too low (Thompson 2006).

Resistance occurs relatively quickly but appears to reduce viral fitness (Lu 2002). Point mutations affecting a short sequence in the gp41 gene are sufficient (Mink 2005). Since T-20 is a large peptide, antibodies are produced. However, these do not impair efficacy (Walmsley 2003).

Can latent reservoirs be emptied with T-20? After initially positive reports, more recent studies dashed these hopes (Gandhi 2010, Morand-Joubert 2012). Cost also remains an important issue. Due to the complex manufacturing process – according to the company, T-20 is "one of the most complicated agents" ever produced – the price of ART is much higher.

Overall, due to the cumbersome application process, T-20 practically no longer plays a role. In salvage, it can be valuable in individual cases, but it can almost always be replaced by INSTIs (De Castro 2009, Grant 2009).

Literature on (approved) entry inhibitors

Ackerman P, Thompson M, Molina JM, et al. Long-term efficacy and safety of fostemsavir among subgroups of heavily treatment-experienced adults with HIV-1. AIDS 2021, 35:1061-1072.

Alessandri-Gradt E, Charpentier C, Leoz M, et al. Impact of natural polymorphisms of HIV-1 non-group M on genotypic susceptibility to the attachment inhibitor fostemsavir. J Antimicrob Chemother 2018, 73:2716-2720.

Alkhatib G, Combadiere C, Broder CC, et al. CC CKR5: a RANTES, MIP-1alpha, MIP-1beta receptor as a fusion cofactor for macrophage-tropic HIV-1. Science 1996;272:1955-8.

Allers K, Hütter G, Hofmann J, et al. Evidence for the cure of HIV infection by CCR5Δ32/Δ32 stem cell transplantation. Blood 2011, 117:2791-9.

Ayoub A, van der Ryst E, Turner K, McHale M. A review of the markers of immune function during the maraviroc phase 1 and 2a studies. Abstract 509, 14th CROI 2007, Los Angeles.

Brumme ZL, Goodrich J, Mayer HB, et al. Molecular and clinical epidemiology of CXCR4-using HIV-1 in a large population of antiretroviral-naive individuals. J Infect Dis 2005, 192:466-74.

Charpentier C, Larrouy L, Visseaux B, et al. Prevalence of subtype-related polymorphisms associated with in vitro resistance to attachment inhibitor BMS-626529 in HIV-1 'non-B'-infected patients. J Antimicrob Chemother. 2012 Mar 1. [Epub ahead of print].

Connor RI, Sheridan KE, Ceradini D, Choe S, Landau NR. Change in coreceptor use coreceptor use correlates with disease progression in HIV-1—infected individuals. J Exp Med 1997, 185:621-8.

Cooper DA, Heera J, Goodrich J, et al. Maraviroc versus Efavirenz, Both in Combination with Zidovudine-Lamivudine, for the Treatment of Antiretroviral-Naive Subjects with CCR5-Tropic HIV-1 Infection. J Infect Dis 2010, 201:803-13.

De Castro N, Braun J, Charreau I, et al. Switch from enfuvirtide to raltegravir in virologically suppressed multidrug-resistant HIV-1-infected patients: a randomized open-label trial. Clin Infect Dis 2009, 49:1259-67.

Dean M, Carrington M, Winkler C, et al. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Science 1996;273:1856-62.

DeJesus E, Richmond G, Merhe M, et al. IV push administration of Ibalizumab: Pharmacokinetics, safety, and efficacy. Abstract 429, CROI 2022.

Deng H, Liu R, Ellmeier W, et al. Identification of a major co-receptor for primary isolates of HIV-1. Nature 1996;381:661-6.

Doranz BJ, Rucker J, Yi Y, et al. A dual-tropic primary HIV-1 isolate that uses fusin and the beta-chemokine receptors CKR-5, CKR-3, and CKR-2b as fusion cofactors. Cell 1996;85:1149-58.

Emu B, Fessel J, Schrader S, et al. Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1. N Engl J Med 2018, 379:645-654.

Fätkenheuer G, Nelson M, Lazzarin A. Subgroup analysis of maraviroc in previously treated R5 HIV-1 infection. N Engl J Med 2008, 359:1442-1455.

Fätkenheuer G, Pozniak AL, Johnson MA, et al. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1. Nat Med 2005, 11:1170-2.

Gandhi RT, Bosch RJ, Aga E, et al. No evidence for decay of the latent reservoir in HIV-1-infected patients receiving intensive enfuvirtide-containing antiretroviral therapy. J Infect Dis 2010, 201:293-6.

Glass WG, McDermott DH, Lim JK, et al. CCR5 deficiency increases risk of symptomatic West Nile virus infection. J Exp Med 2006; 203:35-40.

Grant PM, Palmer S, Bendavid E, et al. Switch from enfuvirtide to raltegravir in Virologically suppressed HIV-1 infected patients: effects on level of residual viremia and quality of life. J Clin Virol 2009, 46:305-8.

Gulick RM, Fatkenheuer G, Burnside R, et al. Five-year safety evaluation of maraviroc in HIV-1-infected treatment-experienced patients. J AIDS 2014, 65:78-81.

Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously untreated patients with R5 HIV-1 infection. N Engl J Med 2008, 359:1429-1441.

Hardy D, Reynes J, Konourina I, et al. Efficacy and safety of maraviroc plus optimized background therapy in treatment-experienced patients infected with CCR5-tropic HIV-1: 48-week combined analysis of the MOTIVATE Studies. Abstract 792, 15th CROI 2008, Boston.

Hardy WD, Gulick RM, Mayer H, et al. Two-year safety and virologic efficacy of maraviroc in treatment-experienced patients with CCR5-tropic HIV-1 infection: 96-week combined analysis of MOTIVATE 1 and 2. J AIDS 2010 Aug 11. [Epub ahead of print].

Hütter G, Nowak D, Mossner M, et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Engl J Med 2009, 360:692-8.

Jubb B, Lewis M, Simpson P, et al. CCR5-tropic resistance to maraviroc is uncommon even among patients on functional maraviroc monotherapy or with ongoing low-level replication. Abstract 639, 16th CROI 2009 Montréal.

Khanlou H, Gathe G, Schrader S, et al. Safety, efficacy, and pharmacokinetics of ibalizumab in treatment-experienced HIV-1 infected patients: A phase 2b study. Abstract H2-794b, ICAAC 2011. Chicago.

Kilby JM, Hopkins S, Venetta TM, et al. Potent suppression of HIV-1 replication in humans by T-20, a peptide inhibitor of gp41-mediated virus entry. Nat Med 1998, 4:1302-1307.

Kilby JM, Lalezari JP, Eron JJ, et al. The safety, plasma pharmacokinetics, and antiviral activity of subcutaneous enfuvirtide (T-20), a peptide inhibitor of gp41-mediated virus fusion, in HIV-infected adults. AIDS Res Hum Retroviruses 2002, 18:685-93.

Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Engl J Med 2003, 348:2175-85.

Landry I, Zhu L, Abu Tarif M, et al. Model-Based Phase 3 Dose Selection for HIV-1 Attachment Inhibitor Prodrug BMS-663068 in HIV-1-Infected Patients: Population Pharmacokinetics/ Pharmacodynamics of the Active Moiety, BMS-626529. Antimicrob Agents Chemother 2016, 60:2782-9.

Lataillade M, Lalezari JP, Kozal M, et al. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced individuals: week 96 results of the phase 3 BRIGHTE study. Lancet HIV 2020, 7:e740-e751.

Lataillade M, Zhou N, Joshi SR, et al. Viral Drug Resistance through 48 Weeks, in a Phase 2b, Randomized, Controlled Trial of the HIV-1 Attachment Inhibitor Prodrug, Fostemsavir. JAIDS 2017 Nov 28.

Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. N Engl J Med 2003, 348:2186-95.

Lelièvre JD, Assoumou L, Aznar E, et al. ANRS 146 – GeSIDA 7211 OPTIMAL: Optimized Phase III Trial of Immuno-Stimulation With Maraviroc, a CCR5 Antagonist, Combined With Anti-Retroviral Therapy (cART) in Advanced, Late Diagnosed HIV-1-Infected Patients With an AIDS-Defining Event and/or CD4 Counts ≤200 Cells/mm^3. Abstract MOAB0102, 9th IAS Paris 2017.

Lin HS, Lee SJ, Wang NC, et al. Intramuscular ibalizumab: pharmacokinetics, safety, and efficacy vs IV administration. Abstract 438, 24th CROI 2017, Seattle.

Liu R, Paxton WA, Choe S, et al. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. Cell 1996;86:367-77.

Low AJ, Dong W, Chan D, et al. Current V3 genotyping algorithms are inadequate for predicting X4 co-receptor usage in clinical isolates. AIDS 2007; 21.

Lu J, Sista P, Cammack N, Kuritzkes D, et al. Fitness of HIV-1 clinical isolates resistant to T-20 (enfuvirtide). Antiviral therapy 2002, 7:S56.

MacInnes A, Lazzarin A, Di Perri G, et al. Maraviroc can improve lipid profiles in dyslipidemic patients with HIV: results from the MERIT trial. HIV Clin Trials 2011, 12:24-36.

Mink M, Mosier SM, Janumpalli S, et al. Impact of human immunodeficiency virus type 1 gp41 amino acid substitutions selected during enfuvirtide treatment on gp41 binding and antiviral potency of enfuvirtide in vitro. J Virol 2005, 79:12447-54.

Morand-Joubert L, Ghosn J, Delaugerre C, et al. Lack of benefit of 3-month intensification with enfuvirtide plus optimized background regimen (OBR) versus OBR alone in patients with multiple therapeutic failures: the INNOVE study. J Med Virol 2012, 84:1710-8.

Nelson M, Arasteh K, Clotet B, et al. Durable efficacy of enfuvirtide over 48 weeks in heavily treatment-experienced HIV-1-infected patients in the T-20 versus optimized background regimen only 1 and 2 clinical trials. J AIDS 2005, 40:404-12.

Nettles RE, Schürmann D, Zhu L, et al. Pharmacodynamics, safety, and pharmacokinetics of BMS-663068, an oral HIV-1 attachment inhibitor in HIV-1-infected subjects. J Infect Dis 2012, 206:1002-11.

Norris D, Morales J, Godofsky E, et al. TNX-355, in combination with optimized background regimen, achieves statistically significant viral load reduction and CD4 cell count increase when compared with OBR alone in phase 2 study at 48 weeks. Abstr. ThLB0218, XVI IAC 2006, Toronto.

Pett SL, Amin J, Horban A, et al. Week 96 results of the randomized, multicentre Maraviroc Switch (MARCH) study. HIV Med 2018, 19:65-71.

Pichenot M, Deuffic-Burban S, Cuzin L, Yazdanpanah Y. Efficacy of new antiretroviral drugs in treatment-experienced HIV-infected patients: a systematic review and meta-analysis of recent randomized controlled trials. HIV Med 2012, 13:148-55.

Poveda E, Hernández-Quero J, Pérez-Elías MJ, et al. Genotypic tropism testing of proviral DNA to guide maraviroc initiation in aviraemic subjects: 48-week analysis of results from the PROTEST study. HIV Med 2017, 18:482-489.

Prahalad S. Negative association between the chemokine receptor CCR5-Delta32 polymorphism and rheumatoid arthritis: a meta-analysis. Genes Immun 2006;7:264-8.

Rabkin CS, Yang Q, Goedert JJ, et al. Chemokine and chemokine receptor gene variants and risk of non-Hodgkin's lymphoma in human immunodeficiency virus-1-infected individuals. Blood 1999, 93:1838-42.

Root MJ, Kay MS, Kim PS. Protein design of an HIV-1 entry inhibitor. Science 2001;291:884-8.

Rossetti B, Gagliardini R, Meini G, et al. Switch to maraviroc with darunavir/r, both QD, in patients with suppressed HIV-1 was well tolerated but virologically inferior to standard antiretroviral therapy: 48-week results of a randomized trial. PLoS One 2017, 21;12:e0187393.

Samson M, Libert F, Doranz BJ, et al. Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature 1996;382:722-5.

Scarlatti G, Tresoldi E, Bjorndal A, et al. In vivo evolution of HIV-1 co-receptor usage and sensitivity to chemokine-mediated suppression. Nat Med 1997, 3:1259-65.

Sierra-Madero J, Di Perri G, Wood R, et al. Efficacy and safety of maraviroc versus efavirenz, both with zidovudine/lamivudine: 96-week results from the MERIT study. 4. HIV Clin Trials 2010, 11:125-32.

Soulié C, Fourati S, Lambert-Niclot S, et al. Factors associated with proviral DNA HIV-1 tropism in antiretroviral therapy-treated patients with fully suppressed plasma HIV viral load: implications for the clinical use of CCR5 antagonists. J Antimicrob Chemother 2010, 65:749-51.

Stellbrink HJ, Le Fevre E, Carr A, et al. Once-daily maraviroc versus tenofovir/emtricitabine each combined with darunavir/ritonavir for initial HIV-1 treatment. AIDS 2016, 30:1229-38.

Thompson M, DeJesus E, Richmond G, et al. Pharmacokinetics, pharmacodynamics and safety of once-daily versus twice-daily dosing with enfuvirtide in HIV-infected subjects. AIDS 2006, 20:397-404.

Thompson M, Lalezari JP, Kaplan R, et al. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in antiretroviral-experienced subjects: week 48 analysis of AI438011, a Phase IIb, randomized controlled trial. Antivir Ther 2017, 22:215-223.

Toma J, Weinheimer SP, Stawiski E, et al. Loss of asparagine-linked glycosylation sites in variable region 5 of human immunodeficiency virus type 1 envelope is associated with resistance to CD4 antibody ibalizumab. J Virol 2011, 85:3872-80.

Trottier B, Walmsley S, Reynes J, et al. Safety of enfuvirtide in combination with an optimized background of antiretrovirals in treatment-experienced HIV-1-infected adults over 48 weeks. JAIDS 2005, 40:413-21.

Tsamis F, Gavrilov S, Kajumo F, et al. Analysis of the mechanism by which the small-molecule CCR5 antagonists SCH-351125 and SCH-350581 inhibit human immunodeficiency virus type 1 entry. J Virol 2003;77:5201-8.

Walmsley S, Henry K, Katlama C, et al. Enfuvirtide (T-20) cross-reactive glycoprotein 41 antibody does not impair the efficacy or safety of enfuvirtide. J Infect Dis 2003, 188:1827-33.

Westby M, Lewis M, Whitcomb J, et al. Emergence of CXCR4-using human immunodeficiency virus type 1 (HIV-1) variants in a minority of HIV-1-infected patients following treatment with the CCR5 antagonist maraviroc is from a pretreatment CXCR4-using virus reservoir. J Virol 2006, 80:4909-20.

Westby M, Smith-Burchnell C, Mori J, et al. Reduced maximal inhibition in phenotypic susceptibility assays indicates that viral strains resistant to the CCR5 antagonist maraviroc utilize inhibitor-bound receptor for entry. J Virol 2007;81:2359-71.

Zhou N, Nowicka-Sans B, McAuliffe B, et al. Genotypic correlates of susceptibility to HIV-1 attachment inhibitor BMS-626529, the active agent of the prodrug BMS-663068. J Antimicrob Chemother 2014, 69:573-81.

Capsid inhibitors

The viral genome and viral enzymes of HIV are enclosed in a capsid, a cone-shaped envelope consisting of p24 rings containing the viral genome and viral enzymes. Although it is still unclear exactly when "uncoating" of the capsid occurs after uptake into the cell, the capsid is essential for replication. It plays a critical role in many aspects of the HIV-1 replication cycle, including reverse transcription, cytoplasmic transport, nuclear entry and maturation of the virion, and interaction with many host factors essential for infection (McFadden 2021, Selyutina 2022).

The p24 gene encodes the gag capsid, which remains highly conserved at key sites across all HIV subtypes. Gag polymorphisms or other mutations in the gag cleavage site do not appear to affect efficacy, nor do mutations against other drug classes (Margot 2021).

Agents that influence the stability of the capsid are known as capsid inhibitors. After many years in which the pharmaceutical industry cut its teeth on developing effective prototypes, there has been movement in research in recent years. With lenacapavir, the first capsid inhibitor was approved in 2022. After NRTIs, NNRTIs, PIs, INSTIs, and entry inhibitors, a sixth class of active ingredients entered the market.

Individual agents

Lenacapavir (Sunlenca®, formerly **GS-6207**) is a novel, potent, and long-acting first-in-class HIV-1 capsid inhibitor granted breakthrough therapy designation by the FDA in 2019. It is manufactured by Gilead Sciences and is an improved analog of the prototype GS-CA1. Mutations selected *in vitro* with GS-6207 remained sensitive to other antiretroviral agents, and some appear to impair replication significantly (Yant 2019). As monotherapy, lenacapavir delivered a mean maximal HIV-1 RNA reduction of an impressive 2.2 logs at ten days (Link 2020). However, the half-life is at least as impressive. Sufficient levels can be achieved over six months with a single subcutaneous administration. Weekly oral administration also appears possible. It was looked at in two large clinical studies, CALIBRATE and CAPELLA.

CALIBRATE, an open-label Phase II trial, enrolled 182 treatment-naïve individuals who received lenacapavir subcutaneously (every six months) or orally (each with different combination partners). In the combined lenacapavir arms, viral load at week 28 was 94% below 50 copies/mL (100% in the control arm with bictegravir). Two of 103 people treated subcutaneously with lenacapavir discontinued treatment due to injection site reactions (Gupta 2021).

In CAPELLA, 72 extensively pre-treated patients on failing ART were treated with lenacapavir SC every six months or placebo (Segal-Maurer 2022). Two weeks after the first injection, viral load had fallen by at least 0.5 log levels in 88% compared with 17% on placebo. Despite very limited options in the optimized background therapy, up to 81% achieved viral loads below 50 copies/mL, including 4/6 individuals in whom lenacapavir was the only active agent (Molina 2021). At 52 weeks, however, 9/72 participants had emergent lenacapavir resistance; four re-suppressed while maintaining lenacapavir use (Ogbuagu 2023). Injection site reactions were the most common problems but rarely led to discontinuation.

Resistance appears to be predominant at codons 67 and 74 (Margot 2022, Bester 2022) and was also observed in 2/157 therapy-naive individuals (Gupta 2022) – possibly indicating that the resistance barrier is not very high with this agent.

Providers should pay attention to drug-drug interactions when initiating lenacapavir. Lenacapavir is a substrate for Pgp, CYP3A, and UGT1A1 and a moderate inhibitor of CYP3A (review: Tuan 2023).

In August 2022, the EMA approved lenacapavir based on the CAPELLA data. The tablets are intended as a "lead-in" before the first depot injection. As with fostemsavir, the indication is limited to "adults with multi-drug-resistant HIV-1 infection in whom no other suppressive antiviral regimen can be composed". For manufacturer Gilead, this is likely just a start: the development project suggests that lenacapavir will be developed further, both as an oral agent (GS6289, an exciting study in combination with bictegravir as STR) and further as a long-acting agent. Studies in combination with broadly neutralizing antibodies are also being planned. In the Purpose Phase III trials, lenacapavir is also tested as PrEP every six months SC compared to TAF/FTC and TDF/FTC in a placebo-controlled setting in women and MSM.

Literature on capsid inhibitors

Bester SM, Adu-Ampratwum D, Annamalai AS, et al. Structural and Mechanistic Bases of Viral Resistance to HIV-1 Capsid Inhibitor Lenacapavir. mBio. 2022 Oct 3:e0180422.

Gupta SK, et al. Long-acting subcutaneous lenacapavir dosed every six months as part of a combination regimen in treatment-naïve people with HIV: interim 16-week results of a randomized, open-label, phase 2 induction-maintenance study (CALIBRATE). IAS 2021. Abstract OALB0302.

Gupta SK, Sims J, Brinson C, et al. Lenacapavir as part of a Combination Regimen in Treatment-Naïve People with HIV: Week 54 Results. Abstract 138, CROI 2022.

Link JO, et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. Nature 2020, 584:614-618.

Margot N, Ram R, Rhee M, Callebaut C. Absence of Lenacapavir (GS-6207) Phenotypic Resistance in HIV Gag Cleavage Site Mutants and in Isolates with Resistance to Existing Drug Classes. Antimicrob Agents Chemother 2021, 65:e02057-20.

Margot NA, Naik V, VanderVeen L, et al. Resistance analyses in Highly Treatment-Experienced People with HIV Treated with the Novel Capsid HIV Inhibitor Lenacapavir. J Infect Dis 2022 Sep 9:jiac364.

McFadden WM, Snyder AA, Kirby KA, et al. Rotten to the core: antivirals targeting the HIV-1 capsid core. Retrovirology 2021, 18:41.

Ogbuagu O, Segal-Maurer S, Ratanasuwan W, et al. Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial. Lancet HIV 2023, S2352-3018(23)00113-3.

Segal-Maurer S, DeJesus E, Stellbrink HJ, et al. Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection. N Engl J Med 2022, 386:1793-1803.

Selyutina A, Hu P, Miller S, et al. GS-CA1 and lenacapavir stabilize the HIV-1 core and modulate the core interaction with cellular factors. iScience 2021, 25:103593.

Tuan J, Ogbuagu O. Lenacapavir: a twice-yearly treatment for adults with multidrug-resistant HIV infection and limited treatment options. Expert Rev Anti Infect Ther 2023; 21:565-570.

5.3. ART 2024+: Beyond the horizon

CHRISTIAN HOFFMANN

Almost all people living with HIV can be treated adequately. Nevertheless, there is still a need for new drugs. Not only for the few for whom the new drug classes do not work but, in principle, for all patients. As things stand, HIV therapy must be taken for the rest of the patient's life; it remains unclear whether the current drugs will suffice. New drugs that are less toxic and easier to take than today's STRs must be developed. To get closer to the long-term goal of eradication, they should be more potent than the current ones. For a while, many companies shifted away from HIV and toward hepatitis C, but there is now renewed movement in HIV research after the end of the HCV boom – the HIV pipeline is full. However, the increasing price erosion of generic drugs will have a negative impact. The incentive to develop new drugs will decrease. It has become tough to show an additional benefit that could justify higher prices. We do not need 20 single-tablet regimens (STRs). The following is an overview of the most exciting agents as of early 2023 – probably incomplete!

Long-acting drugs

Long-acting (LA) drugs are delayed-release and thus have a very long effect. They are mainly being developed to address treatment fatigue from the burden of daily pills and improve convenience. LA drugs could be used both as PrEP and for adherence issues, as well as for anyone who prefers a "monthly injection" or even a "three-monthly injection" *vs*. taking tablets daily (reviews: D'Amico 2020, Clement 2020). With the approval of Vocabria® and Rekambys® (US and Canada: Cabenuva®), the combination of cabotegravir and rilpivirine given every 4 or 8 weeks for pre-treated patients has been available since late 2020; they are discussed later in the de-escalation strategies. Lenacapavir (Sunlenca®, see section above) is also approved as a six-monthly injection for multi-drug resistance, but it must be combined with other oral therapies. Experimental agents are briefly discussed below.

Dolutegravir-LA – is being tested as a nano-formulation. This involves packaging a hydrophobic and lipophilic prodrug of dolutegravir into nanoparticles. In mice, parenteral administration allowed sufficient levels for up to 2 months (Sillman 2018). New manufacturing processes or technologies allow even annual doses in animal models (Deodhar 2022).

Rilpivirine-LA – the NNRTI rilpivirine is well suited as an LA formulation because it accumulates in plasma and other compartments for a long time, more than other antiretroviral agents (Jackson 2013). Rilpivirine is also detectable in vaginal fluid for a long time, which makes it attractive as PrEP (Jackson 2015). It is approved as Recambys®. Nanoformulations also appear possible and feasible; in animal studies, decent levels could be achieved for over 25 weeks by a single intramuscular injection (Hilaire 2019).

Islatravir (formerly **MK-8591** or **EfdA**) is a nucleoside RT translocation inhibitor (NRTTI) that accumulates long in PBMC and macrophages. PK data in monkeys suggest a once-yearly administration may be feasible with an LA formulation (see below for new NRTIs).

Numerous **other agents** are in development as LA formulations. **Raltegravir-LA** was highly protective when injected subcutaneously in animal studies. Two weeks after a single injection, levels were comparable to oral raltegravir (Kovarova 2016). **Atazanavir-LA,** as a nanodispersion, showed higher tissue accumulation in animal studies (IM injection) than by conventional ART even after two weeks (Dash 2012,

Puligijja 2015). The effect is significantly enhanced by a kinase inhibitor (Zhang 2016).

Albuvirtide is a fusion inhibitor. In combination with lopinavir, 5/9 patients achieved a viral load below the detection limit in a pilot study of weekly injections (Zhang 2016). In another study, it worked even in pre-treated patients (Su 2022).

Other long-acting systems: Increasingly, attempts are being made to deliver long-acting HIV drugs by means other than injections. Transdermal is just one way (Review: Weld 2020). Implants with TAF and FTC replenished through the skin have already been tested in monkeys as PrEP (Chua 2017). Degradable implants applied under the skin with an implant have also been successful in animal studies (Durham 2017). The methods are partially similar to long-term contraceptives, in which hormone implants are inserted directly under the skin as a plastic rod a few centimeters long with an applicator (Schlesinger 2016).

Capsid inhibitors

Lenacapavir was the first agent in this class to reach the market in 2022. Therefore, the development of capsid inhibitors is expected to pick up speed. Capsid inhibitors are also used for other viral infections, such as bersacapavir for hepatitis B (in Phase II trials) or vapendavir for enteroviruses. The drugs developed for HIV target different binding sites of the capsid, but almost all are still pre-clinical (review: McFadden 2022).

GS-CA1 was described in 2017 as a substance with a long half-life that binds directly to the HIV-1 capsid. It is the precursor of lenacapavir and appears in many articles; it is mentioned here only for form.

PF74 is Pfizer's prototype (Blair 2010). PF74 never reached the clinic but demonstrated submicromolar efficacy and serves as the backbone for some of the most promising current agents, including PF74 analogs with enhanced efficacy, particularly against CA mutants that exhibit resistance to PF74. The peptidic backbone of PF74 is also at the heart of lenacapavir. Given the rapid development of resistance and a short half-life, work is underway to improve the molecule (McFadden 2022).

VH4004280 is a capsid inhibitor of ViiV that can be given orally. A Phase I study in healthy volunteers is ongoing, and a Phase II study in PLWH is planned to start in late 2023. Another candidate (VH4011499) is also reportedly already in clinical trials. Various administration routes are being explored to extend the dosing schedule beyond every two months via the parenteral route or every week or longer via oral administration.

Ebselen is a capsid inhibitor attributed to have diverse antiviral properties (Thenin-Houssier 2016).

Literature on Long-acting and Capsid Inhibitors

Blair WS, Pickford C, Irving SL, et al. HIV capsid is a tractable target for small molecule therapeutic intervention. PLoS Pathog. 2010;6:e1001220.

Chua CX, Jain P, Hu M, et al. Transcutaneous refillable nanofluidic implant for constant delivery of HIV PrEP. Abstract 422LB, 24th CROI 2017, Seattle.

Clement ME, Kofron R, Landovitz RJ. Long-acting injectable cabotegravir for the prevention of HIV infection. Curr Opin HIV AIDS 2020, 15:19-26.

D'Amico R, Margolis DA. Long-acting injectable therapy: an emerging paradigm for the treatment of HIV infection. Curr Opin HIV AIDS 2020, 15:13-18.

Dash PK, Gendelman HE, Roy U, et al. Long-acting nanoformulated antiretroviral therapy elicits potent antiretroviral and neuroprotective responses in HIV-1-infected humanized mice. AIDS 2012, 26:2135-44.

Deodhar S, Sillman B, Bade AN, et al. Transformation of dolutegravir into an ultra-long-acting parenteral prodrug formulation. Nat Commun 2022, 13:3226.

Durham PG, Gatto G, Johnson L, et al. In Vitro -In Vivo Evaluation of a Biodegradable Implant Containing TAF for HIV PrEP. Abstract 420LB, 24th CROI 2017, Seattle.

Hilaire JR, Bade AN, Sillman B, et al. Creation of a long-acting rilpivirine prodrug nanoformulation. J Control Release 2019 Oct;311-312:201-211.

Jackson A, McGowan I. Long-acting rilpivirine for HIV prevention. Curr Opin HIV AIDS 2015, 10:253-7.

Jackson AG, Else LJ, Mesquita PM, et al. A compartmental pharmacokinetic evaluation of long-acting rilpivirine in HIV-negative volunteers for pre-exposure prophylaxis. Clin Pharmacol Ther 2014, 96:314-23.

Kovarova M, Swanson MD, Sanchez RI, et al. A long-acting formulation of the integrase inhibitor raltegravir protects humanized BLT mice from repeated high-dose vaginal HIV challenges. J Antimicrob Chemother 2016, 71:1586-96.

McFadden WM, Snyder AA, Kirby KA, et al. Rotten to the core: antivirals targeting the HIV-1 capsid core. Retrovirology 2021, 18:41.

Owen A, Rannard S. Strengths, weaknesses, opportunities and challenges for long acting injectable therapies: Insights for applications in HIV therapy. Adv Drug Deliv Rev. 2016 Feb 23.

Puligujja P, Balkundi SS, Kendrick LM, et al. Pharmacodynamics of long-acting folic acid-receptor targeted ritonavir-boosted atazanavir nanoformulations. Biomaterials 2015, 41:141-50.

Schlesinger E, Johengen D, Luecke D. A Tunable, Biodegradable, Thin-Film Polymer Device as a Long-Acting Implant Delivering Tenofovir Alafenamide Fumarate for HIV Pre-exposure Prophylaxis. Pharm Res 2016, 33: 1649–1656.

Sillman B, Bade AN, Dash PK, et al. Creation of a long-acting nanoformulated dolutegravir. Nat Commun. 2018 Feb 6;9:443.

Su B, Yao C, Zhao QX, et al. Long-acting HIV fusion inhibitor albuvirtide combined with ritonavir-boosted lopinavir for HIV-1-infected patients after failing the first-line antiretroviral therapy: 48-week randomized, controlled, phase 3 non-inferiority TALENT study. J Infect 2022, 85:334-363.

Thenin-Houssier S, Mitchelle de Vera I, Pedro-Rosa L, et al. Ebselen, a Small-Molecule Capsid Inhibitor of HIV-1 Replication. Antimicrob Agents Chemother. 2016, 60:2195-208.

Zhang G, Guo D, Dash PK, et al. The mixed lineage kinase-3 inhibitor URMC-099 improves therapeutic outcomes for long-acting antiretroviral therapy. Nanomedicine 2016, 12:109-22.

Zhang H, Jin R, Yao C, et al. Combination of long-acting HIV fusion inhibitor albuvirtide and LPV/r showed potent efficacy in HIV-1 patients. AIDS Res Ther. 2016 Feb 10;13:8.

New nucleoside analogs (NRTIs)

Finding NRTIs with good activity against resistant viruses that do not have mitochondrial toxicity seems challenging. For a long time, it seemed doubtful that a new agent in this class would ever make it to the market, and many have already disappeared into obscurity. With islatravir, an innovative new substance, this could change.

Apricitabine (ATC, AVX-754, formerly SPD-754) is a heterocyclic cytidine analog that remains effective despite many NRTI mutations. With monotherapy, viral load decreased by 1.2–1.4 logs (Cahn 2006), compared with 0.7–0.9 logs for the M184V mutation (Cahn 2010). ATC was well tolerated (Gaffney 2009) and was much less toxic than BCH-10652, which causes severe degenerative dermatopathy in monkeys (Locas 2004). In May 2010, negotiations with major pharmaceutical companies failed, and further development was halted.

Censavudine (festinavir, BMS986001), a thymidine analog, is a purportedly less toxic derivative of d4T. The original name, "festinavir", was changed to avoid confusion with PIs. Censavudine is reported to have good activity against HIV-2 (Smith 2015). In a Phase II trial testing different doses against TDF, there was more resistance and evidence of lipoatrophic changes (Gupta 2016), so BMS lost interest. According to the Japanese company Oncolys, it will now continue in Phase II in neurogenerative diseases (!), while there is no talk of further investigation into HIV.

Elvucitabine (or ACH-126,443) is a cytidine analog from Achillion Pharmaceuticals. It is an enantiomer of dexelvucitabine (Reverset) and is effective *in vitro* for numerous NRTI resistances (Fabrycki 2003). Of interest is its long half-life of 150 hours. In HIV-infected individuals with the M184V mutation, viral load decreased by 0.7–0.8 logs after 28 days in a small, double-blind study. However, the study was terminated because leukopenia and skin rashes occurred with 100 mg elvucitabine (Dunkle 2003). In Phase II in 77 treatment-naive patients (with efavirenz and TDF), elvucitabine was roughly comparable in efficacy to 3TC over 96 weeks (DeJesus 2010). Achillion is reportedly collaborating with companies in China, although further development is unclear.

Fozivudine is a prodrug of AZT that is activated intracellularly to AZT monophosphate. The company Heidelberg Pharma conducted clinical trials. In a Phase II trial, for example, fozivudine was only moderately effective – at the highest dose, the viral load fell by just under 0.7 log levels (Girard 2000) – too little for further development? In one Phase II trial in Tanzania and Côte d'Ivoire published in 2017, combined with 3TC and efavirenz, it was just as effective and, at the same time, less myelotoxic than AZT (Kroidl 2017).

Islatravir (**MK-8591** or **EfdA**, 4′-ethynyl-2-fluoro-deoxyadenosine) is a nucleoside RT translocation inhibitor (NRTTI) that inhibits reverse transcriptase in a complex and novel manner. The mechanism of action relies both on immediate chain termination through inhibition of translocation, a step required for RT before any incorporation of a new nucleotide, and on delayed chain termination once islatravir has been incorporated into the primary strand by RT. The chemical structure and novel mechanism of action thus distinguish it from all previously approved NRTIs and result in a unique resistance and PK profile (Markowitz 2020). The resistance barrier appears to be high (Diamond 2022).

It is being developed by MSD, which acquired islatravir in 2012 from the Japanese company Yamasa, a soy sauce manufacturer (!). The effort is immense; the development has picked up speed compared to other NRTIs. Quite obviously, there seems to be a lot of promise. Mutations such as M184V do not negatively affect islatravir

(Oliveira 2017, Diamond 2022), and HIV-2 is also inhibited. The half-life of orally administered islatravir is 150 hours; the compound accumulates in PBMC and macrophages. With a single dose of only 10 mg, viral load decreased by 1.6 log levels after seven days (Schürmann 2021).
In a Phase IIa trial in treatment-naïve patients, three different doses of islatravir (0.25–2.25 mg daily) were combined with doravirine+3TC and were tested against a standard therapy of doravirine+TDF+3TC (Molina 2021). If virological efficacy was good, randomization to a 2DR of islatravir+doravirine occurred at week 24. At 48 weeks, efficacy was comparable to the standard arm across all subgroups (gender, ethnicity, CD4 T-cells, viral load). 5/90 patients developed virologic failure; all remained below 80 copies and without resistance. Tolerability has been excellent over 96 weeks to date (Molina 2022).
The compound was highly protective in macaques as PrEP (Markowitz 2019). PK data in monkeys, moreover, suggest that with an LA formulation, even once-yearly dosing may become feasible. The dose will be flexible, with long intervals: weekly tablets, tri-monthly injections, and subdermal depot – all seem possible. Seemed. The ambitious Phase III program (in which doravirine and islatravir were tested against bictegravir/TAF/FTC) was abruptly halted in November 2021: completely unexpected lymphopenias and CD4 T-cell declines were seen in some participants. The FDA subsequently halted all ongoing studies. The causes of the lymphopenias remain unclear, but they appear to occur primarily at high doses and are reversible. It may be possible that islatravir triphosphate accumulates in lymphocytes and triggers cell death at very high drug concentrations (Squires 2023). The 0.75 mg dose was initially taken forward for larger phase 3 studies. Still, after the development pause, Merck decided to skip all PrEP studies and focus on testing a 0.25 mg dose of islatravir. A Phase 3 study now compares doravirine and a lower islatravir dose to bictegravir/TAF/FTC in previously untreated PLWH. More studies are planned.
Despite these drawbacks, islatravir remains one of the most interesting new compounds in HIV medicine. It will be interesting to see what is possible with lower drug doses.

Phosphazide (Nikavir) is an NRTI developed in Russia (and approved there since 1999) that closely resembles AZT (Skoblov 2003). After 12 weeks of monotherapy with 400 mg, viral load decreased by 0.7 log levels. Because phosphazide is a prodrug of AZT, an additional activation step is required. The D67N mutation appears to reduce efficacy (Machado 1999). Other studies showed efficacy with ddI and nevirapine (Kravtchenko 2000) or saquinavir (Sitdykova 2003). However, detecting an advantage over AZT is difficult – better tolerability has not been demonstrated.

Racivir is a cytidine analog initially developed by Pharmasset. It is a mixture of FTC and its enantiomer. There may be different resistance pathways for the two enantiomers, which could complicate the development of resistance (Hurwitz 2005). Combined with d4T and efavirenz, a good effect was seen after two weeks (Herzmann 2005). In a study of 42 patients with the M184V mutation, viral load decreased by 0.4 log levels after 28 days (Cahn 2007). After Gilead acquired Pharmasset, nothing more was heard, and further development is questionable.

Rovafovir etalafenamide (or GS-9131) is a new NRTI developed by Gilead Sciences with good efficacy against diverse NRTI resistance (K65R, L74V, M184V, or even combinations) that can be given once daily (White 2017, Ibanescu 2019). Rovafovir is a cyclic nucleoside phosphonate, and the prodrug of GS-9148, but a Phase II trial in Uganda was stopped early in April 2020 due to lack of efficacy – probably the end.

Tenofovir exalidex (TXL, formerly CMX 157) is a pro-drug of tenofovir, "HDP-tenofovir" (hexadecyloxypropyl ester), similar to TAF and probably not as nephro-

toxic. TXL is being developed by ContraVir Pharmaceuticals in New Jersey. *In vitro*, it was effective against TDF resistance, including K65R (Lanier 2010); it may be given once weekly. It is also being developed for hepatitis B; in Phase I studies, it was pretty well-tolerated, with HBV DNA dropping by about 2 logs (Tanwandee 2017). Where it goes from here is unclear. Do we still need tenofovir? The companies involved will watch the development of dual therapies very closely.

Out of sight, out of mind – the following NRTIs will not be developed further:
- Adefovir dipivoxil from Gilead, little effect against HIV, nephrotoxicity
- Amdoxovir (DAPD), too toxic
- Dexelvucitabine (Reverset) from Incyte, 2006, pancreatitis
- Dioxolanthymine (DOT) as a thymidine analog too unattractive
- dOTC from Biochem Pharma, toxicity in monkeys
- FddA (lodenosine) from Bioscience, 1999, liver/kidney damage
- Fosavuldine from Heidelberg Pharma, too toxic
- KP-1461 from Koronis Pharmaceuticals, June 2008, due to ineffectiveness
- Lobucavir from BMS, carcinogenicity
- MIV-210 from Medivir/Tibotec, October 2007, tested as an HBV drug
- MIV-310 (alovudine) from Boehringer, March 2005, disappointing Phase II study
- SPD-756 (BCH-13520) and SPD-761
- Stampidine by Parker Hughes, company broke, nobody wants a new d4T

Literature on new NRTIs

Cahn P, Altclas J, Martins M, et al. Antiviral activity of apricitabine in treatment-experienced HIV-1-infected patients with M184V who are failing combination therapy. HIV Med 2010 Nov 3. [Epub ahead of print]

Cahn P, Cassetti I, Wood R, et al. Efficacy and tolerability of 10-day monotherapy with apricitabine in antiretroviral-naive, HIV-infected patients. AIDS 2006, 20:1261-8.

Cahn P, Sosa N, Wiznia A, et al. Racivir demonstrates safety and efficacy in patients harbouring HIV with the M184V mutation and >3 TAM. Abstract 488, 14th CROI 2007, Los Angeles.

Cihlar T, Laflamme G, Fisher R, et al. Novel nucleotide human immunodeficiency virus reverse transcriptase inhibitor GS-9148 with a low nephrotoxic potential: characterization of renal transport and accumulation. Antimicrob Agents Chemother 2009, 53:150-6.

Cihlar T, Ray AS, Boojamra CG, et al. Design and profiling of GS-9148, a novel nucleotide analog active against nucleoside-resistant variants of human immunodeficiency virus type 1, and its orally bioavailable phosphonoamidate prodrug, GS-9131. Antimicrob Agents Chemother 2008;52:655-65.

DeJesus E, Saple D, Morales-Ramirez J, et al. Elvucitabine phase II 48-week interim results show safety and efficacy profiles similar to lamivudine in treatment-naive HIV-1 infected patients with a unique pharmacokinetic profile. Abstract H-892, 48th ICAAC 2008, 2008.

DeJesus E, Saple D, Morales-Ramirez J, et al. Elvucitabine vs lamivudine with tenofovir and efavirenz in antiretroviral-treatment-naïve HIV-1 infected patients: 96-week final results. Abstract 511, 17th CROI 2010, San Francisco.

Diamond TL, Ngo W, Xu M, et al. Islatravir Has a High Barrier to Resistance and Exhibits a Differentiated Resistance Profile from Approved Nucleoside Reverse Transcriptase Inhibitors (NRTIs). Antimicrob Agents Chemother 2022, 66:e0013322.

Dunkle LM, Gathe JC, Pedevillano DE, et al. Elvucitabine: potent antiviral activity demonstrated in multidrug-resistant HIV infection. Antiviral Therapy 2003, 8:S5.

Fabrycki J, Zhoa Y, Wearne J, et al. In vitro induction of HIV variants with reduced susceptibility to elvucitabine (ACH-126,443,beta-L-Fd4C). Antiviral Therapy 2003, 8:S8.

Gaffney MM, Belliveau PP, Spooner LM. Apricitabine: a nucleoside reverse transcriptase inhibitor for HIV infection. Ann Pharmacother 2009, 43:1676-83

Girard PM, Pegram PS, Diquet B, et al. Phase II placebo-controlled trial of fozivudine tidoxil for HIV infection: pharmacokinetics, tolerability, and efficacy. J AIDS 2000, 23:227-35.

Gupta SK, McComsey GA, Lombaard J, et al. Efficacy, safety, bone and metabolic effects of HIV nucleoside reverse transcriptase inhibitor BMS-986001 (AI467003): a phase 2b randomised, controlled, partly blinded trial. Lancet HIV 2016, 3:e13-22.

Harris KS, Brabant W, Styrchak S, Gall A, Daifuku R. KP-1212/1461, a nucleoside designed for the treatment of HIV by viral mutagenesis. Antiviral Res 2005, 67:1-9.

Herzmann C, Arasteh K, Murphy RL, et al. Safety, pharmacokinetics, and efficacy of (+/-)-beta-2′,3′-dideoxy-5-fluoro-3′-thiacytidine with efavirenz and stavudine in antiretroviral-naive HIV-infected patients. Antimicrob Agents Chemother 2005, 49:2828-33.

Hurwitz SJ, Otto MJ, Schinazi RF. Comparative pharmacokinetics of Racivir, (+/-)-beta-2′,3′-dideoxy-5-fluoro-3′-thiacytidine in rats, rabbits, dogs, monkeys and HIV-infected humans. Antivir Chem Chemother 2005, 16:117-27.

Ibanescu RI, Oliveira M, Spira B, et al. Favourable outcome of in vitro selections with novel prodrug GS-9131. Abstract 482, CROI 2019, Seattle.

Kravtchenko AV, Salamov GG, Serebrovskaya LV, et al. The first experience of HAART with phosphazid + didanosine + nevirapine in HIV-infected patients in Russia. Abstract 3, 5th Int Conf Drug Therapy 2000, Glasgow, Scotland.

Kroidl A, Ello F, Mgaya J, et al. Virological efficacy of 24-week fozivudine-based regimen in ART-naive patients from Tanzania and Côte d'Ivoire. AIDS 2017, 31:501-509.

Lanier ER, Ptak RG, Lampert BM, et al. Development of hexadecyloxypropyl tenofovir (CMX157) for treatment of infection caused by wild-type and nucleoside/nucleotide-resistant HIV. Antimicrob Agents Chemother 2010, 54:2901-9.

Locas C, Ching S, Damment S. Safety profile of SPD754 in cynomolgus monkeys treated for 52 weeks, Abstract 527, 11th CROI 2004, San Francisco. http://www.retroconference.org/2004/cd/Abstract/527.htm

Machado J, Tsoukas C, Salomon H, et al. Antiviral activity and resistance profile of phosphazid – a novel prodrug of AZT. Abstract 594, 6th CROI 1999, Chicago. http://www.retroconference.org/99/abstracts/594.htm

Markowitz M, Gettie A, St Bernard L, et al. Once-weekly Oral Dosing of MK-8591 Protects Male Rhesus Macaques from Intrarectal SHIV109CP3 Challenge. J Infect Dis 2019 Jun 7.

Markowitz M, Grobler JA. Islatravir for the treatment and prevention of infection with the human immunodeficiency virus type 1. Curr Opin HIV AIDS 2020, 15:27-32.

Michailidis E, Marchand B, Kodama EN, et al. Mechanism of inhibition of HIV-1 reverse transcriptase by 4′-Ethynyl-2-fluoro-2′-deoxyadenosine triphosphate, a translocation-defective reverse transcriptase inhibitor. J Biol Chem 2009, 284:35681-91

Molina JM, Yazdanpanah Y, Afani Saud A, et al. Brief Report: Efficacy and Safety of Oral Islatravir Once Daily in Combination With Doravirine Through 96 Weeks for Treatment-Naive Adults With HIV-1 Infection Receiving Initial Treatment With Islatravir, Doravirine, and Lamivudine. J Acquir Immune Defic Syndr 2022, 91:68-72.

Molina JM, Yazdanpanah Y, Afani Saud A, et al. Islatravir in combination with doravirine for treatment-naive adults with HIV-1 infection receiving initial treatment with islatravir, doravirine, and lamivudine: a phase 2b, randomised, double-blind, dose-ranging trial. Lancet HIV 2021, 8:e324-e333.

Oliveira M, Brenner BG, Xu H, et al. M184I/V substitutions and E138K/M184I/V double substitutions in HIV reverse transcriptase do not significantly affect the antiviral activity of EFdA. J Antimicrob Chemother 2017, 72:3008-3011.

Ray AS, Vela JE, Boojamra CG, et al. Intracellular metabolism of the nucleotide prodrug GS-9131, a potent anti-human immunodeficiency virus agent. Antimicrob Agents Chemother 2008, 52:648-54.

Salie ZL, Kirby KA, Michailidis E, et al. Structural basis of HIV inhibition by translocation-defective RT inhibitor 4′-ethynyl-2-fluoro-2′-deoxyadenosine (EFdA). PNAS 2016, 113: 9274-9.

Schürmann D, Rudd DJ, Zhang S, et al. Safety, pharmacokinetics, and antiretroviral activity of islatravir (ISL, MK-8591), a novel nucleoside reverse transcriptase translocation inhibitor, following single-dose administration to treatment-naive adults infected with HIV-1: an open-label, phase 1b, consecutive-panel trial. Lancet HIV 2020 Jan 3.

Sitdykova YR, Serebrovskaya LV, Kravchenko AV. Immune reconstitution on treatment of HIV-infected patients with phosphazid, didanosine and saquinavir/ritonavir once daily in Russia. Abstract 2.7/1. 9th EACS 2003, Warsaw, Poland.

Skoblov Y, Karpenko I, Shirokova E, et al. Intracellular metabolism and pharmacokinetics of 5′-hydrogenphosphonate of 3′-azido-2′,3′-dideoxythymidine, a prodrug of 3′-azido-2′,3′-dideoxythymidine. Antiviral Res 2004;63:107-13.

Smith RA, Raugi DN, Wu VH, et al. The Nucleoside Analog BMS-986001 Shows Greater In Vitro Activity against HIV-2 than against HIV-1. Antimicrob Agents Chemother 2015, 59:7437-46.

Tanwandee T, Chatsiricharoenkul S, Thongsawat S, et al. Pharmacokinetics, Safety and Tolerability of Tenofovir exalidex (CMX157), a Novel Prodrug of Tenofovir, Administered as Ascending Multiple Doses to Healthy Volunteers and HBV-Infected Subjects. Abstract PS040, EASL 2017, Amsterdam.

White KL, Margot M, Stray K, et al. GS-9131 is a novel NRTI with activity against NRTI-resistant HIV-1. Abstract 436, 24th CROI 2017.

New NNRTIs and PIs

There has been some progress in the development of NNRTIs recently (impressive review: Zhuang 2020). With the approval of doravirine, an NNRTI entered the market for the first time in years. However, given the massive use of INSTIs worldwide, the overall share of NNRTIs and PIs is declining. There is hardly anything in sight for PIs; the market seems to have remained saturated since the approval of darunavir (Pokorná 2009).

AIC 292 is a new NNRTI that attracted attention at ICAAC in 2013 (Wildum 2013) and is being developed by AiCuris from Wuppertal. It differs chemically from other NNRTIs as diaryl pyrazole carboxamide and is effective against NNRTI resistances such as K103N or Y181C. In Phase I, the compound was well tolerated up to 1,400 mg, half-life is 20 hours. The decisive factor for further development will be whether one of the major HIV players shows interest. Most recently, this was not the case. AiCuris meanwhile concentrated on preparations against herpes viruses.

Elsulfavirine (Elpida®) is an NNRTI developed by Viriom in Russia and marketed there or in other countries such as Ukraine (Al-Salama 2017). It is the prodrug of the active compound VM-1500A with a long half-life of 8 days. In a phase IIb study, 118 people were randomized to 20 mg of elsulfavirine once daily in a double-blind fashion against efavirenz; all received TDF+FTC. After 48 weeks, 81% versus 74% had achieved viral loads below 400 copies/mL (Murphy 2017). Tolerability was good; in particular, there were few CNS side effects with elsulfavirine. This was sufficient for approval by Russian health authorities. Numerous formulations are under investigation, including fixed combinations and long-acting preparations.

GS-PI1 is a PI from Gilead Sciences still in preclinical stages with the potential for unboosted once-daily administration. It appears to have a high resistance barrier, and common PI mutations do not affect its efficacy (Link 2017). Perhaps Gilead is finally finding interest in developing new PIs.

MK-8507 is being or has been developed as a new NNRTI by MSD with islatravir (Kandala 2021). It probably also has efficacy against NNRTI-RAMs. In a phase I trial, 18 participants were treated. The mean 7-day reduction in HIV-1 RNA after a single dose ranged from 1.2 to 1.5 log10 copies/mL (Schürmann 2022). One study was stopped because of lymphopenia (see islatravir). Currently, the future is unclear.

RDEA806 is an NNRTI from Ardea Bioscience. The resistance barrier is reportedly high, and the interaction potential is low (Hamatake 2007). Monotherapy studies showed a drop of over 1.8 logs after seven days, with good tolerability (Moyle 2010). The data are promising enough for further development. However, after the purchase of Ardea by AstraZeneca, the new owner seems to have lost interest.

TMC-310911 is a PI from Tibotec. *In vitro* data look good (Dierynck 2012). Healthy subjects tolerated the compound well; there was an excellent dose-PK relationship (Hoetelmans 2014). In PLWH, viral load decreased by approximately 1.5 log levels after 14 days of monotherapy (boosted with ritonavir) (Stellbrink 2014). It remains to be seen whether this is sufficient for further development.

The great NNRTI and PI die-off – discontinued agents:
- AG-001859 – PI from Pfizer
- Atevirdine – NNRTI, Upjohn focused on delavirdine
- BIRL355 BS – NNRTI from Boehringer, in 2007 Problems with metabolites
- Brecanavir – PI stopped by GSK in late 2006 due to poor PK data
- Calanolide A – NNRTI from Sarawak, probably too weakly effective
- Capravirine (AG1549) – NNRTI from Pfizer, too weak

- DPC 961 – NNRTI, subjects' suicidal thoughts, DPC 963.
- Emivirine (MKC-442, Coactinon) – from Triangle, too weak (Me-too).
- Fosdevirine (GSK 761, formerly IDX-899), NNRTI of ViiV – seizures.
- HBY-097, NNRTI from Hoechst-Bayer, unfavorable side effects
- JE-2147 (AG1776, KNI-764) – PI from Pfizer, nothing new since 1999.
- KNI-272 (kynostatin) – PI, unfavorable PK data.
- Lersivirin, NNRTI of ViiV, nausea, no benefits (me-too).
- Loviride, NNRTI from Janssen Pharmaceuticals, too weak in CAESAR
- MIV-150, Medivir/Chiron, NNRTI, poorly bioavailable
- Mozenavir (DMP-450) – PI from Gilead, Me-too (no benefits apparent).
- PL-110 (MK8122) – PI from MSD, they are dedicated to other compounds
- PNU 142721, Pharmacia & Upjohn, NNRTI, Efavirenz too similar (Me-too).
- RO033-4649 – PI from Roche, probably too similar to saquinavir
- TMC 120 (dapivirine), NNRTI from Tibotec, poor oral availability.

Literature on new NNRTIs and PIs

Al-Salama ZT. Elsulfavirine: First Global Approval. Drugs 2017, 77:1811-1816.

Dierynck I, Van Marck H, Van Ginderen M, et al. TMC310911, a novel HIV type 1 protease inhibitor, shows in vitro an improved resistance profile and higher genetic barrier to resistance compared with current protease inhibitors. Antimicrob Agents Chemother 2011, 55:5723-31.

Hamatake R, Zhang Z, Xu W, et al. RDEA806, a potent NNRTI with a high genetic barrier to resistance. Abstract 1662, 47th ICAAC 2007, Chicago.

Hoetelmans RM, Dierynck I, Smyej I, et al. Safety and pharmacokinetics of the HIV-1 protease inhibitor TMC310911 coadministered with ritonavir in healthy participants: results from 2 phase 1 studies. JAIDS Acquir 2014, 65:299-305.

Kandala B, Fancourt C, Ananthula HK, et al. Model-informed dose selection for islatravir/MK-8507 oral once-weekly phase 2b study. Poster 376, CROI 2021, 6–10 March 2021.

Link JO, Kato D, Moore M, et al. Novel HIV PI with high resistance barrier and potential for unboosted QD oral dosing. Abstract LB433, CROI 2017, Seattle.

Margolis DA, Eron JJ, DeJesus E, White S, Wannamaker P, Stancil B, Johnson M. Unexpected finding of delayed-onset seizures in HIV-positive, treatment-experienced subjects in the Phase IIb evaluation of fosdevirine (GSK2248761). Antivir Ther. 2014;19(1):69-78.

Moyle G, Boffito M, Stoehr A, et al. Phase 2a randomized controlled trial of short-term activity, safety, and pharmacokinetics of a novel nonnucleoside reverse transcriptase inhibitor, RDEA806, in HIV-1-positive, antiretroviral-naive subjects. Antimicrob Agents Chemother 2010, 54:3170-8.

Murphy RL, A.V. Kravchenko SV, Orlova-Morozova EA, et al. Elsulfavirine as compared to efavirenz in combination with TDF/FTC: 48-week study. Abstract 452LB, 24th CROI 2017, Seattle.

Pokorná J, Machala L, ezá ová P Konvalinka J. Current and Novel Inhibitors of HIV Protease. Viruses 2009, 1:1209-1239. http://www.mdpi.com/1999-4915/1/3/1209/htm

Schürmann D, Jackson Rudd D, Schaeffer A, et al. Single Oral Doses of MK-8507, a Novel Non-Nucleoside Reverse Transcriptase Inhibitor, Suppress HIV-1 RNA for a Week. J Acquir Immune Defic Syndr 2022, 89:191-198.

Stellbrink HJ, Arasteh K, Schürmann D, et al. Antiviral activity, pharmacokinetics, and safety of the HIV-1 protease inhibitor TMC310911, coadministered with ritonavir, in treatment-naive HIV-1-infected patients. J Acquir Immune Defic Syndr 2014, 65:283-9.

Wildum S, Paulsen D, Thede K, et al. In vitro and in vivo activities of AIC292, a novel HIV-1 nonnucleoside reverse transcriptase inhibitor. Antimicrob Agents Chemother 2013, 57:5320-9.

Zhuang C, Pannecouque C, De Clercq E, Chen F. Development of non-nucleoside reverse transcriptase inhibitors (NNRTIs): our past twenty years. Acta Pharm Sin B. 2020 Jun;10(6):961-978.

New integrase inhibitors

Integrase strand transfer inhibitors (INSTIs) have become one of the most essential classes of HIV therapy, if not the most important. However, the efficacy of even second-generation INSTIs is also limited by resistance and thus not infinite. There has now been great progress in better understanding the resistance mechanisms (Cook 2020, Passos 2020), hopefully leading to the development of even better INSTIs. However, inhibition of strand transfer is not the only mechanism of action to inhibit integrase. Integrase inhibitors that target other sites are also being developed.

ALLINIs (or **LEDGINs, NCINIs**) are integrase inhibitors that bind allosterically, i.e., not directly to the catalytically active site of the integrase, but to a conserved binding pocket for a cellular cofactor, called LEDGF/p75 (human lens epithelium-derived growth factor). This supports viral replication by binding the integrase to chromatin. The principle was first described in 2010 (Christ 2010). Currently, there is no consensus on what to call this new class, with some referring to LEDGINs, others to ALLINIs (allosteric INIs), NCINIs (non-catalytic INIs), MINIs (multimerization INIs), or INLAIs (integrase-LEDGF allosteric inhibitors). Currently, the term ALLINI seems to be gaining acceptance.
The binding of HIV-1 integrase to viral RNA, a crucial step for forming infectious viruses, is disrupted (Singh 2022). Non-infectious viruses are formed. Surprisingly, another effect of LEDGINs is later than expected in the replication cycle and is more similar to that of PIs or maturation inhibitors (Tsiang 2012, van Bel 2014, Gupta 2016). Thus, the effect is not only in the interaction between LEDGF/p75 and integrase but additionally in a disruption of a not yet well-characterized function of integrase during maturation and assembly of the nucleus, thus making itself "noticeable" later in the replication cycle.
ALLINIs are still in preclinical studies but appear to be a promising new group of integrase inhibitors. This is also illustrated by the extraordinary abundance of papers published in recent months, where searching for suitable molecules is still on at full speed (Review: Engelman 2019). All major HIV companies are engaged.

STP0404 is currently the most advanced ALLINI. There is no cross-resistance with INSTIs (Maehigashi 2021). An initial study of 65 healthy volunteers showed good tolerability, besides mostly mild headache and diarrhea (Meng 2022). Single daily dosing is possible. According to the Korean manufacturer ST Pharm, a phase II trial was planned in the US for the end of 2022.

GSK-1264 from ViiV Healthcare/GSK is also an allosteric inhibitor of integrase that is still preclinical (Gupta 2014). Another compound is **GSK-3839919** (Parcella 2022).

JTP-0157602 is also a potent agent well characterized preclinically (Ohata 2022).

MK-2048 was developed by MSD in 2009. It appears to have a different resistance profile. However, *in vitro* data might be slightly worse than dolutegravir for specific resistance mutations like R263K (Osman 2015). It also appears to have a short life and is being tested in prevention as a vaginal ring, with phase I trials published in 2019 (Hoesley 2019, Liu 2019). New technologies are also being used (Tong 2022).
Stilbenavir – is a new INSTI that binds to the C-terminal domain of integrase and thus is thought to have a different mechanism of action than the classic INSTIs. Accordingly, there appears to be no cross-resistance, and the compound is still preclinical (Aknin 2019).

Out of sight, out of mind: recently stopped integrase inhibitors
- BI-224436 – an ALLINI, stopped before Phase I
- BMS-707035, probably no advantage over raltegravir apparent
- GSK-364735 (GSK), liver toxicity in monkeys, stopped in Phase IIa in 2007

- GS-9822, urothelial toxicity in monkeys
- L-870810 (MSD), liver toxicity in dogs
- MK-2048 (MSD), poor PK data
- S-1360 (Shionogi/GSK), probably too toxic, stopped in 2005

Literature on new integrase inhibitors

Aknin C, Smith EA, Marchand C, et al. Discovery of Novel Integrase Inhibitors Acting outside the Active Site Through High-Throughput Screening. Molecules. 2019 Oct 12;24(20).

Amadori C, van der Velden YU, Bonnard D, et al. The HIV-1 integrase-LEDGF allosteric inhibitor MUT-A: resistance profile, impairment of virus maturation and infectivity but without influence on RNA packaging or virus immunoreactivity. Retrovirology 2017, 14:50.

Christ F, Voet A, Marchand A, et al. Rational design of small-molecule inhibitors of the LEDGF/p75-integrase interaction and HIV replication. Nat Chem Biol 2010, 6:442–448.

Cook NJ, Li W, Berta D, et al. Structural basis of second-generation HIV integrase inhibitor action and viral resistance. Science. 2020 Jan 30.

Engelman AN. Multifaceted HIV integrase functionalities and therapeutic strategies for their inhibition. J Biol Chem 2019, 294:15137-57.

Gupta K, Brady T, Dyer BM, et al. Allosteric inhibition of human immunodeficiency virus integrase: late block during viral replication and abnormal multimerization involving specific protein domains. J Biol Chem 2014, 289:20477-88.

Gupta K, Turkki V, Sherrill-Mix S, et al. Structural Basis for Inhibitor-Induced Aggregation of HIV Integrase. PLoS Biol 2016, 14:e1002584.

Hassounah SA, Alikhani A, Oliveira M, et al. Antiviral Activity of Bictegravir and Cabotegravir against Integrase Inhibitor-Resistant SIVmac239 and HIV-1. Antimicrob Agents Chemother 2017, 61.

Hoesley CJ, Chen BA, Anderson PL, et al. Phase 1 Safety and Pharmacokinetics Study of MK-2048/Vicriviroc (MK-4176)/MK-2048A Intravaginal Rings. Clin Infect Dis 2019, 68:1136-1143.

Liu AY, Zhang J, Anderson PL, et al. Phase 1 Pharmacokinetic Trial of 2 Intravaginal Rings Containing Different Dose Strengths of Vicriviroc (MK-4176) and MK-2048. Clin Infect Dis 2019, 68:1129-1135.

Maehigashi T, Ahn S, Kim UI, et al. A highly potent and safe pyrrolopyridine-based allosteric HIV-1 integrase inhibitor targeting host LEDGF/p75-integrase interaction site. PLoS Pathog. 2021, 17, e1009671.

Ohata Y, Tomonaga M, Watanabe Y, et al. Antiviral Activity and Resistance Profile of the Novel HIV-1 Non-Catalytic Site Integrase Inhibitor JTP-0157602. J Virol 2022, 96:e0184321.

Osman N, Mesplède T, Quashie PK, et al. Dolutegravir maintains a durable effect against HIV replication in tissue culture even after drug washout. J Antimicrob Chemother 2015, 70:2810-5.

Parcella K, Wang T, Eastman K, et al. Discovery and Preclinical Profiling of GSK3839919, a Potent HIV-1 Allosteric Integrase Inhibitor. ACS Med Chem Lett. 2022 May 9;13(6):972-980.

Passos DO, Li M, Jó wik IK, et al. Structural basis for strand transfer inhibitor binding to HIV intasomes. Science. 2020 Jan 30.

Singh PK, Li W, Bedwell G, et al. Allosteric Integrase Inhibitor Influences on HIV-1 Integration and Roles of LEDGF/p75 and HDGFL2 Host Factors. Viruses 2022, 14, 1883.

Tong X, Patel SK, Li J, et al. Development and Evaluation of Nanoparticles-in-Film Technology to Achieve Extended In Vivo Exposure of MK-2048 for HIV Prevention. Polymers (Basel). 2022, 14:1196.

Tsiang M, Jones GS, Niedziela-Majka A, et al. New class of HIV-1 integrase (IN) inhibitors with a dual mode of action. J Biol Chem 2012; 287:21189–21203.

Van Bel N, van der Velden Y, Bonnard D, et al. The Allosteric HIV-1 Integrase Inhibitor BI-D Affects Virion Maturation but Does Not Influence Packaging of a Functional RNA Genome. PLoS One 2014, 9:e103552

New entry inhibitors

Attachment inhibitors, coreceptor antagonists and fusion inhibitors are currently grouped as entry inhibitors, although they are heterogeneous. Four entry inhibitors are available: maraviroc, T-20, ibalizumab, and fostemsavir (see previous chapter). With the new entry inhibitors, in combination with bNAbs (see below), fascinating new possibilities could open up. On the other hand, much is still little more than basic research – many of the compounds discussed below will disappear into obscurity, and some already have done so.

Albuvirtide (Aikening®) is a fusion inhibitor with a half-life of 11–12 days (Chong 2012). Frontier Biotechnologies presented an interim analysis of a larger trial (TALENT) in late 2016 in which 171 individuals with treatment failure on first-line therapy received therapy consisting of weekly infusions of albuvirtide plus lopinavir/r or standard lopinavir/r-based therapy with 2 NRTIs (Wu 2016). A full paper has since appeared (Su 2022). After 48 weeks, more individuals with albuvirtide as second-line therapy had achieved viral loads below 50 copies/mL (80% versus 66%). Although numerous methodological problems were evident and data are sparse, China approved albuvirtide for HIV in 2018. It is said that the approval will be extended to other countries, and several studies are underway, including PrEP (Nie 2021), but also in combination with bNAbs.

Cenicriviroc (**TBR-652** or previously **TAK-652)** is an orally available CCR5/CCR2 antagonist sold first by Takeda to Tobira and then Allergan. Laboratory data showed that multiple mutations in the V3 region (and in the *env* gene) must be present for complete resistance. Oral bioavailability is good, and the half-life is 35–40 hours (Martin 2012). Cenicriviroc also appears to have activity against CCR2, a receptor on monocytes, dendritic, and memory T-cells. Nevertheless, there are no safety concerns because of this activity. After ten days of monotherapy with different doses, viral load decreased by a maximum of 1.5–1.8 log levels in 54 patients (Marier 2011). In a phase II trial of 150 patients testing cenicriviroc as 100 mg and 200 mg against efavirenz (all receiving TDF+FTC), 68% and 64%, respectively, were below 50 copies/mL after 48 weeks, compared with only 50% on efavirenz. However, virologic treatment failure was more frequent under cenicriviroc. Tolerability was good (Thompson 2016). However, with the overall somewhat unfavorable data on maraviroc in recent years, it is unlikely that cenicriviroc will make it to market. It's also unclear what advantage it would have over maraviroc. The new owner, Allergan, focuses on use in NASH, with moderate success (Ratziu 2020). Phase III trials are ongoing. It is also being positioned against COVID-19 (Files 2022).

GSK3732394 (formerly BMS-986197), a "**Combinectin**", is a new, long-acting compound that inhibits HIV entry into the target cell by three different pathways. Adnectins are small proteins that bind to gp41 and CD4, among others. Three synergistically acting adnectins were bound to human serum albumin to stabilize the compound. The effect could be comparable to classical ART. Favorable PK data in the monkey model suggest that once-weekly subcutaneous injections may become feasible (Krystal 2016). Like several other compounds, GSK3732394 was initially developed by BMS and has since been sold to ViiV. Unfortunately, a phase 1, first-time-in-human study on subcutaneous administrations showed unexpectedly low levels in healthy volunteers. The study was terminated when it became clear that the maximum planned doses would not achieve the desired therapeutic profile (Krystal 2022). Other adnectins are being developed that bind primarily to N17, a highly conserved site on gp41 that is not sterically accessible to antibodies (Wensel 2018). Future studies will expand on these findings to improve PK profiles for other long-acting biologics designed as multivalent proteins.

Leronlimab (formerly **Pro-140**) is a monoclonal antibody developed by Progenics that targets human CCR5 receptors (Trkola 2001). Thus, it is not a chemokine derivative like maraviroc, with which there even appears to be a synergistic effect (Murga 2006). The resistance barrier is probably high (Jacobson 2010). Leronlimab must be given parenterally. The normal function of CCR5 receptors should not be disrupted. Under single intravenous doses ranging from 0.5 to 5.0 mg/kg, viral load at the highest dose decreased by 1.83 log levels at nadir by day 10 (Jacobson 2008). Weekly subcutaneous administration can also achieve comparable effects (Jacobsen 2010, Tenorio 2011). CytoDyn now owns the rights. In a long-term follow-up, viral load remained suppressed for at least two years of maintenance therapy in some patients with R5 viruses; participants injected themselves subcutaneously with the antibody weekly (Dhody 2019). Tolerability has been good so far; IIb/III trials are reportedly ongoing. Weekly or fortnightly injections are likely reasonable, at least in patients with limited options. However, these patients often have X4-tropic viruses, for which Leronlimab is ineffective. Therefore, there are also considerations to use the substance as PrEP; animal studies were encouraging (Chang 2021). In October 2022, however, CytoDyn announced that it had voluntarily withdrawn its pending Biologics License Application. This decision was "based on various factors, including systemic issues related to the quality of the data collection and monitoring of the pivotal clinical trials by the clinical research organization contracted to manage the trials, resulting in significant concerns with achieving a successful FDA BLA approval". Whatever this means. We'll see.

Lipovurtide is a fusion inhibitor developed in China with broad activity against HIV-1 (Lan 2021). Initial human injection studies are underway.

Mavorixafor (**AMD 11070)** is a CXCR4 antagonist from AnorMED. Theoretically, blockade of the CXCR4 receptor is attractive because individuals with X4 viruses and limited options could benefit. However, CXCR4 blockade in animal studies had far-reaching consequences in angiogenesis, hematopoiesis, or brain development (Review: Miao 2020). Healthy subjects tolerated AMD 070 well but often developed leukocytosis (Stone 2004). Two pilot studies (Moyle 2007, Saag 2007) demonstrated efficacy in the dual-tropic virus. After ten days of monotherapy, viral load decreased by at least one log level in 7/15 individuals. However, development was temporarily halted in 2007 due to liver toxicity. Binding to the X4 receptor is localized somewhat differently than that of the prodrug Plerixafor, giving hope that there is scope in the development of new, more potent, and less toxic CXCR4 antagonists – with AMD 11070 at least a start has been made and evidence of efficacy established. The compound is currently under further investigation in oncology (Miao 2020).

Plerixafor (**AMD3100**, **Mozobil®**) is a CXCR4 antagonist (Miao 2020). Plerixafor is now approved as a leukocyte growth factor in combination with G-CSF in certain situations due to its side effects, leukocyte mobilization. As an antiretroviral agent, plerixafor is too weak.

UB-421 is a new antibody from BioPharma that targets the CD4 receptor but at a different domain than ibalizumab, namely the first. UB-421 was tested in phase II in PLWH, whose plasma viremia was below 20 copies/mL (Wang 2019). After ART interruption, 29 subjects received eight intravenous infusions of UB-421 at either 10 mg/kg per week or 25 mg/kg every two weeks. UB-421 maintained virologic suppression in all for 8–16 weeks; however, 8 experienced passive blips below 400 copies/mL. One patient discontinued the study because of a rash. No severe immunologic complications were observed, and CD4 T-cells remained stable – which is noteworthy because UB-421 potentially competes with CD4 function. In August

2022, the FDA gave the green light for a phase II trial in patients with multidrug-resistant viruses.

Vicriviroc (SCH-D) is an orally bioavailable CCR5 antagonist. Schering-Plough halted development in July 2010 after analyzing two phase III trials (Gathe 2010). Of 721 pre-treated patients who received vicriviroc or placebo to optimized therapy, 64% versus 62% were below 50 copies/mL at 48 weeks. Despite significant differences in those down to a maximum of two active drugs (70 versus 55%), the company discontinued development. MSD has since taken up the compound and is testing it as a PrEP option or vaginal ring under the name MK-4179 (Hoesley 2019, Liu 2019).

Virip blocks the entry of HIV-1 into the cell by interacting with the gp41 fusion peptide. It is also known as an anchoring inhibitor. German researchers from Ulm discovered the peptide in hemofiltrate, the fluid filtered from dialysis patients' blood, to replace it with an electrolyte solution. Virip is thus a "natural" entry inhibitor whose antiretroviral activity could be significantly enhanced by slight modifications or replacement of a few amino acids (Munch 2007). Several such Virip derivatives are being explored, including **Virip-576** and -353. Under continuous infusions of Virip-576, viral load decreased by about one log level after ten days at the highest dose (Forssmann 2010). Tolerability was good. However, resistance mechanisms have been reported (González-Ortega 2011), resulting in a significant loss of fitness (Müller 2018). It seems possible that Virip will remain an academic anecdote.

Out of sight, out of mind: stopped entry inhibitors
- AMD 3100 (CXCR4A) from AnorMed, Cardiotoxicity
- Aplaviroc/GW873140/AK602 (CCR5A) from GSK, hepatotoxicity
- BMS-806, BMS-488043 (attachment inhibitor), poor pharmacokinetics
- FP-21399 (FI) from Lexigen or Merck, probably too weak
- Pro-542 (attachment inhibitor) from Progenics focuses on Pro-140
- SCH-C/Ancriviroc (CCR5A) from Schering-Plough, cardiac arrhythmias
- Sifuvirtide (FI) – from China, worse PK than Albuvirtide
- T-1249 and T-649 (FIs) from Roche/Trimeris, lack of likelihood of success
- TAK-779, TAK-220 (CCR5A) from Takeda, replaced by TAK-652
- TRI-1144, TRI-999 (FIs), probably too poor PK data

Literature on new entry inhibitors

Berkhout B, Eggink D, Sanders RW. Is there a future for antiviral fusion inhibitors? Curr Opin Virol 2012, 2:50-9.

Chang XL, Webb GM, Wu HL, et al. Antibody-based CCR5 blockade protects Macaques from mucosal SHIV transmission. Nat Commun 2021, 12:3343.

Chong H, Yao X, Zhang C, et al. Biophysical Property and Broad Anti-HIV Activity of Albuvirtide, a 3-Maleimimidopropionic Acid-Modified Peptide Fusion Inhibitor. PLoS One 2012, 7:e32599.

Dhody K, Pourhassan N, Kazempour K, et al. PRO 140, a monoclonal antibody targeting CCR5, as a long-acting, single-agent maintenance therapy for HIV-1 infection. HIV Clin Trials 2018, 19:85-93.

Files DC, Tacke F, O'Sullivan A, Dorr P, Ferguson WG, Powderly WG. Rationale of using the dual chemokine receptor CCR2/CCR5 inhibitor cenicriviroc for the treatment of COVID-19. PLoS Pathog 2022, 18:e1010547.

Forssmann WG, The YH, Stoll M, et al. Short-term monotherapy in HIV-infected patients with a virus entry inhibitor against the gp41 fusion peptide. Sci Transl Med 2010, 2:63re3.

Gathe J, R Diaz R, Fätkenheuer G, et al. Phase 3 trials of vicriviroc in treatment-experienced subjects demonstrate safety but not significantly superior efficacy over potent background regimens alone. Abstract 54LB, 17th CROI 2010, San Francisco.

Gonzalez E, Ballana E, Clotet B, Esté JA. Development of resistance to VIR-353 with cross-resistance to the natural HIV-1 entry virus inhibitory peptide (VIRIP). AIDS 2011, 25:1557-83.

González-Ortega E, Ballana E, Badia R, Clotet B, Esté JA. Compensatory mutations rescue the virus replicative capacity of VIRIP-resistant HIV-1. Antiviral Res 2011, 92:479-83.

Hoesley CJ, Chen BA, Anderson PL, et al. Phase 1 Safety and Pharmacokinetics Study of MK-2048/Vicriviroc (MK-4176)/MK-2048A Intravaginal Rings. Clin Infect Dis 2019, 68:1136-1143.

Ingallinella P, Bianchi E, Ladwa NA, et al. Addition of a cholesterol group to an HIV-1 peptide fusion inhibitor dramatically increases its antiviral potency. Proc Natl Acad Sci U S A 2009 Mar 18.

Jacobson J, Thompson M, Fischl M, et al. Phase 2a study of PRO 140 in HIV-infected adults. Abstract HG-1220, 49th ICAAC 2009, San Francisco.

Jacobson JM, Lalezari JP, Thompson MA, et al. Phase 2a study of the CCR5 monoclonal antibody PRO 140 administered intravenously to HIV-infected adults. Antimicrob Agents Chemother 2010, 54:4137-42.

Jacobson JM, Thompson MA, Lalezari JP, et al. Anti-HIV-1 activity of weekly or biweekly treatment with subcutaneous PRO 140, a CCR5 monoclonal antibody. J Infect Dis 2010, 201:1481-7.

Krystal M, Chabria S, Austin D, et al. A Phase 1 randomized study of GSK3732394, an investigational long-acting biologic treatment regimen for HIV-1 infection. Antivir Ther 2022, 27:13596535221131164.

Krystal M, Wensel D, Sun YM, et al. HIV Combinectin BMS-986197: A long-acting inhibitor with multiple modes of action. Abstract 97, 16th CROI 2016, Boston.

Lan Q, Pu J, Cai Y, et al. Lipopeptide-based pan-CoV fusion inhibitors potently inhibit HIV-1 infection. Microbes Infect 2021, 23:104840.

Liu AY, Zhang J, Anderson PL, et al. Phase 1 Pharmacokinetic Trial of 2 Intravaginal Rings Containing Different Dose Strengths of Vicriviroc (MK-4176) and MK-2048. Clin Infect Dis 2019, 68:1129-1135.

Marier JF, Trinh M, Pheng LH, Palleja SM, Martin DE. Pharmacokinetics and Pharmacodynamics of TBR-652, a Novel CCR5 Antagonist, in HIV-1-Infected, Antiretroviral Treatment-Experienced and CCR5 Antagonist-Naïve Patients. Antimicrob Agents Chemother 2011 Apr 12. [Epub ahead of print].

Martin D, Beliveau M, Marier JF, et al. Pharmacokinetics of Cenicriviroc following 100- or 200-mg Once-daily Dosing with Open-label Emtricitabine/Tenofovir in HIV 1+ Subjects Enrolled in a Phase 2b Study. Abstract 600, 19th CROI 2012, Seattle.

Miao M, De Clercq E, Li G. Clinical significance of chemokine receptor antagonists. Expert Opin Drug Metab Toxicol 2020, 16:11-30.

Moyle G, DeJesus E, Boffito M, et al. CXCR4 antagonism: proof of activity with AMD 11070. Abstract 511, 14th CROI 2007, Los Angeles.

Müller JA, Glöckle A, Gawanbacht A, et al. Reduced Susceptibility to VIRIP-Based HIV-1 Entry Inhibitors Has a High Genetic Barrier and Severe Fitness Costs. J Virol. 2018 Aug 16;92(17).

Munch J, Standker L, Adermann K, et al. Discovery and optimization of a natural HIV-1 entry inhibitor targeting the gp41 fusion peptide. Cell 2007;129:263-75.

Murga JD, Franti M, Pevear DC, Maddon PJ, Olson WC. The potent antiviral synergy between monoclonal antibody and small-molecule CCR5 inhibitors of human immunodeficiency virus type 1. Antimicrob Agents Chemother 2006, 50:3289-96.

Nie J, Sun F, He X, et al. Tolerability and Adherence of Antiretroviral Regimens Containing Long-Acting Fusion Inhibitor Albuvirtide for HIV Post-Exposure Prophylaxis: A Cohort Study in China. Infect Dis Ther 2021, 10:2611-2623.

Ratziu V, Sanyal A, Harrison SA, et al. Cenicriviroc Treatment for Adults with Nonalcoholic Steatohepatitis and Fibrosis: Final Analysis of the Phase 2b CENTAUR Study. Hepatology. 2020 Jan 13.

Saag M, Rosenkranz S, Becker S, et al. Proof of concept of ARV activity of AMD 11070 (an orally administered CXCR4 entry inhibitor): results of the first dosing cohort A studied in ACTG protocol A5210). Abstract 512, 14th CROI 2007, Los Angeles.

Schneider EL, Ashley GW, Dillen L, et al. Half-life extension of the HIV-fusion inhibitor peptide TRI-1144 using a novel linker technology. Eur J Pharm Biopharm 2015, 93:254-9.

Su B, Yao C, Zhao QX, et al. Long-acting HIV fusion inhibitor albuvirtide combined with ritonavir-boosted lopinavir for HIV-1-infected patients after failing the first-line antiretroviral therapy: 48-week randomized, controlled, phase 3 non-inferiority TALENT study. J Infect. 2022 Sep;85(3):334-363.

Tenorio AR. The monoclonal CCR5 antibody PRO-140: the promise of once-weekly HIV therapy. Curr HIV/AIDS Rep 2011, 8:1-3.

Thompson M, Saag M, DeJesus E, et al. A 48-week randomized phase 2b study evaluating cenicriviroc versus efavirenz in treatment-naive HIV-infected adults with C-C chemokine receptor type 5-tropic virus. AIDS 2016, 30:869-78.

Trkola A, Ketas TJ, Nagashima KA, et al. Potent, broad-spectrum inhibition of HIV type 1 by the CCR5 monoclonal antibody PRO 140. J Virol 2001, 75:579-88.

Wang CY, Wong WW, Tsai HC, et al. Effect of Anti-CD4 Antibody UB-421 on HIV-1 Rebound after Treatment Interruption. N Engl J Med 2019, 380:1535-45.

Wensel D, Sun Y, Davis J, et al. A Novel gp41-Binding Adnectin with Potent Anti-HIV Activity Is Highly Synergistic when Linked to a CD4-Binding Adnectin. J Virol 2018, 92(14).

Wensel D, Sun Y, Davis J, et al. GSK3732394: a Multi-specific Inhibitor of HIV Entry. J Virol. 2019 Sep 30;93(20).

Wong R, Bodard V, Metz M, et al. Understanding the interactions between CXCR4 and AMD 11070, a first-in-class small-molecule antagonist of the HIV coreceptor. Abstract 495, 14th CROI 2007, Los Angeles.

Zhang H, Jin R, Yao C, et al. Combination of long-acting HIV fusion inhibitor albuvirtide and LPV/r showed potent efficacy in HIV-1 patients. AIDS Res Ther 2016, 13:8.

Broadly neutralizing antibodies

FLORIAN KLEIN, CHRISTIAN HOFFMANN

The so-called envelope proteins, or spikes, protrude from the envelope surrounding HIV. These envelope glycoprotein complexes (Env for short) each consist of an outer glycoprotein (gp120) and a transmembrane protein (gp41). Each envelope protein contains three gp120/gp41 molecules, forming a trimeric structure. The HIV envelope protein is directly visible to antibodies and thus forms a central target of the human humoral immune response, hence of vaccine and antibody research. HIV has developed a variety of very effective mechanisms for the envelope proteins or spikes to evade the immune response (Klein 2010+2013). Given the high genetic variance alone, this forms a moving target. In addition, only a relatively small number of spikes are found on each virion, and their vulnerable, conserved regions are often coated with many sugar molecules (glycan shield). Approximately 10–25% of PLWH develop a neutralizing antibody response against various *env* regions sometime after infection – rarely within the first year (Sather 2009, Stamatatos 2009, Mikell 2011). This immune response is more commonly found in individuals exposed to high levels of envelope protein as antigen, i.e., individuals with a plasma viral load over a prolonged period (Doria-Rose 2010, Rusert 2016). Interestingly, it is not only the individual immune system that favors development but also the virus itself: certain viruses seem to induce a broader antibody response than others (Kouvos 2018).
The therapeutic potential was already looked into in the early 1990s; however, studies showed a minimal effect (Trkola 2005) since the antibodies used were limited in their activity. Research has been spurred in recent years by better techniques for cloning human antibodies and the identification of so-called "elite neutralizers," i.e., patients who have a markedly good neutralizing antibody response against HIV in serum (West 2014). Since about 2009, a plethora of new antibodies have been discovered that are significantly more potent than first-generation antibodies and target multiple, vulnerable sites of *env* (Walker 2009, Wu 2010, Scheid 2011, Caskey 2019). The latter include, most notably, the CD4 binding site, but also the loop-like and variable regions in gp120 ("V-loops") and various regions in the gp41 glycoprotein (see Figure 3.1). Because they can recognize and render many HIV variants harmless, these antibodies are called broadly neutralizing antibodies (bNAbs). In addition to the activity against the free virus, antiviral effects of bNAbs against HIV-infected cells have been observed, among others, by blocking the release of HIV (Duflo 2022).

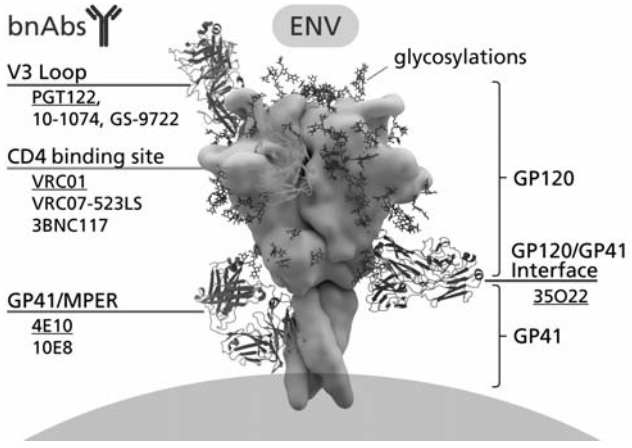

Figure 3.1: The ENV glycoprotein and binding sites of broadly neutralizing antibodies.

Although "broad" remains poorly defined, most bNAbs can neutralize approximately 60% to over 97% of circulating HIV isolates (Wu 2010, Scheid 2011, Klein 2013, Schommers 2020). In 2015, encouraging antiretroviral effects were shown for the first time in humans (Caskey 2015, Lynch 2015), further boosting development. Many clinical trials have already been conducted, testing different bNAbs. In addition to studies for use in prevention, numerous bNAb studies are underway for HIV therapy. Common approaches here are to achieve long-term viral control with a combination of different bNAbs or to eliminate infected cells and reduce the viral reservoir by combining them with ART and drugs for immune activation (current reviews: Caskey 2019, Julg 2021, Gruell 2022). Meanwhile, major companies have also become active in the field of HIV therapy. Here, we will briefly touch upon the clinical experience of the major bNAbs. Given the rapid development in recent years, only a snapshot (as of the beginning of 2023) can be given.

CD4 binding site

One group of bNAbs attacks the CD4 binding site, a protected area surrounded by glycans. They are also abbreviated as "CD4bs bNAbs". Many have broad and particularly potent activity and were the first new-generation bNAbs to be clinically tested.

VRC01 is one of the prototypes of this group. Healthy subjects tolerated various doses well (Ledgerwood 2015). In 6/8 PLWH, viral load decreased by 1.1–1.8 logs, although pre-existing resistance was detectable in two subjects (Lynch 2015). Unfortunately, in two pilot studies, monotherapy showed little effect on viral rebound during analytic therapy breaks despite drug levels still being present (Bar 2016). VRC01-resistant isolates were found during therapy breaks; they were pre-existing and newly selected. Also, in a small, double-blind, randomized trial from Thailand in men with acute HIV, VRC01 remained without effect on viral setpoint during analytic therapy breaks (Crowell 2019). VRC01 has also been studied in two large Phase II trials (HVTN 704 and HPTN 085) as transmission prophylaxis in individuals at high risk for HIV infection. Again, the expected protective effect did not occur: among the 2,699 participants, 32 infections occurred in the low-dose group, 28 in the high-dose group, and 38 in the placebo group (Corey 2021). However, a sub-analysis showed that infections with sensitive viral strains with an IC_{80} of less than 1 µg per milliliter were effectively prevented by VRC01 (efficacy of approximately 75%). Thus, it can be inferred that passive immunization with highly potent bNAbs may well be able to confer protection from HIV infection. However, the neutralizing activity of VRC01 alone was insufficient to produce a significant effect across the study population. Better bNAbs, preferably combined, would need to be used for a successful outcome.

VRC07-523LS is about 5–8 times as potent as VRC01 and can neutralize up to 96% of all HIV-1 variants tested (Rudicell 2014). In addition, the antibody has a mutation in the Fc portion (LS mutation), resulting in a significantly longer half-life, about 33 days intravenously and about 29 days subcutaneously (Mahomed 2022). This mutation is now incorporated in almost all other bNAbs. Single subcutaneous doses of VRC01-523LS were also well tolerated in a Phase I study in healthy individuals (Gaudinski 2019). In a small pilot study in viremic adults, VRC07-523 was shown to have better antiviral activity than VRC01 (both had the LS mutation incorporated). In 3/7 subjects, viral load dropped > 0.5 log under VRC01LS; under VRC07-523LS, 8/9 showed a drop of > 1.2 log (Chen 2019). A study by the IMPAACT pediatric network recently presented PK data as PrEP in 22 HIV-exposed but uninfected infants supporting three months of administration (Cunningham 2022).

Teropavimab (3BNC117 or GS-5423) also targets the binding site for human CD4. A single infusion of 30 mg/kg reduced viral load by 0.8–2.5 logs, and viral load

remained partially reduced for 28 days (Caskey 2015). It is possible that administration also enhances the HIV-specific immune response (Schoofs 2016). During analytic therapy breaks, viral rebound took several weeks longer after 2–4 infusions than in historical controls (Scheid 2016). In monkeys, administration during acute infection resulted in durable control of SIV infection (Nishimura 2017). The immune activation mediated by bNAbs (so-called 'vaccinal effect') of the autologous immune response is currently under further investigation (Tipoe 2022). The cause could be bNAb/HIV immune complexes, which lead to an additional amplification of the immune response. Combination with romidepsin did not affect the latent reservoir (Gruell 2022). Teropavimab is currently being tested mainly in combination with other Gilead bNAbs, such as 10-1074 (see below).

V1/V2 and V3 Loop of gp120

Some bNAbs do not bind to the CD4 binding site but to the V1/V2 loop, a variable glycan-containing region of gp120. These antibodies also interact with the glycan shield, among others. Representatives are **PGDM1400** and **CAP256**. Another critical target is at the base of the V3 loop and surrounding glycans. Representative agents include **zinlirvimab** and **PGT121**. The bNAbs directed against the V-loops are partly more potent but usually less broad (about 60–80%) than the antibodies directed against the CD4bs (Gama 2018). Bispecific bNAbs that simultaneously bind multiple epitopes on V1/V2 and V3 are already being investigated and thus maybe even more broadly effective and potent (Davis-Gardner 2020).

Zinlirvimab (10-1074, GS-2872) binds to the stem of the V3 loop at the *env* protein. In an initial monotherapy study, the highest dose reduced viral load by 1.5 logs (Caskey 2017). However, viral load did not decrease in all individuals. Instead, on monotherapy, resistance was selected in almost everyone. Resistance was much less common when combined with 3BNC117 (Bar-On 2018, Mendoza 2019). This antibody is used by Gilead in various combinations (see below).

PGT121 is a monoclonal antibody isolated from an African "elite neutralizer" in 2011. Like 10-1074, PGT121 targets the base of the V3 loop. In a pilot study, viral load decreased by 1.77 logs, with a median viral load reaching nadir after 8.5 days. Two individuals with low baseline viral loads experienced ART-free viral suppression for more than 168 days (Stephenson 2021). Long-acting versions such as **PGT121,414LS** are being tested in combination with other bNAbs or drugs.

Elipovimab (GS-9722) is a further development of **PGT121** and is designed to be particularly effective in targeting and eliminating HIV-infected cells, thereby reducing the reservoir (Thomsen 2019). It is currently in Phase Ib. Manufacturer Gilead Sciences plans to study GS-9722 in combination with other bNAbs and other immunomodulatory agents.

Regions of gp41

MPER stands for "membrane proximal external region", a binding site on the gp41 transmembrane protein. bNAbs have now also been isolated for this site and for another glycan-rich region on gp41 that arises shortly before fusion and is located at the junction between gp120 and gp41 (Falkowska 2014). **PGT151 targets** this "gp120/gp41 interphase".

10E8 binds to the conserved region in MPER of gp41, neutralizing more than 95% of all HIV-1 variants, making it the bNAb with the broadest activity ever (Huang 2012, Kwon 2016). However, subcutaneous application was associated with skin reactions at the injection site, including grade 3 erythema associated with fever and feeling sick. This led to a halt to ongoing studies (Caskey 2019).

Prediction, pre-existing resistances

Many HIV isolates may be resistant to bNAbs or develop mutations relatively quickly. How well and with what methods can possible resistance or the development of resistance be predicted? Numerous studies are addressing these questions. Genotypic analysis of the *env* gene is a relatively simple method for a possible prediction. For some antibodies, e.g., V3-loop bNAbs like zinlirvimab or PGT121, there is a very good correlation to the actual (phenotypic) susceptibility. This is more difficult for other antibodies like CD4bs bNAbs (Moldt 2021, Pabus 2022). Also, the escape dynamics of HIV-1 during antibody treatment can now be robustly predicted (Meijers 2021).

In a rather large study from the UK, 48% of 147 individuals were found to be resistant to one or both of the bNAbs tested, with 29% resistant to zinlirvimab and 13% resistant to teropavimab. A total of 3.4% were resistant to both bNAbs. Phylogenetic analyses revealed evidence of both transmitted resistance and evolution in the host (Zacharopoulou 2022). In another study, 41/54 (76%) were sensitive to teropavimab, 37/54 (69%) to zinlirvimab and 30/54 (56%) to both bNAbs (Montaner 2022).

Combinations of bNAbs, new approaches

Given the development of resistance to individual bNAbs, combinations are increasingly being tested. In animal models, this has prevented resistance (Klein 2012). In addition, combinations of two to four bNAbs can neutralize up to 100% of the viruses in a panel (Kong 2015). Combining multiple attachment sites on a single molecule has also become possible with newer technologies. In monkey models, such bi- or tri-specific antibodies are highly protective (Gautam 2016, Xu 2017). Human studies with the tri-specific antibody SAR441236 are currently underway. A synergistic effect of some bNAbs also appears to exist when combined with the attachment inhibitor fostemsavir, a small molecule that also binds to gp120, approved in 2021. Thus, bNAb-resistant isolates remain sensitive to fostemsavir and *vice versa* (Zhang 2019).

Teropavimab (**3BNC117**) plus **zinlirvimab (10-1074**, **GS-2872)** shows good tolerability and antiviral activity and is already more commonly used (Cohen 2019, Gruell 2022). In a Phase 1b study, PLWH were given both antibodies at a dose of 30 mg/kg each at weeks 0, 3, and 6. The nine subjects with sensitive virus maintained suppression without classical ART for a median of 21 weeks (in some cases significantly longer). Viral rebound was detected only when antibodies fell below their therapeutic levels. As long as the drug levels were sufficiently high, resistant viruses did not develop (Mendoza 2018). Global licensing rights for both bNAbs were purchased by Gilead Sciences in 2020. In a recently published study, virologic suppression could be maintained for at least 20 weeks without ART in 13/17 individuals with seven administrations of the bNAb combination (Gaebler 2022). In two subjects, viral suppression persisted for one year. There was also a positive effect on the viral reservoir during bNAb administration (Gaebler 2022) and possibly on the T cell response (Niessl 2020). In the monkey model, the combination was protective (Garber 2021). In another study in which both bNAbs were combined with pegylated interferon, 10/14 remained below the detection limit after 26 weeks (Tebas 2022).

Long-acting preparations of the antibodies in which the Fc receptor was modified are being studied (Lee 2022). Initial clinical data were presented at CROI 2022 (Caskey 2022). The modified bNAbs (with half-lives of approximately 62 and 80 days, respectively) were infused into six untreated male PLWH. Two patients with baseline viral loads below 10,000 copies/mL showed long-lasting viral suppression, while four showed transient suppression. The combination is currently also being tested with the long-acting capsid inhibitor lenacapavir.

VRC01-LS plus **zinlirvimab (10-1074, GS-2872):** The Tatelo study tested this combination in infected infants as an alternative to daily oral ART (Shapiro 2022). In this proof-of-concept study, viral load remained below 40 copies/mL in 11/28 children (44%) by week 24. However, in 14/28 children, the median viral load increased again to > 400 copies/mL after four weeks.

VRC07-523LS plus **PGDM1400** plus **PGT121**: What happens when three bNAbs are combined? In a pilot study, five viremic adults received the CD4 binding site antibody VRC07-523LS and two V2/V3 loop-specific antibodies (Julg 2022). Viral load decreased maximally by a mean of 2.04 $\log_{10}$ copies/mL; however, viral rebound occurred in all participants within an average of 20 days after nadir. Rebound viruses showed partial to complete resistance to PGDM1400 and PGT121 *in vitro* while maintaining sensitivity to VRC07-523LS.

Is it possible to let patients produce the bNAbs themselves? Recently, a study was presented in which the transfer of DNA encoding VRC07 was tested using a vector (Casazza 2022). For this, an adeno-associated virus (AAV8) vector encoding both the light and heavy chains of VRC07 was administered to eight adults living with HIV (Casazza 2022). New approaches in which mRNA technologies are also used could further advance this pathway (Naranayan 2022).

Broadly neutralizing antibodies could change antiretroviral therapy as we understand it. The real potential is not yet foreseeable and is not limited to the treatment of HIV infection. Essential roles in prevention and even functional cures are also conceivable. The problems that have come to light – especially resistance and cost – do not seem insoluble. If it were possible to administer such maintenance therapy every 6–12 months with a short infusion (a few minutes), many people with HIV would opt for it. Still, there are other hurdles to overcome. For example, greater neutralizing efficacy and breadth are needed to avoid and overcome resistance. But there is no doubt: this chapter will continue to grow in future issues.

Literature on neutralizing antibodies

Bar KJ, Harrison LJ, Overton ET, et al. ACTG 5340: The Effect of VRC01 on Viral Kinetics After Analytic Treatment Interruption. Abstract 32LB, 23rd CROI 2016, Boston.

Bar KJ, Sneller MC, Harrison LJ, et al. Effect of HIV Antibody VRC01 on Viral Rebound after Treatment Interruption. NEJM 2016, 375:2037-2050.

Bar-On Y, Gruell H, Schoofs T, et al. Safety and antiviral activity of combination HIV-1 broadly neutralizing antibodies in viremic individuals. Nat Med 2018, 24:1701-1707.

Casazza JP, Cale EM, Narpala S, et al. Safety and tolerability of AAV8 delivery of a broadly neutralizing antibody in adults living with HIV: a phase 1, dose-escalation trial. Nat Med 2022, 28:1022-1030.

Caskey M, Klein F, Lorenzi JC, et al. Viraemia is suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. Nature 2015; 522: 487-91.

Caskey M, Klein F, Nussenzweig MC. Broadly neutralizing anti-HIV-1 monoclonal antibodies in the clinic. Nat Med 2019, 25:547-553.

Caskey M, Millard K, Turroja M, et al. Phase 1 study of long-acting 3BNC117 and 10-1074 in viremic adults living with HIV. Abstract 140, CROI 2022.

Caskey M, Schoofs T, Gruell H, et al. Antibody 10-1074 suppresses viremia in HIV-1-infected individuals. Nat Med 2017, 23:185-191.

Chen G, Coates E, Fichtenbaum C, et al. Safety and virologic effect of the HIV-1 broadly neutralizing antibodies, VRC01LS or VRC07-523LS, administered to HIV-infected adults in a phase 1 clinical trial. Abstract WEAA0305LB, IAS 2019, Mexico City.

Cohen YZ, Butler AL, Millard K, et al. Safety, pharmacokinetics, and immunogenicity of the combination of the broadly neutralizing anti-HIV-1 antibodies 3BNC117 and 10-1074 in healthy adults: A randomized, phase 1 study. PLoS One 2019, 14:e0219142.

Corey L, Gilbert PB, Juraska M, et al. Two Randomized Trials of Neutralizing Antibodies to Prevent HIV-1 Acquisition. NEJM 2021, 384:1003-1014.

Crowell TA, Colby DJ, Pinyakorn S, et al. Safety and efficacy of VRC01 broadly neutralising antibodies in adults with acutely treated HIV (RV397): a phase 2, randomised, double-blind, placebo-controlled trial. Lancet HIV 2019, 6:e297-e306.

Cunningham CK, Capparelli E, McFarland EJ, et al. Extended safety and pk of anti-HIV monoclonal Ab VRC07-523LS in HIV-exposed infants. Abstract 732, CROI 2022.

Cunningham CK, McFarland EJ, Morrison RL, et al. Safety, Tolerability, and Pharmacokinetics of the Broadly Neutralizing HIV-1 Monoclonal Antibody VRC01 in HIV-Exposed Newborn Infants. J Infect Dis. 2019 Nov 4.

Davis-Gardner ME, Alfant B, Weber JA, et al. A bispecific antibody that simultaneously recognizes the V2- and V3-Glycan epitopes of the HIV-1 envelope glycoprotein is broader and more potent than its parental antibodies. mBio 2020, 11: e03080-19.

Doria-Rose NA, Klein RM, Daniels MG, et al. Breadth of human immunodeficiency virus-specific neutralizing activity in sera: clustering analysis and association with clinical variables. J Virol 2010, 84: 1631–1636.

Dufloo J, Planchais C, Frémont S, et al. Broadly neutralizing anti-HIV-1 antibodies tether viral particles at the surface of infected cells. Nat Commun 2022, 13:630.

Falkowska E, Le KM, Ramos A, et al. Broadly neutralizing HIV antibodies define a glycan-dependent epitope on the prefusion conformation of gp41 on cleaved envelope trimers. Immunity 2014, 40:657-68.

Gaebler C, Nogueira L, Stoffel E, et al. Prolonged viral suppression with anti-HIV-1 antibody therapy. Nature. 2022 Apr 13.

Gama L, Koup RA. New-Generation High-Potency and Designer Antibodies: Role in HIV-1 Treatment. Annu. Rev Med 2018, 69:14.1–14.11.

Garber DA, Guenthner P, Mitchell J, et al. Broadly neutralizing antibody-mediated protection of macaques against repeated intravenous exposures to simian-human immunodeficiency virus. AIDS 2021, 35:1567-1574.

Gaudinski MR, Houser KV, Doria-Rose NA. Safety and pharmacokinetics of broadly neutralising human monoclonal antibody VRC07-523LS in healthy adults: a phase 1 dose-escalation clinical trial. Lancet HIV 2019, 6:e667-e679.

Gautam R, Nishimura Y, Pegu A, et al. A single injection of anti-HIV-1 antibodies protects against repeated SHIV challenges. Nature 2016, 533:105–9.

Gruell H, Gunst JD, Cohen YZ, et al. Effect of 3BNC117 and romidepsin on the HIV-1 reservoir in people taking suppressive antiretroviral therapy (ROADMAP): a randomised, open-label, phase 2A trial. Lancet Microbe 2022, 3:e203-e214.

Gruell H, Schommers P. Broadly neutralizing antibodies against HIV-1 and concepts for application. Curr Opin Virol 2022 Jun;54:101211.

Julg B, Barouch D. Broadly neutralizing antibodies for HIV-1 prevention and therapy. Semin Immunol. 2021 Jan;51:101475.

Julg B, Stephenson KE, Wagh K, et al. Safety and antiviral activity of triple combination broadly neutralizing monoclonal antibody therapy against HIV-1: a phase 1 clinical trial. Nat Med 2022 May 12.

Klein F, Halper-Stromberg A, Horwitz JA, et al. HIV therapy by a combination of broadly neutralizing antibodies in humanized mice. Nature 2012, 492:118-22.

Klein F, Mouquet H, Dosenovic P, et al. Antibodies in HIV-1 vaccine development and therapy. Science 2013; 341: 1199-204.

Klein JS, Bjorkman PJ. Few and far between: how HIV may be evading antibody avidity. PLoS Pathog 2010;6:e1000908.

Kong R, Louder MK, Wagh K, et al. Improving neutralization potency and breadth by combining broadly reactive HIV-1 antibodies targeting major neutralization epitopes. J. Virol 2015, 89:2659–71.

Kouyos RD, Rusert P, Kadelka C, et al. Tracing HIV-1 strains that imprint broadly neutralizing antibody responses. Nature 2018, 561:406-410.

Ledgerwood JE, Coates EE, Yamshchikov G, et al. Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults. Clin Exp Immunol 2015, 182:289-301.

Lee MJ, Collins S, Babalis D, et al. The RIO trial: rationale, design, and the role of community involvement in a randomised placebo-controlled trial of antiretroviral therapy plus dual long-acting HIV-specific broadly neutralising antibodies (bNAbs) in participants diagnosed with recent HIV infection-study protocol for a two-stage randomised phase II trial. Trials 2022, 23:263.

Lynch RM, Boritz E, Coates EE, et al. Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection. Sci Transl Med 2015, 7:319ra206.

Mahomed S, Garrett N, Capparelli EV, et al. Safety and Pharmacokinetics of Monoclonal Antibodies VRC07-523LS and PGT121 Administered Subcutaneously for Human Immunodeficiency Virus Prevention. J Infect Dis 2022, 226:510-520.

Meijers M, Vanshylla K, Gruell H, Klein F, Lässig M. Predicting in vivo escape dynamics of HIV-1 from a broadly neutralizing antibody. Proc Natl Acad Sci U S A 2021; 118:e2104651118.

Mendoza P, Gruell H, Nogueira L, et al. Combination therapy with anti-HIV-1 antibodies maintains viral suppression. Nature 2018, 561: 479-484.

Mikell I, Sather DN, Kalams SA, et al. Characteristics of the earliest cross-neutralizing antibody response to HIV-1. PLoS Pathog 2011; 7: e1001251.

Moldt B, Parvangada A, Martin R, et al. Evaluation of Broadly Neutralizing Antibody Sensitivity by Genotyping and Phenotyping for Qualifying Participants to HIV Clinical Trials. J AIDS 2021, 88:61-69.

Montaner LJ, Lynn K, Azzoni L, et al. Susceptibility to 3BNC117 and 10-1074 in ART-suppressed chronically infected persons. Abstract 503, CROI 2022.

Narayanan E, Falcone S, Elbashir SM, et al. Rational Design and In Vivo Characterization of mRNA Encoded Broadly Neutralizing Antibody Combinations against HIV-1. Antibodies 2022, 11, 67.

Niessl J, Baxter AE, Mendoza P, et al. Combination anti-HIV-1 antibody therapy is associated with increased virus-specific T cell immunity. Nat Med 2020, 26:222-227.

Nishimura Y, Gautam R, Chun TW, et al. Early antibody therapy can induce long-lasting immunity to SHIV. Nature 2017, 543:559-563.

Pahus MH, Gunst JD, Ramos V, et al. Performance of a phenotype and 2 genotype algorithms for bNAb sensitivity prediction. Abstract 504, CROI 2022.

Rudicell RS, Kwon YD, Ko SY, et al. Enhanced potency of a broadly neutralizing HIV-1 antibody in vitro improves protection against lentiviral infection in vivo. J. Virol 2014, 88:12669–82.

Rusert P, Kouyos RD, Kadelka C, et al. Determinants of HIV-1 broadly neutralizing antibody induction. Nat Med 2016, 22:1260-1267.

Sather DN, Armann J, Ching LK, et al. Factors associated with the development of cross-reactive neutralizing antibodies during human immunodeficiency virus type 1 infection. J Virol 2009, 83: 757–76937.

Scheid JF, Horwitz JA, Bar-On Y, et al. HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption. Nature 2016, 535:556-60.

Scheid JF, Mouquet H, Ueberheide B, et al. Sequence and structural convergence of broad and potent HIV antibodies that mimic CD4 binding. Science 2011, 333:1633-7.

Schommers P, Gruell H, Abernathy ME, et al. Restriction of HIV-1 Escape by a Highly Broad and Potent Neutralizing Antibody. Cell 2020, 180:471-489.e22.

Schoofs T, Klein F, Braunschweig M, et al. HIV-1 therapy with monoclonal antibody 3BNC117 elicits host immune responses against HIV-1. Science 2016, 352:997-1001.

Shapiro R, Maswabi K, Ajibola G, et al. Treatment with broadly neutralizing antibodies in children with HIV in Botswana. Abstract 32, CROI 2022.

Sloan DD, Lam CY, Irrinki A, et al. Targeting HIV Reservoir in Infected CD4 T Cells by Dual-Affinity Re-targeting Molecules (DARTs) that Bind HIV Envelope and Recruit Cytotoxic T Cells. PLoS Pathog 2015, 11:e1005233.

Stamatatos L, Morris L, Burton DR, Mascola JR. Neutralizing antibodies generated during natural HIV-1 infection: good news for an HIV-1 vaccine? Nat Med 2009, 15: 866–87036.

Stephenson KE, Julg B, Tan CS, et al. Safety, pharmacokinetics and antiviral activity of PGT121, a broadly neutralizing monoclonal antibody against HIV-1: a randomized, placebo-controlled, phase 1 clinical trial. Nat Med 2021, 27:1718-1724.

Sung JA, Pickeral J, Liu L, et al. Dual-affinity re-targeting proteins direct T cell-mediated cytolysis of latently HIV-infected cells. J Clin Invest 2015, 125:4077-90.

Tebas P, Azzoni L, Papasavvas E, et al. BEAT2: PEG-IFN-α2B + 3BNC117 and 10-1074 keeps HIV at <20 c/µl during 26 week ATI. Abstract 352, CROI 2022.

Thomsen N, Balakrishnan M, Pace C, et al. GS-9722: First-in-Class, Effector-Enhanced, Broadly Neutralizing Antibody for HIV Cure. Abstract 356, CROI 2019, Seattle.

Tipoe T, Fidler S, Frater J. An exploration of how broadly neutralizing antibodies might induce HIV remission: the 'vaccinal' effect. Curr Opin HIV AIDS 2022, 17:162-170.

Trkola A, Kuster H, Rusert P, et al. Delay of HIV-1 rebound after cessation of antiretroviral therapy through passive transfer of human neutralizing antibodies. Nat Med 2005, 11:615-22.

Walker LM, Phogat SK, Chan-Hui PY, et al. Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. Science 2009, 326:285-9.

West AP Jr, Scharf L, Scheid JF, Klein F, Bjorkman PJ, Nussenzweig MC. Structural insights on the role of antibodies in HIV-1 vaccine and therapy. Cell 2014, 156:633-48.

Wibmer CK, Moore PL, Morris L. HIV broadly neutralizing antibody targets. Curr Opin HIV AIDS 2015;10:135–143.

Wu X, Yang ZY, Li Y, et al. Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. Science 2010;329:856–861.

Xu L, Pegu A, Rao E, et al. Trispecific broadly neutralizing HIV antibodies mediate potent SHIV protection in macaques. Science 2017, 358: 85-90.

Zacharopoulou P, Nogueira L, Oliveira T, et al. Mutational landscape of 10-1074 and 3BNC117 sensitivity in a UK population with PHI. Abstract 505, CROI 2022.

Zhang Y, Chapman JH, Ulcay A, Sutton RE. Neutralization Synergy between HIV-1 Attachment Inhibitor Fostemsavir and Anti-CD4 Binding Site Broadly Neutralizing Antibodies against HIV. J Virol 2019, 93.

Zhou P, Wang H, Fang M. Broadly resistant HIV-1 against CD4-binding site neutralizing antibodies. PLoS Pathog. 2019, Jun 13;15(6):e1007819.

Maturation inhibitors and other mechanisms of action

Maturation inhibitors (MIs) inhibit HIV replication at a later stage, namely when new virions are budding. As with INSTIs, antiviral activity was first demonstrated *in vivo* in 2005. MIs are, thus, undoubtedly an exciting class of compounds. With the development of bevirimat, the pioneer compound, some problems have become apparent, but they are probably surmountable (Review: Reguireo-Ren 2019).

Bevirimat (MPC 4326, formerly also **PA-457)** is a derivative of betulinic acid that can be isolated from a plant-derived natural product. It inhibits the budding or maturation of new virions (Li 2003), specifically, the conversion of the capsid precursor protein p25 to the mature capsid protein p24, resulting in non-infectious viruses. The long half-life allows once-daily oral administration (Smith 2007). To date, bevirimat, tested in over 650 people, has been well tolerated. In an initial placebo-controlled Phase IIa study (Beatty 2005), viral load decreased by a median of 1.03 logs after ten days at 200 mg. However, no effects on viral load were detectable in some subjects, likely due to "natural" polymorphisms in the *gag* gene (Lu 2011). Without polymorphisms, the effect was more than one log, with polymorphisms only 0.2 log (Bloch 2009). With no *gag* polymorphisms, only about 50–70% of patients appear to be without polymorphisms overall. PI resistance also affects efficacy (Verheyen 2010, Fun 2011). Given these problems, Myriad declared in June 2010 that it would not pursue further development. Second-generation MIs are expected to overcome the problem of *gag* polymorphisms (Urano 2019).

GSK-3532795 (formerly **BMS-955176)** is a second-generation MI that demonstrated efficacy in 2015. In a Phase II study, viral load decreased by up to 1.64 log levels after ten days of monotherapy, independent of most known *gag* polymorphisms and PI resistance. However, after purchasing the BMS pipeline, ViiV decided to terminate development in 2016, primarily due to rapid resistance (Morales-Ramirez 2018).

GSK-2838232 is another second-generation MI. In a Phase II trial, 33 PLWH received different doses boosted with cobicistat. After ten days of monotherapy, the maximum viral load was as high as 1.7 log levels; there was a nice dose-response relationship (DeJesus 2019).

Fipravirimat (**GSK-3640254**, **GSK-254**) has been among the most promising candidates and was the first after bevirimat to be given a proper name. Its effect seems to be largely independent of *gag* polymorphisms. Phase II showed a decrease of up to 2 logs and a dose-response relationship (Spinner 2022). Concurrent food intake increases absorption (Johnson 2022). A larger Phase II trial (Dynamic) in combination with dolutegravir has been fully enrolled since June 2022. However, it currently seems that ViiV has decided not to progress. The move to cull fipravirimat was made because the drug was "not differentiated enough in the daily oral HIV market". Meaning: not good enough.

Other mechanisms of action

Obefazimod (**ABX464**) is also a substance with a completely new mechanism of action. It inhibits the activity of *rev* – this protein mediates, among other things, the nuclear export of unspliced viral RNA into the cytoplasm. In a pilot study in Thailand, the viral load fell by more than half a log in 4/6 patients after oral administration of 150 mg for 12 days – not much, but still proof of concept. The substance has been well tolerated so far (Steens 2017). In another small study conducted in Europe, proviral DNA was reduced in some subjects (Rutsaert 2019). However, the company currently seems to be focusing more on other indications, including rheumatoid arthritis and ulcerative colitis, where it is already in Phase III (Vermeire 2022).

Literature on Maturation Inhibitors and Other Agents

Beatty G, Jacobson J, Lalezari J, et al. Safety and Antiviral Activity of PA-457, the First-In-Class Maturation Inhibitor, in a 10-Day Monotherapy Study in HIV-1 Infected Patients. Abstract Abstract H-416D, 45th ICAAC 2005, Washington.

Bloch M, Bodsworth N, Fidler M, et al. Efficacy, safety, and pharmacokinetics of MPC-4326 (bevirimat dimeglumine) 200mg BID and 300mg BID monotherapy administered for 14 days in subjects with HIV-1 infection. Abstract H-1230, 49th ICAAC 2009, San Francisco.

DeJesus E, Harward S, Jewell RC, et al. A Phase IIa Study Evaluating Safety, Pharmacokinetics, and Antiviral Activity of GSK2838232, a Novel, Second-generation Maturation Inhibitor, in Participants With Human Immunodeficiency Virus Type 1 Infection. Clin Infect Dis 2019 Nov 26.

Fun A, van Maarseveen NM, Pokorná J, et al. HIV-1 protease inhibitor mutations affect the development of HIV-1 resistance to the maturation inhibitor bevirimat. Retrovirology 2011, 8:70.

Johnson M, Pene Dumitrescu T, Joshi SR, et al. Relative Bioavailability and Food Effect of GSK3640254 Tablet and Capsule Formulations in Healthy Participants. Clin Pharmacol Drug Dev 2022, 11:632-639.

Lalezari J, Richmond G, Thompson M, et al. Pharmacokinetics and safety of a novel 100 mg tablet formulation of MPC-4326 in subjects with HIV-1 infection. Abstract H-1309/42, 49th ICAAC 2009, San Francisco.

Li F, Goila-Gaur R, Salzwedel K, et al. PA-457: a potent HIV inhibitor that disrupts core condensation by targeting a late step in Gag processing. Proc Natl Acad Sci U S A 2003, 100:13555-60.

Lu W, Salzwedel K, Wang D, Chakravarty S, Freed EO, Wild CT, Li F.A Single Polymorphism in HIV-1 Subtype C SP1 is Sufficient to Confer Natural Resistance to the Maturation Inhibitor, Bevirimat. Antimicrob Agents Chemother. 2011 Apr 18.

Martin DE, Galbraith H, Schettler J, Ellis C, Doto J. Pharmacokinetic properties and tolerability of bevirimat and atazanavir in healthy volunteers: an open-label, parallel-group study. Clin Ther 2008, 30:1794-805.

Morales-Ramirez J, Bogner JR, Molina JM, et al. Safety, efficacy, and dose-response of the maturation inhibitor GSK3532795 (formerly known as BMS-955176) plus tenofovir/emtricitabine once daily in treatment-naive HIV-1-infected adults: Week 24 primary analysis from a randomized Phase IIb trial. PLoS One 2018, 13:e0205368.

Regueiro-Ren A, Dicker IB, Hanumegowda U, Meanwell NA. Second Generation Inhibitors of HIV-1 Maturation. ACS Med Chem Lett 2019, 10:287-294.

Regueiro-Ren A, Sit SY, Chen Y, et al. The Discovery of GSK3640254, a Next-Generation Inhibitor of HIV-1 Maturation. J Med Chem 2022, 65:11927-11948.

Rutsaert S, Steens JM, Gineste P, et al. Safety, tolerability and impact on viral reservoirs of the addition to antiretroviral therapy of ABX464, an investigational antiviral drug, in individuals living with HIV-1: a Phase IIa randomised controlled study. J Virus Erad 2019, 5:10-22.

Smith PF, Ogundele A, Forrest A, et al. Phase I and II study of the safety, virologic effect, and PKs/pharmacodynamics of single-dose 3-o-(3′,3′-dimethylsuccinyl)betulinic acid (bevirimat) against HIV infection. Antim Ag Chemoth 2007;51:3574-81.

Spinner CD, Felizarta F, Rizzardini G, et al. Phase IIa Proof-of-Concept Evaluation of the Antiviral Efficacy, Safety, Tolerability, and Pharmacokinetics of the Next-Generation Maturation Inhibitor GSK3640254. Clin Infect Dis 2022, 75:786-794.

Steens JM, Scherrer D, Gineste P, et al. Safety, Pharmacokinetics, and Antiviral Activity of a Novel HIV Antiviral, ABX464, in Treatment-Naive HIV-Infected Subjects in a Phase 2 Randomized, Controlled Study. Antimicrob Agents Chemother 2017 Jun 27;61(7).

Urano E, Timilsina U, Kaplan JA, et al. Resistance to Second-Generation HIV-1 Maturation Inhibitors. J Virol 2019, 93.

Verheyen J, Verhofstede C, Knops E, et al. High prevalence of bevirimat resistance mutations in protease inhibitor-resistant HIV isolates. AIDS 2010, 24:669-73.

Vermeire S, Sands BE, Tilg H, et al. ABX464 (obefazimod) for moderate-to-severe, active ulcerative colitis: a phase 2b, double-blind, randomised, placebo-controlled induction trial and 48 week, open-label extension. Lancet Gastroenterol Hepatol 2022, S2468-1253(22)00233-3.

Immunomodulatory therapies

In addition to antiretroviral therapies, immunomodulatory therapy strategies are also tested in HIV. Although they are repeatedly discussed as alternatives or supplements, all therapies have failed to provide proof of clear clinical benefit. Nevertheless, some approaches will be briefly outlined below in alphabetical order. Except for checkpoint inhibitors, none of these are in active investigation.

Checkpoint inhibitors: To prevent excessive T cell responses, many cells, including tumor cells, carry T cell inhibitory receptors such as PD-1 (programmed cell death receptor 1). These receptors and their ligands are targeted by antibody-based therapeutics known as checkpoint inhibitors. CPIs are arguably one of the most exciting drugs in oncology at present. Still, they could also play a role in HIV therapy because it may be possible to reach latently infected cells via these checkpoints (review: Gubser 2022). Because of the immunomodulatory properties of CPIs, people with HIV were long excluded from trials. This is now changing. However, the immunological results were moderate in the first pilot study with the anti-PD-1 antibody BMS-936559 (Gay 2017). Also, another study in 32 PLWH with various cancers treated with the already approved CPIs, nivolumab, pembrolizumab, and cemiplimab showed only minimal effects on the reservoir (Baron 2022). Data are still very limited, and it is becoming apparent that combinations will likely be necessary (Gubser 2022).

Corticosteroids have been discussed repeatedly. Results from randomized trials have not been encouraging (McComsey 2001, Wallis 2003). In a study of 236 patients, a slightly increased CD4 T-cell count was matched by an approximately threefold increase in viremia (Kasang 2016).

Cyclosporin A (Sandimmun®), otherwise used as prophylaxis for transplant rejection, could inactivate the immune system and thus reduce the replication possibilities of HIV. However, this did not work in clinical trials in chronically or acutely infected individuals (Markovitz 2010).

G-CSF (granulocyte colony-stimulating factor) is approved, among other things, for persistent neutropenia in advanced HIV infection to prevent bacterial infections. In a randomized trial of 258 PLWH with CD4 T-cells below 200/µl, rates of severe neutropenia and bacterial infections decreased (Kuritzkes 1998). There was no apparent effect on HIV viral load. In CMV retinitis, G-CSF was even shown to have a survival benefit (Davidson 2002). Although severe neutropenia has become rare with ART, G-CSF may be useful today, especially with chemotherapy, interferon, or other myelosuppressive drugs such as valganciclovir.

GM-CSF (granulocyte-macrophage colony-stimulating factor) is available as molgramostim (Leucomax®) or sargramostim (Prokine®). Three double-blind, randomized studies showed a slight decrease in HIV viral load (Angel 2000, Skowron 1999, Brites 2000), but one study in uncontrolled infection showed a slight increase (Jacobson 2003). It is not recommended outside of clinical trials – it is not approved in Europe. Currently, some projects with vaccines are ongoing, as GM-CSF enhances vaccine responses (Yu 2016).

Hydroxyurea (HU, **Litalir®**) is an old chemotherapeutic agent leading to an intracellular deoxynucleoside triphosphate deficiency. After the case of the original "Berlin patient" who took HU in addition to indinavir+ddI during acute infection and later remained off ART and had no plasma viremia (Lisziewicz 1999), HU came into vogue temporarily – until several studies showed no effects except toxicity (Swindells 2005). Even in a study on primary infection, the Berlin patient could not be "reproduced" (Zala 2002).

Interferons have an antiretroviral effect, about 0.5–1 logs with pegylated interferon (Asmuth 2010). In one study of 20 people who discontinued ART, 9 remained below 400 copies/mL at 12 weeks on pegylated interferon (Azzoni 2013). Given the side effects, interferons are admittedly of more academic interest today. They may help to eradicate latent reservoirs (Review: Bourke 2017).

Interleukin-2 (IL-2, **Aldesleukin**, **Proleukin®**) is a cytokine that stimulates proliferation and cytokine production of T, B, and NK cells. This results in sustained CD4 and CD8 T-cell increases. Randomized trials such as ESPRIT and SILCAAT showed no clinical benefit (Abrams 2009). Despite better CD4 T-cells, this did not lead to less opportunistic infections. There was also no reduction in mortality. The effects of IL-2 are laboratory cosmetics, nothing more.

Interleukin-7 plays a fundamental role in T cell homeostasis and influences CD4 T-cell formation and maturation. In Phase II studies, good CD4 T-cell increases were observed with different subcutaneous doses (Thiébaut 2016). Whether this has a clinical effect is doubtful after the experience with IL-2. This is also true for **interleukin-12** (Jacobson 2002), **IL-10** (Angel 2000) and **IL-15** (Ahmad 2005).

Murabutide can induce anti-inflammatory cytokines and growth factors and enhance the antiviral effects of cytokines such as IL-2 or interferon. In HIV, it has been used as an immunomodulator, especially in France, but with moderate effect (Bahr 2003).

Mycophenolate (Cellcept®) inhibits inosine monophosphate (IMP) dehydrogenase and is used to prevent acute transplant rejection and autoimmune diseases. Inhibition of lymphocyte proliferation is thought to reduce target cells and thus inhibit HIV replication. No effect was seen in randomized trials (Sankatsing 2004, Kaur 2006).

Remune®, as a prototype of a therapeutic vaccination, suffered shipwreck years ago. This vaccine, which consists of a virus deprived of its envelope proteins (gp120) and can induce an HIV immune response, does not seem to provide any clinical benefits. A trial involving more than 2,500 patients was terminated prematurely in May 1999 for lack of effect (Kahn 2000).

THC (cannabinoids) do not affect the immune system, as a randomized study showed (Bredt 2002). However, THC, which is degraded via the cytochrome p450 system, did not cause harm in terms of viral load and plasma levels (Abrams 2003). THC might help in sensitive polyneuropathy – a small randomized trial showed pain-relieving effects (Abrams 2007). It may also be useful in wasting syndrome (see *AIDS*).

Vitamins do nothing and may even harm. In a double-blind, randomized African trial, 3,418 patients received a high-dose combination of vitamin B complex, vitamin C, and E or standard doses in parallel with ART initiation. The trial was terminated because there was no effect on clinical events, CD4 T-cells, viral load, BMI, or hemoglobin. In addition, liver elevations were more common with high-dose vitamin administration (Isanaka 2012). Other randomized studies showed immunological benefits (Baum 2013, Guwatudde 2015).

Literature on immunotherapies

Abrams D, Lévy Y, Losso MH, et al. Interleukin-2 therapy in patients with HIV infection. N Engl J Med 2009, 361:1548-59.

Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. Ann Intern Med 2003; 139:258-66.

Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007; 68:515-21.

Ahmad A, Ahmad R, Iannello A, et al. IL-15 and HIV infection: lessons for immunotherapy and vaccination. Curr HIV Res 2005, 3:261-70.

Angel JB, High K, Rhame F, et al. Phase III study of granulocyte-macrophage colony-stimulating factor in advanced HIV disease: effect on infections, CD4 cell counts and HIV suppression. Leukine/HIV Study Group. AIDS 2000, 14:387-95.

Angel JB, Jacobson MA, Skolnik PR, A multicenter, randomized, double-blind, placebo-controlled trial of recombinant human interleukin-10 in HIV-infected subjects. AIDS 2000; 14:2503-8.

Asmuth DM, Murphy RL, Rosenkranz SL, et al. Safety, tolerability, and mechanisms of antiretroviral activity of pegylated interferon Alfa-2a in HIV-1-monoinfected participants: a phase II clinical trial. J Infect Dis 2010, 201:1686-96.

Azzoni L, Foulkes AS, Papasavvas E, et al. Pegylated Interferon alfa-2a monotherapy results in suppression of HIV type 1 replication and decreased cell-associated HIV DNA integration. J Infect Dis 2013, 207:213-22.

Bahr GM, De La Tribonniere X, et al. Clinical and immunological effects of a 6 week immunotherapy cycle with murabutide in HIV-1 patients with unsuccessful long-term antiretroviral treatment. J Antimicrob Chemother 2003, 51:1377-88.

Baron M, Soulié C, Lavolé A, et al. Impact of Anti PD-1 Immunotherapy on HIV Reservoir and Anti-Viral Immune Responses in People Living with HIV and Cancer. Cells. 2022, 11:1015.

Baum MK, Campa A, Lai S, et al. Effect of micronutrient supplementation on disease progression in asymptomatic, antiretroviral-naive, HIV-infected adults in Botswana: a randomized clinical trial. JAMA 2013, 310:2154-63.

Bourke NM, Napoletano S, Bannan C, et al. Control of HIV infection by IFN-α: implications for latency and a cure. Cell Mol Life Sci. 2017 Oct 7.

Bredt BM, Higuera-Alhino D, Shade SB, et al. Short-term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients. J Clin Pharmacol 2002; 42:82S-89S.

Brites C, Gilbert MJ, Pedral-Sampaio D, et al. A randomized, placebo-controlled trial of granulocyte-macrophage colony-stimulating factor and nucleoside analogue therapy in AIDS. J Infect Dis 2000, 182: 1531-5.

Davey RT JR, Murphy RL, Graziano FM, et al. Immunologic and virologic effects of subcutaneous interleukin 2 in combination with ART: A randomized controlled trial. JAMA 2000, 284: 183-9.

Davidson M, Min YI, Holbrook JT, et al. Use of filgrastim as adjuvant therapy in patients with AIDS-related CMV retinitis. AIDS 2002, 16: 757-65.

Gay CL, Bosch RJ, Ritz J, et al. Clinical Trial of the Anti-PD-L1 Antibody BMS-936559 in HIV-1 Infected Participants on Suppressive Antiretroviral Therapy. J Infect Dis 2017, 215:1725-1733.

Gubser C, Chiu C, Lewin SR, et al. Immune checkpoint blockade in HIV. EBioMedicine 2022, 76:103840

Guwatudde D, Wang M, Ezeamama AE, et al. The effect of standard-dose multivitamin supplementation on disease progression in HIV-infected adults initiating HAART: a randomized double-blind placebo-controlled trial in Uganda. BMC Infect Dis 2015, 15:348.

Isanaka S, Mugusi F, Hawkins C, et al. Effect of high-dose vs standard-dose multivitamin supplementation at the initiation of HAART on HIV disease progression and mortality in Tanzania: a randomized controlled trial. JAMA 2012, 308:1535-44.

Jacobson JM, Lederman MM, Spritzler J, et al. GM CSF induces modest increases in plasma HIV type 1 RNA levels and cd4+ lymphocyte counts in patients with uncontrolled HIV infection. J Infect Dis 2003; 188: 1804-14.

Jacobson MA, Spritzler J, Landay A, et al. A Phase I, placebo-controlled trial of multi-dose recombinant human interleukin-12 in patients with HIV infection. AIDS 2002; 16:1147-54.

Kahn JO, Cherng DW, Mayer K, et al. Evaluation of HIV-1 immunogen, an immunologic modifier, administered to patients infected with HIV having 300 to 549 x 10(6)/L CD4 cell counts: A randomized controlled trial. JAMA 2000, 284:2193-202.

Kasang C, Kalluvya S, Majinge C, et al. Effects of Prednisolone on Disease Progression in Antiretroviral-Untreated HIV Infection: A 2-Year Randomized, Double-Blind Placebo-Controlled Clinical Trial. PLoS One 2016, 11:e0146678.

Kaur R, Bedimo R, Kvanli MB, et al. A placebo-controlled pilot study of intensification of antiretroviral therapy with mycophenolate mofetil. AIDS Res Ther 2006 May 26;3:16.

Kuritzkes DR, Parenti D, Ward DJ, et al. Filgrastim prevents severe neutropenia and reduces infective morbidity in patients with advanced HIV infection: results of a randomized, multicenter, controlled trial. AIDS 1998, 12:65-74.

Lisziewicz J, Rosenberg E, Lieberman J, et al. Control of HIV despite the discontinuation of antiretroviral therapy. NEJM 1999, 340:1683-4.

Markowitz M, Vaida F, Hare CB, Boden D, et al. The virologic and immunologic effects of cyclosporine as an adjunct to antiretroviral therapy in patients treated during acute and early HIV-1 Infection. J Infect Dis 2010 Mar 17. [Epub ahead of print].

Marra A, Scognamiglio G, Peluso I, et al. Immune Checkpoint Inhibitors in Melanoma and HIV Infection. Open AIDS J 2017, 11:91-100.

McComsey GA, Whalen CC, Mawhorter SD, et al. Placebo-controlled trial of prednisone in advanced HIV-1 infection. AIDS 2001;15:321-7.

Sankatsing SU, Jurriaans S, van Swieten P, et al. Highly active antiretroviral therapy with or without mycophenolate mofetil in treatment-naive HIV-1 patients. AIDS 2004, 18:1925-31.

Skowron G, Stein D, Drusano G, et al. The safety and efficacy of granulocyte-macrophage colony-stimulating factor (Sargramostim) added to indinavir- or ritonavir-based antiretroviral therapy: a randomized double-blind, placebo-controlled trial. J Infect Dis 1999, 180:1064-71.

Swindells S, Cohen CJ, Berger DS, et al. Abacavir, efavirenz, didanosine, with or without hydroxyurea, in HIV-infected adults failing initial nucleoside/protease inhibitor-containing regimens. BMC Infect Dis 2005, 5:23.

Thiébaut R, Jarne A, Routy JP, et al. Repeated Cycles of Recombinant Human Interleukin 7 in HIV-Infected Patients With Low CD4 T-Cell Reconstitution on Antiretroviral Therapy: Results of 2 Phase II Multicenter Studies. Clin Infect Dis 2016, 62:1178-85.

Wallis RS, Kalayjian R, Jacobson JM, et al. A Study of the immunology, virology, and safety of prednisone in HIV-1-infected subjects with CD4 cell counts of 200 to 700 mm^{-3}. J AIDS 2003; 32: 281-6.

Yu TW, Chueh HY, Tsai CC. Novel GM-CSF-based vaccines: One small step in GM-CSF gene optimization, one giant leap for human vaccines. Hum Vaccin Immunother 2016, 12:3020-3028.

Zala C, Salomon H, Ochoa C, et al. Higher rate of toxicity with no increased efficacy when hydroxyurea is added to a regimen of stavudine plus didanosine and nevirapine in primary HIV infection. J Acquir Immune Defic Syndr 2002, 29: 368-73.

5.4. Goals and principles of therapy

Given the increasingly louder debate about potential cure strategies for HIV infection, fueled by some exciting case reports in recent years (much has been put into perspective again), this chapter will be divided into two parts. The first part deals with the goals and principles of lifelong treatment. The second part will discuss the treatment goal of "HIV cure" and the problems on the way there.

5.4.1. Lifelong treatment

CHRISTIAN HOFFMANN

With the currently available antiretroviral therapies, eradication of HIV (explained in more detail in the second part below) has not yet been achieved. It also remains questionable whether it will ever be achievable for many people with HIV. Right now, this means that ART has to be taken for life. And lifelong can mean several decades because there is much to suggest that – given an otherwise healthy lifestyle – life expectancy for PLWH is now close to normal. This has become evident in industrialized countries, even if there is still a difference of several years compared to the general population, at least in specific sub-populations (Marcus 2016, Wandeler 2016, Gueler 2017, Xia 2022). So, we will have to continue to deal with long-term treatment (and its side effects) for decades. The most important goal remains to prolong the lives of PLWH with as good health and a high quality of life as possible. A treatment that only aims to improve laboratory values and ignores the physical and mental well-being of the person with HIV is not good. Let's treat people, not viral load or CD4 T-cells.

Success and failure of lifelong treatment

Virologic, immunologic, and clinical criteria can evaluate treatment success and failure. Although these are often strongly associated with each other, they should be kept apart. The *virological* success or failure of therapy is usually the first seen. This usually means a drop or lack of drop or even an increase in viral load. This is followed, often with a bit of a delay, by *immunological* therapy success, measured by CD4 T-cells, or immunological therapy failure. The *clinical* therapy failure, if any, usually becomes visible much later – first, the values deteriorate, then the patient. The clinical success of therapy in asymptomatic persons is often not perceived. There is little glory in prevention – although the risk of opportunistic infections is reduced to half after only three months of ART (Ledergerber 1999), the individual may not realize what was avoided by therapy.

Virological treatment success and failure

Virological treatment success is usually understood as reducing viral load below the detection limit (usually 50 copies/mL). This is based on early experience that the faster and, above all, the lower the viral load falls, the more durable the effect of therapy (Raboud 1998, Powderly 1999). The viral load decreases biphasically under therapy. A very rapid drop during the first few weeks is followed by a more extended phase in which plasma viremia decreases only gradually. A value below the detection limit should be reached after 2–4 months, depending on the therapy (see below). This decline may take longer if the viral load is initially very high. A viral load above the detection limit after six months, on the other hand, is almost always to be considered a failure. The same applies to a viral load that is rising again, in which case – after a short-term check – consideration should be given to what can be improved about the therapy (absorption, resistance, compliance?).

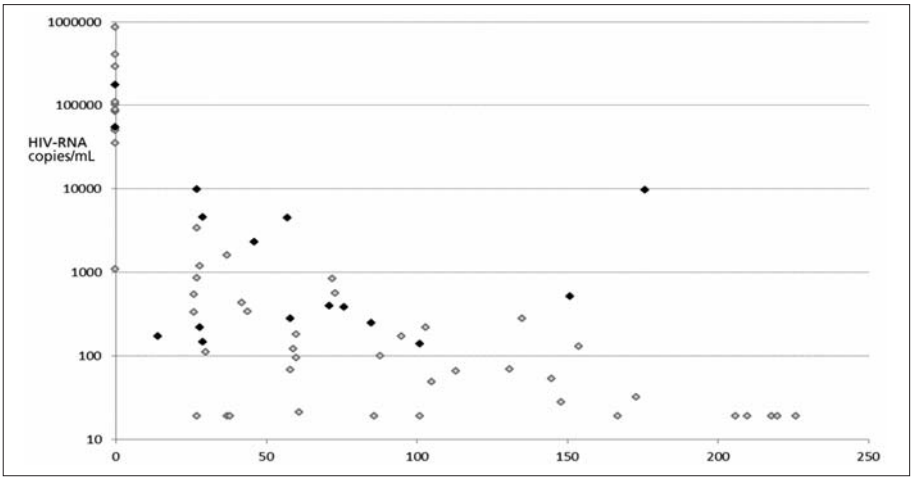

Figure 1: Viral load values in the first 250 days on ART. Gray: Values are from 10 patients who achieved durable viral suppression. Black: 3 patients in whom resistance developed on first-line therapy.

Virological therapy failure can be recognized quite early. A check after four weeks is helpful for psychological reasons ("the virus is going down nicely" is good motivation) and indicates further success. If the viral load is not at least below 5,000 copies/mL after four weeks, later treatment failure is likely (Maggiolo 2000). However, the predictive value of a single absolute measurement, especially at the beginning, remains limited (Brima 2017). This is illustrated by the following figure, which compares cases with and without the development of resistance.

ART regimens also have an impact on viral kinetics. Viral load decreases significantly faster with INSTI-based regimens than others (Murray 2007, Cardozo 2017). In GS-1490, comparing the two INSTIs, bictegravir, and dolutegravir, each combined with TAF+FTC, more than 75% were already below the detection limit by week 4 (Sax 2017). In the DRIVE-FORWARD trial, a comparison of the NNRTI doravirine and the PI darunavir/r, the rates were only 20%. Nevertheless, even in the latter study, more than 80% ultimately achieved a viral load below the limit of detection, and by week 16, the rate was approximately 75% (Molina 2018).

This observation has less to do with potency and more with the mode of action of INSTIs. This implies that clinicians must be more worried about INSTI-based therapies if the viral load is not below 50 copies/mL after two months.

Just above the detection limit: Low-Level Viremia

The cut-off point of 20 or 50 copies/mL as a criterion for success is somewhat arbitrary. It is based on the currently available viral load assays. Whether 60 copies/mL is worse than 30 copies/mL and indicates a lower treatment success has not been proven. In the case of a persistent low-level viremia (LLV) between 20 and 50 copies/mL, the risk of virological failure seems not to be increased for at least one year (Charpentier 2012). Other studies found an association between viral load and subsequent virological failure, even at such low levels (Maggiolo 2012, Pugliese 2013, Elvstam 2022).

LLV was considered predictive of subsequent virologic failure only when above 200 copies/mL (Navarro 2016). This value was also an essential cut-off in the Swiss cohort. If there is a viral load of 21–400 copies/mL at least three times, the risk of virologic failure increases above 200 copies/mL by up to 12% within one year. In

contrast, no virological failure occurred in 26 cases with LLV at 21–49 copies/mL (Boillat-Blanco 2015). These findings are supported by a Swedish study in which an LLV between 200–999 over a 4.5-year period was associated with a threefold increased risk of treatment failure, but an LLV of 51–199 copies/mL was not (Elvstam 2017).
With low values, measurement inaccuracies must always be taken into account, as well as methodological problems (Mortier 2017). A viral load that has risen to low values only once ("blip") is often not relevant (see below) and should be distinguished from LLV. However, some studies suggest that resistance may already be detectable in the case of LLV (Elvstam 2022). Replication, and thus the formation of new resistance, may continue to occur even at such low levels of viral replication (Gunthard 1998, Nettles 2004, Taiwo 2012). However, some studies do not back this up (Vancoillie 2017). Whether immune activation and inflammatory parameters are increased in LLV is also controversial. At least two studies found no unfavorable effect from LLV (Eastburn 2011, Taiwo 2012), while one did (Reus 2013).
In summary, the lower the viremia, the less relevant it is; a critical limit may be around 200 copies/mL. While a low LLV tends to imply no need for action, higher levels should be evaluated for reasons for virological treatment failure. The most critical risk factors are antiretroviral pre-treatment (existing resistance) and poor adherence or sub-optimal drug levels. Resistance testing is often possible with a viral load above 200 copies/mL. Drug level measurement (therapeutic drug monitoring, TDM, see below) of PIs, INSTIs, or NNRTIs is also an option and should preferably be unannounced.
Any LLV should be an opportunity to talk to the patient about potential problems with ART. There is nothing wrong with going over the current treatment plan again. Are medications being taken regularly, or is a dose sometimes skipped? Are intake requirements (fasting or with food) being followed? What additional therapies (PPIs?) are being taken that are not in the chart? All of this should be considered before changing a therapy.
Even with all this said, morbidity and mortality can be significantly reduced even when the virological success of therapy is not reduced below the limit of detection (Grabar 2000, Deeks 2002). Many patients also remain immunologically stable for a relatively long time despite insufficient viral suppression. In a cohort study from Switzerland, CD4 T-cells did not drop as long as the viral load remained below 10,000 copies/mL or at least 1.5 logs below the individual setpoint (Lederberger 2004). Even in intensively pre-treated patients, efforts should be made to reduce the viral load below the detection limit, i.e., with new agents and/or drug classes. Below 50 copies/mL is desirable, and below 200 copies/mL is the minimum goal.

Blips – do they mean virological failure?

Viral blips are transient (and almost always low-level) increases in viral load – provided the viral load was below the detection limit of 50 copies/mL before and after each blip. Therefore, identifying a blip takes at least three viral load measurements. Blips should be distinguished from LLV. They are a common phenomenon under ART and can be observed in up to 20–40% of cases (Sungkanuparph 2005). The more often one looks, the more likely one is to find one. Biological or statistical coincidences are quite possible, at least up to 200 copies/mL (Nettles 2005). Another possibility, as with LLV, is measurement problems with samples left unprocessed for too long. Plasma separation should occur by 24 hours, ideally by 8 hours. Otherwise, viral loads above 400 copies/mL are frequently seen (Portman 2012).
Nevertheless, there is often uncertainty with blips. Is this a sign of treatment failure? The data situation is not clear. While previous studies suggest that this is not the case in the medium term (Sungkanuparph 2005, Dijkstra 2022), the risk of virologic

failure in a recent European cohort with blips was lower than with LLV. Still, it increased overall by about 1.7 (95% confidence interval 1.3–2.2) compared with individuals with constant viral suppression (Elvstam 2022). Little is known about the causes of the blips. Probably many things play a role.

For example, whether there is an association with adherence is unclear. Some studies found no association between adherence and blip frequency (Di Mascio 2003, Miller 2004), while others did (Podsadecki 2007). Immunological mechanisms may also play a role. The earlier in the course of the infection treatment is given or the higher the CD4 T-cells are at the beginning of therapy, the less frequently blips seem to occur (Di Mascio 2003+2004, Sungkanuparph 2005). In our study of 853 successfully treated patients with viral suppression and at least five years of ART experience, the blip rate was high and strongly associated with baseline viral load, even after many years of ART (Erdbeer 2014). In patients with a pre-treatment viremia of more than 100,000, 50,000–100,000, and less than 50,000 copies/mL, the proportions of people with blips during the previous five years were 39.5%, 30.5%, and 21.8% (p=0.007), respectively. The blip level was relatively low in most cases (68%) at 51–200 copies/mL. However, these findings indicate that blips are not always coincidental but probably reflect the individual immunological situation.

Is there an association with specific antiretrovirals? In a large cohort (Sungkanuparph 2005), the blip rates were 34% with NNRTIs and 33% with PIs, occurring at the same levels (median 140 and 144 copies/mL, respectively). In both groups, the risk of virologic failure was approximately 8% at two years. An important finding was that blips did not increase risk even with NNRTIs, which had been theorized, given the rapid development of resistance to NNRTIs. These findings were since confirmed (Martinez 2005). However, a more recent study from the Netherlands indicated that blips are less frequent on INSTIs than with other combinations. Among 1,661 PLWH, compared with an NNRTI anchor, blip incidence was higher for PIs (incidence rate ratio 1.37) and lower for INSTIs (0.64). Again, blips were associated with a higher zenith viral load, higher test frequency, and shorter time since antiretroviral therapy initiation (Dijkstra 2022).

Finally, other factors may be responsible for intermittent viremia. For example, immune activation induced by other infections could increase the risk of blips simply by releasing viruses from latently infected reservoirs (Jones 2007). In a large retrospective analysis, intercurrent infections were the cause of transient viremia in 26% (Easterbrook 2002). Thus, during active syphilis, viral load can increase significantly, and CD4 T-cells can drop (Buchacz 2004). The viral load can also rise temporarily during vaccinations (Kolber 2002).

Overall, ART should not be changed even in case of repeated blips. However, high blips (> 200–500 copies/mL) should be controlled cautiously.

How long does virological treatment success last?

Little is known about how long treatments remain effective. The belief that treatment success is limited to only a few years is widespread. It originated during the early years of ART. Many patients at the time were inadequately pre-treated with mono- or dual-therapy and had thus developed extensive resistance. In such patients, the effect of treatment was often limited, as even a single point mutation was often enough to topple a whole regimen.

In the modern era, things are different. The risk of treatment failure has become much lower. Even more, the risk of virologic failure decreases significantly over time. This is confirmed by cohort studies in which virological therapy failure due to resistance has become significantly less frequent in recent years.

Viral resistance, especially multiple resistance mutations, now almost exclusively affects individuals who have received antiretroviral treatment since the 1990s. This may be illustrated by the Swiss cohort, in which 11,084 PLWH were analyzed. At least one resistance mutation was found in almost 29%. The by far most relevant risk factor was the time at which therapy was started. Of those with three-class resistance (n=471), only 1.7% had started ART after 2006; for two-class resistance (n=1,198), the figure was just 5.0%. Of the 14 individuals with four-class resistance, none had started ART after 2006 (Scherrer 2016). In our evaluation of over 200 patients with resistance to at least three classes, virological suppression was still 90%. Thus, long-term virologic treatment failure is rarely due to resistance – lack of adherence is likely to be the leading cause of lack of virologic control.

Overall, data and experience show that the viral load can remain below the detection limit for decades in most PLWH – provided that therapy does not have to be interrupted. Resistance is by no means inevitable.

Antiretroviral therapy continues to improve, and clinicians are learning as well. In the German ClinSurv cohort (n > 24,000), virologic treatment success (< 50 copies/mL) among treatment-naïve individuals increased from 56.4% in 1999 to 94.1% in 2014 (Schmidt 2017). Thus, most PLWH consistently have a viral load below 50 copies/mL. And it looks like it will stay that way.

However, treatment success must benefit everyone, not only those in therapy. UNAIDS set a goal of "90-90-90" for 2020, meaning that at least 90% of all PLWH would be diagnosed with HIV. Of these, at least 90% would receive antiretroviral therapy, followed by 90% having a viral load below the detection limit. In December 2020, UNAIDS declared a new global target of "95-95-95" for 2025–2030. According to a recent report, many countries have already achieved the "95-95-95" targets, including Botswana, Rwanda, and Zimbabwe. Modeling studies showed that achieving the 2025 targets would reduce new annual infections by 83% (71% to 86% across regions) and AIDS-related deaths by 78% (67% to 81% across regions) by 2025 compared to 2010 (Glover 2021). However, there are many voices now calling for the introduction of a fourth "90" or "95" – meaning that 90% or 95% of all PLWH should have a good quality of life (Popping 2021).

Immunological therapy success and failure

The success of immunological therapy is understood as an increase in CD4 T-cells. However, it is not defined more precisely; a systematic review found 14 different definitions in 20 studies on this topic (Kelly 2016). Depending on the study, increases *of* 50, 100, or 200/µl or increases *to* over 200, 500, or 750/µl are considered as immunological treatment success. Failure is usually described as a lack of increase or a decrease in CD4 T-cells.

It is difficult to individually predict the immunologic success of therapy for patients on ART, as it varies significantly from one person to another. As with the decrease in viral load, the increase in CD4 T-cells also seems to have two phases. After a first, usually rapid increase over the first three to four months, further increases are considerably less pronounced. In EuroSIDA, the greatest mean increase in CD4 count of 100 cells/µl per year was seen in the year after starting ART. Significant, but lower, increases, around 50 CD4 T-cells/µl per year, were seen even five years after starting ART (Mocroft 2007). The COHERE group has published reference curves for the CD4 increase from nearly 30,000 patients. Median CD4 T-cells increase by 133/µl in the first six months (strongly dependent on initial count) and by 38/µl in the following six months (Bouteloup 2017).

The most critical factor predicting immune reconstitution is the CD4 T-cell count before starting therapy (Bouteloup 2017). The lower the CD4 T-cells were, the less

likely normalization becomes. In the Swiss cohort, of 2,235 individuals who started ART in 1996–97, only 39% achieved CD4 T-cells above 500/µl (Kaufmann 2003). The adverse effects of late ART initiation often remain apparent for a long time. For example, about 25% of individuals who started ART with low CD4 T-cells still did not normalize to 500/µl even after 7–10 years despite sustained and good viral suppression (Kelley 2009, Lok 2010). It is unclear whether the immune system continues to restore itself continuously after prolonged viral suppression or whether a plateau is reached after three to seven years (Smith 2004, Mocroft 2007, Lok 2010). In our experience, there may be both: people whose CD4 T-cells continue to rise slowly even after five or six years, but also those whose CD4 T-cells stagnate at a level after a relatively short time.

Immunological treatment success is not necessarily linked to maximal viral suppression. Even with partial suppression, CD4 T-cells can recover (Kaufmann 1998, Ledergerber 2004). The crucial factor seems to be that the viral load remains lower than before therapy (Deeks 2002, Ledergerber 2004). Given the many factors that can influence the regenerative capacity of the immune system (see below), it is usually not beneficial to use CD4 T-cells as a decisive criterion for treatment success. Virological success is better suited for this purpose. Once CD4 T-cells have normalized, significant decline is rare as long as the viral load remains below the detection limit (Phillips 2002). The likelihood of CD4 T-cell counts remaining above the relevant cut-off of 200/µl is over 99% over four years in patients who have once reached 300/µl and who then suppress their viral load to below 200 copies/mL (Gale 2013). Immunological therapy success does not need to be continually monitored if the immune status is good. In the US, the quarterly measurement of CD4 T-cells is no longer mandatory for successfully treated patients. In other countries (such as Spain), it's annual.

Discordant response

A discordant response occurs when the treatment goals – immunological and virological – are not achieved (Table 4.1). Thus, treatment may be successful virologically without showing immunological effects; despite undetectable viral load, CD4 T-cells bobble around (Grabar 2000, Moore 2005, Tan 2007). Conversely, ART can produce substantial CD4 T-cell increases even though viral load remains detectable. Even today, despite ever-improving therapies, discordant responses are still present in about a quarter of all treatment-naïve patients. Particularly in those individuals in whom therapy is successful virologically but not immunologically, it is often unclear how to continue.

Mortality seems slightly higher in patients with discordant responses, but this is probably not only due to AIDS (Gilson 2010, Kelly 2016). In a study of 835 patients who had not reached 200 CD4 T-cells even after three years with viral suppression, this was associated with a 2.6-fold increase in mortality (Engsig 2014).

Table 4.1: Treatment response in prospective cohort studies.

ART response	Grabar 2000 n=2,236	Moore 2005 n=1,527	Tan 2008 n=404
Virological and immunological	48%	56%	71%
Discordant: Immunological only	19%	12%	16%
Discordant: virological only	17%	15%	9%
No therapeutic success	16%	17%	5%

The immunological response was defined as CD4 T-cell increase > 50/µl after six months (Grabar 2000) or at least once during follow-up (Moore 2005, Tan 2007). Virologic response was defined as a viral load < 1,000 (Grabar 2000), < 500 (Moore 2005), or < 50 copies/mL (Tan 2008).

Another study found an increased risk of AIDS only in the first six months in those patients with poor immunological response (Zoufaly 2011).
Different courses over time are shown in the following figure. The risk factors for a lack of immunological success are mostly not heterogeneous (review: Aiuti 2006). Low CD4 T-cells and a low viral load before therapy are only two factors (Kaufmann 2005, Moore 2005, Kelly 2009). Age also plays a role. In older patients, immunological success is often moderate. The immune system's regenerative capacity decreases with age, probably due to thymic degeneration (Lederman 2000, Grabar 2004, Engsig 2016). Several studies showed that the older the patients and the smaller the thymus in CT, the more often immunological success fails (Goetz 2001, Piketty 2001, Teixeira 2001). Regulatory T cells also seem to play a role (Saison 2014).
Other causes may be concomitant immunosuppressive or myelosuppressive therapies. We have seen people who remained below 50/µl for years despite suppressed viral load. In Figure 2, it took about 15 years for the patient (in the upper left) to reach 200/µl! Interestingly, a plateau still does not seem to have been reached here. Sometimes, it may make sense to discontinue potentially myelosuppressive prophylaxis such as cotrimoxazole. Autoimmune diseases (Crohn's disease, lupus erythematosus) or liver cirrhosis may also have a negative impact on immunological success.
In addition, there is evidence that certain antiretroviral drugs are unfavorable. For example, significant CD4 T-cell declines were observed in patients who switched to nevirapine plus TDF+ddI (Negredo 2004), probably due to unfavorable interactions

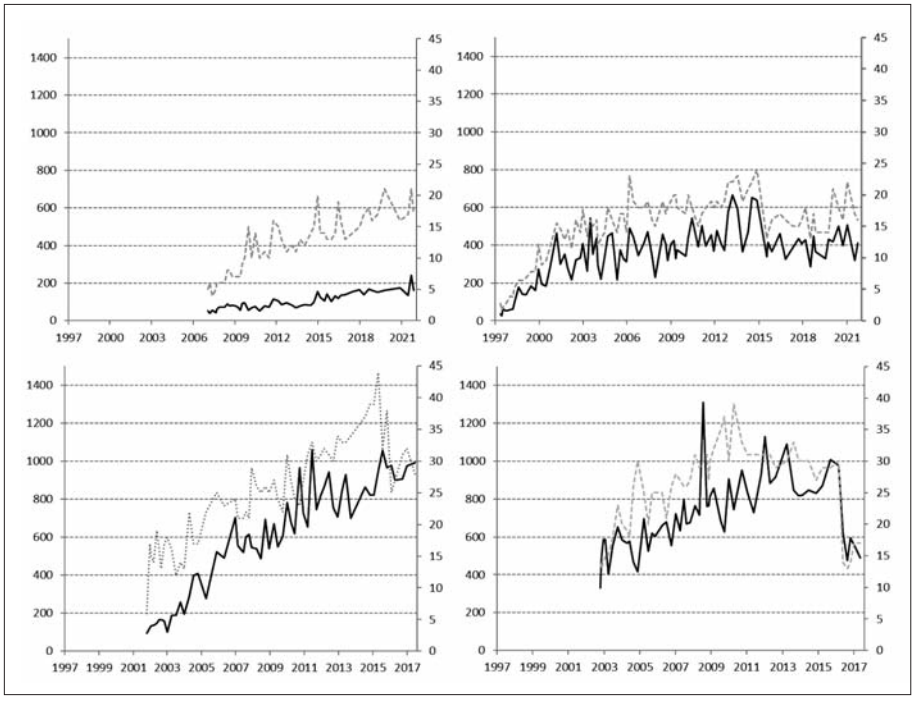

Figure 2: CD4 T-cell trajectories in four patients with sustained viral suppression on ART. Absolute CD4 T-cells/µl (primary axis left, dark), relative CD4 T-cells in % (secondary axis right, gray). Upper left, poor (but still continuous?) immune reconstitution with initially very poor immune status (discordant response). Top right moderate immune reconstitution with a plateau below 500 CD4 T-cells with a very poor immune status initially. Below are two patients with very good immune reconstitution. At the bottom right, however, there was a significant drop during a therapy break of only three months.

between ddI and tenofovir. In two other studies, CD4 T-cells increased more significantly under ABC+3TC and TDF+FTC than AZT+3TC despite comparable virologic success (DeJesus 2004, Pozniak 2006). In the Swiss cohort, individuals on AZT-containing regimens had gained about 60 fewer CD4 T-cells after two years than those without AZT (Huttner 2007). It is doubtful whether, apart from AZT, a therapy change makes sense in case of poor immunological success. There are no differences in the extent of immune reconstitution between NNRTIs and PIs; a switch remains without effect (Torti 2011).
What about INSTIs? Data from the large RESPOND cohort show that better immune reconstitution is observed with INSTIs (Neesgard 2020), and manufacturers always like to emphasize a better immunological response with their drug (when seen!). And yet, a clear trend, at least one that influences therapy selection, has not been shown. Particularly with cohort analyses such as RESPOND, great caution is required, as too many confounding variables are hard to factor out. PIs and NNRTIs are used in different patients than INSTIs.
The same is valid with maraviroc. Early observations of particularly good CD4 T-cell increases with maraviroc led to various randomized trials investigating additional maraviroc administration. The results were consistently sobering. In ANRS 146 (OPTIMAL), a study of 409 late presenters with AIDS or low helper cells, this strategy resulted in no immunologic, virologic, or clinical benefits (Lelievre 2017).

Overall, in the era of modern ART regimens, switching due to a lack of immune reconstitution is not reasonable. Experiments with additional immunostimulants such as St. John's wort, which was popular in the past, or even interleukin-2 (see above, Immunotherapies) should be avoided. It is individual factors that influence immune reconstitution. It is not the therapy.

Practical considerations when dealing with viral load and CD4 T-cells

- The viral load is the most critical parameter for therapy monitoring – it can be influenced directly!
- Stay with one measurement method (in the same laboratory) if possible – take method-related fluctuations (up to half a log) into account!
- After one month of new or switched ART, virologic success should be reviewed.
- After 3–4 months (after six months in case of high viral load), the viral load must be below 50 copies/mL during initial therapy – if not, look for the causes!
- The viral load decreases faster with INSTIs than with NNRTIs or PIs.
- Minor viral load increases (blips or LLV) up to 200 copies/mL usually have no relevance.
- Values above this should be checked in the short term (after 4–6 weeks).
- The higher the age, the more likely a discordant immunological response (viral load well suppressed, CD4 T-cells without relevant increase).
- In contrast to the viral load, the increase in CD4 T-cells, i.e., the immunological success, can hardly be influenced – a change in ART in cases of insufficient CD4 response is useless.
- With good values, CD4 T-cells can be measured less frequently. The higher the CD4 T-cells, the greater the fluctuations.

Clinical therapy success and failure

Clinical treatment success is dependent on virologic and immunologic therapeutic success. In individual patients, clinical response is not always easy to assess. After all, there is no way to show what might have occurred if treatment had not been

started. As an asymptomatic patient cannot feel much better, it may be challenging to find good arguments to continue treatment in the presence of side effects, which, at least temporarily, may affect quality of life.
Clinical success is almost always evaluated via clinical endpoints (AIDS-defining illnesses, death). However, improving ART in a person with considerable constitutional symptoms should also be considered a clinical success. With regard to the risk of disease progression, the immunologic response is at least as critical as the virologic response. However, the extent of virologic success is of great significance. In the Swiss Cohort, in those with a constantly undetectable viral load, the proportion of patients who developed AIDS or died was 6.6% after 30 months. In contrast, this was 9% in patients with viral rebound and up to 20% if the viral load was never suppressed to undetectable levels (Ledergerber 1999). The importance of sustained virological treatment success for clinical benefit has also been reported from other cohorts (Thiebaud 2000, Lohse 2006).

Table 4.2: Morbidity and mortality related to virological and immunological therapy success, respectively. See Table 4.1 for the definition—95% confidence interval in parentheses.

	Grabar 2000	Piketty 2001	Moore 2005
Median CD4 T-cells at baseline	150	73	180–250
Treatment success:			
Complete = Reference	1	1	1
Immunological only, RR	1.6 (1.0–2.5)	6.5 (1.2–35.8)	1.9 (1.1–3.0)
Virological only, RR	2.0 (1.3–3.1)	9.7 (1.6–58.4)	2.5 (1.5–4.0)
No therapeutic success, RR	3.4 (2.3–5.0)	51.0 (11.3–229.8)	3.5 (2.3–5.3)

RR = relative risk.
Clinical endpoints: Progression/death (Grabar 2000, Piketty 2001), death (Moore 2005).

However, even a reasonably effective therapy is still better than none. Even in viremic patients, taking ART is still associated with a significant reduction in morbidity (Mocroft 2012).
Clinical treatment failure is usually understood to mean that the patient develops AIDS or even dies. A distinction must be made between clinical failure that results from ART failure and clinical failure that results from simply starting ART too late. This applies, for example, to immune reconstitution syndromes in which preexisting, subclinical infections manifest in the first few weeks after initiating antiretroviral therapy (see *AIDS*). Therefore, an OI in the presence of rising CD4 T-cells does not necessarily mean ART failure but rather that the immune system is simply resuming its work. On the other hand, the case in which the patient develops severe side effects or even dies is a treatment failure. Fortunately, this is very rarely the case. Finally, other causes must also be taken into account.

Table 4.3: Causes of death among PLWH in France (Morlat 2014). For 2020/21, the analysis was restricted to the Paris area (Sellier 2023).

	2000 (n=964)	2005 (n=1,042)	2010 (n=728)	2020/21 (n=202)*
AIDS-defining diseases	47%	36%	25%	13%
Non-AIDS-defining tumors	11%	17%	22%	31%
Liver disease	13%	15%	11%	4%
Cardiovascular diseases	7%	8%	10%	12%
Suicide	4%	5%	3%	4%

* COVID-19 accounted for more than half of the mortality related to non-AIDS infections over the period (14% of all cases with known causes of death).

Many of the events today on ART are neither ART- nor AIDS-associated but hepatic or cardiovascular. The following table shows the causes of death among deceased PLWH from France from 2000 to 2010. More recently, an update was given for the Paris area only (Sellier 2023). According to this data, less than one in four deaths is AIDS-related. Other diseases, such as tumors or (mostly hepatitis-related) liver diseases, are gaining importance.
As in the case of immunological treatment success, attempts are repeatedly made to evaluate differences between agents or drug classes in the case of clinical success. Given extremely low event rates, this is inevitably done using cohort studies. Sometimes differences are found, as in a recent association of large cohorts from the US and Europe, where higher mortality was observed under INSTI raltegravir than under other agents. This has led to much speculation (Trickey 2022) but could ultimately be because raltegravir is a drug with few side effects and interactions, which is often used in the case of concurrent malignancies and is explicitly recommended there. Overall, there is no clear evidence that there are class-specific differences with regard to clinical treatment success.

What can be achieved?

We should not forget what has been and is being achieved via ART. The success is self-evident; AIDS has become rare. Some diseases that occur only in the most severe immunodeficiencies are practically non-existent today. CMV retinitis or MAC infections are now rare. Today, AIDS almost only affects people who have not received antiretroviral treatment beforehand – because they did not know or did not want to know about their infection. These so-called "late presenters" now account for many AIDS cases (see below).

Table 4.4: Case study (woman, 41 years) showing what ART has made possible*.

		CD4 T-cells/µl	Viral load
Feb 95	AZT+ddC	23 (4%)	NA
Nov 96	AIDS: toxoplasmosis, MAC, candida esophagitis	12 (1%)	815,000
Feb 97	d4T+3TC+SQV	35 (8%)	500
Jun 97	STOP ART due to polyneuropathy		
Jul 97	AZT+3TC+IDV	17 (4%)	141,000
Mar 98		147 (22%)	< 50
Mar 99	AZT+3TC+IDV/r+NVP	558 (24%)	100
Mar 00		942 (31%)	< 50
Apr 05	AZT+3TC+LPV/r+NVP	744 (30%)	130
Jan 12	TDF+FTC+DRV/r	817 (32%)	< 50
Nov 19	TDF+FTC+DRV/c (STR)	715 (27%)	< 50

* Very good immune reconstitution despite severe immunodeficiency and several AIDS-defining diseases. All prophylaxis (MAC, Toxo, PCP) has since been discontinued. Since 2019, the patient has been taking a single-tablet regimen.

In ART-CC, a collaboration of several large cohorts, the average life expectancy of a 20-year-old person living with HIV increased from 36.1 to 49.4 years between 1996–1999 and 2003–2005 (ART-CC 2008). There is little doubt now that the life expectancy of an otherwise healthy PLWH is thus beginning to converge more and more with that of the general population, as has been impressively demonstrated by a flood of analyses from various regions of the world in recent years (review: Wandeler 2016). A more recent analysis from ART-CC showed that for PLWH on ART and with high CD4 T-cell counts who survived to 2015 or started ART after 2015, life expectancy

was only a few years lower than that in the general population, irrespective of when ART was started. However, life expectancy estimates were substantially lower for people with low CD4 counts at the start of follow-up, emphasizing the continuing importance of early diagnosis and sustained treatment of HIV (Trickey 2023).
Even today, there are certain groups for whom there is still a gap compared to the general population. These are not only individuals with hepatitis co-infection or active drug use but also black patients or those with low CD4 T-cells at ART initiation. Comorbidities and alcohol use also worsen the prognosis. Late initiation of therapy also has an unfavorable impact on life expectancy (Marcus 2016). One of the most important negative factors is still often forgotten today: smoking! In a study from Denmark, 2,921 PLWH (only non-IVDUs were included) were examined; this was impressively shown – PLWH today lose more years of life through smoking than HIV-related diseases (Helleberg 2013). There also continue to be marked regional differences. For example, mortality remains significantly higher in North America than Europe, likely due to a higher proportion of socially marginalized people (Wandeler 2016).
However, prospective, controlled studies of the dramatically improved life expectancy are rare. Only a few randomized studies have clinical endpoints (Hammer 1997, Cameron 1998, Stellbrink 2000). Moreover, due to design, the successes in these trials have been comparatively modest. In the ABT-247 trial, in which 1,090 clinically advanced patients received either ritonavir juice or placebo on top of ongoing therapy, the probability of AIDS and death after 29 weeks was 21.9% in the ritonavir arm and 37.5% in the placebo arm – about half as high (Cameron 1998).

Table 4.5: Decline in mortality and morbidity in large cohorts.

	Region (n)	Patients (period)	Mortality (/100 PY)	Morbidity (/100 PY)
Palella 1998	USA (1,255)	<100 CD4 T-cells/µl (1/94–6/97)	29.4 → 8.8	21.9 → 3.7*
Mocroft 2000	Europe (7,331)	All (94–98)	k.A.	30.7 → 2.5
Mocroft 2002	Europe (8,556)	All (94–01)	15.6 → 2.7	n.a.
D'Arminio 2005	Worldwide (12,574)	The first 3 months versus 3rd year *after* ART	n.a.	12.9 → 1.3
D:A:D 2010	Worldwide (33,308)	All (99–07)	1.7 → 1.0	n.a.
May 2016	Worldwide (37,496)	The first 6 months versus 10 years after ART initiation (96-01)	3.3 → 1.4	n.a.

*MAC, PCP, CMV. Mortality/morbidity each per 100 PY = patient-years

Fortunately, the number of clinical endpoints that occur is now extremely low. As a result, the duration of any contemporary study to prove the clinical benefit of one combination over another would have to be extended over a long period. Unrealistically large study populations are now required given the extremely low probability of progression –rarely will such investigations be undertaken in the future (Raffi 2001). Two of the few trials that could confirm the benefits of ART on clinical endpoints were SMART (see chapter 5.11. on Treatment Interruption below) and START (see next section).

In the Swiss cohort, the effect of ART still increased with duration – after more than two years of ART, the risk of progression was only 4% of the risk without ART (Sterne 2005). However, several large cohorts (over 20,000 patients) showed that, especially in recent years, AIDS and death rates have not continued to decline – in both 1997 and 2003, the AIDS risk was about 6%. It is possible that, in many cases, ART is now started too late. In recent years, for example, one in two had fewer than 200 CD4 T-cells at the start of therapy (May 2016). The effect of ART on the incidence of individual AIDS cases is likely to be variable. Viral OIs show the most marked decline but are less pronounced than fungal OIs (D'Arminio 2005).

At least as apparent as the effect on incidence is the effect of ART on its course. Diseases such as cryptosporidiosis or PML can resolve heal without specific therapy, and Kaposi's sarcoma can disappear entirely without specific therapy. Prophylaxis can usually be safely discontinued. These effects are discussed in more detail in the corresponding chapters.

Literature on therapy goals of continuous therapy

Aiuti F, Mezzaroma I. Failure to reconstitute CD4+ T-cells despite suppression of HIV replication under HAART. AIDS Rev 2006; 8: 88-97.

Aan der Heiden M, Marcus U, Kollan C, et al. Schätzung der Zahl der HIV-Neuinfektionen und der Gesamtzahl von Menschen mit HIV in Deutschland.

Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 2008, 372:293-9.

Blanco JR, Alejos B, Moreno S. Impact of dolutegravir and efavirenz on immune recovery markers: results from a randomized clinical trial. Clin Microbiol Infect 2017 Nov 26.

Boillat-Blanco N, Darling KE, Schoni-Affolter F, et al. Virological outcome and management of persistent low-level viremia in HIV-1-infected patients: 11 years of the Swiss HIV Cohort Study. Antivir Ther 2015, 20:165-75.

Bouteloup V, Sabin C, Mocroft A, et al. Reference curves for CD4 T-cell count response to combination antiretroviral therapy in HIV-1-infected treatment-naïve patients. HIV Med 2017, 18:33-44.

Brima N, Lampe FC, Copas A, et al. Early virological response to HIV treatment: Can we predict who is likely to experience subsequent treatment failure? Results from an observational cohort study, London, UK. J Int AIDS Soc 2017, 20:21567.

Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. AIDS 2004, 18:2075-2079.

Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. The Advanced HIV Disease Ritonavir Study Group. Lancet 1998, 351:543-9.

Cardozo EF, Andrade A, Mellors JW, et al. Treatment with integrase inhibitor suggests a new interpretation of HIV RNA decay curves that reveals a subset of cells with slow integration. PLoS Pathog 2017, 13:e1006478.

Charpentier C, Landman R, Laouénan C et al. Persistent low-level HIV-1 RNA between 20 and 50 copies/mL in antiretroviral-treated patients: associated factors and virological outcome. J Antimicrob Chemother 2012, 67:2231-5.

d'Arminio Monforte A, Sabin CA, Phillips A, et al. The changing incidence of AIDS events in patients receiving highly active antiretroviral therapy. Arch Intern Med 2005, 165:416-23.

Data Collection on Adverse Events of Anti-HIV drugs (D:A:D) Study Group, Smith C. Factors associated with specific causes of death amongst HIV-positive individuals in the D:A:D Study. AIDS 2010, 24:1537-48.

Deeks SG, Barbour JD, Grant RM, Martin JN. Duration and predictors of CD4 T-cell gains in patients who continue combination therapy despite detectable plasma viremia. AIDS 2002, 16: 201-7.

DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. Clin Infect Dis 2004;39:1038-46.

Di Mascio M, Markowitz M, Louie M, et al. Dynamics of intermittent viremia during highly active antiretroviral therapy in patients who initiate therapy during chronic versus acute and early HIV type 1 infection. J Virol 2004, 78:10566-73.

Di Mascio M, Markowitz M, Louie M, et al. Viral blip dynamics during highly active antiretroviral therapy. J Virol 2003; 77:12165-72.

Dijkstra S, Hofstra LM, Mudrikova T, et al. Lower Incidence of HIV-1 Blips Observed During Integrase Inhibitor-Based Combination Antiretroviral Therapy. J AIDS 2022, 89:575-582.

Eastburn A, Scherzer R, Zolopa AR, et al. Association of low level viremia with inflammation and mortality in HIV-infected adults. PLoS One 2011, 6:e26320.

Easterbrook PJ, Ives N, Waters A, et al. The natural history and clinical significance of intermittent viraemia in patients with initial viral suppression to <400 copies/mL. AIDS 2002; 16:1521-7.

Elvstam O, Malmborn K, Elén S, et al. Virologic failure following low-level viremia and viral blips during antiretroviral therapy: results from a European multicenter cohort. Clin Infect Dis. 2022 Sep 14:ciac762.

Elvstam O, Medstrand P, Yilmaz A, et al. Virological failure and all-cause mortality in HIV-positive adults with low-level viremia during antiretroviral treatment. PLoS One 2017, 12:e0180761.

Engsig FN, Zangerle R, Katsarou O, et al. Long-term mortality in HIV-positive individuals virally suppressed for 3 years with incomplete CD4 recovery. Clin Infect Dis 2014, 58:1312-21.

Erdbeer G, Sabranski M, Sonntag I, et al. Intermittent viraemia and immune reconstitution in patients with more than 10-15 years of antiretroviral therapy: baseline values still matter. J Int AIDS Soc 2014, 17(4 Suppl 3):19689.

Florence E, Lundgren J, Dreezen C, et al. Factors associated with a reduced CD4 lymphocyte count response to HAART despite full viral suppression in the EuroSIDA study. HIV Med 2003;4:255-62.

Gale HB, Gitterman SR, Hoffman HJ, et al. Editor's choice: Is Frequent CD4+ T-Lymphocyte Count Monitoring Necessary for Persons With Counts ≥300 Cells/μL and HIV-1 Suppression? Clin Infect Dis, 56: 1340-1343.

Gilson RJ, Man SL, Copas A, et al. Discordant responses on starting highly active antiretroviral therapy: suboptimal CD4 increases despite early viral suppression in the UK Collaborative HIV Cohort (UK CHIC) Study. HIV Med 2010, 11:152-60.

Goetz MB, Boscardin WJ, Wiley D, Alkasspooles S. Decreased recovery of CD4 lymphocytes in older HIV-infected patients beginning HAART. AIDS 2001, 15:1576-9.

Grabar S, Kousignian I, Sobel A, et al. Immunologic and clinical responses to HAART over 50 years of age. AIDS 2004, 18:2029-2038.

Grabar S, Le Moing V, Goujard C, et al. Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of HAART. Ann Intern Med 2000, 133: 401-10.

Gueler A, Moser A, Calmy A, et al. Life expectancy in HIV-positive persons in Switzerland: matched comparison with general population. AIDS 2017, 31:427-436.

Gunthard HF, Wong JK, Ignacio CC, et al. Human immunodeficiency virus replication and genotypic resistance in blood and lymph nodes after a year of potent antiretroviral therapy. J Virol 1998, 72:2422-8.

Haas D. Human genetic variability and HIV treatment response. Current HIV/AIDS Reports 2006, 3:53-58.

Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with HIV infection and CD4 cell counts of 200 per cubic millimeter or less. ACTG 320 Study Team. N Engl J Med 1997, 337:725-33.

Helleberg M, Afzal S, Kronborg G, et al. Mortality attributable to smoking among HIV-1-infected individuals: A nationwide, population-based cohort study. Clin Infect Dis 2013, 56:727-34.

Huttner AC, Kaufmann GR, Battegay M, Weber R, Opravil M. Treatment initiation with zidovudine-containing potent antiretroviral therapy impairs CD4 cell count recovery but not clinical efficacy. AIDS 2007;21:939-46.

Jones LE, Perelson AS. Transient viremia, plasma viral load, and reservoir replenishment in HIV-infected patients on antiretroviral therapy. J AIDS 2007;45:483-93.

Kaufmann D, Pantaleo G, Sudre P, Telenti A. CD4-cell count in HIV-1-infected individuals remaining viraemic with HAART. Swiss HIV Cohort Study. Lancet 1998, 351:723-4.

Kaufmann GR, Furrer H, Ledergerber B, et al. Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. Clin Infect Dis 2005;41:361-72.

Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. Arch Intern Med 2003; 163:2187-95.

Kelley CF, Kitchen CM, Hunt PW, et al. Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. Clin Infect Dis 2009, 48:787-94.

Kelly C, Gaskell KM, Richardson M, et al. Discordant Immune Response with Antiretroviral Therapy in HIV-1: A Systematic Review of Clinical Outcomes. PLoS One 2016;11: e0156099.

Kolber MA, Gabr AH, De La Rosa A, et al. Genotypic analysis of plasma HIV-1 RNA after influenza vaccination of patients with previously undetectable viral loads. AIDS 2002, 16: 537-42.

Ledergerber B, Egger M, Opravil M. et al. Clinical progression and virological failure on HAART in HIV-1 patients: a prospective cohort study. Lancet 1999, 353: 863-8.

Ledergerber B, Furrer H, Rickenbach M, et al. Predictors and time trends of stably suppressed viral load among HIV-1 infected individuals on cART in the Swiss HIV Cohort Study (SHCS). Abstract 507, 17th CROI 2010, San Francisco.

Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. Lancet 2004, 364:51-62.

Lederman MM, McKinnis R, Kelleher D, et al. Cellular restoration in HIV-infected persons treated with abacavir and a protease inhibitor: age inversely predicts naive CD4 cell count increase. AIDS 2000, 14: 2635-42.

Lelièvre JD, Assoumou L, Aznar E, et al. ANRS 146 – GeSIDA 7211 OPTIMAL: Optimized Phase III Trial of Immuno-Stimulation With Maraviroc, a CCR5 Antagonist, Combined With Anti-Retroviral Therapy (cART) in Advanced, Late Diagnosed HIV-1-Infected Patients With an AIDS-Defining Event and/or CD4 Counts ≤200 Cells/mm^3. Abstract MOAB0102, 9th IAS Paris 2017.

Lohse N, Hansen AB, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. Ann Intern Med 2007; 146: 87-95.

Lok JJ, Bosch RJ, Benson CA, et al. Long-term increase in CD4+ T-cell counts during combination antiretroviral therapy for HIV-1 infection. AIDS 2010, 24:1867-76.

Maggiolo F, Callegaro A, Cologni G, et al. Ultrasensitive assessment of residual low-level HIV viremia in HAART-treated patients and risk of virological failure. J AIDS 2012, 60:473-82.

Maggiolo F, Migliorino M, Pirali A. Duration of viral suppression in patients on stable therapy for HIV-1 infection is predicted by plasma HIV RNA level after 1 month of treatment. J AIDS 2000, 25:36-43.

Maldarelli F, Palmer S, King MS, et al. ART suppresses plasma HIV-1 RNA to a stable set point predicted by pretherapy viremia. PLoS Pathog 2007, 3:e46.

Marcus JL, Chao CR, Leyden WA, et al. Narrowing the gap in life expectancy between HIV-infected and HIV-uninfected individuals with access to care. J Acquir Immune Defic Syndr. 2016 Mar 29.

Martinez V, Marcelin AG, Morini JP, et al. HIV-1 intermittent viraemia in patients treated by non-nucleoside reverse transcriptase inhibitor-based regimen. AIDS 2005;19:1065-1069.

May MT, Vehreschild JJ, Trickey A, et al. Mortality According to CD4 Count at Start of Combination Antiretroviral Therapy Among HIV-infected Patients Followed for up to 15 Years After Start of Treatment: Collaborative Cohort Study. Clin Infect Dis 2016; 62:1571-7.

Miller LG, Golin CE, Liu H, et al. No evidence of an association between transient HIV viremia ("Blips") and lower adherence to the antiretroviral medication regimen. J Infect Dis 2004, 189:1487-96.

Mocroft A, Bannister WP, Kirk O, et al. The clinical benefits of antiretroviral therapy in severely immunocompromised HIV-1-infected patients with and without complete viral suppression. Antivir Ther 2012, 17:1291-300.

Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994-98: the EuroSIDA study. Lancet 2000, 356:291-6.

Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. Lancet 2003;362:22-9.

Mocroft A, Phillips AN, Gatell J, et al. Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study. Lancet 2007;370:407-13.

Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV 2018, 5:e211-e220.

Moore DM, Hogg RS, Yip B, et al. Discordant immunologic and virologic responses to highly active antiretroviral therapy are associated with increased mortality and poor adherence to therapy. J Acquir Immune Defic Syndr 2005; 40: 288-93.

Morlat P, Roussillon C, Henard S, et al. Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000. AIDS 2014, 28:1181-91.

Mortier V, Vancoillie L, Dauwe K, et al. Meticulous plasma isolation is essential to avoid false low-level viraemia in Roche Cobas HIV-1 viral load assays. Antivir Ther 2017 Oct 24.

Murray JM, Emery S, Kelleher AD, et al. Antiretroviral therapy with the integrase inhibitor raltegravir alters decay kinetics of HIV, significantly reducing the second phase. AIDS 2007, 21: 2315–2321.

Navarro J, Caballero E, Curran A, et al. Impact of low-level viraemia on virological failure in HIV-1-infected patients with stable antiretroviral treatment. Antivir Ther 2016 Jan 12.

Neesgaard B, Mocroft A, Zangerle R, et al. Virologic and immunologic outcomes of treatment with integrase inhibitors in a real-world setting: The RESPOND cohort consortium. PLoS One 2020;15:e0243625.

Negredo E, Molto J, Munoz-Moreno JA, et al. Safety and efficacy of once-daily didanosine, tenofovir and nevirapine as a simplification antiretroviral approach. Antivir Ther 2004, 9:335-42.

Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. JAMA 2005, 293:817-29.

Nettles RE, Kieffer TL, Simmons RP, et al. Genotypic resistance in HIV-1-infected patients with persistently detectable low-level viremia while receiving highly active antiretroviral therapy. Clin Infect Dis 2004, 39:1030-7.

Nottet HS, van Dijk SJ, Fanoy EB, et al. HIV-1 can persist in aged memory CD4+ T lymphocytes with minimal signs of evolution after 8.3 years of effective highly active antiretroviral therapy. J AIDS 2009, 50:345-53.

Palella FJ JR, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced HIV infection. N Engl J Med 1998, 338:853-60.

Phillips AN, Youle M, Lampe F, et al. CD4 cell count changes in individuals with counts above 500 cells/mm and viral loads below 50 copies/mL on antiretroviral therapy. AIDS 2002; 16: 1073-5.

Piketty C, Castiel P, Belec L, et al. Discrepant responses to triple combination antiretroviral therapy in advanced HIV disease. AIDS 1998, 12:745-50.

Piketty C, Weiss L, Thomas F, et al. Long-term clinical outcome of HIV-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen. J Infect Dis 2001, 183:1328-35.

Podsadecki TJ, Vrijens BC, Tousset EP, Rode RA, Hanna GJ. Decreased adherence to antiretroviral therapy observed prior to transient human immunodeficiency virus type 1 viremia. JID 2007;196:1773-8.

Popping S, Kall M, Nichols BE, et al. Quality of life among people living with HIV in England and the Netherlands: a population-based study. Lancet Reg Health 2021, 8:100177.

Portman MD, Lacey CJ. Apparent low-level HIV RNA viraemia related to sample processing time. HIV Med 2012, 13:578-9.

Powderly WG, Saag MS, Chapman S, et al. Predictors of optimal virological response to potent ART. AIDS 1999, 13:1873-80.

Pozniak AL, Gallant JE, DeJesus E, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes—a 96-week analysis. J AIDS 2006; 43: 535-40.

Pugliese P, Delpierre C, Cuzin L, et al. An undetectable polymerase chain reaction signal in routine HIV plasma viral load monitoring is associated with better virological outcomes in patients receiving highly active antiretroviral therapy. HIV Med. 2013 May 8. [Epub ahead of print].

Raboud JM, Montaner JS, Conway B, et al. Suppression of plasma viral load below 20 copies/mL is required to achieve a long-term response to therapy. AIDS 1998, 12: 1619-24.

Raffi F, Chene G, Lassalle R, et al. Progression to AIDS or death as endpoints in HIV clinical trials. HIV Clin Trials 2001, 2:330-5.

Renaud M, Katlama C, Mallet A, et al. Determinants of paradoxical CD4 cell reconstitution after protease inhibitor-containing antiretroviral regimen. AIDS 1999, 13:669-76.

Reus S, Portilla J, Sánchez-Payá J, et al. Low-level HIV viremia is associated with microbial translocation and inflammation. J AIDS 2013, 62:129-34.

Saison J1, Ferry T, Demaret J, et al. Association between discordant immunological response to highly active antiretroviral therapy, regulatory T cell percentage, immune cell activation and very low-level viraemia in HIV-infected patients. Clin Exp Immunol 2014, 176:401-9.

Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet 2017, 390:2073-2082.

Scherrer AU, von Wyl V, Yang WL, et al. Emergence of Acquired HIV-1 Drug Resistance Almost Stopped in Switzerland: A 15-Year Prospective Cohort Analysis. Clin Infect Dis 2016, 62:1310-1317.

Schmidt D, Kollan C, Neuhauss AK, et al. Persistent viraemia – Still an ongoing problem of antiretroviral treatment? Results from the ClinSurv HIV cohort from 1999 to 2014. Abstract 119, DÖAK 2017, Salzburg.

Sellier P, Alexandre-Castor G, Brun A, et al. Updated mortality and causes of death in 2020-2021 in people living with HIV: a multicenter study in France. AIDS. 2023 Jul 10.

Shen L, Peterson S, Sedaghat AR, et al. Dose-response curve slope sets class-specific limits on inhibitory potential of anti-HIV drugs. Nat Med 2008, 14:762-6.

Sigal A, Kim JT, Balazs AB, Dekel E, Mayo A, Milo R, Baltimore D. Cell-to-cell spread of HIV permits ongoing replication despite antiretroviral therapy. Nature 2011, 477:95-8.

Siliciano JD, Kajdas J, Finzi D, et al. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. Nature Med 2003;9:727-728.

Siliciano R. New approaches for understanding and evaluating the efficacy of ARVs. Abstract 16, 16th CROI 2009 Montréal.

Smith CJ, Sabin CA, Youle MS, et al. Factors influencing increases in CD4 cell counts of HIV-positive persons receiving long-term highly active antiretroviral therapy. J Infect Dis 2004, 190:1860-8.

Smith K, Aga E, Bosch RJ, Valdez H, et al. Long-term changes in circulating CD4 T lymphocytes in virologically suppressed patients after six years of highly active antiretroviral therapy. AIDS 2004, 18:1953-6.

SPARTAC Investigators. Short-course antiretroviral therapy in primary HIV infection. N Engl J Med 2013, 368:207-17.

Stellbrink HJ, Hawkins DA, Clumeck N, et al. Randomised, multicentre phase III study of saquinavir plus zidovudine plus zalcitabine in previously untreated or minimally pretreated HIV-infected patients. Clin Drug Invest 2000, 20:295-307.

Stepanyuk O, Chiang TS, Dever LL, et al. Impact of adding maraviroc to antiretroviral regimens in patients with full viral suppression but impaired CD4 recovery. AIDS 2009, 23:1911-3.

Sterne JA, Hernan MA, Ledergerber B, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. Lancet 2005, 366:378-84.

Stover J, Glaubius R, Teng Y, et al. Modeling the epidemiological impact of the UNAIDS 2025 targets to end AIDS as a public health threat by 2030. PLoS Med. 2021 Oct 18;18(10):e1003831.

Sungkanuparph S, Overton ET, Seyfried W, et al. Intermittent episodes of detectable HIV viremia in patients receiving nonnucleoside reverse-transcriptase inhibitor-based or protease inhibitor-based highly active antiretroviral therapy regimens are equivalent in incidence and prognosis. Clin Infect Dis, 41:1326-32.

Taiwo B, Gallien S, Aga E, et al. Antiretroviral drug resistance in HIV-1-infected patients experiencing persistent low-level viremia during first-line therapy. J Infect Dis 2011, 204:515-20.

Taiwo B, Hunt P, Gandhi R, et al. Immune Activation in HIV-1 Patients Experiencing Transiently Detectable Viremia During ART. Abstract 276, 19th CROI 2012, Seattle.

Tan R, Westfall AO, Willig JH, et al. Clinical outcome of HIV-infected antiretroviral-naive patients with discordant immunologic and virologic responses to highly active antiretroviral therapy. J AIDS 2008, 47:553-8.

Teixeira L, Valdez H, McCune JM, et al. Poor CD4 T cell restoration after suppression of HIV-1 replication may reflect lower thymic function. AIDS 2001, 15:1749-56.

Torti C, d'Arminio-Monforte A, Pozniak AL, et al. Long-term CD4+ T-cell counts evolution after switching from regimens including HIV nucleoside reverse transcriptase inhibitors (NRTI) plus protease inhibitors to regimens containing NRTI plus non-NRTI or only NRTI. BMC Infect Dis 2011, 11:23.

Trickey A, Zhang L, Gill J, et al. Associations of modern initial antiretroviral drug regimens with all-cause mortality in adults with HIV in Europe and North America: a cohort study. Lancet 2022, e404-e413.

Trickey A, Sabin CA, Burkholder G, et al. Life expectancy after 2015 of adults with HIV on long-term antiretroviral therapy in Europe and North America: a collaborative analysis of cohort studies. Lancet HIV 2023, 10:e295-e307.

Vancoillie L, Hebberecht L, Dauwe K, et al. Longitudinal sequencing of HIV-1 infected patients with low-level viremia for years while on ART shows no indications of genetic evolution of the virus. Virology 2017, 510:185-193.

Wandeler G, Johnson LF, Egger M. Trends in life expectancy of HIV-positive adults on antiretroviral therapy across the globe: comparisons with the general population. Curr Opin HIV AIDS. 2016 May 31.

Xia Q, Maduro GA, Li W, Huynh M, Torian LV. Life expectancy among people with HIV in New York City, 2009-2018. JAIDS 2022 Sep 8.

Zoufaly A, an der Heiden M, Kollan C, et al. Clinical outcome of HIV-infected patients with discordant virological and immunological response to antiretroviral therapy. J Infect Dis 2011, 203:364-71.

5.4.2. Therapeutic goal: HIV cure

GEORG BEHRENS, CHRISTIAN HOFFMANN

The cure for people living with HIV remains the holy grail of HIV medicine. With the introduction of the first ART combinations, it was calculated that 70 years of therapy should lead to the viral eradication of all reservoirs. Thus, it is clear that we must develop strategies beyond ART to drive HIV and the latently infected cells out of the body. An international group of researchers defined the goals and strategies for the next five years at the end of 2021 (Deeks 2021).

The case of the "Berlin patient" Timothy Brown, published in 2009, shows that it is possible to eradicate HIV infection. Brown had acute myeloid leukemia, and there was an indication for an allogeneic stem cell transplant (allo-SCT). One of the potential stem cell donors was homozygous for the delta 32 mutation in the CCR5 gene. This otherwise harmless gene defect lacks an important co-receptor on the target cells that HIV requires for entry. After two successful transplants using stem cells from the donor, Brown, who had had a very high viral load before starting ART, remained undetectable for many years, even without ART (Hütter 2009). The virus could not be detected in the blood, lymph nodes, or intestinal mucosa (Yukl 2013). Unfortunately, Brown died of leukemia in September 2020, 13 years after transplantation. Other cases of successful remission after transplantation of homozygous deficient stem cells have since been published (Gupta 2020, Jensen 2023), but the observation periods are shorter. A cure (at least for 14 months) was also recently reported with resistant stem cells from umbilical cord blood in one woman (Hsu 2023). These cases have provided essential insights on the way to a cure. Such approaches are generally impractical, given the effort involved and especially the considerable risks (Duarte 2015, Koelsch 2017). There is also an important case in which an allo-SCT was unsuccessful (not able to eradicate HIV), indicating that, at least in some cases, HIV that uses CCR5 receptors can persist and continue to spread (Rubinstein 2023).

What is meant by "cure"?

Eradication of all replication-capable viruses would be the surest path to a cure. But perhaps less is enough – we would already achieve a lot if the body could control HIV without the aid of drugs – like other viral infections, i.e., herpes, where low levels of virus persist throughout life. A distinction is therefore made today between "Sterilizing Cure" and "Functional Cure" (note: the term "sterilizing" terminology has been criticized for being potentially derogatory in its connotations to disinfection and eugenics).

A "functional" cure is achieved in so-called "Post Treatment Controllers", which can maintain viral replication at low or undetectable levels after stopping ART. At least four strategies are currently being pursued or combined to achieve this. These are (1) elimination of latently infected cells, (2) control of residual replication, (3) enhancement of the HIV-specific immune response, and (4) attempts to make cells resistant to HIV infection ultimately.

Some patients succeed at least in the "functional cure" without any therapy. These so-called "elite controllers" (ECs) make up less than 1% of all PLWH. The CD4 T-cells remain normal for many years, and the viral load is, more impressively, below the limit of detection (primarily constant) even without therapy. Responsible for this are usually favorable HLA constellations (especially HLA B57*, B58*, and B27*) and/or other gene variants like heterozygosity for the Δ32 deletion (see *Basics*). In particular, it is from those ECs who lack protective alleles and where control of HIV likely

occurs via CD8 cytotoxic cells that future learning is needed to better understand the immune system (Moyano 2021).
ECs are not a homogeneous group; attenuated viruses can also be the cause, although rarely (review: Lopez-Galindez 2019). There are also at least two case reports in which no intact provirus was found even with extremely sensitive methods – in both cases of such "spontaneous cure", interestingly, women were affected (Jiang 2020, Turk 2022). Using CRISPR/Cas9, a wealth of other potential genes or functional host factors have now been discovered, which will help to understand individual variability in HIV control better (Hiatt 2022).
Despite normal CD4 T-cells and an undetectable viral load, ECs exhibit differences compared to healthy controls. There is evidence for increased systemic inflammation and immune activation. Compared with PLWH, who controlled their infection with ART, ECs had a significantly increased risk of hospitalization even after adjustment for demographics, primarily related to cardiovascular events (Crowell 2015). However, one study found no increased risk of sub-clinical cardiovascular disease in ECs (Brusca 2019).
In a prospective pilot study, 16 ECs received antiretroviral therapy (Hatano 2013). Signs of T cell activation and dysfunction in the lymph node and intestinal mucosa regressed after 24 weeks on ART, even in patients with an undetectable viral load below 40 copies/mL before ART initiation. Thus, it is likely that even extremely low residual replication can result in adverse effects or chronic immune stimulation. If it can be assumed that residual replication is also present in "post-treatment controllers," the question arises whether such a functional cure is desirable. Apart from the fact that no treatments need to be taken, is this equivalent to well-tolerated and cost-effective ART?

Can (very) early ART lead to a cure?

In 2013, the case of the perinatal infected "Mississippi Baby" gained worldwide attention. This infant had been antiretrovirally treated only 31 hours after birth (Persaud 2013). The baseline viral load of 19,812 copies/mL fell to 265 copies/mL at day 19 and was undetectable for 18 months. The baby was then lost to the healthcare system for six months. Unexpectedly, the viral suppression remained undetectable when tested for HIV upon return. For more than two years, this girl had no signs of the virus in her blood despite cessation of treatment. An ultrasensitive assay revealed 4 copies of HIV DNA/million PBMCs but no HIV-specific immune responses. Protective HLA types, as seen in elite controllers, were not observed. The finding encouraged scientists hoping to find a way to save children from a lifetime of ART. However, the virus resurfaced in the patient 27 months after stopping ART (Ledford 2014). It became apparent that the "post-treatment control" had only been transient. It remains unclear what led to the abrupt rebound.
Meanwhile, similar pediatric cases have been published where viral rebound later occurred within a few days after treatment interruption despite immediate ART after birth, with only a few exceptions (Butler 2015, Frange 2016, Vieira 2019).
Before the Mississippi baby case, several PCT cases had been presented from France (Sáez-Cirión 2013). In the so-called VISCONTI cohort (Viro-Immunological Sustained CONtrol after Treatment Interruption), 14 PLWH who had received antiretroviral treatment within 35–70 days of infection and for a median of 3 years showed no viral load rebound during multi-year treatment interruptions, which lasted 7.5 years (48 to 113 months). In all 14 people, the viral load was below 500 copies, and proviral DNA remained detectable in PBMC. In no case were favorable genetic defects or protective alleles detectable, and the patients had worse CD8 responses than "elite controllers". Further French and Thai studies suggested that early therapy could limit

viral reservoirs (Hocqueloux 2013, Crowell 2016). In contrast, in other studies, the effect on the reservoir remained independent of the Fiebig stage of acute HIV infection (Kroon 2018). Even when therapy was started very early (Fiebig 1), HIV RNA increased again after ART was discontinued (Colby 2018). Overall, a clear statement about the potential of a so-called PCT with immediate ART during acute infection is impossible. The probability seems to be low. In an analysis of 14 studies, post-treatment controllers (individuals who underwent treatment interruption with viral loads ≤ 400 copies/mL at two-thirds or more of time points for ≥ 24 weeks) were more frequently identified in those treated during early vs. chronic infection (13% versus 4%). The durability of PCT was heterogeneous. Of post-treatment controllers, 55% maintained HIV control for two years, with approximately 20% maintaining control for ≥ 5 years (Namazi 2018).
Similarly, SPARTAC, a large randomized trial in which 366 people with early HIV infection (less than six months) received ART for 12–48 weeks or remained untreated, showed a slight but only transient benefit in favor of earlier therapy (SPARTAC 2013, Martin 2017). It also remains unclear, especially in acutely treated patients, whether and how long control persists after treatment. Attempts are being made to predict this based on the breadth of the CTL response (Conway 2015), but there is admittedly no reliable predictor. Despite these uncertainties and the overall low probability of achieving something like PTC with immediate ART and favorably influencing the individual natural history of HIV infection, there is nevertheless much to be said for immediate treatment in acute HIV infection. In times of well-tolerated regimens, given the START study, which showed a clinical advantage in early therapy initiation (see chapter 5.5. *When to start with ART?*) and reduced infectivity, there are barely any strong arguments against immediate initiation.

A cure in chronically infected patients?

Acute HIV infection is rarely diagnosed. The main question is what can be achieved in chronic infection. Several barriers to a cure in these patients must be overcome, such as the intrinsic stability of the viral genome in latently infected CD4s and other cells and persistent low-level replication in different compartments. It remains an open question whether surrogate markers and methods can reliably measure the latent reservoir (Crooks 2015, Massanella 2016, Wang 2018). Measuring proviral DNA from lymphocytes by PCR is not sufficient – it leads to values that are significantly (300-fold) higher than the quantifications of so-called viral outgrowth assays (VOA), in which latently infected cells in culture are stimulated to produce HIV. This suggests that many cells are infected with defective viruses. In addition, residual viremia does not correlate with VOA, perhaps putting the importance of low viremia into perspective. According to VOA studies, the frequency of latently infected cells in antiretroviral-treated patients is approximately $1/10^6$. Although many cells are infected with defective viruses, researchers have been able to isolate intact viruses from cells in 12% after maximal *in vitro* stimulation (Ho 2013). These non-induced proviruses possessed unmethylated promoters and were integrated into active transcription units. In short, we cannot rule out the possibility of these viruses being activated *in vivo*. Thus, quantification of the viral reservoir is technically complex (Bruner 2019). Interpretation of these methods for prospective use in clinical trials will remain a major challenge. In the end, there will be no way around so-called analytical antiretroviral therapy breaks to validate measurement methods of latent reservoirs (Julg 2019). However, the timing of viral rebounds and the viral setpoint are subject to numerous influences. In any case, it is good to start ART as early as possible. In the START trial, starting therapy when there were more than 800 CD4 T-cells was associated with a smaller reservoir (Rasmussen 2022).

The latent reservoirs

At this point, eradication of HIV, i.e., the removal of all viruses from the body, is somewhat unrealistic. The main reason is that HIV-infected cells comprise a lifelong reservoir. The reservoir consists of very heterogeneous cell populations, including long-lived CD4-positive memory T cells and their progenitors, stem cells, macrophages, and others, whose stability is probably independent of residual viral replication (McManus 2018).

The reservoir is quickly established after infection. Moreover, viral transcription can still be detected in them even after years of sufficient suppression (Finzi 1999, Furtado 1999, Sigal 2011, Einkauf 2022). This is especially true for cells in the blood; however, replication also occurs in lymph nodes and the gastrointestinal tract, even when nothing is detectable in the blood. Latently infected reservoirs persist even after myeloablative chemotherapy and autologous stem cell transplantation (Cillo 2013, Henrich 2014).

Theoretically, how long does it take until the last latently infected cells are removed? In a study of 62 patients whose viral load had been successfully suppressed for seven years on ART, the half-life was 44.2 months for the latently infected cell reservoir (Siliciano 2003). The calculated time to eradication of these reservoirs was 73.4 years. Even in those patients in whom not a single blip was measurable during at least three years of stable ART and where an overall trend for somewhat faster decline was observed, the eradication time was still 51.2 years. Even after almost nine years on ART, the virus remains in resting CD4 memory cells, with minimal evolution. It is possible that the latently infected cell reservoir is much larger than previously thought (Dolgin 2013) and that the latently infected cells are particularly resistant to immune challenge (Huang 2018). A recent calculation showed that even with effective ART, a total of 10^8 cells with HIV DNA remain (Estes 2017), containing replicable viruses. Controversy continues to surround whether residual replication of HIV, in particular, keeps "filling" the reservoir or whether the homeostatic proliferation of latently infected cells keeps the size of the reservoir from diminishing (Hosmane 2017, Lee 2017, McManus 2018). It has become clear that the reservoir is much more complex and dynamic than initially thought (Cho 2022).

Various strategies are being tested to combat the latent reservoir: the "shock (or kick) and kill" strategy, in which cells are activated and subsequently eliminated, the reduction of the reservoir (by intensification or/and antibodies), the excision of HIV by gene therapies, and "block and lock" approaches, in which latently infected cells are prevented from activation. These approaches often read very promisingly in theory but, in practice – at least so far – have not lived up to their claims.

Intensification studies

Several studies addressed whether viral load reduction can be accelerated by intensive therapy or anything changes at all. Can the remaining viral replication and latent reservoirs be further reduced? Does activation of the latently infected cells make sense? Various strategies have been pursued, including additional administration of integrase and entry inhibitors and agents to help empty latent reservoirs. These are briefly discussed below.

Mega-HAART, entry, and/or integrase inhibitors

In a study of patients with good viral suppression who still intensified their ART with PIs or NNRTIs, ultrasensitive single-copy assays showed no further viral load reduction (Dinoso 2009). The viral load level on ART depends less on the regimen used than on the pre-therapeutic setpoint (Maldarelli 2007). This is also true for maraviroc, which was evaluated as a potential immunomodulatory CCR5 antago-

nist in a prospective study of 40 people with acute HIV infection. In any case, five-drug ART with maraviroc and raltegravir remained without any advantage over classical triple therapy regarding residual viremia, the extent of immune reconstitution, or immune activation (Markowitz 2014). Several prospective studies in which the INSTIs raltegravir or dolutegravir were added to ART showed neither an additional antiviral effect nor an effect on proviral DNA with ultrasensitive viral load assays (Buzon 2010, Chege 2012, Rasmussen 2018). It is not a question of how many ARVs. However, some studies observed an increase in episomal DNA on raltegravir. This DNA, also called "2-long terminal repeat (2-LTR) circular", is formed when INSTIs prevent DNA from being integrated into chromatin. The detection of this episomal DNA ("2 LTR circles") in some patients who added raltegravir to effective ART perhaps means that active viral replication was inhibited in these cases (Buzon 2010, Llibre 2012, Hatano 2013). However, there are also studies where this phenomenon was not found (Besson 2012, Rasmussen 2018).

"Shock and Kill"

According to the studies described above, it is highly doubtful that eradication will be achievable with the current classes of active agents (Shen 2008). Intensification or expansion has not had meaningful results. For this reason, the old "shock and kill" strategy is currently being resumed, in which infected cells are activated and then (hopefully) killed by the immune system (Zerbato 2019).

Valproic acid, an antiepileptic drug that is an inhibitor of histone deacetylases (HDACs) and is thought to lead to flushing of HIV from resting T cells, showed encouraging effects in a pilot study (Lehrman 2005). However, a more extensive study showed no effects (Routy 2012). Romidepsin, which may be more effective, as well as vorinostat (Fidler 2020), panobinostat, and other HDAC inhibitors (Edelstein 2009, Rasmussen 2013) are being studied but appear to lead to HIV reactivation in only some cells (Winckelmann 2017). In particular, Romidepsin was expected to be very effective after *in vitro* studies (Søgaard 2015). In clinical studies, the substance has failed to provide proof (MacMahon 2021), even in combination with vaccines. In a small pilot study, HIV DNA decreased by 40%, and in 8/17 cases, there was an increase in viral load in the sense of a "washout" – but this did not affect the rebound during a therapy break (Leth 2016). The same was true for the combination of romidepsin and monoclonal antibodies (Gruell 2022). Other chemical classes thought to activate latently infected cells include quinoline derivatives or disulfiram. Likely, the "kill" part will also require activation of HIV-specific CTLs, perhaps with therapeutic vaccines (review: Board 2021).

Immune checkpoint inhibitors, which are increasingly used in oncology and are very effective in abrogating negative signals for T cells, could also play a role (review: Gubser 2022). Combinations of different checkpoint inhibitors are probably necessary (Baron 2022).

Approaches using broadly neutralizing antibodies (bNAbs) are also repeatedly postulated. Since 2009, many such antibodies have been discovered that target not only the CD4 binding site, such as VRC01 but also other vulnerable sites of the *env* glycoprotein of HIV (for an updated overview, see *ART*). Numerous clinical trials are planned or underway, both as prevention and with a therapeutic goal, not only complementary to ART but also with the potential to eliminate infected cells and reduce the viral reservoir. In a few people, this approach does seem to be able to reduce the reservoir, but larger controlled studies are lacking (Gaebler 2022). Intriguingly, the still very new field of bifunctional antibodies (BITEs or DARTs) that bind not only to HIV but also to CD3/CD8 could theoretically help empty the viral reservoir. Pre-clinical studies have been published (Pegu 2015, Sung 2015, Ramadoss 2020).

Gene therapy approaches are also being pursued, but CRISPR-based approaches have not yet worked. These involve attempts to modify hematopoietic stem cells so they no longer express CCR5, making them resistant to HIV infection and then preferentially spreading after reinfusion into the donor (Tebas 2014, Xu 2019). It is also likely to be challenging to remove latent reservoirs with "gene scissors", in which specific enzymes are introduced into host cells that seek out the viral genome in the nucleus and selectively excise it from human DNA (Karpinski 2016). What works in animal models (Hauber 2013) is being tested in humans.

Another innovation from oncology, CAR-T cell therapy, is also being discussed as a possibility. This involves taking T cells from patients and genetically modifying them outside the body so that they better recognize tumor cells when returned. Numerous studies are underway on HIV (review: York 2022).

Other approaches

1. enzymatic excision of HIV from latently infected cells via "zinc finger nucleases" or with CRISPR/Cas9 (Zhu 2015).
2. Artificially engineered T cell receptors to enhance the function of HIV-specific lymphocytes (Sahu 2013, Yang 2014).
3. Vector-based vaccination to induce broadly neutralizing antibodies to HIV that then suppress HIV even without ART (Horwitz 2013, Jardine 2015).

Safety

Many PLWH repeatedly ask about the chances of a cure and express their willingness to participate in experimental studies. Especially given the still very present stigmatization and discrimination, many are willing to take considerable risks. A controversy has erupted over the question of what risks are acceptable and reasonable today in times of almost normal life expectancy. There are increasing calls to proceed with great caution; studies must ultimately withstand regulatory and ethical scrutiny (Dubé 2020). Transplantation, checkpoint inhibitors, or CAR-T cells carry significant risks. But even well-known drugs are not without dangers: in a small study, the first two patients recently developed severe (fortunately reversible) neurotoxicity from the combination of high-dose disulfiram and vorinostat; the study was stopped (McMahon 2022). However, it is not only toxicities that need to be considered; the analytic treatment interruption that usually follows curative trials also poses risks, especially in the era of COVID-19 (Fidler 2021). The safety of PLWH is paramount. Open communication about the risks is required; no unrealistic expectations should be raised (Deeks 2021).

Conclusion

The cure is not around the corner. However, we may expect some people to be called PTC or functionally cured in the next few years. Also, in the long run, only particular patients will be considered for cure strategies, i.e., those with well-preserved immune systems (another reason to start ART as early as possible!). Latently infected cells differ from non-infected cells only by a minuteness that is hardly detectable with current means and cannot be specifically targeted. Washing out the reservoirs or eliminating all infected memory cells has been either unsuccessful or too toxic. The excision of the HIV genome from infected cells using special recombinases has been successful in laboratory and animal models; however, clinical application is still a long way off. This also applies to the CRISPR/Cas9 system, which is currently the subject of much discussion. Given the immune system's complexity, which is only gradually beginning to be understood, a solution still seems a long way off.

Literature on HIV cure

Allers K, Hütter G, Hofmann J, et al. Evidence for the cure of HIV infection by CCR5Δ32/Δ32 stem cell transplantation. Blood 2011, 117:2791-9.

Bar KJ, Harrison LJ, Overton ET, et al. ACTG 5340:The Effect of VRC01 on Viral Kinetics After Analytic Treatment Interruption. Abstract 32LB, 23rd CROI 2016, Boston.

Baron M, Soulié C, Lavolé A, et al. Impact of Anti PD-1 Immunotherapy on HIV Reservoir and Anti-Viral Immune Responses in People Living with HIV and Cancer. Cells 2022, 11:1015.

Besson GJ, McMahon D, Maldarelli F, Mellors JW. Short-course raltegravir intensification does not increase 2 long terminal repeat episomal HIV-1 DNA in patients on effective antiretroviral therapy. Clin Infect Dis 2012, 54:451-3.

Board NL, Moskovljevic M, Wu F, Siliciano RF, Siliciano JD. Engaging innate immunity in HIV-1 cure strategies. Nat Rev Immunol 2021 Nov 25.

Bruner KM, Wang Z, Simonetti FR, et al. A quantitative approach for measuring the reservoir of latent HIV-1 proviruses. Nature 2019; 566:120-125.

Brusca RM, Hanna DB, Wada NI, et al. Subclinical cardiovascular disease in HIV controller and long-term non-progressor populations. HIV Med 2019 Nov 14.

Butler KM, Gavin P, Coughlan S, et al. Rapid viral rebound after 4 years of suppressive therapy in a seronegative HIV-1 infected infant treated from birth. Pediatr Infect Dis J 2015, 34:e48-51.

Buzón MJ, Massanella M, Llibre JM, et al. HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects. Nat Med 2010; 16:460-5.

Caskey M, Klein F, Lorenzi JC, et al. Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. Nature 2015; 522:487-91.

Chege D, Kovacs C, la Porte C, et al. Effect of raltegravir intensification on HIV proviral DNA in the blood and gut. AIDS 2012, 26:167-74.

Cho A, Gaebler C, Olveira T, et al. Longitudinal clonal dynamics of HIV-1 latent reservoirs measured by combination quadruplex polymerase chain reaction and sequencing. Proc Natl Acad Sci U S A 2022, 119:e2117630119.

Cillo AR, Krishnan A, Mitsuyasu RT et al. Plasma viremia and cellular HIV-1 DNA persist despite autologous hematopoietic stem cell transplantation for HIV-related lymphoma. J AIDS 2013, 63:438-41.

Colby DJ, Trautmann L, Pinyakorn S, et al. Rapid HIV RNA rebound after antiretroviral treatment interruption in persons durably suppressed in Fiebig I acute HIV infection. Nat Med 2018, 24:923-926.

Conway JM, Perelson AS. Post-treatment control of HIV infection. Proc Natl Acad Sci U S A 2015, 28;112:5467-72.

Crooks AM, Bateson R, Cope AB et al. Precise Quantitation of the Latent HIV-1 Reservoir: Implications for Eradication Strategies. JID 2015, 212:1361-5.

Crowell TA, Fletcher JL, Sereti I, et al. Initiation of antiretroviral therapy before detection of colonic infiltration by HIV reduces viral reservoirs, inflammation and immune activation. J Int AIDS Soc 2016; 19:21163.

Crowell TA, Gebo KA, Blankson JN, et al. Hospitalization Rates and Reasons Among HIV Elite Controllers and Persons With Medically Controlled HIV Infection. J Infect Dis 2015; 211:1692-702.

Deeks SG, Archin N, Cannon P, et al. Research priorities for an HIV cure: International AIDS Society Global Scientific Strategy 2021. Nat Med 2021, 27:2085-2098.

Dinoso JB, Kim SY, Wiegand AM, et al. Treatment intensification does not reduce residual HIV-1 viremia in patients on highly active antiretroviral therapy. Proc Natl Acad Sci U S A 2009, 106:9403-8.

Dolgin E. Underestimate of HIV reservoirs threatens purging approach. Nat Med 2013, 19:384-5.

Duarte RF, Salgado M, Sánchez-Ortega I, et al. CCR5 Δ32 homozygous cord blood allogeneic transplantation in a patient with HIV: a case report. Lancet HIV 2015, 2:e236-42.

Dubé L, Dee L. Willingness to risk death endpoint in HIV cure-related research with otherwise healthy volunteers is misleading. J Vir Erad 2020, 6:81-84.

Edelstein LC, Micheva-Viteva S, Phelan BD, Dougherty JP. Short communication: activation of latent HIV type 1 gene expression by suberoylanilide hydroxamic acid (SAHA), an HDAC inhibitor approved for use to treat cutaneous T cell lymphoma. AIDS Res Hum Retroviruses 2009, 25:883-7.

Einkauf KB, Osborn MR, Gao C, et al. Parallel analysis of transcription, integration, and sequence of single HIV-1 proviruses. Cell 2022, 185:266-282.

Estes JD, Kityo C, Ssali F, et al. Defining total-body AIDS-virus burden with implications for curative strategies. Nat Med 2017, 23:1271-1276.

Fidler S, Lewin S, Deeks S, et al. HIV cure research in the time of COVID-19 – Antiretroviral therapy treatment interruption trials: A discussion paper. J Virus Erad 2021, 7(1):100025.

Fidler S, Stöhr W, Pace M, et al. Antiretroviral therapy alone versus antiretroviral therapy with a kick and kill approach, on measures of the HIV reservoir in participants with recent HIV infection (the RIVER trial): a phase 2, randomised trial. Lancet 2020, 395:888-898.

Frange P, Faye A, Avettand-Fenoël V, et al. HIV-1 virological remission lasting more than 12 years after interruption of early antiretroviral therapy in a perinatally infected teenager enrolled in the French ANRS EPF-CO10 paediatric cohort: a case report. Lancet HIV 2016, 3:e49-54.

Gaebler C, Nogueira L, Stoffel E, et al. Prolonged viral suppression with anti-HIV-1 antibody therapy. Nature 2022, 606:368-374.

Gossez M, Martin GE, Pace M, et al. Virological remission after antiretroviral therapy interruption in female African HIV seroconverters. AIDS 2019; 33:185-197.

Gruell H, Gunst JD, Cohen YZ, et al. Effect of 3BNC117 and romidepsin on the HIV-1 reservoir in people taking suppressive antiretroviral therapy (ROADMAP): a randomised, open-label, phase 2A trial. Lancet Microbe 2022, 3:e203-e214.

Gubser C, Chiu C, Lewin SR, Rasmussen TA. Immune checkpoint blockade in HIV. EBioMedicine. 2022 Feb;76:103840.

Gupta RK, Peppa D, Hill AL, et al. Evidence for HIV-1 cure after CCR5Δ32/Δ32 allogeneic haemopoietic stem-cell transplantation 30 months post-analytical treatment interruption: a case report. Lancet HIV 2020, 7:e340-e347.

Hatano H, Strain MC, Scherzer R, et al. Increase in 2-long terminal repeat circles and decrease in D-dimer after raltegravir intensification in patients with treated HIV infection: a randomized, placebo-controlled trial. J Infect Dis 2013, 208:1436-42.

Hatano H, Yukl SA, Ferre AL et al. Prospective antiretroviral treatment of asymptomatic, HIV-1 infected controllers. PLoS Pathog. 2013, 9:e1003691.

Hauber I, Hofmann-Sieber H, Chemnitz J et al. Highly significant antiviral activity of HIV-1 LTR-specific tre-recombinase in humanized mice. PloS Pathog. 2013, 9:e1003587.

Henrich TJ, Hanhauser E, Marty FM, et al. Antiretroviral-free HIV-1 remission and viral rebound after allogeneic stem cell transplantation: report of 2 cases. Ann Intern Med 2014; 161:319-27.

Hiatt J, Hultquist JF, McGregor MJ, et al. A functional map of HIV-host interactions in primary human T cells. Nat Commun 2022, 13:1752.

Ho YC, Shan L, Hosmane NN et al. Replication-competent noninduced proviruses in the latent reservoir increase barrier to HIV-1 cure. Cell 2013, 155:540-51.

Hocqueloux L, Avettand-Fènoël V, Jacquot S et al. Long-term antiretroviral therapy initiated during primary HIV-1 infection is key to achieving both low HIV reservoirs and normal T cell counts. J Antimicrob Chemother 2013, 68:1169-78.

Horwitz JA, Halper-Stromberg A, Mouquet H et al. HIV-1 suppression and durable control by combining single broadly neutralizing antibodies and antiretroviral drugs in humanized mice. Proc Natl Acad Sci U S A. 2013, 110:16538-43.

Hosmane NN, Kwon KJ, Bruner KM, et al. Proliferation of latently infected CD4(+) T cells carrying replication-competent HIV-1: Potential role in latent reservoir dynamics. J Exp Med 2017, 214:959-972.

Hsu J, Van Besien K, Glesby MJ, et al. HIV-1 remission and possible cure in a woman after haplo-cord blood transplant. Cell 2023, 186:1115-1126.e8.

Huang SH, Ren Y, Thomas AS, et al. Latent HIV reservoirs exhibit inherent resistance to elimination by CD8+ T cells. J Clin Invest 2018, 128:876-889.

Hunt PW, Shulman NS, Hayes TL, et al. The immunologic effects of maraviroc intensification in treated HIV-infected individuals with incomplete CD4+ T-cell recovery: a randomized trial. Blood 2013, 121:4635-46.

Hütter G, Nowak D, Mossner M, et al. Long-term control of HIV by CCR5 Δ32/Δ32 stem-cell transplantation. N Engl J Med 2009, 360:692-8.

Jardine JG, Ota T, Sok D, et al. HIV-1 VACCINES. Priming a broadly neutralizing antibody response to HIV-1 using a germline-targeting immunogen. Science 2015;349:156-61.

Jensen BO, Knops E, Cords L, et al. In-depth virological and immunological characterization of HIV-1 cure after CCR5Δ32/Δ32 allogeneic hematopoietic stem cell transplantation. Nat Med 2023, 29:583-587.

Jiang C, Lian X, Gao C, et al. Distinct viral reservoirs in individuals with spontaneous control of HIV-1. Nature 2020, 585:261-267.

Julg B, Dee L, Ananworanich J, et al. Recommendations for analytical antiretroviral treatment interruptions in HIV research trials-report of a consensus meeting. Lancet HIV 2019; 6:e259-e268.

Julg B, Liu PT, Wagh K, et al. Protection against a mixed SHIV challenge by a broadly neutralizing antibody cocktail. Sci Transl Med 2017, 9(408).

Karpinski J, Hauber I, Chemnitz J, et al. Directed evolution of a recombinase that excises the provirus of most HIV-1 primary isolates with high specificity. Nat Biotechnol 2016; 34:401-9.

Koelsch KK, Rasmussen TA, Hey-Nguyen WJ, et al. Impact of Allogeneic Hematopoietic Stem Cell Transplantation on the HIV Reservoir and Immune Response in 3 HIV-Infected Individuals. J Acquir Immune Defic Syndr 2017, 75:328-337.

Kroon E, de Souza M, Chottanapund S, et al. Persistent detection of HIV RNA+ cells with ART started in Fiebig 1&2 vs Fiebig 3-5. Abstract 66, 25th CROI 2018, Boston.

Ledford H. HIV rebound dashes hope of 'Mississippi baby' cure. Nature doi:10.1038/nature.2014.15535.

Lee GQ, Orlova-Fink N, Einkauf K, et al. Clonal expansion of genome-intact HIV-1 in functionally polarized Th1 CD4+ T cells. J Clin Invest 2017, 127:2689-2696.

Lehrman G, Hogue IB, Palmer S, et al. Depletion of latent HIV-1 infection in vivo: a proof-of-concept study. Lancet 2005, 366: 549-55.

Leth S, Schleimann MH, Nissen SK et al. Combined effect of Vacc-4x, recombinant human granulocyte macrophage colony-stimulating factor vaccination, and romidepsin on the HIV-1 reservoir (REDUC): a single-arm, phase 1B/2A trial. Lancet HIV 2016; 3:e463-72.

Lewin SR, Rouzioux C. HIV cure and eradication: How will we get from the laboratory to effective clinical trials? AIDS 2011, 25:885-97.

Lindkvist A, Edén A, Norström MM, et al. Reduction of the HIV-1 reservoir in resting CD4+ T-lymphocytes by high dosage intravenous immunoglobulin treatment: a proof-of-concept study. AIDS Res Ther 2009, 6:15.

Llibre JM, Buzón MJ, Massanella M, et al. Treatment intensification with raltegravir in subjects with sustained HIV-1 viraemia suppression: a randomized 48-week study. Antivir Ther 2012, 17:355-64.

Lopez-Galindez C, Pernas M, Casado C, et al. Elite controllers and lessons learned for HIV-1 cure. Curr Opin Virol 2019, 38:31-36.

Lynch RM, Boritz E, Coates EE, et al. Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection. Sci Transl Med 2015, 319ra206.

Maldarelli F, Palmer S, King MS, et al. ART suppresses plasma HIV-1 RNA to a stable set point predicted by pretherapy viremia. PLoS Pathog 2007, 3:e46.

Markowitz M, Evering TH, Garmon D, et al. A randomized open-label study of three- versus five-drug combination antiretroviral therapy in newly HIV-1 infected individuals. J Acquir Immune Defic Syndr. 2014 [Epub ahead of print].

Martin GE, Gossez M, Williams JP, et al. Post-treatment control or treated controllers? Viral remission in treated and untreated primary HIV infection. AIDS 2017; 31:477-484.

Massanella M, Richman DD. Measuring the latent reservoir in vivo. Biochem Pharmacol 2016, 106:30-45.

McMahon DK, Zheng L, Cyktor JC, et al. A Phase ½ Randomized, Placebo-Controlled Trial of Romidespin in Persons With HIV-1 on Suppressive Antiretroviral Therapy. J Infect Dis 2021, 224:648-656.

McMahon JH, Evans VA, Lau JSY, et al. Neurotoxicity with high-dose disulfiram and vorinostat used for HIV latency reversal. AIDS. 2022 Jan 1;36(1):75-82.

McManus WR, Bale MJ, Spindler J et al. There is no evidence for ongoing HIV replication in lymph nodes during suppressive ART. Abstract 70, 25th CROI 2018, Boston.

Moyano A, Ndung'u T, Mann JK. Determinants of natural HIV-1 control. AIDS Rev 2021 Jan 12.

Murray JM, Emery S, Kelleher AD, et al. Antiretroviral therapy with the integrase inhibitor raltegravir alters decay kinetics of HIV, significantly reducing the second phase. AIDS 2007;21:2315-21.

Namazi G, Fajnzylber JM, Aga E, et al. The Control of HIV After Antiretroviral Medication Pause (CHAMP) Study: Posttreatment Controllers Identified From 14 Clinical Studies. J Infect Dis 2018, 218:1954-1963.

Pegu A, Asokan M, Wu L, et al. Activation and lysis of human CD4 cells latently infected with HIV-1. Nat Commun 2015 Oct 20;6:8447.

Pegu A, Xu L, DeMouth ME, et al. Potent anti-viral activity of a trispecific HIV neutralizing antibody in SHIV-infected monkeys. Cell Rep 2022, 38:110199.

Persaud D, Gay H, Ziemniak C, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. N Engl J Med. 2013, 369:1828-35.

Ramadoss NS, Zhao NQ, Richardson BA, Grant PM, Kim PS, Blish CA. Enhancing natural killer cell function with gp41-targeting bispecific antibodies to combat HIV infection. AIDS 2020, 34:1313-23.

Rasmussen TA, Ahuja SK, Kuwanda L, et al. Antiretroviral initiation at ≥800 CD4+ cells/mm^3 associated with lower HIV reservoir size. Clin Infect Dis 2022:ciac249.

Rasmussen TA, McMahon JH, Chang JJ, et al. The effect of antiretroviral intensification with dolutegravir on residual virus replication in HIV-infected individuals: a randomised, placebo-controlled, double-blind trial. Lancet HIV 2018; 5:e221-e230.

Rasmussen TA, Schmeltz Søgaard O, Brinkmann C, et al. Comparison of HDAC inhibitors in clinical development: Effect on HIV production in latently infected cells and T-cell activation. Hum Vaccin Immunother 2013, 9(5).

Routy JP, Tremblay CL, Angel JB, et al. Valproic acid in association with highly active antiretroviral therapy for reducing systemic HIV-1 reservoirs: results from a multicentre randomized clinical study. HIV Med 2012, 13:291-6.

Rubinstein P et al. HIV-1 viral reservoir reactivation after CCR5 delta 32/32 stem cell transplantation. Abstract 434, 30th CROI 2023, Seattle.

Sáez-Cirión A, Bacchus C, Lodiueloux L, et al. Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy ANRS VISCONTI Study. PLoS Pathog 2013, 9:e1003211.

Sahu GK, Sango K, Selliah N, et al. Anti-HIV designer T cells progressively eradicate a latently infected cell line by sequentially inducing HIV reactivation then killing the newly gp120-positive cells. Virology 2013, 446:268-75.

Shen L, Peterson S, Sedaghat AR, et al. Dose-response curve slope sets class-specific limits on inhibitory potential of anti-HIV drugs. Nat Med 2008, 14:762-6.

Sigal A, Kim JT, Balazs AB, et al. Cell-to-cell spread of HIV permits ongoing replication despite antiretroviral therapy. Nature 2011, 477:95-8.

Siliciano JD, Kajdas J, Finzi D, et al. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. Nature Med 2003;9:727-728.

SPARTAC Investigators. Short-course antiretroviral therapy in primary HIV infection. N Engl J Med 2013, 368:207-17.

Sung JA, Pickeral J, Liu L, et al. Dual-affinity re-targeting proteins direct T cell-mediated cytolysis of latently HIV-infected cells. J Clin Invest 2015, 125:4077-90

Søgaard OS, Graversen ME, Leth S, et al. The Depsipeptide Romidepsin Reverses HIV-1 Latency In Vivo. PLoS Pathog 2015, 11:e1005142.

Tebas P, Stein D, Tang WW, et al. Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. N Engl J Med. 2014, 370:901-10.

Turk G, Seiger K, Lian X, et al. A Possible Sterilizing Cure of HIV-1 Infection Without Stem Cell Transplantation. Ann Intern Med 2022, 175:95-100.

Tyagi M, Iordanskiy S, Ammosova T, et al. Reactivation of latent HIV-1 provirus via targeting protein phosphatase-1. Retrovirology 2015, 12:63.

Vieira VA, Zuidewind P, Muenchhoff M, et al. Strong sex bias in elite control of paediatric HIV infection. AIDS 2019; 33:67-75.

Wang Z, Simonetti FR, Siliciano RF, Laird GM. Measuring replication competent HIV-1: advances and challenges in defining the latent reservoir. Retrovirology 2018, 15:21.

Winckelmann A, Barton K, Hiener B, et al. Romidepsin-induced HIV-1 viremia during effective antiretroviral therapy contains identical viral sequences with few deleterious mutations. AIDS 2017, 31:771-779.

Xu L, Wang J, Liu Y, et al. CRISPR-Edited Stem Cells in a Patient with HIV and Acute Lymphocytic Leukemia. N Engl J Med 2019; 381:1240-1247.

Yang H, Buisson S, Hancock G, et al. Elimination of Latently HIV-infected Cells from Antiretroviral Therapy-suppressed Subjects by Engineered Immune-mobilizing T-cell Receptors. Mol Ther 2016; 24:1913-1925.

York J, Gowrishankar K, Micklethwaite K, Palmer S, Cunningham AL, Nasr N. Evolving Strategies to Eliminate the CD4 T Cells HIV Viral Reservoir via CAR T Cell Immunotherapy. Front Immunol. 2022 Apr 29;13:873701.

Yukl SA, Boritz E, Busch M, et al. Challenges in detecting HIV persistence during potentially curative interventions: a study of the Berlin patient. PLoS Pathog 2013, 9:e1003347.

Zerbato JM, Purves HV, Lewin SR, Rasmussen TA. Between a shock and a hard place: Challenges and developments in HIV latency reversal. Curr Opin Virol. 2019 Oct;38:1-9.

Zhu W, Lei R, Le Duff Y, et al. The CRISPR/Cas9 system inactivates latent HIV-1 proviral DNA. Retrovirology 2015 Feb 27;12:22.

5.5. When to start with ART?

CHRISTIAN HOFFMANN

The optimal time point to start ART has been debated for many years. Possible side effects of antiretroviral agents had to be weighed against the potential risk of evolution to AIDS without ART. CD4 T-cells and viral load were essential decision-making tools. Finally, the results of the START study published in 2015 changed this. What used to be "the most important question in HIV medicine" (Anthony Fauci) has since become easy to answer – **all PLWH, even those without symptoms, should be offered ART regardless of CD4 T-cells or viral load**. The European guidelines still allow an exception for individuals with high and stable CD4 T-cells and a low viral load of less than 1,000 copies/mL (EACS 2022). However, this is rarely seen. Today, the main decisive factor is the patient's willingness to start ART. Even today, some persuasion is still necessary. There are still people with considerable reservations about antiretroviral therapy.

The risk of progression

It is pretty simple – the higher the viral load, the faster the CD4 T-cells decline (COHERE 2014). The higher the viral load, the higher the risk of AIDS (Mellors 1997, Lyles 2000). It may be helpful to know about the current AIDS risk if ART is not started. Table 5.1 lists (selected) risks; the data are from over 3000 individuals in the "pre-HAART era" (Phillips 2004). The range of risk of progression, calculated based on age, CD4 T-cell count, and viral load, is high.

Table 5.1: Probability (%) of developing AIDS within six months without therapy, by age, viral load level, and CD4 T-cells (data from the "pre-HAART era").

	100 CD4/µl	200 CD4/µl	350 CD4/µl
35 years old			
HIV-RNA 10,000 copies/mL	5.3	2.0	1.1
HIV-RNA 100,000 copies/mL	10.6	4.1	2.3
55 years old			
HIV-RNA 10,000 copies/mL	10.7	4.6	1.8
HIV-RNA 100,000 copies/mL	20.5	9.2	3.6

From: Phillips A, CASCADE Collaboration. AIDS 2004, 18:51-8.

However, different risks remain even after ART initiation, as shown in Table 5.2 for different age groups. Data for these calculations were generated from 12 cohorts in Europe and North America in which over 20,000 individuals had started ART between 1995–2003 (May 2007).

It should be noted that the risks apply only to asymptomatic non-IVDU patients; otherwise, the risks of progression may increase, in some cases, significantly. On the other hand, given the data from the early days of ART, it is conceivable that the risks are lower today, thanks to modern treatments. The fact that ART interruptions were not considered could also lead to an overestimation of the risk of progression. Thus, the risks are only rough guidelines but can aid any discussion. At the same time, we don't want to frighten patients or put them under pressure.

Nevertheless, it is still essential that all asymptomatic patients with good values are monitored regularly – especially if they decide not to start ART. Data from the COHERE database of 34,384 treatment-naïve individuals describe the course of untreated HIV infection. The mean CD4 T-cell drop was 78 (95% confidence interval,

Table 5.2: Probability (%) of AIDS or death in the year *after starting ART* (in parentheses: in the next five years). The risk applies to non-IVDU patients without AIDS.

	<25 CD4/µl	25–49 CD4/µl	50–99 CD4/µl	100–199 CD4/µl	200–350 CD4/µl	>350 CD4/µl
16–29 years						
VL<100,000	10 (19)	8 (17)	7 (16)	5 (11)	2 (7)	2 (6)
VL>100,000	12 (23)	10 (21)	9 (19)	6 (13)	3 (8)	2 (7)
30–39 years						
VL<100,000	12 (22)	10 (19)	8 (18)	5 (12)	3 (8)	2 (6)
VL>100,000	14 (26)	12 (23)	10 (22)	6 (15)	3 (10)	2 (8)
40–49 years						
VL<100,000	13 (25)	11 (22)	10 (20)	6 (14)	3 (9)	2 (7)
VL>100,000	16 (29)	13 (26)	12 (24)	7 (17)	4 (11)	3 (9)
>50 years						
VL<100,000	16 (29)	13 (26)	12 (24)	7 (17)	4 (11)	3 (9)
VL>100,000	19 (35)	16 (31)	14 (29)	9 (21)	5 (13)	3 (11)

VL = viral load (HIV RNA copies/mL). From: http://www.art-cohort-collaboration.org

–80 to –76) cells/µl per year. It is closely associated with viral load. With every additional log of viral load, 38 CD4 T-cells/µl per year are added (COHERE 2014). No association exists with gender, ethnicity, drug use, or transmission route. Incidentally, the viral load increased slightly over the years.

Interestingly, an unusual viral variant (the VB variant) was described in early 2022 and has been circulating in the Netherlands for years (Wymant 2022). CD4 T-cell counts dropped twice as fast as expected in more than one hundred individuals. This subtype B virus line, which emerged *de novo* at the turn of the millennium, has extensive changes in the genome. According to the authors, these findings "emphasize the importance of access to frequent testing for at-risk individuals and adherence to recommendations for immediate treatment initiation for every PLWH". No more, no less.

Practical experiences, rapid start

Treatment practice has changed significantly in recent years. In Europe, the median CD4 count at ART initiation was around 200/µl for many years, having been as high as 270/µl in 1998 (May 2006). In recent years, an opposite trend has been seen; the pendulum is swinging back – given the increasingly better, more tolerable drugs, people are starting earlier. In the German PROPHET study, which enrolled nearly 450 treatment-naïve PLWH from almost 30 priority centers in 2014/15, median CD4 T-cells at therapy initiation were already slightly above 350/µl. In resource-poor countries, however, most patients have well below 200 CD4 T-cells/µl at therapy initiation (Mugglin 2012). In Europe, male immigrants, in particular, start ART later (COHERE 2017).

In recent years, initiating ART as early as the day of HIV diagnosis has become a strategy for increasing global interest in controlling the HIV epidemic and optimizing the health of PLWH. No detrimental effects of rapid-start ART have been identified in randomized controlled trials undertaken in low- or middle-income countries or cohort studies performed in high-income countries (review Boyd 2019). However, there is insufficient evidence for guidelines to recommend universal test-and-treat strategies for all people, in all settings, on HIV diagnosis.

Before starting any ART, whether the person concerned is ready should be clarified. Assessment for readiness is critical. Sometimes, the decision is made hastily, often prematurely. The risk of AIDS is often low. Prescribing ART to a person with HIV at the first presentation can be unwise. Clinicians should get a picture of the person's situation and learn about lifestyle and motives, why they went to the doctor, and what is expected. It also often happens that patients harbor misconceptions. Not everyone knows that ART has to be taken for life. A few weeks is not enough. This is often difficult to convey to people from other cultures in particular. The question of sexual partners is essential, and any wish for parenthood should also be discussed. Is there a negative partner? The fact that ART offers the best protection for others motivates many people more than anything else to start with ART (see TasP in chapter *Prevention*). Treatment as prevention has been included in almost all guidelines.

If a vacation is imminent, it is possible to wait, provided the values are decent since the success of the therapy and side effects cannot be monitored from afar. On the other hand, patients sometimes give new reasons (job stress, exams, job change). Many are afraid of AIDS, but often just as afraid of the therapy ("the pills are the beginning of the end!"). This may lead to irrational and false expectations of ART and its consequences – the beginning of a therapy does not mean that one will be subjected to daily infusions and unable to work. Therefore, it should be made clear to every person with HIV what ART means in daily routine, nothing more, nothing less.

Defining individual thresholds from the beginning is also helpful, especially with hesitant people. It is good to convey to many people that immediate ART is also a strategic decision. Often, there are concerns about potential long-term toxicity. But what is gained in terms of quality of life in waiting? The CD4 T-cell drop is between 50 and 100 cells/µl annually, even at an average viral load. What is saved in long-term toxicities over the next twenty or thirty years by one, two, or three therapy-free years? Will it still be relevant in 2040 or 2050, whether therapy started in 2023 or 2025? Probably not. This makes sense to many.

Practical tips for starting therapy

Below 500 CD4 T-cells/µl and in AIDS patients

- Start as soon as possible with ART. The lower the CD4 T-cells, the sooner!
- Assess readiness: Take time to get to know the person (why did they wait so long?), examine, educate, and start prophylaxis if CD4 T-cells are very poor (< 200/µl).
- Address all fears and reservations about therapy.
- With > 200/µl, there is a little more time, but talk about timelines for decision-making (vacation, etc.).

Above 500 CD4 T-cells/µl if the patient is hesitant

- Talk about ART early (and repeatedly), and explain administration (number of tablets).
- Set thresholds for onset (according to older guidelines, e.g., at 350 CD4/µl).
- Don't just evaluate absolute CD4 T-cells; look at other factors. Clinical progression? Rapid decline? Any co-infection? Age > 50? Malignancies? Pregnancy? Starting ART is more important!
- Is there an HIV-negative partner? A hope for parenthood? Talk about the decreasing infectivity on ART – this can be a good reason for many.
- Check on any clinical studies that may be interesting and/or relevant!

Patients should be involved in the decision-making process. It may be useful to see patients several times to prepare them for ART. Only two situations are an exception: acute HIV infection (see *Acute HIV Infection*) and severe immunodeficiency (see below). But even then, it is not a matter of one or two visits; therapy must be discussed and chosen. Will the person come back at all? In these cases, we start with PCP prophylaxis and use the first days for examinations (funduscopy! X-ray thorax, sonography) and informational talks about maybe a clinical study. A picture of the psychosocial situation should also be obtained. Needs regarding the number of pills and their modalities should be addressed. ART is not started until these issues have been clarified.

Asymptomatic patients below 500 CD4 T-cells/µl

For this group, all guidelines strongly recommend starting therapy. Even though the overall risk of disease is relatively low, at least above 350 CD4 T-cells/µl, one should not be complacent above these limits. We have seen patients who developed Kaposi's sarcoma, PML, or lymphoma at almost normal levels. In the START study, some AIDS events occurred with high CD4 T-cells.

A look at the calculator described above (May 2007) gives a rough idea about the individual risk. A 45-year-old, asymptomatic patient with 200–350 CD4 T-cells/µl, a viral load below 100,000 copies/mL, and no drug use has a combined AIDS/death risk after five years of ART initiation of 8.7%. With more than 350 CD4 T-cells/µl at ART initiation, the risks decrease to 7.3%. If the patient is over 50 years old and the viral load is over 100,000 copies/mL, the five-year risk is reduced from 13.1% to 11.0%. This "reduction" of 1–2% may seem marginal at first glance. And yet, in today's era of well-tolerated ART, such a risk of developing AIDS or death has become relevant. The 1–2% has become avoidable and unnecessary.

Before START, essential data were provided by HTPN-052, a study of 1,763 HIV-discordant couples in the US, Africa, and Asia. The HIV-positive partners had to be antiretroviral naïve and have CD4 T-cells between 350 and 550/µl. They were randomized to start ART immediately or only when CD4 T-cells fell below 250/µl or at the onset of AIDS (Cohen 2011, Grinsztejn 2014). Although HIV transmission was the primary endpoint, in an interim evaluation, severe illness, and death were decreased in the immediate ART group (57 versus 77, p=0.07). The difference was significant for AIDS cases (40 versus 61, p=0.03). However, this difference was primarily caused by extrapulmonary tuberculosis (17 versus 34), which was also mainly observed in India.

Asymptomatic patients over 500 CD4 T-cells/µl

The WHO or US guidelines always recommend starting ART even if the immune status is normal (above 500 CD4 T-cells/µl in most cases). Some guidelines, however, keep a backdoor open for those with low viremia. However, the following additional criteria make the indication clearer even in those with no evidence of any immune defect:

- Viral load above 100,000 copies/mL
- HCV or HBV coinfection
- Pregnancy
- Age over 50
- Framingham score above 20% within the next ten years
- Rapidly decreasing CD4 T-cell count
- Patient's wish or need for reduction of infectivity

There appears to be a risk of AIDS or death closely related to CD4 T-cells, even above 500/µl. In a large British cohort of therapy-naïve individuals, the risk per 1,000 person-years was 24.9 at 350–499/µl, compared with 15.4 at 500–649/µl and 9.6 at more than 650/µl. Nevertheless, there has long been an emotional debate about the optimal initiation of therapy at normal immune status, even in the face of conflicting data from cohort studies. In contrast to a US study (Kitahata 2009), European studies had shown no benefit of ART above 450–500/µl (Sterling 2003, Sterne 2009).

START Study

Rarely has a study had such an impact on HIV therapy. Since 2009, START, or Strategic Timing of Antiretroviral Therapy, has followed 4,685 otherwise healthy PLWH with more than 500 CD4 T-cells/µl in two strategy arms. One-half immediately began ART, which was selected by the treating physician (regimens included TDF in 89% and efavirenz in 62%), and the other half waited until CD4 T-cells fell below the previously accepted threshold of 350/µl. The primary clinical endpoint was defined as not only all deaths and severe AIDS events (excluding herpes infections and thrush esophagitis, but scoring Hodgkin's lymphoma) but also non-AIDS events such as cardiovascular disease, renal and hepatic decompensation, and cancer.

The results were surprising in their clarity: patients in the delayed therapy arm developed more AIDS and more serious non-AIDS-defining events; the hazard ratios in favor of early ART were 0.28 and 0.61, respectively. Despite the low incidence rates, the differences were so stark that the randomized phase was terminated early in May 2015 after only three years of observation. The Data Safety Monitoring Board found that the original question of the study had been clearly answered in these three years and recommended ART for all PLWH in the future.

Regardless of whether male or female, young or old, black or white – all participants benefited from early ART. Interestingly, the benefit was seen even at very high CD4 T-cell counts and low viral loads (below 5,000 copies/mL). In a more recent subanalysis, however, the benefit did disappear at viral loads below 3,000 copies/mL. These patients also had significantly higher CD4 T-cell counts (Sereti 2019).

Table 5.3: Clinical endpoints in START, each per 100 patient-years (INSIGHT 2015).

	Immediate ART n=2,326	Delayed ART n=2,359	Hazard ratio (95% CI), p-values
Primary endpoints (see text)	0.60 (n=42)	1.38 (n=96)	0.43 (0.30–0.62), p < 0.001
Serious AIDS events	0.20 (n=14)	0.72 (n=50)	0.28 (0.15–0.50), p < 0.001
Serious non-AIDS events	0.42 (n=29)	0.67 (n=47)	0.61 (0.38–0.97), p=0.04
Deaths	0.17 (n=12)	0.30 (n=21)	0.58 (0.28–1.17), p=0.13

CI, confidence interval.

AIDS events were rare but occurred in both arms, even those with very high CD4s. Most events were lymphoma, Kaposi's sarcoma, and tuberculosis (41/50 in the delayed arm versus 10/14 in the immediate arm). 16/26 (62%) of the TB cases were observed in Africa. Tumor diseases accounted for a relevant proportion of non-AIDS events (18/47 versus 9/29). In total, 22/27 (81%) of these tumors were observed in Australia, Europe, and the United States, as were 19/26 (73%) of the cardiovascular diseases. However, these events did not differ between the two strategy arms, likely due in part to the young age of the participants (36 years at baseline). Mortality overall, as well as severe grade IV outcomes, were equally common in both arms.

Given the impressive trial size, START holds a wealth of exciting data examining early ART's benefit in other aspects. Many sub-analyses are ongoing, and preliminary data showed a benefit in quality of life (Lifson 2017), bacterial infections, and infection-associated tumors. No benefit was seen in other cancers or concerning cardiovascular risk scores (Baker 2017) or neurocognitive testing. Some disadvantage of immediate therapy was instead seen in increased bone density decline during the first year of ART (Hoy 2017).

Initial sub-analyses suggest that the positive effect of ART may have been significantly underestimated in the first publication (Sharma 2019). START was known to have included many long-term stable patients, which implies selection (clinically stable people without ART). A detailed analysis of the delayed arm showed that newly infected patients (less than six months) had more clinical events than those infected for more than two years. Longer follow-up of START also revealed that serious AIDS and non-AIDS risks were diminished after ART initiation, but the persistent excess risk remained evident even for years (Lundgren 2023).

In summary, the START data do not mean that every patient MUST receive ART immediately. However, it is recommended to all since there is some clinical benefit even with high CD4 T-cells, and one can now at least be sure not to do any harm.

Practical tips for untreated patients

- Are the CD4 T-cells falling, and if so, how fast? → Always note relative values (percentages) and CD4/8 ratio; absolute values often fluctuate.
- How high is the viral load? Does the picture fit together? → at low viral loads (< 1,000 copies/mL), "true" CD4 T-cell count drops are rather unusual.
- What kind of values does the affected person come from? → if the CD4 T-cells were always 1,000 and have now dropped to 350, the immunodeficiency is probably more pronounced than in someone who comes from 450 CD4 T-cells.
- How ready is the person for ART, how well informed, and how adherent is she or he? → the more negative and fearful the person is, the more time must be allowed, and the better the start of therapy must be prepared in discussions.
- How old is the patient? The immunological regeneration capacity decreases with age → the older the person, the earlier the onset.
- Are there any symptoms that have gone unnoticed so far → regular physical examination! OHL, oral thrush, mycoses, etc.?
- A drop of more than 50–100 CD4 T-cells/µl per year is too much! Do not wait too long! Talk with the patient.

Late presenters: AIDS and/or below 350 CD4 T-cells/µl

Despite dramatically improved treatment options, many people present still late in the course of their HIV infection. Although not yet clearly defined, the term "late presenter" has also become established in many countries. In most cases, a CD4 T-cell count below 350/µl and/or manifest AIDS disease at HIV diagnosis is considered a criterion (Antinori 2011). However, what "at HIV diagnosis" means varies in scope, ranging from three months to three years. In addition, some studies distinguish between "late testers" and also "very late presenters" or "long-term non-presenters". In the US and Europe, and probably in other countries, about half of patients are still late presenters. In COHERE, an association of European cohorts, 84,524 PLWH were followed between 2000 and 2011. The proportion with less than 350 CD4 T-cells at initial presentation declined slowly, from 57% in 2000 to 52% in 2010/2011 (Mocroft 2013). In a more recent evaluation, the rate remained broadly stable between 2010 and 2013, most recently at 49% (Mocroft 2015).

The cut-off value of 350 CD4 T-cells sometimes raises problems, as heterogeneous groups are thus pooled. Due to the often very low CD4 T-cells during acute HIV infection, the numbers are probably somewhat overestimated (Sasse 2016); on the other hand, the consequences of the very late onset tend to be underestimated by this high value. In the following, the term "late presenter" is therefore primarily restricted to persons with AIDS or with less than 200 CD4 T-cells/µl.

Incidence and risk factors for late HIV diagnosis

How common are true late presenters? Without a uniform definition, 10–44% rates are reported in Europe and the US, with a recent slight downward trend, at least in some countries (Table 5.4). With the FindHIV study, data for Germany have also recently become available (Valbert 2022). Of 706 people diagnosed as HIV-positive for the first time (within the last six months) in 40 study centers between January 2019 and May 2020, 55% had a CD4 T-cell count below 350/µl, and 20% even had an AIDS diagnosis.

The risk factors for late diagnosis (Table 5.5) are similar worldwide: older age, immigration, and heterosexual transmission route. These observations suggest that the reasons for late presentation are complex. Presumably, both patients (reduced access to the health care system, lack of education, fear of stigmatization) and healthcare professionals (i.e., reduced "HIV-awareness" among some) contribute to this.

Several studies have shown that even in people at high risk for HIV infection, many missed opportunities exist to diagnose HIV earlier (Duffus 2009, Jenness 2009). For example, of 263 African patients in London, 76% had visited their GP the year before their initial HIV diagnosis. As many as 38% and 15% had been treated in an outpatient clinic and as inpatients, respectively (Burns 2008).

Table 5.4: Frequency of (very) late diagnoses in Western countries.

Country	Period (n)	Definition of late diagnosis	% (AIDS)	Trend over time
France (Delpierre 2008)	1996–2006 (6,805)	CD4 < 200 cells/µl or AIDS < 1 year	38 (17)	Decline from 43 to 32
USA (CDC 2009)	1996–2005 (281,421)	CD4 < 200 cells/µl or AIDS < 1 year	38	Decline from 43 to 36
Great Britain (UK Chic 2010)	1996–2006 (15,775)	CD4 < 200 cells/µl	27 (10)	n.a.
Italy (Rafetti 2016)	1985–2013 (19,391)	CD4 < 200 cells/µl or AIDS < 6 mo	38	Slight decrease
Netherlands (Coul 2016)	1996–2014 (20,965)	CD4 < 200 cells/µl or AIDS < 3 mo	35	Decline from 46 to 26
Spain (Rava 2021)	2004–2018 (14,876)	CD4 < 200 cells/µl or AIDS < 6 mo	26	Decline from 34 to 24
Switzerland (Hachfeld 2016)	2009–2012 (1,366)	CD4 < 200 cells/µl	25	No clear trend

AIDS = AIDS-defining disease. Mo = months.

Of 270 late presenters admitted to a Berlin Hospital in 2009–2013, 21% had previously presented with indicator illnesses at other facilities without being tested for HIV (Tominski 2017). In the FindHIV study, 45% of study physicians saw at least one opportunity in the healthcare system where the initial HIV diagnosis could have been made earlier (Valbert 2022).

Table 5.5: Risk factors for late diagnosis in Western countries.

Country (reference)	Risk factors
USA (CDC 2009)	Male sex, older age, ethnicity non-white
Germany (Zoufaly 2011)	Older age, heterosexual transmission, migration
France (Wilson 2014)	Migration, heterosexual transmission route, older age
Italy (Rafetti 2016)	Male sex, older age, heterosexual transmission route, migration
Netherlands (Coul 2016)	Male sex, older age, heterosexual transmission route, foreign origin
Spain (Rava 2021)	Male sex, older age, IVDU, or heterosexual transmission
Switzerland (Hachfeld 2016)	Female gender, origin sub-Saharan Africa. Protective: high school education, MSM
Belgium (Darcis 2018)	Male sex, sub-Saharan African origin, age, heterosexual transmission

A primary focus of prevention is, therefore, on earlier identification of people who are not yet aware of their infection – especially about the first 95 of the 95-95-95 UNAIDS goals; there is room for improvement.

Morbidity, mortality – consequences of late HIV diagnosis

Up to 90% of AIDS-defining diseases today occur in viremic – i.e., primarily untreated – PLWH. This is especially true for classical opportunistic infections such as PCP or CMV retinitis, but also, although less strictly, for tuberculosis or non-Hodgkin lymphomas (ART CC 2009). About two-thirds of patients with newly diagnosed NHL in our lymphoma cohort had not received ART previously. Nearly 40% were diagnosed with NHL and HIV infection simultaneously (Hoffmann 2015). In a UK analysis of 387 deaths in 2004/2005, late HIV diagnosis accounted for as many as 24% of all deaths and 35% of all HIV/AIDS-related deaths (Lucas 2008). In a cost analysis, treatment costs increased by 200% with fewer than 200 CD4 T-cells at the time of HIV diagnosis (Krentz 2004). This is also likely due to immune reconstitution syndrome (IRIS), common among late presenters (see *AIDS*).

There is no doubt that late HIV diagnosis is associated with an increased mortality risk and morbidity. The worse the CD4 T-cells or CD4/CD8 ratio at therapy initiation, the higher the risk (Sterne 2009, Mocroft 2013, Domínguez-Domínguez 2022). In individuals with less than 350 CD4 T-cells, mortality increased 10-fold in the first year, with no significant differences observed until after four years (Sobrino-Vegas 2016). However, there is no question that the prognosis of late presenters has improved in recent years. In an Italian study, the 1- and 5-year survival rates of individuals with fewer than 200 CD4 T-cells and/or AIDS increased from 63% and 17% in 1985–1991 to 95% and 91% in 2004–2009 (Raffetti 2016). Even in the severely ill, everything should be tried. For most people, ART will be timely! Of 270 late presenters with AIDS from 2009–2013 in a Berlin hospital, only 6 died as inpatients (Tominski 2017). However, when CD4 T-cells are very low, mortality remains elevated for many years (ART CC 2007, Lanoy 2007).

Moreover, immune reconstitution rarely remains complete in the case of severe immune deficiency. The worse the immune system, the less likely complete restoration. Even long-term viral suppression for decades does not change this. In a study of individuals who had achieved a consistently low viral load of less than 1,000 copies/mL over at least four years on ART, 44% of patients with less than 100/µl at ART initiation failed to achieve the average value of 500 CD4 T-cells/µl even after

7.5 years. For 100–200 CD4 T-cells/µl, the rate was still 25% (Kelley 2009). In addition to low CD4 T-cells, older age, often observed in late presenters, is a risk factor. With increasing age, the regenerative capacity of the immune system decreases, probably due to thymic degeneration (Lederman 2000, Grabar 2004). A late start may also result in poor antigen-specific immune reconstitution, both against HIV and opportunistic pathogens. Many studies have suggested that qualitative immune reconstitution often fails to keep pace with quantitative immune reconstitution (Gorochov 1998, Lange 2002). But why then does the AIDS risk decrease so significantly and so rapidly with increasing CD4 T-cells? Why can even severely immunosuppressed patients discontinue their prophylaxis relatively safely as soon as CD4 T-cells have risen above 200/µl? Clinical observations seem to show otherwise, and the relevance of impaired immune reconstitution in the long term is unclear. A large cohort study showed that discordant response (despite good viral suppression and low CD4s) is associated with an increased risk of AIDS only in the first months. In virally well-suppressed individuals, CD4 T-cells are no longer an excellent surrogate marker for AIDS risk (Zoufaly 2012).

In contrast to the immunological response, the virological response of late presenters is usually no worse (Rava 2021). Of 760 patients with AIDS at the time of HIV diagnosis, 89% achieved a viral load of less than 500 copies/mL (Mussini 2008).

Start with ART – always immediately?

PLWH with poor immune status and/or symptoms should start ART as soon as possible. For a long time, many treatment providers preferred to focus initially only on OIs and to wait a few weeks before starting ART to avoid risk therapeutic options given the high complication potential of OI therapies. The first large randomized trial on this made this strategy questionable (Zolopa 2009). In ACTG A5164, 282 patients with an acute OI (63% PCP, TB cases were excluded) were randomized to start ART immediately or at the earliest after completion of OI therapy. On median, the "immediately" treated group started ART 12 days after initiation of OI therapy, and the "delayed" treated group started ART after 45 days. Despite this short period, significant differences emerged after 48 weeks: significantly fewer deaths or new AIDS cases occurred in the immediately treated group. The risk of switching ART was slightly increased, but not the number of serious adverse events, hospitalizations, or IRIS cases. The authors concluded that ART should be initiated immediately in persons with acute OIs (at least PCP). Another smaller study found no relevant differences in PCP and toxoplasmosis, but case numbers were too small, given slow recruitment (Schäfer 2019).

In tuberculosis, at least five randomized trials have addressed the optimal timing of ART (Abdool 2011, Blanc 2011, Havlir 2011, Török 2011, Wondwossen 2012). The main results are that immediate therapy does not significantly improve mortality or AIDS-related morbidity. The only exception seems to be in individuals whose CD4 T-cells are below 50 cells/µl at TB diagnosis. In these cases, immediate initiation is strongly recommended. Of note, immediate initiation always carries the risk of paradoxical TB exacerbation in the setting of IRIS, which reached up to 30% in some studies.

Adverse effects on survival were seen with immediate ART initiation in tuberculous meningitis (Török 2012). This is also true for cryptococcal meningitis (Makadzange 2010) – it may be necessary to differentiate the OI (Lawn 2011). Another controversial issue is whether to start ART in patients with malignant lymphomas immediately or only after completion of chemotherapy (see *Malignant Lymphomas*).

Which ART to start with for late presenters?

Active OI is often an exclusion criterion for clinical trials. People with OIs are thus chronically underrepresented. Therefore, optimal therapy is an individual decision (Manzardo 2007) (see chapter 5.6. *First-line Therapy*). Regarding immunological success, no relevant differences between NNRTI- and PI-based regimens are seen in late presenters (Samri 2007). In addition to the low interaction potential and good tolerability, the main argument favoring INSTIs is the rapid reduction in viral load. However, some cohort studies showed clinical benefits with INSTIs (Martin-Iguacel 2022), while others showed just the opposite (Rava 2021). Controlled, prospective studies are lacking. The LAPTOP trial, ongoing in various European countries, randomizing between bictegravir and darunavir/c in advanced immunodeficiency or AIDS, will hopefully clarify this issue shortly. There have been some reports of increased risk among INSTIs regarding possible immune reconstitution syndromes. However, a large meta-analysis recently concluded that the overall IRIS risk is not higher than in other drug classes (Zhao 2022).

Intensification with an INSTI such as raltegravir has no effect. The African REALITY study impressively proved this in 1,805 patients with severe immunodeficiency of less than 100 CD4 T-cells (Kityo 2018). Through 48 weeks, there was no evidence of differences in mortality, serious adverse events, or events judged compatible with IRIS or in hospitalizations. There is also no evidence supporting the additional administration of maraviroc; this has neither an effect on IRIS nor immune reconstitution (Sierra-Madera 2014, Belaunzarán-Zamudio 2017 (See *Chapter 5.4*).

In summary, no evidence exists that late presenters require a specific ART regimen. ART selection should be guided by factors that affect other patients (see next chapter).

Literature on starting therapy and late presenters

Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med 2010, 362:697-706.

Antinori A, Coenen T, Costagiola D, et al. Late presentation of HIV infection: a consensus definition. HIV Med 2011, 12:61-4.

ART Cohort Collaboration. Importance of baseline prognostic factors with increasing time since initiating highly active antiretroviral therapy: collaborative analysis of cohorts of HIV-1-infected patients. J AIDS 2007;46:607-15.

ART-CC, Mocroft A, Sterne JA, et al. Variable impact on mortality of AIDS-defining events diagnosed during combination antiretroviral therapy: not all AIDS-defining conditions are created equal. Clin Infect Dis 2009, 48:1138-51.

Baker JV, Hullsiek KH, Engen NW, et al. Early Antiretroviral Therapy at High CD4 Counts Does Not Improve Arterial Elasticity: A Substudy of the Strategic Timing of Antiretroviral Treatment (START) Trial. Open Forum Infect Dis 2016, 3:ofw213.

Belaunzarán-Zamudio PF, Azzoni L, Canaday DH, et al. Immunologic Effects of Maraviroc in HIV-Infected Patients with Severe CD4 Lymphopenia Starting Antiretroviral Therapy: A Sub-Study of the CADIRIS Trial. Pathog Immun 2017, 2:151-177.

Blanc FX, Sok T, Laureillard D, et al. CIPRA KH001) Study Team. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med 2011, 365:1471-81.

Boyd MA, Boffito M, Castagna A, Estrada V. Rapid initiation of antiretroviral therapy at HIV diagnosis: definition, process, knowledge gaps. HIV Med 2019, Suppl 1:3-11.

Burns FM, Johnson AM, Nazroo J, et al. Missed opportunities for earlier HIV diagnosis within primary and secondary healthcare settings in the UK. AIDS 2008, 22:115-22.

Centers for Disease Control and Prevention (CDC). Late HIV testing – 34 states, 1996-2005. MMWR Morb Mortal Wkly Rep 2009,58:661-5.

Cohen MS, Ying QC, McCauley M, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. N Engl J Med 2011; 365:493-505.

COHERE. Factors associated with short-term changes in HIV viral load and CD4(+) cell count in antiretroviral-naive individuals. AIDS 2014, 28:1351-6.

Darcis G, Lambert I, Sauvage AS, et al. Factors associated with late presentation for HIV care in a single Belgian reference center: 2006-2017. Sci Rep 2018, 8:8594.

Domínguez-Domínguez L, Rava M, Bisbal O, et al. Low CD4/CD8 ratio is associated with increased morbidity and mortality in late and non-late presenters: results from a multicentre cohort study, 2004-2018. BMC Infect Dis 2022, 22:379.

Duffus WA, Youmans E, Stephens T, Gibson JJ, Albrecht H, Potter RH. Missed opportunities for early HIV diagnosis in correctional facilities. AIDS Patient Care STDS 2009, 23:1025-32.

EACS: Guidelines for the clinical management and treatment of HIV-infected adults in Europe. November 2022. http://www.eacs.eu.

Emery S, Neuhaus JA, Phillips AN, et al. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. J Infect Dis 2008, 197:1133-44.

Garcia F, De Lazzari E, Plana M, et al. Long-Term CD4+ T-Cell Response to Highly Active Antiretroviral Therapy According to Baseline CD4+ T-Cell Count. J AIDS 2004, 36:702-713.

García-Deltoro M. Rapid Initiation of Antiretroviral Therapy after HIV Diagnosis. AIDS Rev 2019, 21:55-64.

Gorochov G, Neumann AU, Kereveur A, et al. Perturbation of CD4+ and CD8+ T-cell repertoires during progression to AIDS and regulation of the CD4+ repertoire during antiviral therapy. Nat Med 1998; 4: 215-21.

Grinsztejn B, Hosseinipour MC, Ribaudo HJ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. Lancet Infect Dis. 2014;14:281-290.

Hachfeld A, Ledergerber B, Darling K, et al. Reasons for late presentation to HIV care in Switzerland. J Int AIDS Soc 2015, 18:20317.

Havlir DV, Kendall MA, Ive P, Kumwenda J, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. NEJM 2011, 365:1482-91.

Hoffmann C, Hentrich M, Gillor D, et al. Hodgkin lymphoma is as common as non-Hodgkin lymphoma in HIV-positive patients with sustained viral suppression and limited immune deficiency: a prospective cohort study. HIV Med 2015;16:261-4.

Hoy JF, Grund B, Roediger M, et al. Immediate Initiation of Antiretroviral Therapy for HIV Infection Accelerates Bone Loss Relative to Deferring Therapy: Findings from the START Bone Mineral Density Substudy, a Randomized Trial. J Bone Miner Res 2017, 32:1945-1955.

INSIGHT START Study Group, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015 Aug 27;373:795-807.

Jenness SM, Murrill CS, Liu KL, Wendel T, Begier E, Hagan H. Missed opportunities for HIV testing among high-risk heterosexuals. Sex Transm Dis 2009, 36:704-10.

Kelley CF, Kitchen CM, Hunt PW, et al. Incomplete peripheral CD4+ cell count restoration in HIV-infected patients receiving long-term antiretroviral treatment. Clin Infect Dis 2009, 48:787-94.

Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med. 2009 Apr 1.

Kityo C, Szubert AJ, Siika A, et al. Raltegravir-intensified initial antiretroviral therapy in advanced HIV disease in Africa: A randomised controlled trial. PLoS Med 2018, 15:e1002706.

Krentz HB, Auld MC, Gill MJ. The high cost of medical care for patients who present late (CD4 <200 cells/microL) with HIV infection. HIV Med 2004, 5:93-8.

Lange CG, Valdez H, Medvik K, Asaad R, Lederman MM. CD4+ T-lymphocyte nadir and the effect of highly active antiretroviral therapy on phenotypic and functional immune restoration in HIV-1 infection. Clin Immunol 2002, 102:154-61.

Lanoy E, Mary-Krause M, Tattevin P, et al. Frequency, determinants and consequences of delayed access to care for HIV infection in France. Antivir Ther 2007, 12:89-96.

Lawn SD, Török ME, Wood R. Optimum time to start antiretroviral therapy during HIV-associated opportunistic infections. Curr Opin Infect Dis 2011, 24:34-42.

Lifson AR, Grund B, Gardner EM, et al. Improved quality of life with immediate versus deferred initiation of antiretroviral therapy in early asymptomatic HIV infection. AIDS 2017, 31:953-963.

Lucas SB, Curtis H, Johnson MA. National review of deaths among HIV-infected adults. Clin Med 2008, 8:250-2.

Lundgren JD, Babiker AG, Sharma S, et al. Long-Term Benefits from Early Antiretroviral Therapy Initiation in HIV Infection. NEJM Evid 2023;2(3):10.1056/evidoa2200302.

Lyles RH, Munoz A, Yamashita TE, et al. Natural history of HIV type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men. J Infect Dis 2000, 181:872-880.

Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-Saharan Africa. Clin Infect Dis 2010, 50:1532-8.

Manzardo C, Zaccarelli M, Agüero F, Antinori A, Miró JM. Optimal timing and best antiretroviral regimen in treatment-naive HIV-infected individuals with advanced disease. J Acquir Immune Defic Syndr 2007, 46 Suppl 1:S9-18.

Martin-Iguacel R, Reyes-Urueña J, Bruguera A, et al. Determinants of long-term survival in late HIV presenters: The prospective PISCIS cohort study. EClinicalMedicine. 2022 Aug 3;52:101600.

May M, Sterne JA, Sabin C, et al. Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: Collaborative analysis of prospective studies. AIDS 2007;21:1185-97.

May MT, Sterne JA, Costagliola D, et al. HIV treatment response and prognosis in Europe and North America in the first decade of highly active antiretroviral therapy: a collaborative analysis. Lancet 2006; 368: 451-8.

Mellors JW, Munoz AM, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med. 1997, 126:946-954.

Mocroft A, Lundgren J, Antinori A, et al. Late presentation for HIV care across Europe: update from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study, 2010 to 2013. Euro Surveill 2015, 20(47).

Mocroft A, Lundgren JD, Sabin ML, et al. Risk factors and outcomes for late presentation for HIV-positive persons in Europe: results from the Collaboration of Observational HIV Epidemiological Research Europe Study (COHERE). PLoS Med 2013;10:e1001510.

Mugglin C, Althoff L, Wools-Kaloustian K, et al. Immunodeficiency at the Start of ART: Global View. Abstract 100, 19th CROI 2012, Seattle.

Murray JM, Emery S, Kelleher AD, et al. Antiretroviral therapy with the integrase inhibitor raltegravir alters decay kinetics of HIV, significantly reducing the second phase. AIDS 2007, 21:2315-21.

Mussini C, Manzardo C, Johnson M, et al. Patients presenting with AIDS in the HAART era: a collaborative cohort analysis. AIDS 2008, 22:2461-9.

Op de Coul EL, van Sighem A, Brinkman K, et al. Factors associated with presenting late or with advanced HIV disease in the Netherlands, 1996-2014: results from a national observational cohort. BMJ Open 2016, 6:e009688.

Phillips A, CASCADE Collaboration. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. AIDS 2004, 18:51-8.

Raffetti E, Postorino MC, Castelli F, et al. The risk of late or advanced presentation of HIV-infected patients is still high, and associated factors evolve. Still, the impact on overall mortality is vanishing over calendar years: results from the Italian MASTER Cohort. BMC Public Health 2016, 16:878.

Rava M, Bisbal O, Domínguez-Domínguez L, et al. Late presentation for HIV impairs immunological but not virological response to antiretroviral treatment. AIDS 2021, 35:1283-1293.

Rava M, Domínguez-Domínguez L, Bisbal O, et al. Late presentation for HIV remains a major health issue in Spain: Results from a multicenter cohort study, 2004-2018. PLoS One 2021, 16:e0249864.

Samri A, Goodall R, Burton C, et al. Three-year immune reconstitution in PI-sparing and PI-containing antiretroviral regimens in advanced HIV-1 disease. Antivir Ther 2007, 12:553-8.

Sasse A, Florence E, Pharris A, et al. Late presentation to HIV testing is overestimated when based on the consensus definition. HIV Med 2016, 17:231-4.

Schäfer G, Hoffmann C, Arasteh K, et al. Immediate versus deferred antiretroviral therapy in HIV-infected patients presenting with acute AIDS-defining events (toxoplasmosis, Pneumocystis jirovecii-pneumonia): a prospective, randomized, open-label multicenter study (IDEAL-study). AIDS Res Ther 2019, 16:34.

Sereti I, Gulick RM, Krishnan S, et al. ART in HIV-Positive Persons With Low Pretreatment Viremia: Results From the START Trial. J Acquir Immune Defic Syndr 2019, 81:456-462.

Sharma S, Schlusser KE, de la Torre P, et al. The benefit of immediate compared with deferred antiretroviral therapy on CD4+ cell count recovery in early HIV infection. AIDS 2019, 33:1335-1344.

Siegfried N, Uthman OA, Rutherford GW. Optimal time for initiation of antiretroviral therapy in asymptomatic, HIV-infected, treatment-naive adults. Cochrane Database Syst Rev 2010, 17;(3):CD008272.

Sierra-Madero JG, Ellenberg S, Rassool MS, et al. A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of a Chemokine Receptor 5 (CCR5) Antagonist to Decrease the Occurrence of Immune Reconstitution Inflammatory Syndrome in HIV-Infection: The CADIRIS Study. Lancet HIV 2014, 1:e60-e67.

Sterling TR, Chaisson RE, Moore RD. HIV-1 RNA, CD4 T-lymphocytes, and clinical response to HAART. AIDS 2001, 15:2251-7.

Sterne JA, May M, Costagliola D, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet 2009, 373:1352-63.

Tominski D, Katchanov J, Driesch D, et al. The late-presenting HIV-infected patient 30 years after the introduction of HIV testing: spectrum of opportunistic diseases and missed opportunities for early diagnosis. HIV Med 2017, 18:125-132.

Török ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)—associated tuberculous meningitis. CID 2011, 52:1374-83.

UK Collaborative HIV Cohort (UK CHIC) Steering Committee. Late diagnosis in the HAART era: proposed common definitions and associations with mortality. AIDS 2010, 24:723-7.

Valbert F, Wolf E, Preis S, et al. HIV-Epidemiologie in Deutschland: Späte Diagnostik. Dtsch Arztebl 2021, 118: A-1994 / B-1644.

Wilson Kd1KD, Dray-Spira R, Aubrière C, et al. Frequency and correlates of late presentation for HIV infection in France: older adults are a risk group – results from the ANRS-VESPA2 Study, France. AIDS Care 2014, 26 Suppl 1:S83-93.

Wondwossen AD, Lindquist L, Aderaye G, et al. Randomized Clinical Trial to Determine Efficacy and Safety of ART 1 Week after TB Therapy in Patients with CD4 Counts <200 Cells/µL. Abstract 144, 19th CROI 2012, Seattle.

Wymant C, Bezemer D, Blanquart F, et al. A highly virulent variant of HIV-1 circulating in the Netherlands. Science 2022, 375:540-545.

Zhao Y, Hohlfeld A, Namale P, Meintjes G, Maartens G, Engel ME. Risk of Immune Reconstitution Inflammatory Syndrome With Integrase Inhibitors Versus Other Classes of Antiretrovirals: A Systematic Review and Meta-analysis of Randomized Trials. J AIDS 2022, 90:232-239.

Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS 2009, 4:e5575.

Zoufaly A, an der Heiden M, Marcus U, et al. Late presentation for HIV diagnosis and care in Germany. HIV Med 2012, 13:172-81.

5.6. The optimal first-line therapy

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Given the more than thirty drugs, the number of possible combinations in first-line therapy hardly seems manageable at first glance. Moreover, different guidelines such as those of the International AIDS Society (IAS, Gandhi 2023), US Department of Health and Human Services (DHHS 2022), European AIDS Society (EACS 2022) or German-Austrian AIDS Society (GAAS 2021) – all recommend different regimens.
However, INSTI-based regimens are recommended first-line for all PLWH worldwide (where they are available). These include BIC/TAF/FTC and DOL-containing regimens plus TDF/FTC or TAF/FTC. Beyond these regimens, some critical differences are still evident. For example, DHHS and EACS (but not IAS) also recommend dolutegravir plus ABC/3TC for individuals who are HLA-B*5701 negative and without chronic hepatitis B virus (HBV) co-infection. EACS is the only international guideline to recommend NNRTI-based regimens (doravirine). According to DHHS, boosted darunavir plus (TAF or TDF) plus (FTC or 3TC) is possible – "pending the results of the genotype test".
In the German-Austrian recommendations, at least ten therapies (based on INSTIs, NNRTIs, and PIs) are recommended as equivalent, and others are considered alternatives. In contrast, WHO states that only "DTG in combination with an NRTI backbone is recommended as the preferred first-line regimen". Due to this recommendation in 2021, and thanks to access-oriented voluntary licensing agreements worldwide, the combination of TDF/3TC/dolutegravir ("TLD") has become the most widely used HIV regimen globally.
However, this may not always be the best choice (and is unavailable in Western Europe). There are other options. And there is still space for improvement. For this reason alone, it remains sensible for therapy-naïve people to participate in clinical trials: this is the only way to improve therapy further. But sometimes studies are not possible. For these cases, we summarize the data situation (beyond availability).

Recommended first-line therapies

Assuming a few things, the seemingly complex situation quickly becomes clearer. Let us assume that in first-line therapy
1. So-called single-tablet regimes (STRs) are to be preferred
2. 3TC and FTC are equivalent
3. Abacavir is more and more likely to be avoided because of cardiovascular risk
4. Food restrictions are somewhat unfavorable

Only a few combinations remain (Table 6.1). They consist of a backbone with one or two NRTIs and a third compound and are discussed in detail below. The third substance is either a boosted PI with darunavir, an NNRTI with doravirine, or a second-generation integrase inhibitor, namely dolutegravir or bictegravir.

Table 6.1: Useful STR combinations in first-line therapy (no ranking).

NRTIs	plus	Third (or second) agent		Brand name
TAF + FTC		PI:	Darunavir/c	Symtuza®
TAF + FTC		INSTI:	Bictegravir	Biktarvy®
3TC		INSTI:	Dolutegravir	Dovato®[1]
TDF + 3TC		NNRTI:	Doravirine	Delstrigo®

[1] only if viral load is below 500,000 copies/mL, if there are more than 200 CD4 T-cells, and in the absence of hepatitis B

These four STRs can be used in almost all clinically conceivable situations. In addition, many other therapies or agents are possible (some of which are approved), although they are only used in exceptional cases in practice. These include agents that have been recommended for many years, such as rilpivirine, but also elvitegravir or raltegravir, whose resistance barriers are probably lower than those of doravirine, dolutegravir and bictegravir. Abacavir, which used to be widely used, should also be avoided because of the cardiovascular risk, especially in first-line therapy.

First-line therapy: practical and important aspects

A compelling virological superiority of a specific combination has not been shown even in recent years; there is no *gold standard*. Therefore, other things often play a role in the choice: individual adherence, concomitant diseases, concomitant medication, and individual needs should be considered. Even tablet size or restrictions regarding food intake can influence the decision.
The right first-line therapy is vital and must be well-prepared. Especially in highly viremic patients, there is a relevant risk of resistance in the first few weeks, as it takes several weeks for replication to be slowed down. It should not be forgotten that for many people, the start of therapy is a drastic event: the realization that from now on, they will probably be treated for life makes them nervous and uncertain. Reservations can, therefore, often be great. It is not uncommon for people to have unclear ideas about what antiretroviral therapy means nowadays.

Practical tips for first-line therapy

- The first shot should be successful, i.e., the viral load must be below the detection limit – at the latest, after 3–6 months!
- Is the patient motivated? Will they come back at all? An immediate start makes sense in principle but is rarely necessary. In case of doubt, it may be better to wait and check the values further.
- Be sure to address likely adherence and work and eating habits (shift work?).
- Pros and cons (side effects!) of different combinations can be discussed openly – there is almost always time for this. Each patient may learn why the particular therapy was chosen.
- Ask about concomitant medication (and drug use; see below) – are relevant interactions to be expected?
- Check concomitant diseases – what about liver (hepatitis?), kidney?
- Is a resistance test available? Caution: Transmitted resistances are possible.
- Check if participation in a clinical trial is possible!

What should be clarified first?

It is often the little things that influence the decision. Patients should be involved as far as possible. It has proven beneficial to ask openly, "What is important to you? How regularly do you eat? Do you have a particular diet? Does taking pills daily cause you problems in principle, or do you not care whether it is one or three pills daily? Do you trust yourself to take them regularly, or are you someone who might forget to do so? When would taking it during the day be optimal for you? Would mild and/or temporary diarrhea be a big problem?"

Table 6.2: Factors influencing the choice of first-line therapy, differences between drug classes. The choice of backbone may also play a role.

	NNRTI DOR	PI DRV	INSTIs DTG, BIC
Number of tablets per day	1	1	1
Once-daily dose	yes	yes	yes
Food restrictions	no	partly	no
Viral load reduction	medium	often slow	quickly
Interaction potential	medium	high	low
Resistance risk during first-line	1–2%	0%	0%
Main side effect of the class	allergies	diarrhea	weight gain
Preferred NRTI backbone	TDF+3TC	TAF+FTC	TAF+FTC/3TC
Long-term experience (class)	> 20 years	> 20 years	5–10 years

People living with HIV have become more demanding. And rightly so. There are many alternatives. As in the early days of ART, multiple daily doses are obsolete; the once-daily administration of an STR is the rule. Lifelong ART must fit as perfectly as possible into everyday life. And cause little disruption. It is not about a few months, but about years, about decades. Of the combinations listed below, only the PI should be taken with a meal; with the other three, it does not matter.

Adherence

Compliance is defined as a patient's consent and acceptance of therapy. In the mid-'90s, a new term, "compliance", was adopted. Since then, the more politically correct term – "adherence" is frequently used. This term refers to the physician and patient working together to set up a treatment concept acceptable to both parties. It emphasizes that responsibility for the failure of the therapy is not automatically the patient's fault. Adherence includes all factors that influence staying on a regimen in terms of acceptability under these three buckets:

1. The success of a treatment is endangered if medication is taken irregularly
2. Clinicians tend to overestimate a patient's adherence
3. Adherence diminishes with the complexity of the treatment

Is the patient able to take the therapy on his own? Do they understand that ART is a life-long treatment that should not be stopped when they feel better? Do they realize that there is no need to tolerate severe side effects? What is realistic, given their private and social background?

No doubt, adherence is the Achilles' heel of every antiretroviral therapy. Poor adherence is the main if not the primary, factor for developing resistance and treatment failure (Turner 2002). However, adherence can be improved! Resistance is virtually bred by only partial viral suppression and insufficient drug levels. ART should be taken consistently. All or nothing: Regarding the development of resistance, sometimes it is better not to take any therapy. The reasons for poor adherence are complex. They range from being overwhelmed with the intake (number of tablets, timing of intake, food intake) to side effects or concerns about them. A poor doctor-patient relationship also plays a role. Sometimes, it is just the hurdle of keeping regular doctor's appointments and getting prescriptions. Not everyone ensures that there is always enough medication in the house.

Patients at risk for poor adherence are not only drug users, alcoholics, or those with side effects. Depressed people, people living alone, and younger people have also been identified as problem groups in many studies (Glass 2006). Favorable factors, on the other hand, are the physician's experience, the understanding of ART, and

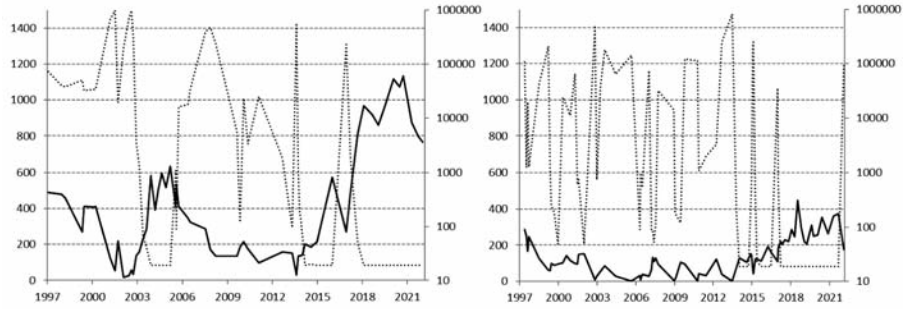

Figure 6.1: Two cases with adherence problems, CD4 T-cells/µl (dark, primary axis left, cells/µl), and viral load (dashed, primary axis right, RNA copies/mL). In both, initially, inconsistent ART use for many years, as indicated by high viral loads. In both cases, several HIV-associated problems and resistance mutations occurred over time.

social support. In contrast, ethnicity, gender, or stage of disease do not seem to play a role. Further factors include the individual worldview of disease and health, the acceptance of conventional medicine, or the fear of side effects. However, there is a large variance. Ultimately, adherence is difficult to predict in individual cases; experience and intuition are essential factors.

Countless studies have shown that it is crucial to take medication regularly. However, the previously propagated need for at least 95% adherence (95% of doses taken) can no longer be proven. Modern agents with a high resistance barrier, such as darunavir, dolutegravir, or bictegravir, probably have a high forgiveness – they "forgive" significantly more "non-compliance" (Nelson 2010, Bezabhe 2016). Recent studies investigating regular treatment interruptions also show that absolute adherence is not always required, especially in patients treated for many years. In the French QUATUOR trial (ANRS 170), 647 successfully treated patients were randomized to continue taking their ART daily or only on 4/7 days (every Friday to Sunday off). After 48 weeks, 96% remained below the limit of detection in the experimental arm, and resistance had occurred in only 3/318 patients (Landman 2022). Although one can argue about the ethical aspects of such a human experiment – it shows that repeated treatment interruptions can remain without consequences for most individuals over a longer period. Concepts of Directly-Observed-Therapy (DOT) or DAART (directly administered antiretroviral therapy) discussed in the past are mostly obsolete today. Moreover, the effect of DOT usually disappears as soon as the patients are left to themselves (Berg 2011).

Poor adherence does not only mean virological failure. It also has immunological consequences and clinical consequences beyond surrogate markers. In a Spanish study, patients who failed to take more than 10% of their medications had an almost 4-fold increased risk of mortality (Garcia 2002). Increased mortality and more hospitalizations were also found in other studies (Wood 2004). It is likely that non-adherence also increases the risk that resistant viruses will be transmitted.

The essential features of developing resistance should be explained to the patients. Education is key! A large randomized study in 400 PLWH proved that intensive early adherence counseling at ART initiation (three counseling sessions) had a sustained, significant impact on adherence, and virologic treatment failure during the 18-month follow-up while using an alarm device had no effect (Chung 2011)! Participants who received counseling were 29% less likely to have monthly adherence < 80% (hazard ratio 0.71, p=0.055) and 59% less likely to experience viral failure (HR 0,41; p=0.01) compared to those who received no counseling.

It is crucial to explain that once resistance has been generated, it does not disappear but is likely to persist for life. And that this is an essential difference from other chronic diseases. The comparison with diabetes or hypertension has proven itself – while it is forgivable to skip a tablet in these diseases, it is different with HIV. Blood sugar or blood pressure can be lowered again easily the next day, but this is not certain with HIV. "Sloppiness" can have irreversible consequences, and the therapy becomes more complicated with each resistance mutation. The reminder should be repeated occasionally and be a part of routine care. Diverse adherence-promoting strategies range from additional nurses and the community to regular text messages or even phone calls. The effect of such strategies depends heavily on individual factors; on the other hand, social media interventions can be useful, especially for younger people (reviews: Locher 2019, Shah 2019). However, often, this is not practical – and with a good education, it is mostly unnecessary. The effects of these interventions are limited.

Twelve steps to improve adherence

- Every patient receives a written (comprehensible) treatment plan, which is reviewed at the end of the visit. The plan contains a telephone number (or email) for queries.
- Patient and physician agree on the treatment plan. The patient's concerns and questions have been discussed.
- It is clear to the patients that the therapy was not chosen arbitrarily but tailored to their needs.
- Explaining a new therapy or a change takes time and should not happen haphazardly – all questions must be answered.
- The patient has learned in broad terms why adherence is essential – not only when starting or when or why changing therapy! Repeated discussions about adherence are part of routine care.
- It should be explained what side effects can be expected and how to deal with them. Support Groups and local associations have been mentioned or referred.
- It is essential to note that the individual can and should come in immediately if there are problems with the ART.
- It has been discussed that the therapy should never be partially reduced ("I left out the big pills last month…").
- Irregularities in prescriptions should be addressed openly.
- Just at the beginning, when viral load is dropping, and CD4 T-cells are rising, communicating this success can be motivating.
- Treat depression!

If adherence remains poor

Despite all efforts, some patients will fail to improve adherence. Physicians and other healthcare providers should not take this personally or feel offended. Although accepting the patient's views on life, disease, and treatment may be difficult, healthcare providers must keep tolerance and acceptance as key components in their interactions with patients. Some providers, especially those who treat selective patient populations in university settings, tend to forget the reality of routine medical practice. Rigidly upholding the principles of modern medicine usually does not help here, and putting patients under pressure will achieve even less. It is essential to clearly outline and explain, advise, help, question, and listen.

One's positions must be clearly represented and well justified. Whether non-compliant patients should continue to be treated with antiretroviral therapy can be challenging to address. On the one hand, some patients benefit even from sub-optimal therapy; on the other hand, drugs are expensive and should not be prescribed too readily. Restraint should be applied until the reason for poor compliance is understood. A referral to counseling (peer support?) may be needed.
Clinicians should also be aware of criminal schemes – there are always reports of deals with pharmacies in which those involved procured other drugs (methadone, etc.) or money. Prescriptions issued should be documented. If there are reasonable doubts about compliance or honesty, one can also arrange for plasma levels to be measured (TDM, preferably without notice).

The Duesberg Sect

Patients who refuse antiretroviral treatment on principle are a special case. These patients are frequently not on treatment thanks to (shockingly misdirected) doctors, who call themselves "Duesbergians" (after the US virologist and AIDS dissident Peter Duesberg, who denies any association between AIDS and illness). In such cases, leaving patients to their fate can be very difficult. Informative consultations should be as detailed as possible and preferably documented in writing.
An example: an approximately 40-year-old patient with a long history of untreated HIV, 30 CD4 T-cells/µl, and cerebral toxoplasmosis (TE), which improved significantly after four weeks of acute treatment (the last MRI still showed scattered lesions) introduced his case to the HIV outpatient department. Clinically, he was relatively well and fully oriented and due for discharge that day. In a conversation, the patient categorically refused to start the urgently recommended antiretroviral therapy. His Duesbergian physician had advised him against HIV therapy ("You can die from AZT, and the other drugs are not much better, etc."). He refused antibiotics on principle as well. This was why the patient would not continue the TE maintenance therapy, which had made him suffer from diarrhea (NB, probably cryptosporidiosis), skin problems (seborrhoeic dermatitis, thrush), and extreme loss of weight (MAC?) since his first day in hospital. It was imperative for him to have a break from all medication.
In such cases, we make sure the patients sign the information sheets. Every patient is allowed to and should decide for himself (if fully cognizant and capable) – they must be fully informed about what they are doing. It is vital to give the patient control: if they change their mind, they may return! In our experience, arguing with medical Duesbergians leads nowhere. This sect has a very restricted view of the world and sticks to its repetitive mantra-like arguments. Discussing with them is time-consuming and a waste of energy. Fortunately, these cases have become rarer. The initial widespread skepticism towards ART has decreased significantly due to its overwhelming success in recent years. Concerning Peter Duesberg, he is relatively quiet as far as his HIV activities go. The sect is in decline.

Pre-existing (transmitted) resistance

At least one genotypic resistance test should be available before ART initiation. In Europe, pre-existing resistance mutations that have been transmitted and are therefore present even though the affected person has not yet taken ART can be expected to be constant at about 10–15% (see *Resistance*). These resistance mutations must be considered in any treatment decisions. A single resistance mutation such as K103N, found in just under 2% in Europe among untreated individuals, can throw an NNRTI regimen into disarray, with the threat of further mutations. Since some mutations, such as M184V, that reduce viral replication fitness may disappear over time, old

tests should also be considered. If no test has been available to date, it should be performed. Suppose ART needs to be started urgently, for example, in cases of advanced immunodeficiency or initial diagnosis in pregnancy. In that case, waiting for the result may be optional, often taking 7–14 days. It may be better to start a high resistance barrier ART regimen with, for example, darunavir and adjust it if necessary (Huhn 2020).

Concurrent illnesses

Before starting therapy, all concurrent illnesses should be known (medical history, examination). This is important: someone with consistent diarrhea is likelier not to be given a boosted PI. Latent diabetes mellitus may become insulin-dependent with PIs. Is obesity present? In these cases, remember that significant weight gain has been described in some studies under both INSTIs and TAF (Sax 2019, Venter 2019, see next chapter). Caution is advised with TDF in renal disease or osteoporosis, especially with boosted PIs. Caution with abacavir is warranted in the presence of high cardiovascular risk (Behrens 2010). Liver disease or chronic hepatitis should also be considered. The risk of severe hepatotoxicity with nevirapine or ritonavir increases (Sulkowski 2000). However, our co-infected patients have not seen an increased risk (Mauelshagen 2012).

Table 6.3: Concurrent illnesses where specific agents may be problematic (not limited to first-line therapies) exist.

Disease	Caution with
Active hepatitis B	Nevirapine, boosted PIs (instead, favorable: TDF or TAF plus FTC!)
Active hepatitis C	Nevirapine, boosted PIs
Active drug use, substitution	NNRTIs, ritonavir (possibly favorable: raltegravir)
Anemia	AZT
Chronic diarrhea, intestinal diseases	All PIs
Diabetes mellitus	All PIs
Myocardial infarction	Abacavir, darunavir, lopinavir
Kidney diseases	TDF, atazanavir, cobicistat
Psychoses, other CNS disorders	Efavirenz, possibly dolutegravir, bictegravir
Osteoporosis	TDF

In case of an active hepatitis B co-infection, the high anti-HBV potency of TDF and TAF (and also FTC and 3TC) should be used. Long-term control of hepatitis B over many years is possible with tenofovir (de Vries-Sluijs 2010). However, we always recommend combining it with a cytidine analog such as 3TC or FTC. In contrast, the weakly effective, resistance-prone 3TC alone (in Kivexa®, Dovato®, Triumeq®) should be avoided in patients with hepatitis B. In all PLWH, the current hepatitis B status should be known and well documented. It is common for the rebound to occur with 3TC alone or an NRTI-free regimen.

Finally, the desire to have children must also be considered, and women of childbearing potential should refrain from taking efavirenz. With INSTIs such as bictegravir and doravirine, experience during pregnancy is still limited. Even if the neural tube defects described in a 2018 cohort on dolutegravir have not been confirmed (Zash 2019), it still seems advisable to use proven agents (see chapter *ART in children*). However, this is in flux, and more pregnant women are likely to be below detection at term on dolutegravir in particular than on other therapies (Lockman 2021, Patel 2022).

Interactions with medications and drugs

Interactions also play an essential role when choosing individual regimens (see *Interactions*). Knowledge of these is often limited. How strong interactions can be may be illustrated by a study in which ritonavir increased the plasma levels of simvastatin by 3059% in healthy individuals (Fichtenbaum 2002). Severe rhabdomyolysis with statins and PIs has been described (review: Chauvin 2013). Severe side effects have also been described with chemotherapies, especially with vinca alkaloids. They should not be combined with boosters such as ritonavir or cobicistat. The same applies to some hepatitis drugs and some DAAs (see chapter 11). Many other agents should not be combined with ART because of the potential for unpredictable interactions. These also include certain contraceptives. Even preparations with which one would not have suspected any problems at first glance can be unfavorable: for example, Cushing's syndromes have been observed with steroid-containing asthma sprays and PIs (Saberi 2013). Cumarins can also be problematic; ritonavir significantly lowers levels (Llibre 2002). Some NOAKs should also be used cautiously; severe bleeding has been described with rivaroxaban and boosted PIs (Egan 2014, Lakatos 2014).

Even professionals make mistakes, and interactions are common (Lopes 2020). In the Swiss cohort, the proportion of boosted regimens decreased significantly between 2008–2018, but simultaneously, the number of co-medications increased. Polypharmacy is a growing problem. Concomitant use of five or more non-HIV medications was observed in 14%, with older individuals more frequently affected (6%, 18%, and 33% in the 18–49, 50–64, and ≥ 65 age groups). The proportion of unfavorable interactions was 29%, and the proportion of critical interactions was 2% (Deutschmann 2021). The most common errors were the combination of boosted ART with steroids (fluticasone, mometasone, triamcinolone: Cushing's syndrome), quetiapine, and domperidone (QT prolongations in each case). Also common were combinations of PPIs with unboosted atazanavir or rilpivirine. Typical problematic medications included migraine medications, prokinetics, and sedatives/hypnotics. One death has been described with ergotamine and ritonavir (Pardo 2003). Simultaneous administration of ART and PDE-5 inhibitors also has issues (see *Sexual Dysfunction*). At this point, it is not possible to refer to every substance. Many can be found in the *Drugs* section and the *Interactions* chapter. However, it is always advisable to also look at the drug information. The start of ART is always an excellent opportunity to reflect on the existing co-medication. If interactions are imminent and co-medication is mandatory, unboosted, TDF-free INSTI regimens may be the best choice (Lopes 2020).

However, the best way to check possible interactions with ART is the Liverpool Drug Interactions website, established in 1999 by members of the Department of Pharmacology at the University of Liverpool. This is a clinically useful, reliable, comprehensive, up-to-date, evidence-based drug-drug interaction resource that is freely available to everybody. It can be found at https://www.hiv-druginteractions.org/checker.

Interactions with drugs

Drugs or alcohol also interact with ART (review: Kumar 2015), party drugs, especially with boosted regimens, and NNRTIs (review: Bracchi 2015). "Chemsex" is now integral to many patients' lives; it describes sexual contact under psychoactive agents such as mephedrone, crystal methamphetamine, and gamma-hydroxybutyrate (see *Sexual Dysfunction*). Adherence is often impaired. Patterns of use range from occasional use to complete loss of control with social decline. Counseling services are rare, and there is often no awareness of the problem ("I'm not a junkie"). Drug

use is associated with higher educational attainment, a steady seropositive partner, younger age, and poor ART adherence. In a survey of 2,248 HIV-infected MSM in London, 51% had used party drugs in the previous three months (Daskalopoulou 2015). These figures will likely be transferable to other local metropolitan areas in Western countries. Of 453 PLWH (22% female, mean age 46 years) in Germany, 56% reported recreational drug use in the previous six months: nitrite inhalants ("poppers"), cannabis, and PDE-5 inhibitors were common in all age groups; ecstasy, methamphetamine, and gamma-hydroxybutyrate were predominantly reported by younger people (Funke 2021). Only 7% considered drug use combined with ART a problem. Strikingly, 44% and 42% had received medical treatment or were hospitalized for drug use.

Clinicians should know about these drugs in basic terms. Before starting ART, one should talk openly about drugs. The patient does not always desire this. However, it is crucial to know the indicators of the hidden use of party drugs (see box).

Indicators for (hidden) use of party drugs

- Frequent missed doctor's appointments, frequent appearances without appointments.
- Frequent incapacity to work, especially after the weekend.
- Congested noses and nosebleeds, "funny" stories.
- Frequently occurring STDs (especially hepatitis C!).
- Recurrent thrombophlebitis, abscesses (for example, see picture section).
- Desire for sleeping pills

Interactions can have dangerous consequences. Several deaths following concomitant use of ritonavir and amphetamines or MDMA/ecstasy or gamma hydroxybutyrate have been published (Henry 1998, Harrington 1999, Hales 2000). In particular, ritonavir and cobicistat inhibit the metabolism of amphetamines (speed or MDMA/ecstasy), ketamines, or LSD (Bracchi 2015). ART regimens with boosters (ritonavir, cobicistat) should be avoided for people who use party drugs. Compared with party drugs, marijuana, and THC probably have little interaction potential (Kosel 2002). For methadone-substituted individuals, nevirapine and efavirenz may significantly increase the need for methadone. This is also true to a weaker extent for ritonavir. Data are inconsistent for lopinavir, but dose adjustments may also be required. In contrast, raltegravir and dolutegravir do not affect methadone levels (Anderson 2010, Song 2013).

Additive toxicities

Additive toxicities should also be considered when selecting therapy. In the case of potentially nephrotoxic agents, caution is advised, especially with TDF; in these cases, TAF is preferable. Cobicistat or even dolutegravir, although not nephrotoxic, may provide falsely low GFR values by inhibiting tubular secretion of creatinine, and monitoring may become difficult. If myelotoxic agents (valganciclovir, cotrimoxazole) are necessary simultaneously, AZT should generally no longer be used.

Finally, potentially allergenic agents are unfavorable in first-line therapy if anti-infective prophylaxis with cotrimoxazole or other sulfonamides is required simultaneously. These include all NNRTIs, abacavir, as well as darunavir. Otherwise, it may be challenging to identify the causative agent without doubt in the case of drug exanthema.

Overall, the toxicity of the newer antiretroviral agents is significantly reduced compared to the past. Discontinuation rates have decreased (see *Side Effects*).

Literature on adherence and practical aspects of first-line therapy

Anderson MS, Mabalot Luk JA, Hanley WD, et al. Effect of Raltegravir on the Pharmacokinetics of Methadone. J Clin Pharmacol 2010, 50:1461-6.

Behrens GM, Reiss P. Abacavir and cardiovascular risk. Curr Opin Infect Dis 2010, 23:9-14.

Berg KM, Litwin AH, Li X, Heo M, Arnsten JH. Lack of sustained adherence or viral load improvement following a directly observed antiretroviral therapy intervention. Clin Infect Dis 2011, 53:936-43.

Bezabhe WM, Chalmers L, Bereznicki LR, Peterson GM. Adherence to Antiretroviral Therapy and Virologic Failure: A Meta-Analysis. Medicine (Baltimore) 2016, 95:e3361.

Bracchi M, Stuart D, Castles R, et al. Increasing use of 'party drugs' in people living with HIV on antiretrovirals: a concern for patient safety. AIDS 2015, 29:1585-92.

Chauvin B, Drouot S, Barrail-Tran A, Taburet AM. Drug-Drug Interactions Between HMG-CoA Reductase Inhibitors (Statins) and Antiviral Protease Inhibitors. Clin Pharmacokinet. 2013 May 24.

Daskalopoulou M, Rodger A, Phillips AN, et al. Recreational drug use, polydrug use, and sexual behaviour in HIV-diagnosed men who have sex with men in the UK: results from the cross-sectional ASTRA study. Lancet HIV 2014;1:e22-31.

De Vries-Sluijs TE, Reijnders JG, Hansen BE, et al. Long-term therapy with tenofovir is effective for patients co-infected with human immunodeficiency virus and hepatitis B virus. Gastroenterology 2010, 139:1934-41.

Deutschmann E, Bucher HC, Jaeckel S, et al. Prevalence of Potential Drug-Drug Interactions in Patients of the Swiss HIV Cohort Study in the Era of HIV Integrase Inhibitors. Clin Infect Dis 2021, 73:e2145-e2152.

Deutschmann E, Bucher HC, Jaeckel S, et al. Prevalence of potential drug-drug interactions in patients of the Swiss HIV cohort study in the era of HIV integrase inhibitors. PS13/3, EACS 2019, Basel.

DHHS. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. September 2022. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf.

EACS. GUIDELINES Version 11.1. October 2022. www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf.

Egan G, Hughes CA, Ackman ML. Drug interactions between antiplatelet or novel oral anticoagulant medications and antiretroviral medications. Ann Pharmacother 2014, 48:734-40.

Fichtenbaum CJ, Gerber JG, Rosenkranz SL, et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. AIDS 2002, 16:569-77.

Funke B, Spinner CD, Esser S, et al. High prevalence of recreational and illicit drug use in German people living with HIV with a potential for drug-drug interactions with antiretroviral therapy. Int J STD AIDS 2021, 32:75-82.

Gandhi RT, Bedimo R, Hoy JF, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2022 Recommendations of the International Antiviral Society-USA Panel. JAMA 2023, 329:63-84.

Garcia de Olalla P, Knobel H, Carmona A, et al. Impact of adherence and HAART on survival in HIV-infected patients. J AIDS 2002, 30:105-10.

Glass TR, De Geest S, Weber R, et al. Correlates of Self-Reported Nonadherence to Antiretroviral Therapy in HIV-Infected Patients: The Swiss HIV Cohort Study. J AIDS 2006, 41:385-392.

Hales G, Roth N, Smith D. Possible fatal interaction between protease inhibitors and methamphetamine. Antivir Ther 2000, 5:19.

Harrington RD, Woodward JA, Hooton TM, Horn JR. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and gamma-hydroxybutyrate. Arch Intern Med 1999, 159:2221-4.

Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. Lancet 1998, 352:1751-2.

Huhn GD, Crofoot G, Ramgopal M, et al. Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in a Rapid-Initiation Model of Care for Human Immunodeficiency Virus Type 1 Infection: Primary Analysis of the DIAMOND Study. Clin Infect Dis 2020, 71:3110-3117.

Kosel BW, Aweeka FT, Benowitz NL, et al. The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. AIDS 2002, 16:543-50.

Kumar S, Rao PS, Earla R, Kumar A. Drug-drug interactions between anti-retroviral therapies and drugs of abuse in HIV systems. Expert Opin Drug Metab Toxicol 2015, 11:343-55.

Lakatos B, Stoeckle M, Elzi L, et al. Gastrointestinal bleeding associated with rivaroxaban administration in a treated patient infected with human immunodeficiency virus. Swiss Med Wkly 2014 Jan 22;144:w13906.

Landman R, de Truchis P, Assoumou L, et al. A 4-days-on and 3-days-off maintenance treatment strategy for adults with HIV-1 (ANRS 170 QUATUOR): a randomised, open-label, multicentre, parallel, non-inferiority trial. Lancet HIV 2022, 9:e79-e90.

Lerner BH, Gulick RM, Dubler NN. Rethinking nonadherence: Historical perspectives on triple-drug therapy for HIV. Ann Int Med 1998, 129:573-8.

Llibre JM, Romeu J, Lopez E, Sirera G. Severe interaction between ritonavir and acenocoumarol. Ann Pharmacother 2002, 36:621-3.

Locher C, Messerli M, Gaab J, et al. Long-Term Effects of Psychological Interventions to Improve Adherence to Antiretroviral Treatment in HIV-Infected Persons: A Systematic Review and Meta-Analysis. AIDS Patient Care STDS 2019, 33:131-144.

Lockman S, Brummel SS, Ziemba L, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet 2021, 397:1276-1292.

Lopes S, O'Day K, Meyer K, et al. Comedication prescription patterns and potential for drug-drug interactions with antiretroviral therapy in people living with human immunodeficiency virus type 1 infection in Germany. Pharmacoepidemiol Drug Saf. 2020 Jan 16.

Malaba TR, Nakatudde I, Kintu K, et al. 72 weeks post-partum follow-up of dolutegravir versus efavirenz initiated in late pregnancy (DolPHIN-2): an open-label, randomised controlled study. Lancet HIV 2022, 9:e534-e543.

Mauelshagen A, Horst HAH, Stellbrink HJS, Hoffmann C. Long-term safety and tolerability of nevirapine and efavirenz-containing regimens in HIV/HCV-coinfected patients. Journal of the International AIDS Society 2012, 15(Suppl 4):18416.

Miller LG, Liu H, Hays RD, et al. How well do clinicians estimate patients' adherence to combination antiretroviral therapy? J Gen Int Med 2002; 17: 1-11.

Nelson M, Girard PM, Demasi R, et al. Suboptimal adherence to darunavir/ritonavir has minimal effect on efficacy compared with lopinavir/ritonavir in treatment-I, HIV-infected patients: 96-week ARTEMIS data. J Antimicrob Chemother 2010, 65:1505-9.

Pardo REY C, Yebra M, Borrallo M, et al. Irreversible coma, ergotamine, and ritonavir. Clin Infect Dis 2003; 37: e72-3.

Patel K, Huo Y, Jao J, et al. Dolutegravir in Pregnancy as Compared with Current HIV Regimens in the United States. N Engl J Med 2022, 387:799-809.

Saberi P, Phengrasamy T, Nguyen DP. Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: a review of pharmacokinetics, case reports and clinical management. HIV Med 2013, 14:519-29.

Sax PE, Erlandson KM, Lake JE, et al. Weight Gain Following Initiation of Antiretroviral Therapy: Risk Factors in Randomized Comparative Clinical Trials. Clin Infect Dis. 2019 Oct 14. Pii: ciz999.

Shah R, Watson J, Free C. A systematic review and meta-analysis in the effectiveness of mobile phone interventions used to improve adherence to antiretroviral therapy in HIV infection. BMC Public Health 2019, 19:915.

Song I, Mark S, Chen S, et al. Dolutegravir does not affect methadone pharmacokinetics in opioid-dependent, HIV-seronegative subjects. Drug Alcohol Depend 2013, 133:781-4.

Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with HIV and the role of hepatitis C or B virus infection. JAMA 2000, 283: 74-80.

Turner BJ. Adherence to antiretroviral therapy by HIV-infected patients. J Infect Dis 2002; 185 Suppl 2: S143-51.

Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med 2019, 381:803-815.

Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. Lancet HIV 2020, 7:e666-e676.

WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. 16 July 2021. www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hiv/treatment.

Wood E, Hogg RS, Yip B, et al. The impact of adherence on CD4 cell count responses among HIV-infected patients. J AIDS 2004, 35:261-8.

Zash R, Holmes L, Diseko M, et al. Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. N Engl J Med 2019, 381:827-840.

Which drug classes should be used?

Once all practical aspects have been considered and the options remain unlimited, the appropriate first-line therapy must be selected. Currently, recommended combinations include two NRTIs plus either the PI darunavir, the NNRTI doravirine, or one of the two integrase inhibitors (INSTIs), dolutegravir and bictegravir. They are discussed in more detail here.

The German-Austrian guidelines recommend a total of 18 different combinations at the end of 2021, including some multiple-tablet regimens. Much of this appears dispensable. However, guidelines focusing on INSTIs only may unnecessarily limit treatment decisions. For rilpivirine or elvitegravir, it is increasingly difficult to identify situations in which they might still be useful or justifiable. TAF/FTC (Descovy®) should be avoided because of the high costs. Large randomized trials directly comparing different drug classes in treatment-naïve patients can be found in Table 6.4.

Table 6.4: Randomized, cross-drug class comparisons in first-line therapy.

Study	Drugs (n)	Results on virological failure (VF) and adverse events (AEs)
NNRTIs versus PIs		
ACTG 5142 (Riddler 2008)	EFV versus LPV/r (250 + 253)	VF less with EFV, severe AEs same (but more lipoatrophy with EFV)
ACTG 5202 (Daar 2011)	EFV versus ATV/r (929 + 928)	VF same, more severe AEs with EFV (with ABC+3TC), but better lipid profile
ARTEN (Soriano 2011)	NVP versus ATV/r (376 + 193)	VF same, but more severe AEs and resistance with NVP, better lipid profile
DRIVE-FORWARD (Molina 2020)	DOR versus DRV/r (385 + 384)	VF slightly less with DOR (but overall high drop-out rates), better lipid profile
NNRTIs versus INSTIs		
STARTMRK (Rockstroh 2011)	EFV versus RAL (282 + 281)	VF same, more total AEs with EFV
GS 236-102 (Wohl 2014)	EFV versus EVG/c (352 + 348)	VF and tolerability same (more CNS AEs, less nausea with EFV)
SINGLE (Walmsley 2013)	EFV versus DTG (419 + 411)	VF less with DTG, more AEs, and discontinuations with EFV
ADVANCE (Venter 2019)	EFV versus DTG (351 + 702)	VF less with DTG, more AEs and discontinuations with EFV, weight gain with DTG
NAMSAL (Calmy 2020)	EFV 400 versus DTG (303 + 310)	VF and tolerability same; more weight gain with DTG
INIs versus PIs		
ACTG 5257 (Lennox 2014)	RAL versus ATV/DRV/r (603 + 1206)	VF similar, tolerability better with RAL than with both PIs
GS 236-103 (Clumeck 2014)	EVG/c versus ATV/r (353 + 355)	VF and tolerability same
FLAMINGO (Clotet 2014)	DTG versus DRVr (217 + 200)	VF low (no resistances!), tolerability slightly worse with DRV/r
ARIA (Orrell 2017)	DTG versus ATV/r (250 + 249, women only)	VF less with DTG, more AE-related discontinuations with ATV/r

Notes: Different NRTI backbones (some randomized) were used; some had additional study arms. VF = Virological Failure, AEs = Adverse Events.

It is striking that the currently recommended (and broadly used) therapies are underrepresented. For bictegravir and rilpivirine, large, valid cross-class comparisons still need to be made. Most studies used agents that are no longer first-line today, including efavirenz, atazanavir, or lopinavir. In most class-comparative studies, antiviral potency was broadly comparable, at least as measured by the proportion of patients with viral loads below the detection limit. Although some differences emerged, especially regarding tolerability (and risk of resistance), the results are not likely to compromise any of the three classes. In a review of 29 studies involving 9047 PLWH, no differences were found between NNRTIs and boosted PIs in terms of clinical and immunological-virological success (Borges 2016).

NNRTIs versus PI/s

In various studies such as ACTG 5142/5202, FIRST, ARTEN, or DRIVE-FORWARD, the NNRTI was at least as effective as the respective PI. In some cases, even more patients achieved a viral load below the detection limit, primarily due to better tolerability of the NNRTIs. Some patients discontinued PIs due to gastrointestinal side effects. However, resistance occurs more rapidly and frequently with NNRTIs than with PIs, probably due to the lower resistance barrier. A meta-analysis of 20 studies involving 7,940 subjects found comparably frequent virologic failure among NNRTIs (4,9%) and PIs (5.3%) among PIs. Where genotypic resistance testing was successful, resistance was observed significantly more frequently among NNRTIs. This was true not only for resistance mutations to NNRTIs or PIs but also for NRTI key mutations such as M184V and K65R (Gupta 2008). This phenomenon was particularly evident in the ARTEN study (Soriano 2011). While not a single resistance occurred under the PI atazanavir/r, 6% developed two-class resistance while on nevirapine. With doravirine, the risk of resistance is likely lower (Molina 2020). In two studies (DRIVE-FORWARD and -AHEAD), only 9/747 developed resistance (1.2%), less than is usually seen with NNRTIs.

INSTIs versus NNRTIs

In three large randomized trials, STRTMRK, GS102, and SINGLE, the three INSTIs raltegravir, elvitegravir/c, and dolutegravir each measured up against the standard of care, namely efavirenz (Rockstroh 2011, Walmsley 2013, Wohl 2014). All three INSTIs were better tolerated. Efavirenz tended to be inferior or, in the case of dolutegravir in SINGLE, significantly inferior in each case, primarily due to increased discontinuations due to CNS side effects. Admittedly, tolerability was also dependent on the particular setting. For example, the discontinuation rate of efavirenz due to CNS side effects increased in recent studies, and in SINGLE, it was as high as 10%! Similarly, in ADVANCE, a comparison of dolutegravir and efavirenz in South Africa, discontinuations were higher with efavirenz and partly responsible for differences in efficacy (Venter 2019). The broader choice of therapies likely lowers everyone's "tolerance level" and causes treatment discontinuations more quickly than before for understandable reasons.

INSTIs versus PIs

In FLAMINGO, GS103, and ACTG 5257, the integrase inhibitors each also competed against boosted PIs such as atazanavir/r and darunavir/r, respectively (Clotet 2014, Clumeck 2014, Lennox 2014). Dolutegravir and raltegravir showed better tolerability, reflected in the overall response. Thus, raltegravir was superior to PIs darunavir/r and atazanavir/r in ACTG 5257 primarily due to better tolerability – although slightly more resistance was observed (Lennox 2014). Two large trials in women in resource-poor countries tested dolutegravir (ARIA, Orrell 2017) and elvitegravir/c against

atazanavir/r (WAVE, Squires 2016). In both, more patients achieved viral loads below 50 copies/mL with INSTIs than with atazanavir (ARIA 11%, WAVE 6%). Toxicity-related discontinuations were also slightly more common with the PI.
Beyond virologic response and tolerability, what have we learned from these studies? The sub-analyses of ACTG 5257 in particular, a large three-arm study, are very informative. For example, after 96 weeks, there were differences between raltegravir and the two PIs, darunavir and atazanavir, concerning lipid profile (Ofotokun 2015), but no differences concerning body fat changes (McComsey 2016). Biomarkers regarding atherosclerosis also showed no differences (Kelesidis 2017). Bone density decreased slightly less with raltegravir than with PIs (Brown 2015). Of note was another sub-analysis on body weight. A significant body weight/BMI increase was observed less frequently on either PI than on raltegravir (Bhagwat 2018). This trend to the disadvantage of INSTIs was also confirmed in many other studies (Hester 2022), especially in women and blacks and in combination with TAF. The opposite was expected, as metabolic disturbances from INSTIs had not been expected and PIs had been associated with lipodystrophy – there is undoubtedly a need for further research here (see *Side Effects*).

Resistance among different first-line therapies

What about the most important endpoint of these studies, virologic treatment failure with the development of new resistance? So far, virtually no new resistance has been found with three agents in first-line therapy: darunavir/r, bictegravir, and dolutegravir. Here, the resistance barrier is very high, and the risk is extremely low. With doravirine, raltegravir, and elvitegravir, the risk is about 1–2%, while with rilpivirine, depending on the viral load, it is significantly higher.
However, cross-comparisons between studies are problematic, as not only are different populations studied, but virological failure is defined differently, as is the cut-off for genotypic resistance testing. For example, in a meta-analysis of 14 randomized trials, 29% of patients with virologic failure did not undergo resistance testing (Llibre 2018). In other words, some trials look hard for resistance to treatment failure, while others look less hard. The closer you look, the more you'll find. Unfortunately, almost no study has reported what happened to those affected by virologic failure in the long term.
The occurrence of a single resistance mutation may be regarded as a regrettable case of limited significance. In contrast, two-class resistance is significant since it destroys some crucial options and significantly impacts the treatment of those affected – for years and even decades. Even if these cases are rare, they do exist! The following table shows selected pivotal studies and the frequency of two-class resistance in each case. The rate was lowest among boosted PIs such as darunavir/r (and atazanavir/r), but also among the two second-generation INSTIs, dolutegravir, and bictegravir: not a single case has been described among these first-line therapies.
With raltegravir and elvitegravir, on the other hand, the rate is about 1%, as with doravirine. The rates are unacceptably high, especially with nevirapine and rilpivirine in cases of high viremia. These options are no longer considered in first-line therapy.
Individual strategies have pros and cons – the competition for the best first-line therapy continues. Thus, the pros and cons of the different strategies continue, and controversy over the best first-line therapy persists. One should be warned against cross-trial comparisons, often used as marketing strategies to influence health providers' effectiveness of a specific treatment ("We achieved over 90% tolerance rates in our study"). In a systematic evaluation of 10 large-scale randomized trials with 2,341 therapy-naïve patients receiving AZT+3TC+efavirenz, the success rates (viral load in the ITT analysis < 50/copies/mL at 48 weeks) ranged between 37% and

Table 6.5: Two-class resistance (affecting NRTI backbone and third agent, respectively) emerging in first-line therapy. Not a single case has been described so far in the comparator arms with atazanavir/r, darunavir/r, and dolutegravir.

Combination	Study (reference)	n	%
TDF+FTC+nevirapine	ARTEN (Soriano 2011)	23/376	6.1%
2 NRTIs + rilpivirine*	ECHO/THRIVE (Rimsky 2013)	43/686	6.3%
2 NRTIs + efavirenz	ECHO/THRIVE (Rimsky 2013)	8/686	1.2%
2 NRTIs + doravirine	DRIVE (Molina 2018, Orkin 2019)	6/751	0.8%
2 NRTIs + raltegravir	ARDENT (Lennox 2014)	10/599	1.7%
TDF/FTC/elvitegravir/c	Pooled II-III (Margot 2016)	4/867	0.5%
TAF/FTC/elvitegravir/c	Pooled II-III (Margot 2016)	5/866	0.6%

* In persons with > 100,000 HIV RNA copies/mL, 10.7%; in others, 2.4%.

77%. This broad range was seen using the same combination in ART-naïve patients! The rates of adverse events also differed considerably. Heterogeneous patient populations and study designs (definition of therapy failure), clinician experience, and patient adherence may lead to variations (Hoffmann 2007).
The following is a more detailed discussion of the study data regarding the most critical first-line therapies. These include:

1. **Two NRTIs plus one NNRTI** (Delstrigo® and others).
2. **Two NRTIs plus one protease inhibitor** (Symtuza® and others)
3. **Two NRTIs plus one integrase inhibitor** (Biktarvy® and others)
4. **NRTI-reducing therapies** (Dovato® and others).
5. **Unfavorable first-line therapies that should be avoided**

1. Two NRTIs plus one NNRTI

The advantages of NNRTI-containing regimens are good long-term tolerability and lack of (or lesser) weight gain. The disadvantage, at least of rilpivirine, is the rapid development of resistance. This is why NNRTIs are generally no longer recommended as first-line therapy in some countries, such as the US. Allergies, typical in the past, have become less frequent with rilpivirine and doravirine.

Recommended combination

TDF/3TC/doravirine was approved as a fixed combination Delstrigo® in late 2018. In two partially double-blind randomized Phase III trials of first-line therapy, doravirine was comparable to or tended to outperform darunavir/r and efavirenz. In DRIVE-FORWARD, doravirine response was good, and resistance rates were low, even in high viremia or severe immunodeficiency. Overall tolerability was the same, including gastrointestinal side effects such as diarrhea or nausea. In contrast, the lipid profile was more favorable than with darunavir/r (Molina 2018+2020). In DRIVE-AHEAD, Delstrigo® was non-inferior to Atripla® as a fixed combination and was better tolerated overall, mainly due to fewer CNS side effects. Again, the lipid profile was more favorable than the comparator arm with efavirenz (Orkin 2019). Unlike rilpivirine, there are no food restrictions; however, because of TDF, caution is advised in patients with renal problems. In patients with no renal issues, we believe it is the first NNRTI choice in first-line therapy.

Alternatives

TAF/FTC or **TDF/FTC plus rilpivirine**, the fixed-dose combinations Eviplera® and Odefsey® (the latter containing TAF instead of TDF) have long been an important option. In large trials, they were comparably effective and better tolerated than

TDF/FTC and efavirenz, especially concerning lipids and CNS side effects (Molina 2011, Cohen 2012+2014). Neither Eviplera® nor Odefsey® have been tested in first-line therapy against PIs or INSTIs. The main disadvantage is the rapid development of resistance, often affecting rilpivirine and the NRTI backbone simultaneously. In the ECHO/THRIVE trials, the rate exceeded 10% in patients with high viremia (see Table 6.5). Thus, approval is limited to individuals with viral loads below 100,000 copies/mL. In our opinion, rilpivirine can only be considered in first-line therapy if viremia is very low (well below 10,000 copies/mL) and adherence is perfect. Why unnecessarily expose individuals to a risk of resistance? Rilpivirine is more suitable as maintenance therapy. A fat-containing meal of at least 400 calories is also mandatory for intake. Otherwise, absorption is poor – this is another problem for some people. Choosing other ART regimens for patients with chronic gastritis or long-term PPI co-medication is also preferable.

TDF/FTC/efavirenz or Atripla® was the first single-tablet regimen (STR) and has been used as the standard arm in countless trials. Generic STR regimens are now available. However, this combination has taken a back seat in recent years, mainly due to the CNS side effects typical of efavirenz. In our opinion, it no longer has any place in first-line therapy. The exception is when starting TB therapy simultaneously – in this setting, its use can still make sense.

TDF/FTC plus nevirapine was quite frequently used in the past. Generics are available in Europe, but no STR. The risk of resistance is substantial (Soriano 2011), as is the risk of allergy: like efavirenz, nevirapine no longer has a place in first-line therapy. On the other hand, nevirapine has been on the market since 1996. People who can tolerate it and who are adherent may stay on it. There is little data for TAF and nevirapine.

Reasons *for* NNRTI-containing regimens in first-line therapy

- Low viremia below 10,000 copies/mL, preferably lower (rilpivirine).
- No food restrictions (doravirine).
- High risk of interactions with co-medication, such as TBC (good data for efavirenz)
- Cardiovascular disease (favorable lipid profile for doravirine).

Reasons *against*

- High viremia (rilpivirine should be avoided at all costs).
- Pre-existing resistance or lack of resistance testing (in Europe, approx. 3–5% of all treatment-naïve patients have transmitted NNRTI resistance, in other countries even higher rates).
- Adherence problems, expected treatment interruptions.
- Irregular life or irregular food intake (rilpivirine).
- Chronic gastritis requiring PPI use (rilpivirine).

2. Two NRTIs plus one protease inhibitor

This combination is the only triple combination whose efficacy has been demonstrated by clinical endpoints in randomized trials (Hammer 1997, Cameron 1998, Stellbrink 2000). Symtuza®, the first PI-containing single-tablet regimen (STR), was approved in 2017. Given the high resistance barrier of boosted PIs, they remain attractive for first-line therapy, especially in highly viremic AIDS patients. Resistance among boosted PIs is virtually non-existent. The most important PI is darunavir. Atazanavir and lopinavir are still considered alternatives to some extent; all others no longer play a role. Lopinavir is co-formulated with ritonavir, and darunavir and atazanavir can also be boosted with cobicistat. Choosing the lower TAF dose of

10 mg is important for boosted PI regimens. Disadvantages of PI-containing first-line therapies include somewhat higher pill counts, at least for atazanavir and lopinavir, and often gastrointestinal side effects as well as an unfavorable lipid profile.

Recommended combination

TAF/FTC/darunavir/c (**Symtuza®**). Since February 2009, darunavir has been approved for first-line therapy and is now the only PI recommended in the guidelines. Darunavir has been available as a component of the STR Symtuza® since September 2017. Symtuza® has been successfully tested against TDF+FTC plus darunavir/c in treatment-naïve patients in the AMBER trial (Orkin 2019); comparisons against other approved STRs are not yet available. Most darunavir trials were conducted with ritonavir (rather than cobicistat), and TDF rather than TAF was mainly used in the backbone. Nevertheless, these data can likely apply to Symtuza® – it has already primarily supplanted all other PI regimens due to its simplicity (one tablet, with a meal). In AMBER, the TAF-containing STR Symtuza® was less nephrotoxic than TDF+FTC plus darunavir/c.

TDF/FTC plus darunavir/r was as effective and especially better gastrointestinally tolerated than TDF/FTC plus lopinavir/r in ARTEMIS (Orkin 2013). The lipid profile was better compared with lopinavir/r but less favorable compared with doravirine (Molina 2020). In two larger studies, gastrointestinal symptoms resulted in a slightly worse virologic outcome than with the INSTIs dolutegravir and raltegravir, respectively (Clotet 2014, Lennox 2014). Exanthem, usually moderate, may occur in about 5–10%; abacavir should be avoided in the backbone. Although dyslipidemias are mostly moderate, cohort studies suggest a slightly increased cardiovascular risk (Lundgren 2017).

The resistance barrier of darunavir is very high, and resistance is practically nonexistent in first-line therapy. Therefore, Symtuza® is an option, especially for highly viremic AIDS patients and in cases of doubtful adherence. It should be noted, however, that viremia often declines much more slowly than with INSTIs. Sometimes, it takes up to 6 months to get below 50 copies/mL. Other disadvantages, as with all boosted combinations, are potential interactions.

Alternatives

TDF/TAF+FTC plus atazanavir/c/r is not available as a fixed combination. Atazanavir is now only available generically; the original Reyataz® is off the market. The main drawback is hyperbilirubinemia. In ACTG 5257, atazanavir was inferior to darunavir because of this side effect (Lennox 2014). In two large trials WAVE and ARIA in treatment-naive women, this was also true compared to elvitegravir and dolutegravir (Squires 2016, Orrell 2017). Resistance, however, is a rarity. Atazanavir is the only PI for which boosting is not mandatory (Malan 2008, Squires 2009) – perhaps an advantage, although numerous limitations apply (no PPIs or resistance). The low-dose TAF (10 mg) must be used. In most countries, atazanavir is no longer part of any reasonable combination.

TDF/TAF+FTC plus lopinavir/r offer generics for these previously widely used regimens. However, following the results from ARTEMIS and ACTG 5142 (see above), they have been downgraded in many guidelines. Due to dyslipidemias (cardiovascular risk?), gastrointestinal side effects (diarrhea!), and pill count (four daily, plus backbone), they no longer play a role.

Reasons *for* Symtuza® in first-line therapy

- High viremia (PIs have a high resistance barrier!).
- Low CD4 T-cells, AIDS disease ("late presenter").
- Pre-existing resistance mutations (especially NNRTIs), lack of resistance testing.
- Unsteady adherence ("high forgiveness"), breaks in therapy.

Reasons *against*

- Interacting co-medication, e.g., chemotherapies, DAAs, but also some calcium antagonists, statins, etc.
- Use of party drugs (possible interactions).
- Cardiovascular history (elevated lipids, possibly slightly increased risk of myocardial infarction for darunavir).
- Gastrointestinal problems before ART initiation.
- If the viral load needs to be reduced very rapidly.

3. Two NRTIs plus one integrase inhibitor

Raltegravir was the first integrase strand transfer inhibitor (INSTI) approved for first-line therapy in 2009, and there are now four (the fifth, cabotegravir, is not licensed for first-line, see below). The second-generation INSTIs bictegravir and dolutegravir are strongly recommended, and raltegravir and elvitegravir are considered alternatives (Table 6.6). The tolerability and efficacy of these regimens are excellent; however, except for raltegravir, long-term data over more than ten years still need to be provided. In the PROPHET trial, 407 patients from 24 centers started ART for the first time in 2014/2015; the INSTI arm was recruited more than twice as fast as the PI and NNRTI arms combined (Wolf 2015). Besides good tolerability, one advantage of INSTI-based regimens is rapid viral load reduction, which is faster than with other classes. A disadvantage may be weight gain, which may be greater with dolutegravir and bictegravir than with first-generation INSTIs (Hester 2022).

Table 6.6: Factors influencing the selection of a specific INSTI-containing first-line therapy (the long-acting INSTI cabotegravir is approved only for pre-treated patients).

	Dolutegravir	Bictegravir	Elvitegravir	Raltegravir
Pill count plus NRTIs/day	1–2	1	1	3
Once a day?	yes	yes	yes	yes
Taking with a meal?	no	no	yes	no
Resistance risk	0%	0%	1%	1–2%
Interaction risk	low	low	high	very low
Most important side effect	Sleep disorders	Sleep disorders	Diarrhea, headache	?
Long-term experience, years	5–8	5	8–10	> 10
Preferred backbone	(ABC)+3TC	TAF+FTC	TAF+FTC	none
STR	Triumeq®, Dovato®	Biktarvy®	Genvoya®, Stribild®	–

Recommended combinations

TAF/FTC/bictegravir has rapidly become a major option in first-line therapy with the approval of the fixed combination Biktarvy® in June 2018. Biktarvy® was compared against dolutegravir in two large Phase III trials. In GS-1489, the

comparator was ABC/3TC/dolutegravir (Triumeq®), in GS-1490 it was TAF/FTC plus dolutegravir. In both studies, Biktarvy® was virologically non-inferior to comparator therapy at 96 weeks. There were few discontinuations and/or virologic failures and not a single case of resistance. The resistance barrier is expected to be similar to that of dolutegravir. Tolerability is good and slightly better compared to Triumeq®. In GS-1489, however, probably TAF versus abacavir made the difference; there seems to be virtually no difference between bictegravir and dolutegravir (Wohl 2018+2019, Stellbrink 2019). Nor, incidentally, with regard to the effect on bone, lipids, kidneys, and weight gain. In both studies, patients gained 4–5 kg in weight after 144 weeks (Orkin 2020). Neuropsychiatric side effects are also similarly common (Hoffmann 2020). Extensive studies in first-line therapy comparing INSTIs with PIs or NNRTIs are lacking. A disadvantage is that bictegravir is only available in a fixed combination.

ABC/3TC (or TAF/FTC, TDF/FTC) plus dolutegravir is an essential option in first-line therapy since the approval of dolutegravir in early 2014. The fixed combination ABC/3TC/dolutegravir (Triumeq®) was the first STR without tenofovir in mid-2014. As with all abacavir-containing regimens, prior HLA testing should be considered; if the decision is made to use tenofovir, the TAF dose of 25 mg should be selected. In comparison with other agents, dolutegravir-containing combinations always performed well. In the SINGLE trial, Triumeq® was more effective because it was more tolerable than Atripla® (Walmsley 2013). In SPRING-2, the non-inferiority of dolutegravir to raltegravir was demonstrated in a double-blind design (Raffi 2014). Impressively, data from the FLAMINGO trial showed not only a slightly better response than under a boosted PI regimen with darunavir but also no single resistance mutation appeared (Clotet 2014) – although neither did with darunavir – this trial set the bar very high for resistance. In the ARIA trial, dolutegravir showed better efficacy in women (Orrell 2017). In 1489/1490, it was equal to bictegravir (see above). The resistance barrier of dolutegravir is probably higher than that of first-generation INSTIs; however, it is also not unlimited and insufficient for monotherapies. Tolerability is good, and gastrointestinal side effects are rare. In about 5–6%, mild, reversible CNS side effects (sleep and other neurologic disturbances such as paresthesias, dizziness, and depression) with dolutegravir lead to discontinuation. The mechanism is unclear; dolutegravir probably penetrates the blood-brain barrier better than other INSTIs. In our experience, adverse events are more common in women, the elderly, and when abacavir is initiated concomitantly (Hoffmann 2017). In these, discontinuation rates are as high as 15%. The combination with TAF/FTC means two pills; moreover, because of the patent protection of TAF/FTC, over 300 euros in therapy costs more monthly.

Following the WHO recommendation 2021, TDF/FTC/dolutegravir ("TLD") has since become the most widely used HIV regimen in the world. In Europe, TLD is not available. Before considering TDF/FTC and dolutegravir, it may be wiser to use dolutegravir/3TC (see below).

Alternatives

TDF/FTC or TAF/FTC plus raltegravir have the most long-term experience; raltegravir was the first INSTI in 2007. In the first years, raltegravir was given twice daily only. In STARTMRK, raltegravir was at least as effective as efavirenz (Lennox 2010). Viral load decreased more rapidly, and CD4 T-cells increased more significantly. Moreover, tolerability was better, with effects lasting 196 weeks (Rockstroh 2011). Data on raltegravir to date are predominantly data on TDF-based NRTI backbones. However, a pilot study with ABC/3TC plus raltegravir did not show anything negative (Young 2010), so one is probably relatively free with the choice of NRTI. In SPRING-2, raltegravir was slightly weaker than dolutegravir. In the double-blind design in which

the NRTI backbone (TDF/FTC or ABC/3TC individually selected) was given open-label, about 5% fewer achieved a viral load below 50 copies/mL after 48 weeks (Raffi 2014). The resistance barrier is likely lower than for dolutegravir. In the three-arm, open-label ARDENT trial, raltegravir was superior to the PIs atazanavir/r and darunavir/r overall, but more resistance occurred (Lennox 2014). Resistance is expected to occur in 1–2% in first-line therapy, somewhat more frequently than with darunavir/r or second-generation INSTIs.

Raltegravir-based therapies are excellently tolerated. Discontinuations due to side effects are virtually non-existent. Another advantage is the very low interaction potential, which can be used with vulnerable co-medication (chemotherapies, tuberculostatics, etc.). The main disadvantage is the lack of an STR. Raltegravir is the only recommended substance yet to be given as a single agent. Until 2017, even single-dose administration was not possible (Eron 2011). With a new formulation, two tablets of 600 mg each have been possible since July 2017, allowing single-dose administration. The double-blind, randomized ONCEMRK trial demonstrated non-inferiority in 802 PLWH (Cahn 2017). Nevertheless, the "convenience disadvantage" remains: raltegravir plus NRTIs is three daily tablets.

TAF/FTC/elvitegravir/c: The fixed combination with TAF (Genvoya®), approved in January 2016, has largely displaced the old fixed combination with TDF (Stribild®). However, in most trials, elvitegravir/c was still combined with TDF; in two large Phase III trials, it was comparably effective to efavirenz or atazanavir over 144 weeks (Clumeck 2014, Wohl 2014) and even better than atazanavir in women in the WAVE trial (Squires 2016). Direct comparisons in first-line therapy with other INSTIs are lacking. Renal problems evident under Stribild® are no longer relevant under Genvoya® – there were significantly fewer renal and osseous side effects in two significant Phase III trials (Sax 2015). Genvoya® can also be dosed normally in moderate renal insufficiency (GFR up to 30 mL/min). Mild increases in creatinine due to inhibition of tubular secretion usually do not indicate renal dysfunction, but renal monitoring is more complicated. Other tolerabilities of either are good, with nausea, moderate headache, and mild diarrhea most likely to occur. Resistance is rare, although more common than with dolutegravir, occurring in about 1–2% and often affects two classes. In cases of poor adherence, Genvoya® should be avoided. Another (and probably the most relevant) disadvantage is the pharmacoenhancer cobicistat. Therefore, agents metabolized by CYP3A are contraindicated or should be used cautiously. This is a particular problem in the elderly with extensive co-medications. Bictegravir, which is also combined with TAF+FTC and does not require boosting, has already partially replaced elvitegravir. There is probably no future for Genvoya® in first-line therapy.

Rationale *for* INSTI regimens in first-line therapy

- High viremia, rapid viral load reduction required.
- Interaction-prone co-medications such as chemotherapies and tuberculostatics (especially raltegravir is suitable).
- Cardiovascular pre-existing conditions (favorable lipid profile).

Reasons *against*

- Pre-existing resistance (sporadic).
- High risk of interactions with co-medication (applies only to elvitegravir/c!).
- Renal insufficiency (more difficult monitoring with elvitegravir, dolutegravir, and bictegravir).
- Sleep disorders (dolutegravir, bictegravir).
- Planned pregnancy (especially for bictegravir, less experience than with other classes).

4. NRTI-sparing therapies

The fact that most classic ART regimens in the first line contain two NRTIs each as the backbone is historical. NRTIs were the first drugs on the market, and by the time NNRTIs and PIs were in development, treatment with two NRTIs was the standard. With growing knowledge of the high resistance barrier of modern agents, the omission of NRTIs is also being investigated in first-line therapy. In this so-called dual therapy, only one (or even no) NRTI is given – this is usually 3TC, as it is the least toxic and generically available. Dovato®, a dual therapy ("2DR"), was approved for the first time in 2019; since 2021, it has been recommended in the EACS guidelines for specific conditions and no longer only as an alternative (see below).

Recommended combination (as an alternative)

Dolutegravir/3TC: Dovato®, the fixed combination of dolutegravir and 3TC, became available in August 2019 as the first 2DR for treatment-naïve patients. It is licensed from 12 years of age (at least 40 kg), provided there is no resistance to INSTIs or 3TC, is based on the two GEMINI trials. These compared dolutegravir/3TC in a double-blind fashion with dolutegravir plus TDF/FTC in 1,433 patients with viral loads less than 500,000 copies/mL (Cahn 2019). At 96 weeks, 89% versus 86% were below the limit of detection, and at 144 weeks, 84% versus 82%. Non-inferiority was thus achieved. Virtually no resistance was seen in the few cases of treatment failure to date. Serious adverse events were equally frequent, with only a slight difference in "drug-related AEs" at 96 weeks (20% versus 25%) and in some renal and bone biomarkers. The fact that response rates were worse with low CD4 T-cells below 200 (79% versus 93% at 48 weeks, small case numbers) led to intensive research. Probably no trial in recent years was studied more closely than GEMINI. There were no differences at high viral loads, either in terms of blips or low viremia, even when measured with ultrasensitive assays (Li 2019). Viral shedding under Dovato® is virtually identical to a standard regimen in the first few weeks (Gillman 2019), both in plasma and semen (Charpentier 2019). Interestingly, even with poor adherence, the response was no worse than with triple therapy (Ait-Khaled 2021).

Overall, a relevant difference between 2DR and conventional regimens is rather unlikely. However, there are no clear advantages to report so far either. With the introduction of TAF, the need for 2DR has decreased. The EACS guidelines recommend the combination, limited to patients with less than 500,000 copies/mL, no HBsAg, and no history of PrEP. We use Dovato® relatively often, though rather infrequently as first-line. It would be nice if a study could show better tolerability compared to TAF-containing combinations. A lower weight gain under 2DR would be a start (up to now, no evidence supports this, however).

2-drug combinations or Dual therapy

In addition to dolutegravir plus 3TC, other 2DR regimens have been tried, mostly with moderate success. Moreover, the studies were often insufficiently powered.

Darunavir/r plus raltegravir: In NEAT001, 805 PLWH received either darunavir/r plus raltegravir or standard therapy of darunavir/r plus TDF/FTC (Raffi 2014). At 96 weeks, tolerability and virologic failure were approximately equal (19% versus 15%). However, a slight virologic disadvantage was seen with low CD4 T-cells and high viral load. Over 96 weeks, the cumulative risk of resistance for darunavir/r plus raltegravir was 3,9%. No resistance was observed in the standard arm (Lambert-Niclot 2016). Lipids were also slightly worse. Regarding renal and osseous side effects, Nuke-Sparing fared better in return (Bernadino 2015). The EACS guidelines briefly included darunavir/r plus raltegravir as an alternative first-line therapy in 2015, but this approach has since been removed. There is no argument for this 4-pill ART.

Lopinavir/r or darunavir/r plus 3TC: All the individual agents are generically available. The best data are available for lopinavir/r. For example, in the GARDEL trial, lopinavir/r+3TC was tested against lopinavir plus 2 NRTIs in 426 patients (Cahn 2014). After 48 weeks, 88% versus 84% were below 50 copies/mL in the dual arm (as high as 87% versus 79% in the high viral load arm) – more patients in the standard arm discontinued due to side effects. Lopinavir/r+3TC could save costs in resource-poor countries. For darunavir/r, there is only preliminary data (Sued 2017). In Europe, these combos do not make sense.

Darunavir/r plus maraviroc: Yielded disappointing results in the MODERN study (Stellbrink 2016). After 48 weeks, only 77% were below 50 copies/mL, compared to 87% in the standard arm with TDF/FTC plus darunavir/r. Especially at high viral loads, nuke sparing was clearly inferior (65% versus 80%). Although the results were independent of the tropism assay used, it is likely that tropism assay only sometimes provided valid results. Tolerability was comparable. Although resistance was mostly absent, this nuke-sparing strategy has no place in first-line therapy. It is weaker, after all, regardless of the reason.

Dual therapy in first-line therapy

- Sufficient data only for dolutegravir+3TC (Dovato®), which was tested against the triple combination containing TDF, not TAF.
- Dovato® is approved for first-line since 2019.
- It should not be used with patients with fewer than 200 CD4 T-cells or an HIV RNA greater than 500,000 copies/mL, with a history of HBsAg, or with previous PrEP use.
- Other dual therapies (with maraviroc or raltegravir) were somewhat weaker than standard therapies in some cases, especially in high viremia.
- So far, there is no evidence for better tolerability or any other relevant benefit in the long term.

5. Unfavorable first-line therapies that should be avoided

T-20, maraviroc, etravirine, and tipranavir are not approved for first-line therapy, nor is Juluca®. Toxic agents like AZT and ddI (withdrawn from the market) should also be avoided, as should old PIs such as fosamprenavir or saquinavir (QT prolongation!). Unfavorable combinations also include all monotherapies – and apart from Dovato®, all dual therapies. NRTIs should not compete for the same bases; two cytidine analogs (FTC+3TC) act antagonistically. TAF plus TDF is also nonsense, of course. Previously studied strategies such as "swing therapies" (changing regimen at regular intervals) or cautious "creep-in" (starting every other day or not with a complete combination) also make no sense in modern times and should be avoided.

Monotherapies: Mainly, PIs were tested. In MONARK, only 64% achieved a viral load below 50 copies/mL after 48 weeks on lopinavir/r (Ghosn 2010). Darunavir/r was also weak in a pilot study (Patterson 2009). For dolutegravir, there are isolated cases (Lanzafame 2017). In most cases, low viremia is measurable. Given the many well-tolerated combinations, this strategy has no rationale (Gallant 2017).

Induction therapies: Occasionally, even today, the question is raised as to whether more intensive approaches are necessary when the viral load is high. Given theoretical concerns for the rapid development of resistance, an "induction" of four or five drugs is then started, which is later de-escalated. The effect of this approach, however, has never been validated; a 2000–2016 meta-analysis showed no benefits (Feng 2016). More single agents do no good. Two PIs or NNRTIs each instead of one even had negative consequences. There is also no reason for three NRTIs instead of

two. ACTG 5095 showed no differences between Combivir® and Trizivir® in 765 patients on efavirenz (Gulick 2004). But maybe just more than two drug classes? The larger trials of three drug classes instead of two – mostly with outdated agents such as nelfinavir and ddI+d4T – found no benefits. The addition of raltegravir to conventional triple ART was of no benefit (Kityo 2019). This was also the case in at least two studies in which acutely infected individuals had their PI/r-based triple therapy intensified by maraviroc and raltegravir, respectively (Markovitz 2014, Chéret 2015). Induction therapies that only produce toxicity and cost should be avoided. Cases with multiple primary (transmitted) resistances are an exception.

Triple- or quadruple-nuke no longer have a place in first-line therapy. They are too toxic and less effective (Gulick 2004). Under AZT-free combinations such as TDF+3TC+ABC, there is also a risk of early virological treatment failure, probably due to low genetic resistance barrier (Gallant 2005, Khanlou 2005).

Easily avoidable errors in first-line therapy

- All monotherapy or dual therapy (except dolutegravir+3TC), but also a "gradual introduction" – always start with the full ART!
- T-20, tipranavir, etravirine, maraviroc, long-acting (not approved for first-line therapy).
- Old drugs: AZT, ddI, saquinavir, fosamprenavir, nevirapine.
- 3TC+FTC (antagonistic), TAF+TDF, Triple- or Quadruple-Nuke.
- Induction with more than 3 drugs, even with high viremia.
- Simultaneous initiation of abacavir, darunavir, and NNRTIs (allergy potential).

Literature

Ait-Khaled M, Sierra Madero J, Estrada V, et al. Impact of treatment adherence on efficacy of dolutegravir plus lamivudine and dolutegravir plus tenofovir disoproxil fumarate/emtricitabine: pooled analysis of the GEMINI-1 and GEMINI-2 clinical studies. HIV Res Clin Pract 2021, 23:9-14.

Behrens GM, Reiss P. Abacavir and cardiovascular risk. Curr Opin Infect Dis 2010, 23:9-14.

Bernardino JI, Mocroft A, Mallon PW, et al. Bone mineral density and inflammatory and bone biomarkers after darunavir-ritonavir combined with either raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults with HIV-1: a substudy of the NEAT001 randomised trial. Lancet HIV 2015, 2:e464-73.

Bhagwat P, Ofotokun I, McComsey GA, et al. Changes in Waist Circumference in HIV-Infected Individuals Initiating a Raltegravir or Protease Inhibitor Regimen: Effects of Sex and Race. Open Forum Infect Dis 2018, 5:ofy201.

Borges ÁH, Lundh A, Tendal B, et al. Nonnucleoside Reverse-transcriptase Inhibitor- vs Ritonavir-boosted Protease Inhibitor-based Regimens for Initial Treatment of HIV Infection: A Systematic Review and Metaanalysis of Randomized Trials. Clin Infect Dis 2016, 63:268-80.

Cahn P, Andrade-Villanueva J, Arribas JR, et al. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48-week results of the randomised, open-label, non-inferiority GARDEL trial. Lancet Infect Dis 2014, 14:572-80.

Cahn P, Kaplan R, Sax PE, et al. Raltegravir 1200 mg once daily versus raltegravir 400 mg twice daily, with TDF and emtricitabine, for previously untreated HIV-1 infection: a randomised, double-blind, parallel-group, phase 3, non-inferiority trial. Lancet HIV 2017, 4:e486-e494.

Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48. Lancet 2019, 393:143-155.

Cahn P, Madero JS, Arribas JR, et al. Durable Efficacy of Dolutegravir Plus Lamivudine in Antiretroviral Treatment-Naive Adults With HIV-1 Infection: 96-Week Results From the GEMINI-1 and GEMINI-2 Randomized Clinical Trials. J AIDS 2019 Dec 10.

Cahn P, Sierra Madero J, Arribas JR, et al. Three-year durable efficacy of dolutegravir plus lamivudine in antiretroviral therapy – naive adults with HIV-1 infection. AIDS 2022; 36:39-48.

Calmy A, Tovar Sanchez T, Kouanfack C, et al. Dolutegravir-based and low-dose efavirenz-based regimen for the initial treatment of HIV-1 infection (NAMSAL): week 96 results from a two-group, multicentre, randomised, open label, phase 3 non-inferiority trial in Cameroon. Lancet HIV. 2020 Oct;7(10):e677-e687.

Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. Lancet 1998, 351:543-9.

Charpentier C, Peytavin G, Burdet C, et al. Seminal HIV-1 RNA and drug concentrations in DTG+3TC dual therapy (ANRS167 LAMIDOL). MOPEB268, IAS 2019, Mexico City.

Chéret A, Nembot G, Mélard A, et al. Intensive five-drug antiretroviral therapy regimen versus standard triple-drug therapy during primary HIV-1 infection (OPTIPRIM-ANRS 147): a randomised, open-label, phase 3 trial. Lancet Infect Dis 2015, 15:387-96.

Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet 2014, 383:2222-31.

Cohen C, Molina J, Cahn P, et al. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naïve, HIV-1-infected patients: Pooled results from the phase 3 double-blind, randomized ECHO and THRIVE trials. JAIDS. 2012 Feb 16.

Cohen C, Wohl D, Arribas JR, et al. Week 48 results from a randomized clinical trial of rilpivirine/emtricitabine/tenofovir disoproxil fumarate vs. efavirenz/emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV-1-infected adults. AIDS 2014, 28:989-97.

Daar ES, Tierney C, Fischl MA, et al. Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1. Ann Intern Med 2011, 154:445-56.

EACS: Guidelines for the clinical management and treatment of HIV-infected adults in Europe. October 201520172019. http://www.eacs.eu.

Eron J, Hung CC, Baril JG, et al. Virologic Response by Baseline Viral Load With Dolutegravir Plus Lamivudine vs Dolutegravir Plus Tenofovir Disoproxil Fumarate/Emtricitabine: Pooled Analysis. J Acquir Immune Defic Syndr. 2020 Jan 16.

Eron JJ Jr, Rockstroh JK, Reynes J, et al. Raltegravir once daily or twice daily in previously untreated patients with HIV-1: a randomised, active-controlled, phase 3 non-inferiority trial. Lancet Infect Dis 2011, 11:907-15.

Feng Q, Zhou A, Zou H, et al. Quadruple versus triple combination antiretroviral therapies for treatment naive people with HIV: systematic review and meta-analysis of randomised controlled trials. BMJ 2019, 366:l4179.

Gallant J, Sugarman J. Dolutegravir monotherapy: when should clinical practice be clinical research? Antivir Ther 2017, 22:93-95.

Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. J Infect Dis 2005, 192:1921-30.

Ghosn J, Flandre P, Cohen-Codar I, et al. Long-term (96-week) follow-up of antiretroviral-naïve HIV-infected patients treated with first-line lopinavir/ritonavir monotherapy in the MONARK trial. HIV Med 2010, 11:137-42.

Gillman J, Janulis P, Gulick R, et al. Comparable viral decay with initial dolutegravir plus lamivudine versus dolutegravir-based triple therapy. J Antimicrob Chemother 2019, 74:2365-2369.

Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. N Engl J Med. 2004, 350:1850-1861.

Gupta R, Hill A, Sawyer AW, Pillay D. Emergence of drug resistance in HIV type 1-infected patients after receipt of first-line highly active antiretroviral therapy: a systematic review of clinical trials. Clin Infect Dis 2008, 47:712-22.

Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with HIV infection and CD4 cell counts of 200 per cubic millimeter or less. N Engl J Med 1997, 337: 725-33.

Haubrich RH, Riddler SA, DiRienzo AG, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. AIDS 2009, 23:1109-18.

Hester EK, Greenlee S, Durham SH. Weight Changes With Integrase Strand Transfer Inhibitor Therapy in the Management of HIV Infection: A Systematic Review. Ann Pharmacother 2022, 8:10600280211073321.

Hoffmann C, Schewe K, Fenske S, et al. Short-term neuropsychiatric tolerability of bictegravir combined with emtricitabine/tenofovir alafenamide in clinical practice. Antivir Ther 2020, 25:83-90.

Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med 2017, 18:56-63.

Hoffmann C, Wolf E. Pitfalls of cross-trial comparisons: a systematic review of randomized clinical trials using zidovudine, lamivudine and efavirenz in treatment naive HIV infected patients. Abstract P7.9/05, 11th EACS 2007, Madrid.

Kelesidis T, Tran TTT, Brown TT, et al. Changes in plasma levels of oxidized lipoproteins and lipoprotein subfractions with atazanavir-, raltegravir-, darunavir-based initial antiviral therapy and associations with common carotid artery intima-media thickness: ACTG 5260s. Antivir Ther 2017, 22:113-26.

Khanlou H, Yeh V, Guyer B, Farthing C. Early virologic failure in a pilot study evaluating the efficacy of once-daily abacavir, lamivudine, and tenofovir in treatment-naive HIV-infected patients. AIDS Pat Care STD 2005, 19:135-40.

Kityo C, Szubert AJ, Siika A, et al. Raltegravir-intensified initial antiretroviral therapy in advanced HIV disease in Africa: A randomised controlled trial. PLoS Med 2018, 15:e1002706.

Lambert-Niclot S, George EC, Pozniak A, et al. Antiretroviral resistance at virological failure in the NEAT 001/ANRS 143 trial: raltegravir plus darunavir/ritonavir or tenofovir/emtricitabine plus darunavir/ritonavir as first-line ART. J Antimicrob Chemother 2016, 71:1056-62.

Lanzafame M, Nicolè S, Gibellini D, et al. Dolutegravir monotherapy in HIV-infected naive patients with an HIV-RNA load <100 000 copies/mL: a medium-term follow-up. J Antimicrob Chemother 2017, 72:2136-2138.

Lennox JL, Dejesus E, Berger DS, et al. Raltegravir versus Efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. J AIDS 2010, 55:39-48.

Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet 2009; 374:796-806.

Lennox JL, Landovitz RJ, Ribaudo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. Ann Intern Med 2014, 161:461-71.

Li JZ, Sax PE, Marconi VC, et al. No Significant Changes to Residual Viremia After Switch to Dolutegravir and Lamivudine in a Randomized Trial. Open Forum Infect Dis 2019, 11;6:ofz056.

Llibre JM, Álvarez H, Yzusqui M. Clinical Impact of Virological Failure and Resistance Analysis Definitions used in Pivotal Clinical Trials of Initial Antiretroviral Treatment: A Systematic Review. AIDS Rev 2018, 20:158-170.

Llibre JM, Pulido F, García F, et al. Genetic barrier to resistance for dolutegravir. AIDS Rev 2015, 17:56-64.

Lundgren J, Mocroft A, Ryom L. Contemporary protease inhibitors and cardiovascular risk. Curr Opin Infect Dis. 2017 Dec 9.

Malan DR, Krantz E, David N, et al. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naive patients. J AIDS 2008, 47:161-7.

Margot NA, Kitrinos KM, Fordyce M, et al. Rare emergence of drug resistance in HIV-1 treatment-naïve patients after 48 weeks of treatment with elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. HIV Clin Trials 2016, 17:78-87.

Markowitz M, Evering TH, Garmon D, et al. A randomized open-label study of 3- versus 5-drug-combination antiretroviral therapy in newly HIV-1-infected individuals. J Acquir Immune Defic Syndr 2014, 66:140-7.

Markowitz M, Nguyen BY, Gotuzzo E, et al. Sustained antiretroviral effect of raltegravir after 96 weeks of combination therapy in treatment-naive patients with HIV-1 infection. J AIDS 2009, 52:350-6.

McComsey GA, Moser C, Currier J, et al. Body Composition Changes After Initiation of Raltegravir or Protease Inhibitors: ACTG A5260s. Clin Infect Dis 2016, 62:853-62.

Mills A, Mildvan D, Podzamczer D, et al. Maraviroc once-daily nucleoside analog-sparing regimen in treatment-naive patients: randomized, open-label pilot study. J AIDS 2013, 62:164-70.

Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. Lancet 2008, 372:646-655.

Molina JM, Cahn P, Grinsztejn B, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. Lancet 2011, 378:238-46.

Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial. Lancet HIV 2020, 7:e16-e26.

Molina JM, Squires K, Sax PE. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV 2018, 5:e211-e220.

Ofotokun I, Na LH, Landovitz RJ, et al. Comparison of the metabolic effects of ritonavir-boosted darunavir or atazanavir versus raltegravir, and the impact of ritonavir plasma exposure: ACTG 5257. Clin Infect Dis 2015, 60:1842-51.

Orkin C, DeJesus E, Khanlou H, et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naïve patients in the ARTEMIS trial. HIV Med 2013, 14:49-59.

Orkin C, Eron JJ, Rockstroh J, et al. Week 96 results of a phase 3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naïve HIV-1 patients. AIDS 2019 Dec 10.

Orkin C, DeJesus E, Sax PE, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials. Lancet HIV 2020, 7:e389-e400.

Orkin C, Squires KE, Molina JM, et al. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate is Non-inferior to Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Treatment-naive Adults With HIV-1 Infection: Week 48 Results of the DRIVE-AHEAD Trial. Clin Infect Dis 2019, 68:535-544.

Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA).: week 48 results from a randomised, open-label, non-inferiority, phase 3b study. Lancet HIV 2017, 4:e536-e546.

Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. J AIDS 2010, 55:49-57.

Punekar YS, Radford M, Parks D, et al. Is DTG+3TC and DTG+RPV effective and safe in clinical practice? Evidence from real world data. MOPEB267, IAS 2019, Mexico City.

Raffi F, Babiker AG, Richert L, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir–emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ ANRS143 randomised non-inferiority trial. Lancet 2014, Aug 5, epub ahead of print.

Rimsky L, Van Eygen V, Hoogstoel A, et al. 96-Week resistance analyses of rilpivirine in treatment-naive, HIV-1-infected adults from the ECHO and THRIVE Phase III trials. Antivir Ther 2013, 18:967-77.

Rockstroh JK, DeJesus E, Henry K, et al. A randomized, double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/TDF vs ritonavir-boosted atazanavir plus coformulated emtricitabine and TDF for initial treatment of HIV-1 infection: analysis of week 96 results. J AIDS 2013, 62:483-6.

Rockstroh JK, Dejesus E, Lennox JL, et al. Durable Efficacy and Safety of Raltegravir Versus Efavirenz When Combined With Tenofovir/Emtricitabine in Treatment-Naive HIV-1-Infected Patients: Final 5-Year Results From STARTMRK. J AIDS 2013, 63:77-85.

Saberi P, Phengrasamy T, Nguyen DP. Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: a review of pharmacokinetics, case reports and clinical management. HIV Med 2013, 14:519-29.

Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet 2015, 385:2606-15.

Soriano V, Arastéh K, Migrone H, et al. Nevirapine versus atazanavir/ritonavir, each combined with tenofovir disoproxil fumarate/emtricitabine, in antiretroviral-naive HIV-1 patients: the ARTEN Trial. Antivir Ther 2011, 16:339-48.

Squires K, Kityo C, Hodder S et al. Integrase inhibitor versus protease inhibitor based regimen for HIV-1 infected women (WAVES): a randomised, controlled, double-blind, phase 3 study. Lancet HIV 2016, 3:e410-e420.

Squires KE, Young B, Dejesus E, et al. Similar efficacy and tolerability of atazanavir compared with atazanavir/ritonavir, each with abacavir/lamivudine after initial suppression with abacavir/lamivudine plus ritonavir-boosted atazanavir in HIV-infected patients. AIDS 2010, 24:2019-27.

Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. NEJM 1999, 341:1865-73.

Stellbrink HJ, Arribas JR, Stephens JL, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection. Lancet HIV 2019;6:e364-e372.

Stellbrink HJ, Hawkins DA, Clumeck N, et al. Randomised, multicentre phase III study of saquinavir plus zidovudine plus zalcitabine in previously untreated or minimally pretreated HIV-infected patients. Clin Drug Invest 2000, 20:295-307.

Stellbrink HJ, Le Fevre E, Carr A, et al. Once-daily maraviroc versus tenofovir/emtricitabine each combined with darunavir/ritonavir for initial HIV-1 treatment. AIDS 2016; 30:1229-38.

Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. Clin Infect Dis 2010, 51:963-72.

Sued O, Figueroa MI, Gun A, et al. Dual therapy with darunavir/ritonavir plus lamivudine for HIV-1 treatment initiation: week 24 results of the randomized ANDES study. Abstract MOAB0106LB. 9tth IAS 2017, Paris.

van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. AIDS 2003, 17:987-99.

Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. NEJM 2019, 381:803-815.

Walmsley SL, Antela A, Clumeck N, et al; SINGLE Investigators. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med 2013, 369:1807-18.

Wohl D, Clarke A, Maggiolo F, et al. Patient-Reported Symptoms Over 48 Weeks Among Participants in Randomized, Double-Blind, Phase III Non-inferiority Trials of Adults with HIV on Co-formulated Bictegravir, Emtricitabine, and Tenofovir Alafenamide versus Co-formulated Abacavir, Dolutegravir, and Lamivudine. Patient 2018, 11:561-573.

Wohl DA, Cohen C, Gallant JE, et al. A randomized, double-blind comparison of STR elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. J AIDS 2014;65:e118-e120.

Wohl DA, Yazdanpanah Y, Baumgarten A, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet HIV 2019;6:e355-e363.

Wolf E, Schewe K, Klauke S, et al. First-line antiretroviral therapies in HIV-infected patients in Germany: Treatment decisions in the PROPHET study. 15th EACS 2015, Barcelona.

Young B, Vanig T, Dejesus E, et al. A pilot study of abacavir/lamivudine and raltegravir in antiretroviral-naïve HIV-1-infected patients: 48-week results of the SHIELD trial. HIV Clin Trials 2010, 11:260-9.

5.7. Management of side effects

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The first generation of antiretroviral therapies has come and gone. AZT, d-drugs, efavirenz, nevirapine, or most PIs are hardly or not used anymore. Modern therapies are much better tolerated. Adverse drug reactions, which used to require a change in almost half of the patients, have become considerably less important. On the other hand, the choice has increased, and there is greater flexibility in responding to mild side effects or those for which a relationship is questionable. In European cohorts, the rate of side effect-related treatment modifications is around 20–25% after one year, with a recent slight downward trend (Helleberg 2012, Pantazis 2015). On the other hand, some side effects become apparent only after approval – think of lipodystrophy, neuropsychiatric events, or weight gain. In addition, there is concern about long-term toxicities.

Switching due to acute adverse events

It is not always necessary to change ART immediately. Gastrointestinal side effects in the first weeks are not dangerous, can be treated well, and often improve. This is also true for mild CNS disturbances under INSTIs. For mild allergies, one can also wait on antihistamines. However, ART must be changed rapidly for some problems (see box).

Side effects that usually require discontinuation/switch

- Severe diarrhea persisting despite loperamide (lopinavir, darunavir, less pronounced other PIs, but also elvitegravir, dolutegravir).
- Severe nausea (most likely AZT, rarely TDF).
- Persistent sleep disturbances and other neuropsychiatric events (efavirenz, but also dolutegravir, bictegravir).
- Polyneuropathies (formerly d-drugs, regression often very slow).
- Severe anemias (AZT).
- Progressive muscle weakness, pancreatitis (formerly d-drugs, now rare).
- Lactic acidosis (formerly d4T+ddI, now very rare).
- Severe allergies with mucosal involvement and/or fever (most likely ABCs, NNRTIs, less commonly fosamprenavir, darunavir).
- Renal failure (TDF).
- Severe osteoporosis, osteomalacia (TDF, all PIs).
- QT prolongations (saquinavir, also rilpivirine, in principle many others).
- Hepatotoxicity with transaminases > 100 U/l (nevirapine, tipranavir).
- Manifest icterus (nevirapine, atazanavir, tipranavir).
- Rhabdomyolysis (raltegravir).
- Depression, psychosis (efavirenz, possibly also dolutegravir).

Switching due to side effects on virologically successful ART is usually straightforward. The suspected drug is replaced by another from the same class. It becomes more complex, however, if other drugs are contraindicated or resistant. Especially in complex cases with often more than 20 years of previous therapy, decisions can only be made on an individual basis. In some centers, therefore, "switch consultation rounds" have been established, in which complex cases are discussed jointly by virologists (who usually know what might make sense in the specific resistance situation) and clinicians (who usually know what does not make sense in any particular case).

Switch due to potential long-term toxicity

Virologically successful and well-tolerated combinations have been (and still are) often switched due to concern for potential long-term toxicities such as lipodystrophy or renal or bone problems. Unfortunately, in many cases, the evidence for any benefit of a treatment switch is poor, and switching is just done to do something. Although the complaints of the patient cannot be attributed to a specific agent (classic examples: fatigue syndrome, loss of libido or weight gain, etc.), ART is modified anyway, according to the slogan, "If it gets better, we were right, if not, we can switch back again".

The many switch studies conducted in the past decade prove that the market is very competitive. Every company is trying to bring its products to market with the broadest possible license, including both naïve and the larger group of pre-treated patients. As a result, huge switch studies are designed in which patients are switched to the company's own drug immediately or later. The efforts are enormous, but the information value remains often limited. In most studies, patients are on successful ART regimens before switching. Simply showing that a new therapy is not virologically inferior is not a convincing reason to switch.

In open-label randomized trials, it should be noted that all participants (and their treating physicians) are influenced by the current setting and access to ART. The larger the options outside the trial, the more likely even moderate side effects play a role. Who wants to take an "old" combination today, especially in a clinical trial? If a patient is then randomized to the efavirenz arm or the arm with "continuation of the old combination" and not to the new fancy STR, the switch is made quickly if there are only moderate CNS problems – and already the discontinuation rates of the old combination are rising, while the new preparation is doing well. One example is efavirenz, which was used as a comparator arm for many years: the discontinuation rates have sharply risen in recent years. If, on the other hand, new side effects occur with the new preparation, the manufacturers like to argue that a certain percentage of patients can always be expected to develop problems after a switch. Cleverly launched "reviews" financed by the industry suggest that one should "proactively" think about "contemporary" treatment changes – without it being clear why. Keeping one's head clear in this setting is not always easy.

Again, simply showing that a new therapy is not virologically inferior in successfully treated patients is no longer sufficient today. The more important questions are actually, "What is the benefit to switching?", "Are there data on long-term toxicity? Is there any argument for switching in the long run?", "Who should not switch, when is the risk too high?", "How relevant are the prior therapies?" Unfortunately, these questions are either not answered at all or only partially.

Overall, continuing a virologically successful, well-tolerated ART is not malpractice. Nevirapine still has its fans. Not everyone needs to switch to a new, expensive STR. The most important recent switch studies are discussed below. A particular focus will be on what is improved by such strategic switches.

Replacement of the protease inhibitor

PIs undoubtedly have some potential for long-term side effects. The often significant dyslipidemias could increase cardiovascular risk in the long term. Insulin resistance cases of diabetes mellitus have been described. Lipodystrophy has also long been attributed to PIs. However, whether it is due to PIs has been increasingly questioned recently (McComsey 2016). Interestingly, excessive weight gain is also significantly more common among INSTIs than PIs (see below).

Table 7.1: Randomized studies on protease inhibitor replacement (selection).

Study (reference)	n	Last ART	Significant effect of the switch
INSTIs			
SWITCHMRK (Eron 2010)	702	100% LPV/r	Switch to raltegravir (NRTIs same): AEs same (rare), lipids better. Study was prematurely terminated (more VF with RAL).
STRATEGY-PI (Arribas 2014)	443	40% ATV/r 40% DRV/r	Switch to elvitegravir (Stribild®): AEs same (including diarrhea), lipids slightly better (triglycerides), slight creatinine increase.
NEAT022 (Gatell 2017)	415	51% DRV/r 37% ATV/r	Switch to dolutegravir (NRTIs same): DR-AEs more frequent (13% vs 7%, mostly mild), lipids better, GFR slightly worse, more weight gain.
GS-1878 (Daar 2018)	578	48% DRV/r 36% ATV/r	Switch to TAF/FTC/bictegravir (Biktarvy®): DR-AEs more frequent (19% vs. 2%, mostly mild), lipids little changed, GFR slightly worse.
NNRTIs			
SPIRIT (Palella 2014)	476	37% ATV/r 33% LPV/r	Switched to rilpivirine (Eviplera®): AEs overall same (but 7 vs. 0 discontinuations), lipids significantly better.
DRIVE-SHIFT (Johnson 2019)	670	37% DRV/r 22% ATV/r	Switch to doravirine (Delstrigo®): DR-AEs more frequent (22% vs. 2%), mostly mild, lipids better*.
Maraviroc			
MARCH (Pett 2016)	395	35% ATV/r 28% LPV/r	Switch to maraviroc (NRTIs same): Lipids better, bone mineral density slightly better.

All studies were randomized open-label against continuation of PI. Where available, 48-week data are shown. All patients had been on PIs for several months at the switch time point and had a viral load below the detection limit. VF = Virologic Failure. DR AEs = Drug-related Adverse Events. PI/r can also mean PI/c. *29 were on non-PI regimens at baseline.

The study situation on replacing a virologically successful PI with other classes currently provides the following picture: it is largely virologically safe for INSTIs and NNRTIs if the viral load was previously constantly suppressed and no resistance exists (Table 7.1). Lipids are almost always favorably affected by the replacement of the PI, although the backbone also plays specific roles: TDF has a favorable effect, TAF none. In lipodystrophy, the effects of PI replacement are weaker and less well characterized so far. In other respects, too, one should not expect too much benefit. INSTIs are not always better tolerated; in NEAT22 or GS-1878, more subjective side effects occurred under dolutegravir or bictegravir, respectively. This also applies to doravirine. Replacing the PI can also pose virologic risks, especially with long-term pre-treatment. This was the bitter experience MSD made with raltegravir in 2010 in the SWITCHMRK trials (Eron 2010). A total of 702 PLWH on stable lopinavir/r therapy were randomized to switch to raltegravir or continue lopinavir/r. Inclusion criteria were not very strict; the only requirement was a viral load below 50 copies/mL with at least three months of lopinavir/r therapy. After 24 weeks, only 82% remained below 50 copies/mL with raltegravir, compared with 88% with continued PI. The study was terminated early. Breakthroughs were primarily seen in pre-treated patients with prior treatment failure. Unfortunately, data on resistance, type, and duration of pre-treatment were unavailable; the study was designed somewhat naively. Although the experience could not be replicated in a small Spanish study (Martinez

2010), something stuck after SWITCHMRK. Companies became more cautious. Since then, in studies similar to STRATEGY-PI and switch studies with STRs (see below), patients with previous failure have been consistently excluded, i.e., often precisely those in whom it would have been interesting to see whether the PI is necessary.

Replacement of NNRTIs

The first-generation NNRTIs nevirapine and especially efavirenz, have some side effects. In GS-1160, patients switched from TDF/FTC/efavirenz (Atripla®) to TAF/FTC/rilpivirine (Odefsey®); the switch was safe, but the other effects were moderate. Interestingly, GFR decreased, but less proteinuria and increased bone density were measured. Lipids remained very similar (positive effect of switching efavirenz to rilpivirine, adverse effect of TAF instead of TDF). If switching to rilpivirine is not desired because of dietary restrictions, doravirine may be an option. However, in DRIVE-SHIFT, only a subgroup of around 100 patients was on older NNRTIs (mainly efavirenz), and the switch remained without any changes (Johnson 2019).

A switch to INSTIs may also be considered. In STRATEGY-NNRTI, 439 patients either remained on their NNRTI therapy (mostly efavirenz) or switched to Stribild®, the co-formulation of TDF/FTC/elvitegravir/c. The CNS side effects seen with efavirenz improved, and virologic control persisted (Pozniak 2014). The latter was also true for patients in STRIVING (Trottier 2017), who had switched from mostly NNRTI-based regimens to ABC/3TC/dolutegravir (Triumeq®). However, adverse events occurred more frequently in the switch arms in both studies. For elvitegravir/c, these were headaches and nausea; for dolutegravir, they were primarily CNS problems. Again, it became clear that well-tolerated NNRTI regimens do not need to be switched.

Replacement of NRTIs (with each other)

Thymidine analogs such as d4T and AZT thought to play a leading role in mitochondrial toxicity, should be replaced by other NRTIs. d4T and ddI no longer have any place in HIV therapy, and their distribution has been discontinued. Lipoatrophy improves by switching to TDF or abacavir, as well as lipids, to a large extent (review: Curran 2011). In particular, subcutaneous adipose tissue in arms and legs increases, although the improvements are often not visible and only detectable in DEXA scans. The situation is also evident for AZT: it should be replaced whenever possible, and lipoatrophy should be improved (Ribera 2013).

What about TDF? It appears to have a direct lipid-lowering effect. In the double-blind, randomized ACTG A5206 trial, simply adding TDF to ongoing ART improved lipids versus placebo (Tungsiripat 2010). This was also the case in randomized trials when switching from ABC+3TC to TDF+FTC, both in patients on PIs (Behrens 2012) and efavirenz (Moyle 2015). The cause of the lipid-lowering effect remains unclear, however. A negative effect of switching to TDF is a reduction in bone density (McComsey 2011, Haskelberg 2012, Rasmussen 2012), which improves after replacement of TDF (Bloch 2014). The potential nephrotoxicity of TDF should also be noted. With TAF, at least the renal problems are obsolete. In several studies, switching from TDF to TAF was favorable regarding osseous and renal problems in patients with and without renal insufficiency (Mills 2016, Pozniak 2016). However, lipid-lowering effects are no longer present with TAF; in one study, lipids increased significantly after switching from TDF to TAF (Mills 2016). In GS-1717, a large double-blind, randomized trial, switching from abacavir to TAF (unlike TDF) did not affect lipids or renal and bone biomarkers (Winston 2018). Weight gain with TAF is discussed, and an analysis of multiple studies found a significant effect (DeJesus 2019). However, it is debated whether TAF merely lacks TDF's, catabolic effect (which would also need to be proven).

Switching to triple-nuke combinations containing tenofovir should be avoided for virologic reasons alone; the risk of virologic treatment failure is too high (see below).

Switch due to (potential) side effects: What do we know?

- Virological control is almost always maintained.
- Risk of virological failure may be higher with a long treatment history, with resistance in the NRTI backbone, especially with regimens with lower resistance barriers (raltegravir).
- In PI replacement, lipids improve after switching to rilpivirine, INSTIs, or maraviroc, but the clinical relevance of these changes remains unclear.
- It is unclear whether lipodystrophy also gets better (probably not).
- New drugs are not always better; there is a risk of "new" (usually mild) side effects.
- Most agents can be replaced by agents of the same class if mutations are absent.
- Other NRTIs should replace AZT due to its toxicity.
- Lipids are improved after replacing ABC with TDF (but not TAF).
- Replacing TDF with TAF or ABC improves renal function and mitigates the adverse effects on bone density.

Side effects, classified by organ system

In the following, a practice-oriented overview will be given, which mainly discusses the consequences with regard to ART. For space reasons, the often remarkably detailed recommendations on management that go beyond ART modifications are omitted. The box summarizes the most important things.

Side effects of modern ART, management at a glance

- **Dyslipidemia:** Replace PIs and efavirenz if possible, preferably use unboosted ART plus statins, consider TDF instead of TAF, possibly also metformin (caveat: dolutegravir), strict LDL target values as in HIV-negative patients (maybe even lower).
- **Gastrointestinal:** Nausea almost only with AZT, diarrhea mostly with PIs and elvitegravir. ART change is better than symptomatic treatment (loperamide if necessary).
- **Weight gain:** all INSTIs (mostly dolutegravir, bictegravir), but maybe also TAF. Women and blacks are more affected, and the effect of ART switch is still unclear/unproven.
- **Skin:** Consider allergies with NNRTIs, darunavir/r, and abacavir (HLA typing obligatory!) in the first weeks; no prophylaxis is beneficial, and simultaneous start is not recommended.
- **Cardiovascular:** myocardial infarctions due to abacavir, possibly PIs. Consider other regimens if patients are at high risk (the higher, the more urgent).
- **Bone:** osteoporosis, osteomalacia with TDF, PIs. If there is evidence or risk for osteoporosis, replace if possible! Use vitamin D; if necessary, also biphosphonates.
- **Liver:** transaminases mainly elevated with nevirapine, tipranavir, less frequently all other ARVs (caveat: viral hepatitis, common among MSM!). Bilirubin elevated with atazanavir, GGT with nevirapine.
- **Lipodystrophy:** old NRTIs, old PIs. Resolves slowly, incomplete. In case of severe lipoatrophy, Sculptra®.
- **Kidney:** TDF!, especially in combination with boosted PIs. Caveat: creatinine elevation under INSTIs (inhibition of secretion).
- **Neuropsychiatric:** efavirenz, but also less pronounced, dolutegravir, bictegravir (mainly sleep disorders, but various clinical manifestations).

Lipid metabolism disorders

Hyperlipidemias are common, especially on boosted PIs (especially lopinavir/r), triglycerides, and triglyceride-rich lipoproteins (VLDL) increase, accompanied by LDL elevations (Carr 1998, Maggi 2017). This is often compounded by hyperinsulinemia and insulin resistance. The mechanism is multifactorial and due to both inhibition of the GLUT4 transporter and increased ApoB release with increased free fatty acid turnover and lipolysis (Liang 2001). Darunavir or atazanavir have significantly fewer metabolic side effects than old PIs (Spinner 2016). Dyslipidemias are also typical under efavirenz; it should be replaced by other NNRTIs or INSTIs. In contrast, (moderate) lipid-lowering effects are observed with TDF but not with TAF (Santose 2019, Milinkovic 2019). Standard scoring systems (Procam or Framingham) should be used for cardiovascular risk evaluation. If glucose levels are elevated, HbA1c should be determined.

If the ten-year cardiovascular risk is above 10%, diet, exercise, and replacement of the PI (see above) should be discussed. Of course, smoking must also be discussed (Petoumenos 2016).

The threshold values are stricter than previously defined. The EACS guidelines (2019) recommend LDL levels of < 80 mg/dl and even < 55 mg/dl in secondary prevention, high-risk, and/or diabetes mellitus. Admittedly, this is usually not achievable without statins. Rosuvastatin or atorvastatin are preferable to others; caution is advised because of interactions, especially if the PI or a booster must remain in the ART regimen (choose the lowest statin doses). Statins may be of even higher benefit in PLWH than in HIV-negative people.

Table 7.2: Options for HIV-associated lipodystrophy and metabolic complications.

General measures (adjust diet, physical activity, nicotine cessation).
Switching ART – replacement of PIs, efavirenz, old NRTIs, TDF instead of TAF?
Statins, e.g., atorvastatin or rosuvastatin (generics!), preferably without booster ART (also consider Genvoya®) because of interactions.
Metformin (generic) – caution with dolutegravir (choose lower metformin doses).
Surgical procedures in cases of severe lipodystrophy.

Metformin (2 x 500–1,000 mg daily) showed a positive effect on insulin resistance in two studies and a tendency to reduce intra-abdominal (but subcutaneous) adipose tissue. In addition, it can reverse muscular adiposity when taken together with endurance training. Interactions with dolutegravir may lead to higher metformin levels (caveat in renal insufficiency).

Gastrointestinal tract

Gastrointestinal complaints used to be expected, nausea on AZT classic. Instead of symptomatic treatment with metoclopramide (Paspertin®) or dimenhydrinate (Vomex®), AZT should just be removed. With TDF or modern antiretrovirals, intervention is very rarely needed. Usually, there is a psychological aversion of the affected person that leads to nausea or even vomiting. Talk with the patient! Diarrhea is more likely, observed with all PIs, especially lopinavir, less so under darunavir. Diarrhea is also seen with elvitegravir and rarely with dolutegravir or bictegravir. If possible, the PI or elvitegravir should be replaced; symptomatic therapies such as psyllium (Mucofalk®, 1–2 times daily, one tablespoon, max. 30 g/day) or probiotics (controversial) are rarely helpful. Loperamide or opium tinctures help in the short term, but there are habituation effects and potential for abuse. Depending on the temporal occurrence of diarrhea, infectious and other causes such as lactose/fructose intolerance should also be ruled out, primarily if a change in ART does not provide relief.

Weight gain

Weight gain is probably one of the most important topics of recent years (reviews: Hester 2022, Kanters 2022). The sheer mass of (mostly) cohort studies is confusing. The results as well. Several confounding variables need to be considered, and the causes of weight gain are complex. The potential for bias is large, especially if weight is not systematically recorded (which is the case in very few cohorts). Who was weighed, why, and how often? The genesis of obesity is multifactorial.

In addition, most people gain weight over time, which makes it difficult to separate the additional effects of ART, especially the effect of a single antiretroviral agent. Moreover, with an average weight gain of one to two kilos, some people have gained quite substantially, others have a relatively stable weight, and others have even lost weight. There are increasing calls for standardized evaluations to shed more light on the problem (Venter 2021).

Especially dolutegravir and bictegravir, but also older INSTIs are probably involved. Women and black people seem more affected; in the ADVANCE study, South African women had gained an average of over 9 kg after two years (Venter 2020), predominantly fat, as evidenced by DEXA scans. In the large Gilead 1489/90 trials, weight gain was about 4–5 kg after three years with bictegravir and dolutegravir (Orkin 2020). In a pooled analysis of 8 randomized trials of 5,680 treatment-naïve PLWH 2003–2019, over 17% had gained more than 10% of body weight in just two years (Sax 2019). In the OPERA cohort (US outpatient centers, 5,536 individuals), 18% gained more than 5% of their weight within 28 weeks, and 9% gained more than 10% within 54 weeks (Hsu 2022). In a nationwide cohort from Greece, the prevalence of obesity was 5.7% at ART treatment initiation and 12.2%, 14.2%, and 18.1% after four years of treatment with NNRTIs, PIs, and INSTIs, respectively (Pantazis 2022).

In treatment-naïve patients, however, a "return-to-health" effect has to be considered. This effect is possibly greater among INSTIs due to their more rapid viral load reduction. Those who start their ART with an INSTI and who are in an advanced clinical stage will quickly lower their viral load – and first gain weight, viewed positively. However, the "return to health" effect does not explain everything. Even with good viral suppression, more significant weight gain is common with INSTIs. After switching to dolutegravir, there was a moderate but significant increase in weight in the Swiss cohort (n=2,186); overall, 22% had gained at least 5% body weight, with risk factors again being women and blacks (Mugglin 2019). In NEAT22, patients switched from darunavir/r to dolutegravir; within one year, this resulted in one kilo of weight gain (Waters 2018). Several studies have now looked at mechanisms. It is speculated that INSTIs affect adipocytes, adiponectin, mitochondria, insulin resistance, and melanocortin receptors (Domingo 2020, Ayissi 2022, Jung 2022). Partly, there is good evidence from animal models; partly, it is conjecture. There is probably also a genetic predisposition (Cindi 2021), and the gut microbiome may also be involved.

However, it's probably not only an INSTI problem. The NRTI backbone also plays a role, especially TAF. In ADVANCE, weight gain was particularly pronounced on dolutegravir plus TAF (Venter 2019), and a pooled analysis of 7 studies showed a weight gain of at least one kilo per year, compared with TDF (DeJesus 2019). The effects do not appear to be related to HIV. Participants also gained weight in the largest (and double-blind randomized) PrEP trial, DISCOVER: by 1.7 kg after 96 weeks on TAF+FTC, compared with only 0.5 kg on TDF+FTC (Ogbuagu 2021).

In switch studies, low baseline weight was identified as a risk factor for severe weight gain. In addition, more significant weight gain occurred when switching from

efavirenz or TDF (Erlandson 2022). It is possible, then, that "catabolic" effects play a role in addition to INSTI effects. There are good arguments for this as well. Weight loss with TDF-containing PrEP (review: Shah 2022), a lack of any visible effect from stopping TAF in the randomized TANGO trial (Osiyemi 2022), and more gain with dolutegravir+3TC than with TDF-containing dolutegravir regimens in the GEMINI studies (Cahn 2022).

In summary, the data situation is growing rapidly, to the disadvantage of INSTIs and partly also TAF. However, the mechanisms remain unclear (effect or side effect?); they are possibly heterogeneous. Little is known about the consequences of weight gain (diabetes? hypertension? CVD?). There is an urgent need for standardized and detailed weight measurements in all future pivotal trials with longer follow-ups. We also need well-controlled switch studies and more basic research (predisposition, CNS effects – e.g., melanocortin-4 receptors). Much work remains to be done. Standardized parameters must be defined. Opinions about acceptable weight gain may differ, both among patients and among their clinicians. The only consensus today is that the effects probably have nothing to do with lipodystrophy (see below) but are somewhat due to increased food intake (appetite!).

What we know (and don't know) about weight gain

- Mostly, INSTIs such as bictegravir and dolutegravir are involved.
- Many mechanisms are suspected (including "return to health"), and a predisposition is likely.
- The effects are either enhanced by TAF or reduced by TDF; there are now good arguments for both theories.
- Weight gains can be substantial in some cases (10–20%), but the clinical consequences have not yet been worked out.
- It is unclear whether switching to other therapies can slow, stop, or reverse weight gain or metabolic changes

Skin and allergic reactions

Allergies have become rarer than before. They still occur mainly with NNRTIs, darunavir, and abacavir in the absence of HLA testing. NNRTI allergy is a reversible, immunologically mediated, systemic reaction. It typically manifests as maculopapular, pruritic, and confluent exanthema – particularly on the trunk and arms. It is most commonly seen with nevirapine but also with other NNRTIs. Fever may precede; other symptoms include myalgias, fatigue, and mucosal ulceration. Allergy usually begins in the second or third week of therapy. Women are more frequently and severely affected, especially with nevirapine (Bersoff-Matcha 2001). Symptoms more than eight weeks after initiation of therapy almost always have other causes. Severe courses such as Stevens-Johnson syndrome, acute toxic epidermolysis (Lyell syndrome), or anicteric hepatitis are rare. Alarm signals of a severe skin reaction include mucosal involvement, blistering, exfoliation, transaminase elevation (> 5-fold above average), or fever > 39 °C. The NNRTI must then be discontinued immediately and forever. Approximately 50% of NNRTI allergies remit despite continuation of therapy. Antihistamines can be helpful, but prophylactic administration of corticosteroids or antihistamines is ineffective.

The exanthema with the sulfonamide-containing PI darunavir is clinically indistinguishable from NNRTI rash. It is reversible and responds well to antihistamines or steroids. In most cases, darunavir can be continued (Nishijima 2014). The incidence is about 10%, so darunavir should not be started concurrently with NNRTIs or abacavir.

Abacavir hypersensitivity reaction (HSR) is a systemic event that manifests during the first weeks of treatment, often in the first few days, and can be fatal (see above). HSR is closely associated with the HLA-B*5701 allele, which shows a prevalence of 5%, with country-specific estimates ranging from 1.5 to 7.8% (Orkin 2010). HLA-B*5701 prevalence is highest in the self-reported white population (6.5%) and lowest in the black population (0.4%). Abacavir interacts with the allele and induces a polyclonal T-cell response (Illing 2013). In the prospective Predict study in 1956 individuals from 19 countries, HLA-B*5701 testing prevented HSR when abacavir was omitted if the test was positive (Mallal 2008). HSR without the allele is extremely rare. The diagnosis is made clinically. Skin is involved in 70%, and fever is in 80%. Gastrointestinal symptoms with nausea and diarrhea are often associated. Stevens-Johnson syndrome has also been described (Bossi 2002). After cessation of abacavir therapy, symptoms should remit rapidly. Specific therapeutic options for HSR do not exist. After documented or suspected HSR, re-exposure is contraindicated.

Cardiovascular system

As noted in the drug review of this book (Section 5.2), various cohort studies (Young 2015, Marcus 2016, Dorjee 2018, Jaschinski 2022) found increased myocardial risk with abacavir. It was moderate and was increased about 1.5–2.5-fold, especially if there had been an exposure within the previous six months. Whereas potential confounders should be considered in the analysis of cohort studies, the prothombogenic pathomechanisms are now well explained, making the observations plausible. The mechanisms include increased platelet aggregation and activation (Mallon 2018, O'Halloran 2018, Taylor 2018).

We have moved to replace abacavir with other options, especially for high cardiovascular risk. The higher the risk, the faster and more active. In this era of dual therapies, the drug seems largely dispensable. Triumeq®, the combination of dolutegravir plus ABC/3TC, has largely disappeared from everyday use and has been replaced by Dovato® (dolutegravir plus 3TC) and other agents.

Increased cardiovascular risk has also been consistently described in cohorts for PIs such as darunavir (Lundgren 2017), possibly due to dyslipidemia – but the effect is likely weaker than for abacavir and tends not to influence treatment decisions.

Bones

A loss of bone density of 2–6% is observed in the first two years after ART initiation on all regimens (Brown 2015, Hoy 2017). The magnitude of this demineralization is similar to that seen in women in the first two years after menopause (Finkelstein 2008). After the first years, bone density remains relatively stable (Bolland 2011). Causes include increased osteoclastogenesis and bone turnover (Seminari 2005), and the risk of osteoporosis is increased 2–3-fold (Brown 2015). The SMART study also showed significantly higher bone density loss and fracture rates with continuous therapy compared to breaks in therapy (Grund 2009). In contrast, other studies found no increased fracture rate (Mundy 2002). In the START trial, bone density loss was one of the few disadvantages of early ART initiation (Hoy 2017).

Although bone loss is always multifactorial, there is evidence for some antiretroviral drugs. PIs, as potent cytochrome P450 inhibitors, also interact with vitamin D-1α hydroxylase, among others. A meta-analysis found a slightly increased risk of osteoporosis among PIs (Brown 2015), but this disappeared after adjustment for risk factors. Cohort studies also yielded conflicting data. Some found an increased risk of fracture (Womack 2013), while others did not (Costaglia 2019).

TDF is also involved (review: Shiau 2020); bone density decreases more than under other agents. In some cases, increased fracture rates were found (Horizon 2011, Borges

2016), but not in others (Cooper 2010, Hill 2018). After switching to TAF, bone density and osseous activation markers improve, sometimes significantly, but overall fracture risk remains the same. Biphosphonates appear more effective than TDF replacement in osteopenia (Hoy 2019).
In addition to osteoporosis, TDF is also involved in osteomalacia, an insufficient mineralization of bone. This usually results from impaired uptake, activation, or receptor action of vitamin D or a deficiency of calcium and phosphate mineralization substrates. Vitamin D deficiency is much more common in HIV-infected individuals than in the general population. TDF leads to renal phosphate loss via mitochondrial tubulopathy, which is usually reversible after discontinuation (Wanner 2009).
What remains as a consequence of ART? According to the current EACS guidelines (EACS 2021), consideration should be given to replacing TDF in the following situations: manifest osteoporosis, progressive bone loss, and previous fragility fracture. We would further advise reconsidering the need for TDF if classic risk factors exist. These include older age, female sex, hypogonadism, family history of hip fracture, low BMI, smoking, physical inactivity, history of fracture with minor trauma, increased alcohol consumption, and prolonged steroid use.

Liver

For all PIs, NNRTIs, NRTIs, but also maraviroc, and all INSTIs, there are reports of liver enzyme elevations up to severe hepatotoxic reactions (Núñez 2010). However, they are rare and tend to affect high-risk patients with viral hepatitis, alcohol problems, or potentially hepatotoxic comedication. Liver injury has different mechanisms, and important clues are provided by the onset time (Cai 2019).
Hypersensitivity reactions with liver involvement are typical for abacavir (HLA status?), NNRTIs, especially nevirapine, and darunavir. They are dose-independent and occur in the first 4 to 12 weeks. Particularly with nevirapine, caution is always advised (see above)! Rapid normalization can be expected upon discontinuation. In contrast, direct drug toxicity develops slowly within months (Price 2010). Also, hepatic steatosis caused by mitochondrial toxicity under NRTIs often manifests only after years. This is also true for the hepatotoxicity of some PIs, especially in chronic hepatitis (Sulkowski 2004). Tipranavir causes the most marked liver elevations of all PIs, and fatal courses have been described (Chan-Tack 2008). Inhibition of UDP-glucuronyltransferase is typical for atazanavir, which often leads to hyperbilirubinemia and icterus – it should no longer be used. Liver value changes (usually moderate) have also been described for all INSTIs. Increased GGT is typical for nevirapine (less commonly efavirenz) and can be tolerated if moderate. However, it sometimes exposes patients to the suspicion of excessive alcohol consumption.
Elevated liver values are not always an expression of specific toxicity. Thus, an immune reconstitution syndrome may be the cause; it usually occurs in severe immunodeficiency in the first months under ART, regardless of the regimen (Price 2010). Differentially, viral hepatitis should always be considered: Is there acute hepatitis A, C, or E? Is there a rebound of hepatitis B with discontinuation of HBV-active drugs such as TDF or TAF? Or an initial flair under hepatitis C therapy, especially with hepatitis B coinfection (Bersoff-Matcha 2017)? Ultimately, other causes are possible, and it is not uncommon for athletic activity to have caused a moderate GPT elevation.
Liver enzymes should be monitored before and during ART, preferably after Four weeks and then every three months. Without clinical symptoms, ART can be continued with moderate GPT elevation under closer monitoring. Liver biopsy can differentiate NRTI-induced steatosis from other liver damage. However, it is now only considered in exceptional situations.

Lipodystrophy

Although the syndrome includes morphologic and laboratory chemical changes (Carr 1998), this section will focus on fat distribution abnormalities. Classical lipodystrophy is now rare, predominantly caused by D-drugs, AZT, and probably older PIs such as indinavir or saquinavir (Srinivasa 2014). However, regression often remains incomplete, placing a heavy burden on many patients treated for many years. Often, clinical diagnosis is complicated by physiological aging processes that can be misinterpreted as lipodystrophy. A good definition or classification is still lacking. Diagnostically, a DEXA scan, CT, or MRI can objectify changes. Simpler – but less accurate – are anthropometric measurement methods such as waist circumference or waist-to-hip ratio. However, these tests are rarely helpful in individual cases.

Typical is the simultaneous loss of subcutaneous adipose tissue (lipoatrophy) in the face (periorbital, buccal, temporal), buttocks, and extremities ("stork legs"), often combined with an accumulation of visceral adipose tissue ("buffalo hump", "crix-belly") (Grunfeld 2010). In addition, there are metabolic changes, such as insulin resistance, diabetes mellitus, and dyslipidemia. Lipodystrophy is explained by the mitochondrial toxicity of NRTIs in adipose tissue (Brinkman 1999).

Therapy of lipodystrophy remains difficult. NRTIs and old PIs should be removed from ART if possible. Peripheral fat loss often takes years to improve (see above). Recombinant human growth hormone (HGH, e.g., Serostim®, 4–6 mg/d s.c.) has been tested in studies over 8–12 weeks to reduce marked visceral fat accumulation. Unfortunately, the effects were not durable after discontinuation. Surgical intervention (e.g., liposuction) is only indicated in isolated cases (Guaraldi 2011). In cases of pronounced facial lipoatrophy, repeated injection with poly-L-lactic acid (Sculptra®) may be useful (Lafaurie 2005). However, it belongs in experienced hands.

Neuropsychiatric adverse events (NPAEs)

With efavirenz, central nervous symptoms such as dizziness, sleep disturbances, and nightmares occur in up to 40% (Ford 2015). It should be replaced whenever possible. A switch can be considered even in the absence of symptoms under efavirenz. Often, affected individuals have become "accustomed" to the side effects and only notice them after discontinuation.

There is also increasing evidence of NPAEs for INSTIs, particularly dolutegravir and bictegravir (Hoffmann 2020). They are less pronounced than seen with efavirenz but may lead to discontinuation in 5–10% of cases, depending on the vigilance and alertness of the treatment provider. Raltegravir and elvitegravir are less commonly implicated. NPAEs with INSTIs may be unspecific, comprising vague feelings such as "helmet on my head", "foggy-brained", "tetchy" or "prone to tears". Those events are often not written in electronic records or even considered drug-related by the patients. Thus, they are commonly not captured with retrospective studies checking the electronic medical records or prospective RCTs without specific questionnaires. With heightened awareness of health care providers and patients, reports of NPAEs will probably increase in the future.

Sometimes, affected persons describe these problems only when asked. Much is challenging to distinguish from psychiatric diagnoses; however, in our experience, people without any previous psychiatric illness are also affected. NPAEs among INSTIs are difficult to objectify and not defined, so the true prevalence is difficult to determine. The symptoms can occur even after years; they are by no means limited to the first weeks of exposure. Cross-intolerance does not appear to be high: those who cannot tolerate bictegravir may tolerate dolutegravir, and vice versa (Hoffmann 2020).

The causes continue to be controversial. It is discussed whether there is a genetic predisposition or a connection with plasma levels. There are no valid diagnostic tests.

If neuropsychiatric side effects occur or are suspected, ART can be switched empirically for a few weeks in most cases. Affected individuals should be taken seriously, and the possibility of NPAEs should be addressed openly. Of course, not every psychiatric problem is a side effect. However, an empirical switch of ART is often the easiest solution. NPAEs are reversible: improvement can be expected after a few days if the problems are indeed due to ART. A randomized trial showed clear improvement in several sleep and depression scores when switching from dolutegravir to darunavir (Cabello-Úbeda 2022).

Kidneys

Tenofovir-DF (TDF) usually causes mild and reversible renal dysfunction (see chapter *HIV and nephrology*). For all TDF-containing preparations, there are detailed instructions for renal monitoring. Before initiation, calculate creatinine clearance and monitor renal function at 2–4 weeks, three months, and every 3 to 6 months after that – or more frequently if abnormalities and/or renal risk are present. Severe renal impairment is rare (Cooper 2010). In a meta-analysis, discontinuation rates due to renal events were 0.6% (17/2,689) on TDF (Hill 2018). An increased risk was found only with boosted regimens. In the Swiss cohort, 46 of 2,592 patients (1.6%) had to discontinue TDF due to renal toxicity after a mean of 442 days (Fux 2008). Renal failure is also observed in the setting of Fanconi syndrome, a defect of proximal tubule transport. TDF should be avoided in the presence of renal damage. Elderly and lightweight PLWH are also at risk, as are those with boosted PIs (Young 2012) and potentially nephrotoxic comedication. Concurrent administration of amphotericin B, foscarnet, vancomycin, or cidofovir should be avoided. NSAIDs such as ibuprofen, diclofenac, or even ASA can lead to renal failure requiring dialysis in high doses together with TDF. Tenofovir-AF (TAF), approved in 2016, causes complications much less frequently (Gupta 2019) and can be used in renal failure up to a GFR of 30 mL/min. Switching from TAF to TDF significantly improved eGFR in patients with and without renal impairment (Mills 2016, Pozniak 2016). TAF is always preferable to TDF for renal problems.

Older PIs such as atazanavir can lead to nephrolithiasis; they should no longer be used. The INSTIs dolutegravir, bictegravir, and elvitegravir (as well as the booster cobicistat) often cause a moderate increase in serum creatinine because they inhibit proximal tubular creatinine secretion. Cystatin-C or protein/creatinine ratio are then better markers of renal function.

Varia (rare)

Hematologic changes: AZT is myelosuppressive and may lead to anemia. Even without anemia, mean corpuscular red cell volume (MCV) is regularly increased. When AZT is combined with other myelosuppressive drugs such as cotrimoxazole, ribavirin, or interferon, the effect may be potentiated. AZT should be avoided today.

Coagulopathies: Very rare. In hemophiliacs, spontaneous bleeding into joints and soft tissues has been observed in increased numbers during PI-containing therapies. Rarely, intracranial and gastrointestinal bleeding occurs. The hemorrhages occurred several weeks after the initiation of PI therapy (Wilde 2000), and the cause remained unclear. Far more common are (overlooked) interactions between some NOAKs and boosted ART regimens, some of which can cause life-threatening bleeding. Caveat: Rivaroxaban plus ritonavir or cobicistat!

Lactic acidosis: This potentially life-threatening complication used to be observed with d4T and ddI and less frequently with AZT. Since the d-drugs have disappeared, ART-associated lactic acidosis is a rarity.

Myositis: Rare, formerly with AZT. Isolated cases with raltegravir. Cave rhabdomyolysis in combination with simvastatin and boosted ART. Differential diagnosis comparatively harmless macro-CK under TDF (Schmidt 2013).

Polyneuropathy: Also due to the d-drugs, unfortunately, occasionally persisting, even after many years. Treatment is often complex (see *Neuro*).

Literature

Arranz Caso JA, Lopez JC, Santos I, et al. A randomized controlled trial investigating the efficacy and safety of switching from a protease inhibitor to nevirapine in patients with undetectable viral load. HIV Med 2005, 6:353-9.

Behrens G, Maserati R, Rieger A, et al. Switching to tenofovir/emtricitabine from abacavir/lamivudine in HIV-infected adults with raised cholesterol affects lipid profiles. Antivir Ther 2012, 17:1011-20.

Bersoff-Matcha SJ, Cao K, Jason M, et al. Hepatitis B Virus Reactivation Associated With Direct-Acting Antiviral Therapy for Chronic Hepatitis C Virus: A Review of Cases Reported to the U.S. Food and Drug Administration Adverse Event Reporting System. Ann Intern Med 2017,166:792-798.

Bersoff-Matcha SJ, Miller WC, Aberg JA, et al. Sex differences in nevirapine rash. CID 2001; 32:124-9.

Bhagwat P, Ofotokun I, McComsey GA, et al. Predictors of Severe Weight/Body Mass Index Gain Following Antiretroviral Initiation. Abstract 695, CROI 2017, Boston.

Bloch M, Tong W, Hoy J, et al. Switching from tenofovir to raltegravir increases low bone mineral density and decreases markers of bone turnover over 48 weeks. Improved Low BMD and Bone Turnover Markers with Switch from Tenofovir to Raltegravir in Virologically Suppressed HIV-1+ Adults at 48 Weeks: The TROP Study. Abstract 878, 19th CROI 2012, Seattle.HIV Med 2014, 15:373-80.

Bolland MJ, Wang TK, Grey A, et al. Stable bone density in HAART-treated individuals with HIV: a meta-analysis. J Clin Endo Metab 2011; 96: 2721-31.

Borges ÁH, Hoy J, Florence E, et al. Antiretrovirals, Fractures, and Osteonecrosis in a Large International HIV Cohort. CID 2017, 64:1413-1421.

Bossi P, Roujeau JC, Bricaire F, et al. Stevens-Johnson syndrome associated with abacavir therapy. Clin Infect Dis 2002; 35:902.

Brinkman K, Smeitink JA, Romijn JA, Reiss, P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. Lancet 1999; 354:1112-1115.

Brown TT, Hoy J, Borderi M, et al. Recommendations for evaluation and management of bone disease in HIV. Clin Infect Dis 2015, 60:1242-51.

Cabello-Úbeda A, Baeza AG, García JT, et al. Changes in Quality of Sleep, Mood, and Other Neuropsychiatric Symptoms After Switching Dolutegravir/Lamivudine/Abacavir to Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in a Randomized Study of People With Human Immunodeficiency Virus With Poor Sleep Quality: GESIDA 10418. Open Forum Infect Dis 2022, 9:ofac345.

Cahn P, Sierra Madero J, Arribas JR, et al. Three-year durable efficacy of dolutegravir plus lamivudine in antiretroviral therapy – naive adults with HIV-1 infection. AIDS 2022; 36:39-48.

Cai J, Osikowicz M, Sebastiani G. Clinical significance of elevated liver transaminases in HIV-infected patients. AIDS 2019, 33:1267-1282.

Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 1998; 12:F51-8.

Chan-Tack KM, Struble KA, Birnkrant DB. Intracranial hemorrhage and liver-associated deaths associated with tipranavir/ritonavir: review of cases from the FDA's Adverse Event Reporting System. AIDS Patient Care STDS 2008; 11:843-50.

Cindi Z, Maartens G, Bradford Y, et al. Genetic Associations with Weight Gain among South Africans who Initiated Dolutegravir-Containing and Tenofovir-Containing Regimens. J Acquir Immune Defic Syndr 2021, 87:1002-1009.

Cooper RD, Wiebe N, Smith N, et al. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. Clin Infect Dis 2010; 51:496-505.

Costagliola D, Potard V, Lang S, et al. Impact of Antiretroviral Drugs on Fracture Risk in HIV-Infected Individuals: A Case-Control Study Nested Within the French Hospital Database on HIV (FHDH-ANRS CO4). J Acquir Immune Defic Syndr 2019, 80:214-223.

Curran A, Ribera E. From old to new nucleoside reverse transcriptase inhibitors: changes in body fat composition, metabolic parameters and mitochondrial toxicity after the switch from thymidine analogs to tenofovir or abacavir. Expert Opin Drug Saf 2011, 10:389-406.

DeJesus E, Villanueva JF, Arribas JR. Tenofovir Alafenamide (TAF) Versus Tenofovir Disoproxil Fumarate (TDF) in Hispanic/Latinx and Black Participants: Efficacy, Bone and Renal Safety Results from a Pooled Analysis of 7 Clinical Trials. Abstract 318, ID Week 2019, Washington.

Domingo P, Villarroya F, Giralt M, Domingo JC. Potential role of the melanocortin signaling system interference in the excess weight gain associated to some antiretroviral drugs in people living with HIV. Int J Obes (Lond) 2020, 44:1970-1973.

Dorjee K, Choden T, Baxi SM, et al. Risk of cardiovascular disease associated with exposure to abacavir among individuals with HIV: A systematic review and meta-analyses of results from 17 epidemiologic studies. Int J Antimicrob Agents 2018, 52:541-553.

Daar ES, DeJesus E, Ruane P, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1. Lancet HIV 2018;5:e347-e356.

EACS. European Guideline for HIV-infected adults in Europe 2021. http://www.eacsociety.org.

Erlandson KM, Carter CC, Melbourne K, et al. Weight Change Following Antiretroviral Therapy Switch in People With Viral Suppression: Pooled Data from Randomized Clinical Trials. Clin Infect Dis. 2021, 73:1440-1451.

Eron JJ, Young B, Cooper DA, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2). Lancet 2010, 375:396-407.

Finkelstein JS, Brockwell SE, Mehta V, et al. Bone mineral density changes during the menopause transition in a multiethnic cohort of women. J Clin Endocrinol Metab 2008; 93:861-8.

Ford N, Shubber Z, Pozniak A, et al. Comparative Safety and Neuropsychiatric Adverse Events Associated With Efavirenz Use in First-Line Antiretroviral Therapy: A Systematic Review and Meta-Analysis of Randomized Trials. J Acquir Immune Defic Syndr.AIDS 2015, Aug 1;69(4):422-9.

Fux CA, Rauch A, Simcock M, et al. Tenofovir use is associated with an increase in serum alkaline phosphatase in the Swiss HIV Cohort Study. Antivir Ther 2008, 13:1077-82.

Gatell JM, Assoumou L, Moyle G, et al. Switching from a ritonavir-boosted protease inhibitor to a dolutegravir-based regimen for maintenance of HIV viral suppression in patients with high cardiovascular risk. AIDS 2017, 31:2503-14.

Grund B, Peng G, Gibert CL, et al. Continuous antiretroviral therapy decreases bone mineral density. AIDS 2009;23:1519-1529.

Grunfeld C, Saag M, Cofrancesco J Jr, et al. Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). Regional adipose tissue measured by MRI over 5 years in HIV-infected and control participants indicates persistence of HIV-associated lipoatrophy. AIDS 2010; 24:1717-26.

Guaraldi G, Fontdevila J, Christensen LH, et al. Surgical correction of HIV-associated facial lipoatrophy. AIDS. 2011; 25:1-12.

Gupta SK, Post FA, Arribas JR, et al. Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: A pooled analysis of 26 clinical trials. AIDS 2019, 33:1455-1465.

Haskelberg H, Hoy JF, Amin J, STEAL Study Group. Changes in bone turnover and bone loss in HIV-infected patients changing treatment to tenofovir-emtricitabine or abacavir-lamivudine. PLoS One. 2012;7:e38377.

Helleberg M1, Kronborg G, Larsen CS, et al. Decreasing rate of multiple treatment modifications among individuals who initiated antiretroviral therapy in 1997-2009 in the Danish HIV Cohort Study. Antivir Ther. 2012 Oct 16.

Hester EK, Greenlee S, Durham SH. Weight Changes With Integrase Strand Transfer Inhibitor Therapy in the Management of HIV Infection: A Systematic Review. Ann Pharmacother 2022, 8:10600280211073321.

Hill A, Hughes SL, Gotham D, Pozniak AL. Tenofovir alafenamide versus tenofovir disoproxil fumarate: Is there a true difference in efficacy and safety? J Virus Erad 2018, 4:72-79.

Hoffmann C, Llibre J. Neuropsychiatric adverse events with dolutegravir and other integrase strand transfer inhibitors. AIDS Reviews 2019, 21:4-10.

Hoffmann C, Schewe K, Fenske S, et al. Short-term neuropsychiatric tolerability of bictegravir combined with emtricitabine/tenofovir alafenamide in clinical practice. Antivir Ther 2020, 25:83-90.

Horizon AA, Joseph RJ, Liao Q, et al. Characteristics of foot fractures in HIV-infected patients previously treated with tenofovir versus non-tenofovir-containing highly active antiretroviral therapy. HIV AIDS (Auckl). 2011;3:53-59.

Hoy JF, Grund B, Roediger M, et al. Immediate Initiation of Antiretroviral Therapy for HIV Infection Accelerates Bone Loss Relative to Deferring Therapy: Findings from the START Bone Mineral Density Substudy, a Randomized Trial. J Bone Miner Res 2017, 32:1945-1955.

Hoy JF, Richardson R, Ebeling PR, et al. Zoledronic acid is superior to tenofovir disoproxil fumarate-switching for low bone mineral density in adults with HIV. AIDS 2018, 32:1967-1975.

Hsu RK, Brunet L, Fusco JS, Mounzer K, Lamori JC, Fusco GP. Excessive Weight Gain: Current Antiretroviral Agents in Virologically Suppressed People with HIV. AIDS Res Hum Retroviruses. 2022 Sep 1.

Illing PT, Vivian JP, Purcell AW, et al. Human leukocyte antigen-associated drug hypersensitivity. Curr Opin Immunol 2013;25:81-9.

Jaschinski N, Greenberg L, Neesgaard B, et al. Recent abacavir use and incident cardiovascular disease in contemporary treated people living with HIV. AIDS. 2022 Aug 24.

Johnson M, Kumar P, Molina JM, et al. Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial. J Acquir Immune Defic Syndr 2019, 81:463-472.

Jung I, Tu-Sekine B, Jin S, et al. Dolutegravir Suppresses Thermogenesis via Disrupting UCP1 Expression and Mitochondrial Function in Brown/Beige Adipocytes in preclinical models. J Infect Dis 2022 May 4:jiac175.

Kanters S, Renaud F, Rangaraj A, et al. Evidence synthesis evaluating body weight gain among people treating HIV with antiretroviral therapy – a systematic literature review and network meta-analysis. EClinicalMedicine 2022, 48:101412.

Lafaurie M, Dolivo M, Porcher R, et al. Treatment of facial lipoatrophy with intradermal injections of polylactic acid in HIV-infected patients. J AIDS 2005;38:393-8.

Lebrecht D, Venhoff AC, Kirschner J, et al. Mitochondrial tubulopathy in tenofovir disoproxil fumarate-treated rats. J AIDS 2009; 51: 258-63.

Liang JS, Distler O, Cooper DA, et al. HIV protease inhibitors protect apolipoprotein B from degradation by the proteasome: A potential mechanism for protease inhibitor-induced hyperlipidemia. Nat Med 2001; 7:1327-1331.

Lucas GM, Ross MJ, Stock PG, et al. Clinical practice guideline for the management of chronic kidney disease in patients infected with HIV: 2014 update by the HIV Medicine Association of the IDSA. Clin Infect Dis 2014, 59:e96-138.

Lundgren J, Mocroft A, Ryom L. Contemporary protease inhibitors and cardiovascular risk. Curr Opin Infect Dis. 2017 Dec 9

Maggi P, Di Biagio A, Rusconi S, et al. Cardiovascular risk and dyslipidemia among persons living with HIV: A review. BMC Inf Dis 2017, 17:551.

Mallal S, Phillips E, Carosi G, et al. HLA B5701 Screening for hypersensitivity to abacavir. N Engl J Med 2008, 358:568-79.

Mallon PW, Maughan RT, Garcia AA, et al. Change in soluble glycoprotein VI (SGPVI) when switching from ABC/3TC to TAF/FTC. Abstract 677LB, 25th CROI 2018, Boston.

Marcus JL, Neugebauer RS, Leyden WA, et al. Use of Abacavir and Risk of CVD Among HIV-Infected Individuals. J AIDS 2016, 71:413-9.

Martinez E, Arnaiz JA, Podzamczer D, et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with HIV infection. N Engl J Med 2003; 349:1036-46.

Martínez E, Larrousse M, Llibre JM, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. AIDS 2010, 24:1697-707.

McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: ACTG A5224s, a substudy of A5202. JID 2011, 203:1791-801.

McComsey GA, Moser C, Currier J, et al. Body Composition Changes After Initiation of Raltegravir or Protease Inhibitors: ACTG A5260s. Clin Infect Dis 2016, 62:853-62.

Milinkovic A, Berger F, Arenas-Pinto A, Mauss S. Reversible effect on lipids by switching from tenofovir disoproxil fumarate to tenofovir alafenamide and back. AIDS 2019, 33:2387-2391.

Mills A, Arribas JR, Andrade-Villanueva J, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. Lancet Infect Dis 2016; 16:43–52.

Moyle GJ, Orkin C, Fisher M, et al. A randomized comparative trial of continued abacavir/lamivudine plus efavirenz or replacement with efavirenz/emtricitabine/tenofovir DF in hypercholesterolemic HIV-1 infected individuals. PLoS One 2015, 10:e0116297.

Mugglin C, Calmy A, Gunthard H, et al. Changes in weight after switching to dolutegravir containing antiretroviral therapy in the Swiss HIV Cohort Study. 17th EACS 2019, Basel.

Mundy LM, Youk AO, McComsey GA, et al. Overall benefit of antiretroviral treatment on the risk of fracture in HIV: nested case control analysis in a health-insured population. AIDS 2012; doi: 10.1097/QAD.0b013e 328351997f.

Nan C, Shaefer M, Urbaityte R, et al. Abacavir Use and Risk for Myocardial Infarction and Cardiovascular Events: Pooled Analysis of Data From Clinical Trials. Open Forum Infect Dis 2018, 5:ofy086.

Ngono Ayissi K, Gorwood J, Le Pelletier L, et al. Inhibition of Adipose Tissue Beiging by HIV Integrase Inhibitors, Dolutegravir and Bictegravir, Is Associated with Adipocyte Hypertrophy, Hypoxia, Elevated Fibrosis, and Insulin Resistance in Simian Adipose Tissue and Human Adipocytes. Cells 2022, 4;11:1841.

Nishijima T, Gatanaga H, Teruya K et al. Skin rash induced by ritonavir-boosted darunavir is common, but generally tolerable in an observational setting. J Infect Chemother. 2014 Feb 5.

Núñez M. Clinical syndromes and consequences of antiretroviral-related hepatotoxicity. Hepatology 2010, 52:1143-55.

Ogbuagu O, Ruane PJ, Podzamczer D, et al. Long-term safety and efficacy of emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV-1 pre-exposure prophylaxis: week 96 results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet HIV 2021, 8:e397-e407.

O'Halloran JA, Dunne E, Tinago W, et al. Switching from abacavir to tenofovir disoproxil fumarate is associated with rises in soluble glycoprotein VI, suggesting changes in platelet-collagen interactions. AIDS 2018, 32:861-866.

Orkin C, DeJesus E, Sax PE, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials. Lancet HIV 2020, 7:e389-e400.

Orkin C, Wang J, Bergin C, et al. An epidemiologic study to determine the prevalence of the HLA-B*5701 allele among HIV-positive patients in Europe. Pharmacogenet Genomics 2010; 20:307-14.

Osiyemi O, De Wit S, Ajana F, et al. Efficacy and Safety of Switching to Dolutegravir/Lamivudine Versus Continuing a Tenofovir Alafenamide-Based 3- or 4-Drug Regimen for Maintenance of Virologic Suppression in Adults Living With Human Immunodeficiency Virus Type 1: Results Through Week 144 From the Phase 3, Noninferiority TANGO Randomized Trial. Clin Infect Dis 2022, 75:975-986.

Pantazis N, Papastamopoulos V, Antoniadou A, et al. Changes in Body Mass Index after Initiation of Antiretroviral Treatment: Differences by Class of Core Drug. Viruses 2022, 14:1677.

Pantazis N, Psichogiou M, Paparizos V, et al. Treatment Modifications and Treatment-Limiting Toxicities or Side Effects: Risk Factors and Temporal Trends. AIDS Res Hum Retroviruses 2015, 31:707-17.

Petoumenos K, Law MG. Smoking, alcohol and illicit drug use effects on survival in HIV-positive persons. Curr Opin HIV AIDS 2016, 11:514-520.Curr Opin HIV AIDS. 2016 Sep;11(5):514-520.

Pett SL, Amin J, Horban A, et al. Maraviroc, as a Switch Option, in HIV-1-infected Individuals With Stable, Well-controlled HIV Replication and R5-tropic Virus on Their First Nucleoside/Nucleotide Reverse Transcriptase Inhibitor Plus Ritonavir-boosted Protease Inhibitor Regimen. CID 2016, 63:122-32.

Pozniak A, Arribas JR, Gathe J, et al. Switching to Tenofovir Alafenamide, Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, in HIV-Infected Patients With Renal Impairment: 48-Week Results From a Single-Arm, Multicenter, Open-Label Phase 3 Study. J AIDS 2016, 71:530-7.

Price JC, Thio CL.Liver disease in the HIV-infected individual. Clin Gastroenterol Hepatol 2010;8:1002-12.

Rasmussen TA, Jensen D, Tolstrup M, et al. Comparison of bone and renal effects in HIV-infected adults switching to abacavir or tenofovir based therapy in a randomized trial. PLoS One 2012; 7:e32445.

Ribera E, Larrousse M, Curran A, et al. Impact of switching from zidovudine/lamivudine to tenofovir/emtricitabine on lipoatrophy: the RECOMB study. HIV Med 2013, 14:327-36.

Santos JR, Saumoy M, Curran A, et al. The lipid-lowering effect of tenofovir/emtricitabine: a randomized, crossover, double-blind, placebo-controlled trial. Clin Infect Dis 2015, 61:403-8.

Schmid H, Tokarska-Schlattner M, Füeßl B, et al. Macro CK2 accumulation in tenofovir-treated HIV patients is facilitated by CK oligomer stabilization but is not predictive for pathology. Antivir Ther 2013;18:193-204.

Seminari E, Castagna A, Soldarini A, et al. Osteoprotegerin and bone turnover markers in heavily pretreated HIV-infected patients. HIV Med 2005; 6: 145-150.

Shah S, Pilkington V, Hill A. Is tenofovir disoproxil fumarate associated with weight loss? AIDS 2021, 35(Suppl 2):S189-S195.

Shiau S, Arpadi SM, Yin MT. Bone Update: Is It Still an Issue Without Tenofovir Disoproxil Fumarate? Curr HIV/AIDS Rep 2020, 17:1-5.

Spinner CD, Kern KE, et al. Neither boosted elvitegravir nor darunavir with emtricitabine/tenofovir disoproxil fumarate increase insulin resistance in healthy volunteers: results from the STRIBILD-IR study. Antivir Ther 2016, 21:627-631.

Srinivasa S, Grinspoon SK. Metabolic and body composition effects of newer antiretrovirals in HIV-infected patients. Eur J Endocrin 2014;170:R185-202.

Sulkowski MS. Drug-induced liver injury associated with antiretroviral therapy that includes HIV-1 protease inhibitors. Clin Infect Dis 2004; 38:S90-7.

Taylor KA, Rauzi F, Smyth E, et al. Comparative impact of antiretrovirals on human platelet activation. Abstract 673, 25th CROI 2018, Boston.

Tungsiripat M, Kitch D, Glesby MJ, et al. A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: ACTG 5206. AIDS 2010, 24:1781-4.

Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV. N Engl J Med 2019, 381:803-815.

Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. Lancet HIV 2020, 7:e666-e676.

Venter WDF, Sokhela S, Calmy A, et al. Weight gain stopping/switch rules for antiretroviral clinical trials. AIDS 2021, 35(Suppl 2):S183-S188.

Wanner DP, Tyndall A, Walker UA. Tenofovir induced osteomalacia. Clin Exp Rheumatol 2009; 27: 1001-1003.

Waters L, Assoumou L, Rusconi S, et al. Switch to dolutegravir from a boosted protease inhibitor associated with significant weight gain over 48 weeks in NEAT-022, a randomised 96-week trial. Abstract P102, Glasgow 2018.

Wilde JT. Protease inhibitor therapy and bleeding. Haemophilia 2000; 6:487-90.

Winston A, Post FA, DeJesus E, et al. Tenofovir alafenamide plus emtricitabine versus abacavir plus lamivudine for treatment of virologically suppressed HIV-1-infected adults: a randomised, double-blind, active-controlled, non-inferiority phase 3 trial. Lancet HIV 2018, 5:e162-e171.

Womack JA, Goulet JL, Gibert C, et al. Physiologic frailty and fragility fracture in HIV-infected male veterans. Clin Infect Dis 2013; 56: 1498-1504.

Young J, Schäfer J, Fux CA, et al. Renal function in patients with HIV starting therapy with tenofovir and either efavirenz, lopinavir or atazanavir. AIDS 2012, 26:567-575.

Young J, Xiao Y, Moodie EE, et al. Effect of Cumulating Exposure to Abacavir on the Risk of Cardiovascular Disease Events in Patients From the Swiss HIV Cohort Study. J AIDS 2015, 69:413-21.

5.8. Simplification, de-escalation

CHRISTIAN HOFFMANN

Simplification: Switching to a single-tablet regime (STR)

Not only therapy-naïve but also pre-treated patients are asking about STRs today. Can they switch? The power of the large studies conducted to date (Table 8.1) remains limited for two reasons. First, the patients were mostly heterogeneously pre-treated, sometimes with different drug classes and different backbones – possible positive and negative effects of switching are not always clear. Secondly, care was taken in most studies to ensure that neither resistance nor previous virological failure was present. A maximum of two prior therapies was almost always allowed; in GS-109, participants came from three previous Gilead studies (and were highly selected). Not surprisingly, virological control was maintained by almost all participants in all studies.

Table 8.1: Randomized studies on the switch to so-called single-tablet regimens (STRs) in virologically successfully treated patients (mostly > six months).

STR, study (reference)	n	Last ART	Significant effects of switching to an STR, week 48
Triumeq® STRIIVING (Trottier 2017)	551	42% PIs 26% INIs 31% NNRTIs	DRAEs more frequent (21% vs. 1%), more Nausea (10% vs. 1%), Fatigue (7% vs. 1%), Psychiatric (13% vs. 3%)
Biktarvy® GS-1878 (Daar 2018)	578	56% DRV/r/c 44% ATV/r/c	DRAEs more frequent (19% vs. 2%), mainly headache (12% vs. 4%), lipid changes dependent on prior therapy
Biktarvy® (women only) GS-1961 (Kityo 2019)	472	53% Genvoya® 42% Stribild®	DRAEs slightly more frequent (9% vs. 6%), lipids and renal values idem
Biktarvy® GS-1844 (Molina 2019)	567	96% Triumeq®	DRAEs less frequent (8% vs. 16%), mainly gastrointestinal (0% vs. 5%), lipids and renal values minimally better
Genvoya® GS-109 (Mills 2016)	1,443	42% ATV/r/c 32% Stribild® 26% EFV	DRAEs more frequent (21% vs. 16%, primarily mild), GFR +3.3 mL/min, bone density better, lipids worse
Symtuza® EMERALD (Orkin 2017)	1,141	58% DRV/r 21% ATV/r 13% DRV/c	DRAEs more frequent (18% vs. 7%, primarily mild), GFR idem, bone density better, lipids slightly worse
Delstrigo® DRIVE-SHIFT (Johnson 2019)	670	37% DRV/r 22% ATV/r 17% EFV	DRAEs more frequent (20% vs. 2%, primarily mild), headache (7% vs. 2%), lipids slightly better vs PIs
Eviplera® SPIRIT (Palella 2014)	476	37% ATV/r 33% LPV/r 20% DRV/r	AEs overall same (but 7 vs. 0 discontinuations), lipids overall significantly better
Odefsey® GS-1160/1216 (Hagins 2018)	1,505	58% Atripla® 42% Eviplera®	AEs same, renal values, bone density better, lipids hardly changed

The exclusion criteria were always virological failure and/or resistance – except for EMERALD.
DR AEs = Drug-Related Adverse Events. GFR = Glomerular Filtration Rate.

In EMERALD, the only study in which prior treatment failure was allowed, 70% of the participants were pre-treated with darunavir/r or darunavir/c and then switched to a darunavir/c-containing STR (good to know, but little could go wrong).
The effects on kidneys, bones, and lipids were partly due to the backbone. When switching to TAF, lipids increase; when switching to TDF, they decrease – and *vice versa*. Notably, "drug-related AEs" (DRAEs) were more common in many studies due to the switch – no surprise since most studies switched from stable therapies. In GS-1844, the only study in which fewer DRAEs were observed as a result of the intervention (switching from Triumeq® to Biktary®), the switch was precisely not only from dolutegravir to bictegravir but also from the possibly gastrointestinally less tolerated NRTI abacavir to TAF (Molina 2019).
STR is possible if no resistance or previous therapies have failed. In the case of a therapy that has worked well up to now, however, a change is likely to result in new (usually mild) side effects. Thus, the argument used by the manufacturers in these cases that the patients had previously been on stable, well-tolerated ART can be read differently: not every satisfied patient needs to switch to an STR. It is not malpractice to remain on a functioning therapy, even if it consists of more than one pill.

De-escalation to less than three drugs

Can HIV infection be treated with a sequence of intensive induction therapy followed by reduced (potentially less toxic, cheaper) maintenance therapy? The question was asked as far back as the 1990s, and the answer was always no. Randomized trials such as Trilège, ADAM, or ACTG 343 consistently disappointed. However, they used outdated drugs such as saquinavir, indinavir, or nelfinavir. Only in recent years has the question of maintenance therapy been raised again. Agents with a high resistance barrier are now available and are being investigated as part of dual or monotherapies.
It is time to dedicate a new chapter to de-escalation strategies. De-escalate is admittedly a strong word. It is also misleading: it implies that escalation has taken place beforehand. Ultimately, however, standard therapies – most of which are well tolerated – are reduced by one or two agents. These strategies are described below.

Officially approved STR options for dual therapy

In 2018, Juluca®, the combination of dolutegravir and rilpivirine, was approved as the first dual maintenance therapy. In 2019, Dovato® was added, the combination of dolutegravir and 3TC, for which the indication has since been expanded to include treatment-naïve individuals (see above). Since the end of 2020, the long-acting combination of Vocabria® and Rekambys®, the combination of cabotegravir and rilpivirine given every 4–8 weeks, is the first long-acting option for pre-treated patients, also consisting of only two agents.

Dolutegravir plus rilpivirine (Juluca®) was the first official combination to forgo NRTIs entirely. Two large Phase III trials (SWORD I+II, n=1,028) tested Juluca® against continuation of successful first-line or second-line ART (Llibre 2018, Aboud 2019). Virologic failure was sporadic, and INSTI resistance did not occur at all. However, after 148 weeks in a long-term follow-up, six people (0.6%) had developed NNRTI resistance (van Wyk 2020) despite stringent inclusion criteria: a maximum of two prior therapies, no virological failure, no resistance, and no hepatitis B. In other words, patients would certainly not expect treatment failure. Another downer: CNS side effects from dolutegravir were more likely to lead to discontinuation (9 versus 1 case), and mild side effects were also more common, at 17% versus 2%. In one sub-study, bone density did improve, especially when TDF was discontinued (McComsey 2017).

To ensure adequate absorption of rilpivirine, Juluca® must be taken with food. It remains unclear so far who would benefit from such a choice. The argument that switching to TAF-based regimens may have the same benefits on bone density is also valid. Thus, at the moment, Juluca® seems particularly useful if one wants to be nuke-free and, for example, prevent the progression of lipoatrophy – but these are often people with extended previous therapy and resistance – so they are not eligible. WISARD, a large Phase III study with Juluca® in pre-treated PLWH, in which specific resistance is allowed, is still ongoing (and suffers from slow enrollment), and results are pending.

Apart from Juluca®, other combinations of INSTIs and NNRTIs have been tested in mostly uncontrolled trials, including raltegravir plus nevirapine (Calcagno 2016) or etravirine (Casado 2015). These strategies have little role now. Due to unfavorable PK data, Dolutegravir and etravirine should not be combined (Song 2011).

Dolutegravir plus 3TC (Dovato®): In treatment-naïve patients in the GEMINI trials, this 2DR therapy was so effective that it was approved, with certain restrictions, in first-line therapy (see above). Of course, it can also be considered for pre-treated patients. In two large, open, randomized trials, non-inferiority was shown for switching to Dovato®.

In TANGO, 743 PLWH were randomized to open-label switching to Dovato® or to remain on their successful triple regimen (TAF-based regimen only, 66% Genvoya®). Inclusion criteria were strict: first-line therapy, including viral load below the limit of detection for at least six months, no AIDS-related illness, no hepatitis B, no resistance or prior treatment failure. After 144 weeks, viral suppression was maintained in all subjects, and no resistance occurred. Blips were also not observed to increase with dual therapy (Osiyemi 2022). Of note, adverse events occurred more frequently with Dovato® (15%; 4% led to discontinuation) than with TAF-based therapies (5%; 1%). No relevant changes in renal function and inflammatory and bone biomarkers were observed.

The SALSA trial had a similar design, but non-TAF therapies were allowed (often efavirenz-based). None of the 493 participants met the criteria for virologic failure (Llibre 2022). Again, adverse events occurred more frequently with Dovato® (20%) than with continued ART (6%). Renal function and bone turnover biomarkers improved on Dovato® (unlike TANGO, 44% had TDF on existing ART here). Changes in lipids and inflammatory biomarkers remained minimal. Similar results to SALSA and TANGO were also obtained in the somewhat smaller Spanish DOLAM study (Rojas 2021).

In the absence of resistance and hepatitis B, the switch is quite possible. However, a real advantage has not been seen either. Inflammatory or atherogenic parameters remained almost unchanged (Llibre 2022). Thus, Dovato® currently continues to serve the intuition of patients and their clinicians: less is more, especially with life-long therapy. What is not necessary (tenofovir) can be saved.

De-escalation to dual therapy with Dovato® and Juluca®

- Strict selection: No hepatitis B, first-line or at most second-line therapy, no prior treatment failure, no resistance, no adherence problems.
- De-escalation carries some risk of new side effects from dolutegravir (especially neuropsychiatric events).
- Significant advantages have not been seen so far; however, 2DR is a long-term therapy with as little toxicity as possible.
- Nutritional restrictions for Juluca® should be observed.
- Close monitoring of viral load can be considered to minimize the risk of resistance.

Long-acting

The administration of depot injections, also known as "long-acting", is undoubtedly an innovative, forward-looking concept in HIV medicine. It is especially interesting for those patients who (unfortunately still) are worried that their HIV infection will become known to family, friends, or roommates. These people willingly visit the HIV center every 4–8 weeks for injections. However, according to surveys, many other patients would also accept the injections – so they do not have to worry about taking their daily pill for the remaining month. Coming to the doctor's office once a month to pick up a shot (or two) seems surprisingly attractive: in a French survey, 64% said they preferred monthly injections to pills, and the figure was as high as 76% for bi-monthly doses (Khuong-Josses 2019).

But is this also true after careful explanation? This new depot therapy harbors a whole series of potential problems in everyday life. The logistical effort is significant; different dosages of cabotegravir may be a potential source of error. The drugs must be stored in a cool place in the pharmacy and brought to room temperature (not above 25 °C) before use. Two deep intramuscular injections of 2–3 mL per month are pretty planning- and labor-intensive, not free of risks and painless. Following administration, patients should be monitored for a few minutes. The management at the beginning and the end of such a therapy, in case of delayed administration or in case of potential interactions, is complex. Moreover, it remains unclear which patients are at risk for virological failure, which occurs in 0.5–1% per year and is often accompanied by INSTI and NNRTI resistance (see below).

However, especially for people with adherence problems, parenteral administration will usually not be a good solution. People who find it challenging to comply with today's standard antiretroviral therapy of only one tablet a day will find it more difficult to keep regular and fixed appointments for injections. In the case of depot doses, this bears a high risk for resistance. If doses are missed, a prolonged decline in plasma levels is to be expected – unlike with tablets. The agents are often still detectable in subtherapeutic ranges for many months, which provides the virus with ideal conditions for selecting resistance mutations. With such resistance mutations to cabotegravir and rilpivirine, two of the most important antiretroviral substance classes would be permanently compromised.

It is also unclear whether there is any other advantage for the depot administration apart from convenience. The price is probably not – it is no lower than conventional STRs. The assumption of a lower "burden" that is often widespread among patients, which is still partly fueled by lay media ("monthly injection instead of pill cocktail"), is also not tenable. However, this may be true for frequent travelers. Both agents come from conventional antiretroviral drug classes; the exposure is the same, and a similar therapy has been available for years as STR.

Cabotegravir plus rilpivirine LA: Dual therapy of monthly injections with cabotegravir (Vocabria®) and rilpivirine (Rekambys®), colloquially CARLA (in the US: Cabenuva®), demonstrated non-inferiority to conventional therapies in two significant Phase III trials. In ATLAS, 705 people were successfully pre-treated with different ART regimens for a mean of four years; in FLAIR, 629 treatment-naïve people had initially received several months of induction therapy with ABC/3TC/dolutegravir (Triumeq®), and 566 were randomized (Review: Bares 2022). In November 2017, ATLAS was expanded to include ATLAS-2M. This study compared four- versus eight-week injections and demonstrated non-inferiority of the 8-week arm at 96 weeks (Jäger 2021). Virologic failure was rarely seen but was mainly accompanied by resistance in 9/522 cases. Nevertheless, approval for CARLA spans both 4- and 8-weekly injections. Tolerability has been good so far, and problems at the injection site (pain, swelling, redness) only led very rarely (less than 1%) to discontinuation.

As mentioned above, whether and which people are at increased risk of treatment failure is not yet fully understood. Data from participants randomized to long-acting CARLA Q4W or Q8W dosing within the Phase 3 FLAIR, ATLAS, and ATLAS-2M studies through Week 48 were pooled in a post-hoc analysis. There were three risk factors for virological failure, namely a pre-existing rilpivirine resistance (from proviral DNA analysis at baseline), the presence of HIV subtype A6 or A1, and a BMI of at least 30 kg/m² (Cutrell 2021). The risk of virological failure (often with resistance against both INSTI and NNRTI) was 1% during the first year and increased significantly in the presence of at least two factors. Of all participants with at least two factors, the rate was 26% (n=9/35). Of note, plasma levels in cases of treatment failure were relatively low but not too low to explain the failure. Plausible explanations thus remain lacking.

Although there are now also some centers that use long-acting on a large scale, many continue to shy away from the effort. The industry is taking note of this. It is no coincidence that alternative routes of administration are being investigated, both subcutaneous injections and those into the thigh, and initial results have already been published (Benn 2022, Han 2022). Subcutaneous administration, in particular, should significantly increase acceptance, as should longer intervals.

De-escalation of long-acting agents, practical aspects

- Note strict selection as with all dual therapies: only first-line or, at most, second-line therapy with virological suppression, no prior treatment failure, no resistance, no hepatitis B.
- "Lead-in" with oral cabotegravir and rilpivirine for one month, then two injections at one-month intervals, then every two months thereafter.
- Use the same side for each injection ("Rekambys right side"), trained personnel!
- Indicate possible pain at the injection site; use longer hypodermic needles in obese patients.
- Accurate scheduling (plus/minus seven days allowed), including "oral bridging" if necessary.
- If discontinued within 4–8 weeks, start new ART.
- Rarely, failure and development of resistance occur, sometimes unexplained – it is better to check viral load every 1–2 months in the beginning.
- Possibly more co-payments, indeed more doctor's visits for those affected.

More options

Given the approval of two STR options, other 2DR concepts are increasingly moving into the background. Nevertheless, they will be briefly discussed here.

Darunavir (and other PIs) plus 3TC worked well in therapy-naïve patients in the GARDEL study (see above) and pre-treated patients. Four larger studies examined de-escalation to atazanavir/r, lopinavir/r, and darunavir/r plus 3TC (see Table 8.2). The combination proved similarly effective, and blips were not observed more frequently. Limitations remain, however: all studies examined only the discontinuation of TDF and abacavir, not TAF. Patients with resistance to 3TC or the PI, previous virologic failure, and hepatitis B were excluded. Switching had, at best, only moderate effects on the kidney and bone when TDF was discontinued and mainly resulted in risk-neutral increases in HDL + LDL. The clinical relevance of these changes remained questionable. Apart from cost considerations (no longer relevant after the price decline of TDF), there is little argument for this approach other than intuition ("less is better"). Moreover, 2DR is not entirely correct: the PI is boosted with ritonavir, so there are still three agents, strictly speaking.

Table 8.2: Randomized trials of dual therapy in virologically successfully suppressed patients (TDF was omitted in 61–82%, abacavir in 15–26%).

Study, reference	Dual therapy (n)	Main results
DUAL GESIDA Pulido 2017	DRV/r+3TC (n=249)	AEs equal, lipids idem (increase in HDL/LDL), GFR idem
ATLAS-M Di Giambenedetto 2017	ATV/r+3TC (n=266)	AEs same, lipids idem (increase in HDL/LDL), GFR slightly better
SALT Perez-Molina 2015	ATV/r+3TC (n=286)	AEs same, lipids slightly worse, GFR/BMD unchanged
OLE Arribas 2015, Crespo 2016	LPV/r+3TC (n=250)	AEs same, lipids slightly worse, GFR/BMD slightly better (if switching from TDF)

Exclusion criteria in all studies: hepatitis B, resistance to 3TC and the PIs in question. * In SALT, patients switched from different therapies, including NNRTIs. GFR = glomerular filtration rate, AE = adverse events.

Experimental 2DR combinations

A variety of dual combinations, as well as monotherapies, have been tested in recent years. Benefits are currently not apparent, and some participants lost virological control in some studies. Such experiments are not recommended outside of trials, and participation in such studies must also be justified. The following is a brief overview.

Darunavir/r plus raltegravir: The NEAT study showed promising efficacy in treatment-naive patients (see above). In pre-treated patients, the data are much more limited. In a pilot study, darunavir/r+raltegravir did not improve renal function (Nishijima 2014).

Darunavir/r plus dolutegravir: Was investigated in the DUALIS study, which was underpowered (Spinner 2020). Neither showed advantages over classical ART with regard to weight, renal function, or lipids (Monin 2020). Other PIs, such as atazanavir or lopinavir, should not be used, and neither treatment failure (van Lunzen 2016) nor lipid deterioration was observed (Martin 2013).

Darunavir/r plus etravirine or rilpivirine: These combinations have also not shown any benefit. According to small studies, they seem possible in selected cases (Bernadino 2014, Maggiolo 2016). Combinations with lopinavir and older NNRTIs, on the other hand, were too weak and/or toxic (Fischl 2007).

PIs plus maraviroc: Probably not the best idea. In the three-arm MARCH trial, patients either switched from a PI-based regimen to a PI plus maraviroc, replaced the PI with maraviroc, or maintained their previous PI-based regimen; the failure rate was worryingly high (Pett 2016). This was also true in the smaller GUSTA trial (Rossetti 2017). Although very little resistance occurred, there is currently little to be said for this strategy. Incidentally, both studies are also arguments against the concept that a drug with a high resistance barrier (in this case, the PI) is sufficient as maintenance therapy.

INSTIs plus maraviroc: These nuke-saving combinations are experimental; their benefit is questionable. That they can also go wrong was shown by ROCnRAL, a pilot study in 44 people with lipodystrophy (Katlama 2014). These had received a median of 15 years of ART and a median of 5 years of viral load below the detection limit. After switching to "Nuke+PI sparing" with raltegravir+maraviroc, 7 individuals developed treatment failure, including 3 with RAL resistance, so the study had to be discontinued. Unfortunately, ROCnRAL shows too well that not everything works,

and one must remain cautious even with longstanding viral suppression. In 33 highly selected individuals who switched to raltegravir+maraviroc after initial quadruple therapy, one developed INSTI resistance (Pradat 2016).

TDF plus efavirenz: Bad idea! In the COOL study, several breakthroughs occurred (Girard 2006).

Experimental monotherapies

Monotherapies have been investigated and, in some cases, propagated in numerous, primarily underpowered studies. Those times are over. Monotherapies should be avoided whenever possible; there is rarely anything to be said against at least maintaining 3TC in the backbone. Lopinavir/r was too toxic; low viremia was common (Pulido 2008, Meynard 2010).

Darunavir/r: With MONET, MONOI, and PROTEA, there are several larger randomized trials. In MONET, at least for the primary endpoint, non-inferiority was not fully demonstrated at 96 weeks (Clumeck 2011). At 96 weeks, 82% in the standard arm were below the detection limit of 50 copies/mL, compared with 78% in the darunavir arm. At 144 weeks, the difference had increased from 4% to 6% (Arribas 2012). The PROTEA study also showed a slight difference (Girard 2017). The difference was no longer present unless virologically successful treatment switches were counted as failures. In MONOI, transient viremia was slightly more common with monotherapy after 96 weeks, and durable control with continuous VL below 50 copies/mL without any blip was found at 59% vs. 70% (Valantin 2012). Treatment failure was associated with shorter prior therapy and reduced compliance (Lambert-Niclot 2011). In MONOI, lipoatrophy improved in some patients (Valantin 2012).
In an analysis of more than 2,000 subjects from 13 randomized trials, PI monotherapy was slightly worse regarding virologic control, with an average of 8.3% more virologic failure. However, with subsequent re-intensification, these differences were no longer present. New resistance was rare, occurring in 14/1091 compared with 7/1109 in standard therapies (Arribas 2016). No options were lost in a pragmatic trial (PIVOT) in which 587 individuals were randomized to continue their PI-containing triple combination or to continue with the PI only (Paton 2015).

Dolutegravir: The relatively high resistance barrier of this INSTI initially made monotherapy seem possible. It is probably not sufficient. In four studies of 416 people (Fournier 2022), dolutegravir monotherapy significantly increased the risk of virologic failure (7% versus 0%). Dolutegravir monotherapies are no longer recommended. Those who still propagate them and expose patients – for no reason – to the risk of resistance must accept harsh criticism (Gallant 2017).

Monotherapies

- A monotherapy with PI/r is slightly less effective than triple therapies – the difference is consistently observed in all studies (about 8%). Whether PI monotherapies actually save long-term toxicity is not evident either.
- Low viremia without resistance usually occurs and disappears with re-intensification; the risk of resistance is low (< 1%) with PIs.
- The risk of resistance is higher with dolutegravir mono! Generally not recommended!
- Poor adherence, prior virologic failure, and low CD4 nadir are considered risk factors for failure.

Simplification and de-escalation literature

Aboud M, Orkin C, Podzamczer D, et al. Efficacy and safety of dolutegravir-rilpivirine for maintenance of virological suppression in adults with HIV-1: 100-week data from the randomised, open-label, phase 3 SWORD-1 and SWORD-2 studies. Lancet HIV. 2019 Jul 12.

Arribas J, Clumeck N, Nelson M, et al. The MONET trial: week 144 analysis of the efficacy of darunavir/ritonavir (DRV/r) monotherapy versus DRV/r plus two nucleoside reverse transcriptase inhibitors, for patients with viral load < 50 HIV-1 RNA copies/mL at baseline. HIV Med 2012 Mar 14.

Arribas JR, Girard PM, Landman R, et al. Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open-label, non-inferiority trial. Lancet Infect Dis 2015, 15:785-92.

Arribas JR, Girard PM, Paton N, Winston A, Marcelin AG, Elbirt D, Hill A, Hadacek MB. Efficacy of protease inhibitor monotherapy vs. triple therapy: meta-analysis of data from 2303 patients in 13 randomized trials. HIV Med 2016, 17:358-67.

Bares SH, Scarsi KK. A new paradigm for antiretroviral delivery: long-acting cabotegravir and rilpivirine for the treatment and prevention of HIV. Curr Opin HIV AIDS 2022, 17:22-31.

Benn P, Han L, Sievers J, et al. A study evaluating the safety, tolerability, and pharmacokinetics of a high-concentration (CAB 400mg/mL) cabotegravir long-acting injectable formulation following subcutaneous and intramuscular administration in healthy adult participants. Abstract PESUB24/6276, 24th IAC 2022, Montreal.

Bernardino JI, Zamora FX, Valencia E, et al. Efficacy of a dual therapy based on darunavir/ritonavir and etravirine in ART-experienced patients. J Int AIDS Soc 2014, 17(4 Suppl 3):19787.

Casado JL, Bañón S, Rodriguez MA, et al. Efficacy of dual therapy with lamivudine plus darunavir boosted with ritonavir once daily in HIV-infected patients with nucleoside analogue toxicity. J Antimicrob Chemother. 2015, Feb;70(2):630-2.

Casado JL, Bañón S, Rodriguez MA, Moreno A, Moreno S. Efficacy and pharmacokinetics of the combination of etravirine plus raltegravir as novel dual antiretroviral maintenance regimen in HIV-infected patients. Antiviral Res 2015, 113:103-6.

Clumeck N, Rieger A, Banhegyi D, et al. 96 week results from the MONET trial: a randomized comparison of darunavir/ritonavir with versus without nucleoside analogues, for patients with HIV RNA <50 copies/mL at baseline. J Antimicr Chemother 2011, 66:1878-85.

Crespo M, Navarro J, Martinez-Rebollar M, et al. Improvement of BMD after Switching from Lopinavir/R Plus Two Nucleos(T)ide Reverse Transcriptase Inhibitors to Lopinavir/R Plus Lamivudine: OLE-LIP Substudy. HIV Clin Trials 2016, 17:89-95.

Cutrell AG, Schapiro JM, Perno CF, et al. Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis. AIDS 2021, 35:1333-1342.

Daar ES, DeJesus E, Ruane P, et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1. Lancet HIV 2018; 5:e347-e356 29925490.

Di Giambenedetto S, Fabbiani M, Quiros Roldan E, et al. Treatment simplification to atazanavir/ritonavir + lamivudine versus maintenance of atazanavir/ritonavir + two NRTIs in virologically suppressed HIV-1-infected patients: 48 week results from a randomized trial (ATLAS-M). J Antimicrob Chemother 2017, 72:1163-1171.

Fischl MA, Collier AC, Mukherjee AL, et al. Randomized open-label trial of two simplified, class-sparing regimens following a first suppressive three or four-drug regimen. AIDS 2007; 21: 325-333.

Fournier AL, Hocqueloux L, Braun DL, et al. Dolutegravir Monotherapy as Maintenance Strategy: A Meta-Analysis of Individual Participant Data From Randomized Controlled Trials. Open Forum Infect Dis 2022, 9:ofac107.

Gallant J, Sugarman J. Dolutegravir monotherapy: when should clinical practice be clinical research? Antivir Ther 2017, 22:93-95.

Gatell J, Salmon-Ceron D, Lazzarin A, et al. Efficacy and safety of atazanavir-based HAART in pts with virologic suppression switched from a stable, boosted or unboosted PI treatment regimen: the SWAN Study. CID 2007;44:1484-92.

Girard PM, Antinori A, Arribas JR, et al. Week 96 efficacy and safety of darunavir/ritonavir monotherapy vs. darunavir/ritonavir with two nucleoside reverse transcriptase inhibitors in the PROTEA trial. HIV Med. 2016 Jun 9.

Girard PM, Cabié A, Michelet C, et al. TenofovirDF + efavirenz (TDF+EFV) vs tenofovirDF+ efavirenz + lamivudine (TDF+EFV+3TC) maintenance regimen in virologically controlled patients (pts): COOL Trial. Abstract H-1383, 46th ICAAC 2006, San Francisco.

Hagins D, Orkin C, Daar ES, et al. Switching to coformulated rilpivirine (RPV), emtricitabine (FTC) and tenofovir alafenamide from either RPV, FTC and tenofovir disoproxil fumarate (TDF) or efavirenz, FTC and TDF: 96-week results from two randomized clinical trials. HIV Med 2018, 19:724-733.

Han K, Shaik JS, Crauwels H, et al. Pharmacokinetics (PK) and tolerability of cabotegravir (CAB) and rilpivirine (RPV) long-acting (LA) intramuscular (IM) injections to the vastus lateralis (lateral thigh) muscles of healthy adult participants. Abstract EPB176/9906, 24th IAC 2022, Montreal.

Jaeger H, Overton ET, Richmond G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 96-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. Lancet HIV 2021, 8:e679-e689.

Johnson M, Kumar P, Molina JM, et al. Switching to Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DOR/3TC/TDF) Maintains HIV-1 Virologic Suppression Through 48 Weeks: Results of the DRIVE-SHIFT Trial. J Acquir Immune Defic Syndr 2019, 81:463-472.

Katlama C, Assoumou L, Valantin MA, et al. Maraviroc plus raltegravir failed to maintain virological suppression in HIV-infected patients with lipohypertrophy: results from the ROCnRAL ANRS 157 study. J Antimicrob Chemother 2014, 69:1648-52.

Khuong-Josses MA, Charpentier C, Sayre N, et al. Will HIV-infected patients taking oral ARV switch to long-acting injectable ART when it becomes available? Abstract PE30/3, 17th EACS 2019, Basel.

Kityo C, Hagins D, Koenig E, et al. Switching to Fixed-Dose Bictegravir, Emtricitabine, and Tenofovir Alafenamide (B/F/TAF) in Virologically Suppressed HIV-1 Infected Women: A Randomized, Open-Label, Multicenter, Active-Controlled, Phase 3, Noninferiority Trial. J AIDS 2019, 82:321-328. 31609930.

Lambert-Niclot S, Flandre P, Valantin MA, et al. Factors associated with virological failure in HIV-1-infected patients receiving darunavir/ritonavir monotherapy. J Infect Dis 2011, 204:1211-6.

Lambert-Niclot S, Flandre P, Valantin MA, et al. Resistant minority species are rarely observed in patients on darunavir/ritonavir monotherapy. J Antimicrob Chemother. 2012 Mar 5. [Epub ahead of print].

Llibre JM, Brites C, Cheng CY, et al. Efficacy and Safety of Switching to the 2-Drug Regimen Dolutegravir/Lamivudine Versus Continuing a 3- or 4-Drug Regimen for Maintaining Virologic Suppression in Adults Living With HIV-1: Week 48 Results From the Phase 3, Non-inferiority SALSA Randomized Trial. Clin Infect Dis. 2022 Mar 2:ciac130.

Llibre JM, Cahn PE, Lo J, et al. Changes in Inflammatory and Atherogenesis Biomarkers With the 2-Drug Regimen Dolutegravir Plus Lamivudine in Antiretroviral Therapy-Experienced, Virologically Suppressed People With HIV-1: A Systematic Literature Review. Open Forum Infect Dis. 2022 Feb 10;9:ofac068.

Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. Lancet 2018 Jan 5.

Maggiolo F, Di Filippo E, Valenti D, Ortega PS, Callegaro A. NRTI Sparing Therapy in Virologically Controlled HIV-1 Infected Subjects: Results of a Controlled, Randomized Trial (Probe). J AIDS 2016, 72:46-51.

Martin A, Moore CL, Mallon PW, et al. HIV lipodystrophy in participants randomised to lopinavir/ritonavir (LPV/r) +2-3 nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTI) or LPV/r + raltegravir as second-line antiretroviral therapy. PLoS One 2013, 8:e77138.

McComsey GA, Lupo S, Parks D, et al. Switch from tenofovir disoproxil fumarate combination to dolutegravir plus rilpivirine improves parameters of bone health. AIDS. 2017 Dec 12.

Meynard JL, Bouteloup V, Landman R, et al. Lopinavir/ritonavir monotherapy versus current treatment continuation for maintenance therapy of HIV-1 infection: the KALESOLO trial. J Antimicrob Chemother 2010, 65:2436-44.

Mills A, Arribas JR, Andrade-Villanueva J, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. Lancet Infect Dis 2016, 16:43-52.

Molina JM, Ward D, Brar I, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1. Lancet HIV 2018;5:e357-e365. 29925489.

Monin M, Kümmerle T, Schneider J, et al. Switching to a NRTI-free 2 drug regimen (2DR) -a sub-analysis of the 48 weeks DUALIS study on metabolic and renal changes. Open Forum Infect Dis 2020, 7:ofaa356.

Nishijima T, Gatanaga H, Shimbo T, et al. Switching tenofovir/emtricitabine plus lopinavir/r to raltegravir plus Darunavir/r in patients with suppressed viral load did not result in improvement of renal function but could sustain viral suppression: a randomized multicenter trial. PLoS One 2013, 8:e73639.

Osiyemi O, De Wit S, Ajana F, et al. Efficacy and Safety of Switching to Dolutegravir/Lamivudine Versus Continuing a Tenofovir Alafenamide-Based 3- or 4-Drug Regimen for Maintenance of Virologic Suppression in Adults Living With Human Immunodeficiency Virus Type 1: Results Through Week 144 From the Phase 3, Noninferiority TANGO Randomized Trial. Clin Infect Dis 2022, 75:975-986.

Palella FJ Jr1, Fisher M, Tebas P, et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. AIDS 2014, 28:335-44.

Paton NI, Stöhr W, Arenas-Pinto A, et al. Protease inhibitor monotherapy for long-term management of HIV infection: a randomised, controlled, open-label, non-inferiority trial. Lancet HIV 2015, 2:e417-26.

Perez-Molina JA, Rubio R, Rivero A, et al. Dual treatment with atazanavir-ritonavir plus lamivudine versus triple treatment with atazanavir-ritonavir plus two nucleos(t)ides in virologically stable patients with HIV-1 (SALT): 48 week results from a randomised, open-label, non-inferiority trial. Lancet Infect Dis 2015, 15:775-84.

Perez-Molina JA, Rubio R, Rivero A, et al. Simplification to dual therapy (atazanavir/ritonavir+lamivudine) versus standard triple therapy [atazanavir/ritonavir+two nucleos(t)ides] in virologically stable patients on antiretroviral therapy: 96 week results from an open-label, non-inferiority, randomized clinical trial (SALT study). J Antimicrob Chemother 2017, 72:246-253.

Pett SL, Amin J, Horban A, et al. Maraviroc, as a Switch Option, in HIV-1-infected Individuals With Stable, Well-controlled HIV Replication and R5-tropic Virus on Their First Nucleoside/Nucleotide Reverse Transcriptase Inhibitor Plus Ritonavir-boosted Protease Inhibitor Regimen: Week 48 Results of the Randomized, Multicenter MARCH Study. Clin Infect Dis 2016, 63:122-32.

Pradat P, Durant J, Brochier C, et al. Maraviroc/raltegravir simplification strategy following 6 months of quadruple therapy with tenofovir/emtricitabine/maraviroc/raltegravir in treatment-naive HIV patients. J Antimicrob Chemother 2016, 71:3235-3241.

Pulido F, Delgado R, Pérez-Valero I, et al. Long-term (4 years) efficacy of lopinavir/ritonavir monotherapy for maintenance of HIV suppression. J Antimicrob Chemother 2008, 61:1359-61.

Pulido F, Ribera E, Lagarde M, et al. Dual Therapy With Darunavir and Ritonavir Plus Lamivudine vs Triple Therapy With Darunavir and Ritonavir Plus Tenofovir Disoproxil Fumarate and Emtricitabine or Abacavir and Lamivudine for Maintenance of Human Immunodeficiency Virus Type 1 Viral Suppression: Randomized, Open-Label, Noninferiority DUAL-GESIDA 8014-RIS-EST45 Trial. Clin Infect Dis 2017; 65:2112-18.

Rojas J, Blanco JL, Marcos MA, et al. Dolutegravir monotherapy in HIV-infected patients with sustained viral suppression. J Antimicrob Chemother 2016, 71:1975-81.

Rojas J, de Lazzari E, Negredo E, et al. Efficacy and safety of switching to dolutegravir plus lamivudine versus continuing triple antiretroviral therapy in virologically suppressed adults with HIV at 48 weeks (DOLAM): a randomised non-inferiority trial. Lancet HIV 2021, 8:e463-e473.

Rossetti B, Gagliardini R, Meini G, et al. Switch to maraviroc with darunavir/r, both QD, in patients with suppressed HIV-1 was well tolerated but virologically inferior to standard antiretroviral therapy: 48-week results of a randomized trial. PLoS One 2017 , 21;12:e0187393.

Song I, Borland J, Min S, et al. Effects of etravirine alone and with ritonavir-boosted protease inhibitors on the pharmacokinetics of dolutegravir. Antimicrob Agents Chemother. 2011 Jul;55(7):3517-21.

Spinner CD, Kümmerle T, Schneider J, et al. Efficacy and Safety of Switching to Dolutegravir With Boosted Darunavir in Virologically Suppressed Adults With HIV-1: A Randomized, Open-Label, Multicenter, Phase 3, Noninferiority Trial: The DUALIS Study. Open Forum Infect Dis 2020, 7:ofaa356.

Spinner CD, Kümmerle Z, Schneider J, et al. A switch to dolutegravir in combination with boosted darunavir is safe and effective in suppressed patients with HIV – a subanalysis of the DUALIS study. Abstract MOPEB269, IAS 2019, Mexico.

Trottier B, Lake JE, Logue K, et al. Dolutegravir/abacavir/lamivudine versus current ART in virally suppressed patients (STRIIVING): a 48-week, randomized, non-inferiority, open-label, Phase IIIb study. Antivir Ther 2017, 22:295-305.

Valantin M, Kolta S, Flandre P, et al. Body fat distribution in HIV-infected patients treated for 96 weeks with darunavir/ritonavir monotherapy versus darunavir/ritonavir plus nucleoside reverse transcriptase inhibitors: the MONOI-ANRS136 Substudy. HIV Med. 2012, 13:505-15.Mar 14.

van Lunzen J, Pozniak A, Gatell JM, et al. Brief Report: Switch to Ritonavir-Boosted Atazanavir Plus Raltegravir in Virologically Suppressed Patients With HIV-1 Infection: A Randomized Pilot Study. J Acquir Immune Defic Syndr 2016, 71:538-43.

Van Wyk J, Ajana F, Bisshop F, et al. Efficacy and Safety of Switching to Dolutegravir/Lamivudine Fixed-Dose Two-Drug Regimen Versus Continuing a Tenofovir Alafenamide-Based Three- or Four-Drug Regimen for Maintenance of Virologic Suppression in Adults With HIV-1: Phase 3, Randomized, Non-inferiority TANGO Study. Clin Infect Dis. 2020 Jan 6.

van Wyk J, Orkin C, Rubio R, et al. Brief Report: Durable Suppression and Low Rate of Virologic Failure 3 Years After Switch to Dolutegravir + Rilpivirine 2-Drug Regimen: 148-Week Results From the SWORD-1 and SWORD-2 Randomized Clinical Trials. J AIDS 2020, 85:325-330.

5.9. Virological failure

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Virologic treatment failure has fortunately become rare. However, many mistakes can be made when it does occur: experience, finesse, and decisiveness help. On the one hand, there is a risk of further resistance; on the other hand, rapid change is not always the right solution, as rapid changes in therapy can be unsettling and confusing. If a given ART regimen – for whatever reason – is not taken correctly, the new one often will not be either. A switch can provoke new misunderstandings and further resistance. It is essential to explain to patients who are often skeptical about when and why treatment changes must be made.

As a rule, ART should be changed quickly if viral suppression is insufficient. The virus continues to mutate, resistance mutations accumulate, and further options may be permanently lost. Virologic failure should be assumed if the viral load is repeatedly not below the detection limit of 50 HIV RNA copies/mL. The limit above which action should be taken is 200 copies/mL. Very high values above 1,000 copies/mL usually indicate a break in therapy. Values below 200 copies/mL must be clarified to determine whether they are transient viremia (blips) or persistently low viremia. These usually do not require a change (see *Therapy Principles*). Individual resistance mutations must be considered: for example, with the K65R mutation, which is frequently selected by tenofovir, both abacavir and 3TC/FTC lose significant efficacy. Viral replication at insufficient plasma levels is an ideal ground for resistance. However, the reality is often different: in an analysis from Great Britain, 34% of 694 persons remained on a virologically failing combination for more than six months. Factors associated with rapid switching were low CD4 T-cells, high viral load, and older age (UK Chic 2008).

However, the situation looks different once the first resistance mutations are present. There are, of course, only a few good studies on whether to switch immediately or delay the switch in the setting of virological failure. Randomized trial results suggest that waiting a little is possible (Nasta 2006, Tenorio 2009). However, these studies suffered from small case numbers – motivating patients for such strategy studies is difficult.

Arguments for a rapid switch in the case of virologic failure	Arguments for a later switch in the case of virologic failure
The virus becomes incapable of generating further resistance	New therapies bear the risk of new intolerances/toxicities
Options are maintained	With low viremia, patients often remain immunologically stable for a long time (also clinically, anyway)
The switch is more successful with less resistance	Replication fitness is sometimes reduced with resistance
The lower the viral load at the time of the switch, the better the response to the new therapy	With a low viral load, resistance testing is often not yet possible (although resistance is already present)
Often, the subsequent regime does not have to be more complex than the current one – some things can be simplified!	Switching from a well-tolerated, simple regimen can be challenging to communicate to patients

At least with failing PI therapies, there is probably a bit more time. In the prospective Johns Hopkins cohort, there was no association between delay in ART modification and mortality during virologic failure, at least for PI treatment (Petersen 2008). In the TITAN study, the number of acquired PI mutations did not play a role in the success of darunavir (De Meyer 2008).
In case of clinical or immunological failure (AIDS, CD4 drop/lack of increase), the success of switching is questionable if the viral load is below 50 copies/mL. However, some agents, such as TDF+DDI or AZT, tend to be unfavorable for immunologic reconstitution; switching should be used in such a combination. However, ART switches alone are unlikely to improve immunologically (see *Treatment Principles*).

What to clarify before the switch

In the case of virological failure, it is crucial to analyze the situation in detail. Specifically, one should ask some questions:

What is the reason for the measurable viral load? A viral load above 50 copies/mL does not necessarily mean that resistance has occurred. A common (if not the most common) cause is blips or transient viral load increases. These blips are usually insignificant (see detailed discussion in chapter 5.4.) and almost always below 200 (maximum 400) copies/mL. Thus, a treatment switch should be considered only if the viral load remains detectable after a short-term check after four weeks. Of course, the viremia may also be due to insufficient plasma levels (measure plasma levels!), which in turn may have different causes: malabsorption (is the patient taking PPIs?) or even too low dosage (for example, in very tall, heavy people). Interactions are also important.

How is the patient's adherence? Adherence is critical. It should be addressed openly, and possible problems with taking the therapy should be discussed. Is the therapy taken every day, as discussed? If not, why not? Is it the number of pills and the pill size? Is it possible to take food at the same time? Would once daily be better? Are there other causes (depression)? Misunderstanding about the dosages? Many patients do not know their medication, even after years. The risk of resistance due to poor adherence should be addressed repeatedly.

How vulnerable is the present combination? NNRTIs are very sensitive, and cross-resistance can develop rapidly for the whole class. A prompt change in therapy is more vital than the other drug classes. Delaying the switch a few days and weeks can already be too long! The rapid development of resistance can also be expected quickly with 3TC and FTC, but probably also with raltegravir and elvitegravir. With PI- or dolutegravir-containing regimens, one probably has more time for the switch. Again, however, the higher the viral load at the time of switching, the lower the chances of success – one should not wait too long.

What options does the patient have, and what are the consequences of the treatment change? The more available options and accessible they are to implement, the sooner they should be utilized. Therapy can sometimes be intensified quite quickly. Using agents with a high resistance barrier, such as darunavir/r, bictegravir, or dolutegravir, is essential. Especially if and as long as the patient's adherence is uncertain, it makes little sense to waste new drug classes. Therefore, it should always be clarified before the change whether the patient is capable of switching.

Virological failure: What to consider pre-switch

- How vulnerable to resistance is the current therapy? NNRTIs, 3TC/FTC, raltegravir, elvitegravir: rapid development of resistance – rapid switch recommended!
- The lower the viral load, the greater the success of treatment change.
- Always use agents with a high resistance barrier: darunavir/r, dolutegravir, bictegravir! If NNRTIs are to be included, use etravirine, doravirine.
- Are you sure it is a virological failure, not a temporary blip? Check viral load within 2–4 weeks!
- Are there other reasons for a detectable viral load? Resorption problems? What concurrent therapies are taken? Whether "stomach pill from the family doctor" (PPIs?) or "herbal agents from the alternative practitioner": it all should be on the table.
- Is the present ART taken correctly, or are there possibly misunderstandings?
- Was the therapy interrupted? What do the plasma levels say? What does the patient say?
- What options are available, and what does a change mean? Can the patient take a new therapy?
- Is a reasonably up-to-date resistance test available? (if not, do one!)
- If relevant mutations to the current agents have already developed, calmly wait and prepare the person for a new regimen, possibly with more adherence counseling.

Choice of the follow-up regime

In principle, the same conditions apply to first-line therapy. Adherence, intake modalities, concomitant diseases, and co-medications/interactions should be considered. In addition, prior therapy and possibly existing resistance now play a decisive role. Resistance testing is desirable in cases of virologic failure before any switch but is not always practical. Knowing the essential resistance mutations is helpful, especially for the nucleoside analogs (Table 9.1).

Table 9.1: Resistance mutations are to be expected with different NRTI backbones.

Failing Nuke Backbone	Mutations
AZT or d4T plus 3TC AZT/3TC/ABC	M184V and sequential thymidine analog mutations (the longer the failure)
TDF or TAF plus 3TC or FTC	K65R and/or M184V
ABC/3TC	M184V and/or L74V > K65R
AZT or d4T plus ddI	TAMs, Q151M, T69ins
TDF plus ABC or ddI	K65R

The following applies to any switch in case of virological failure: the faster, the better. The virus should not be given too much time to generate further resistance mutations. The longer one waits, the more complex the resistance pattern becomes (Wallis 2010). And, the more agents that are switched, the greater the likelihood that the new therapy will take hold. It is also crucial that agents with a high resistance barrier are used whenever therapy fails. These include, above all, darunavir/r, dolutegravir and bictegravir. Especially in uncertainty about the existing resistance situation, these three agents are preferable to first-generation INSTIs or NNRTIs (see Table 9.2).

Table 9.2: Possible switch of first-line therapy without knowledge of the resistance situation*.

Failing First-line therapy	Promising switch
2 NRTI + 1 NNRTI	Replace NNRTI with preferably darunavir/r (or also bictegravir, dolutegravir) or darunavir/r plus dolutegravir.
2 NRTI + 1 PI/r	1–2 new nukes plus INSTI (preferably dolutegravir or bictegravir) or possibly doravirine+dolutegravir (data more scarce).
2 NRTI + 1 INSTI	1–2 new nukes plus darunavir/r (if acted upon quickly).

* In individual cases, other modifications or even a wait-and-see approach may be appropriate. Chose drugs with a high resistance barrier if possible: darunavir/r, dolutegravir, bictegravir. For more complex resistance situations, see also *Salvage*.

Virologic treatment failure with NNRTIs. With nevirapine or efavirenz, cross-resistance is usually present, and the development of resistance also occurs very rapidly. This is also true for rilpivirine, which is very vulerable to high viral loads. Continuation of an NNRTI in the presence of resistance is useless, as it does not affect the replicative fitness of the viruses. More so, since cumulative resistance could also affect the efficacy of second-generation NNRTIs, the NNRTI should be stopped immediately in case of virological failure, especially in the case of resistance: etravirine and doravirine can be considered later; other options should be used first. There is now a large amount of data on NNRTI failure, mainly from Africa. Preference should be given to a boosted PI regimen and/or a second-generation INSTI. Darunavir/r is better than lopinavir/r (Aboud 2019). The PI can be combined with two NRTIs but also with raltegravir alone. In at least two large randomized trials (SECOND-LINE 2013, La Rosa 2016), the combination of lopinavir/r plus raltegravir was shown to be equivalent to standard PI/r therapy. In EARNEST (Paton 2014), 1,277 individuals were randomized in a three-arm design to receive either a PI/r regimen (lopinavir/r plus 2–3 NRTIs = standard), a PI/r plus raltegravir (mostly lopinavir/r or darunavir/r = nuke sparing), or a PI/r alone after 12 weeks of raltegravir induction (= mono). The rate with viral load below 400 copies/mL at 96 weeks was 86% in the standard arm, 86% with nuke-sparing, and 61% in the mono arm. The data may not be generalizable to Europe. Though the data may not be generalizable to Europe, they show that nuke sparing can be an alternative. However, they also show that monotherapies are not a good idea in cases of (possibly adherence-related) virological treatment failure. Newer data have described the potential of second-generation INSTIs:
In NADIA, 465 people were assigned to dolutegravir or darunavir/r and 3TC plus either tenofovir or AZT in a randomized 2x2 design (Patel 2022). Dolutegravir was non-inferior to darunavir/r at 96 weeks (90% versus 87% below 400 copies/mL); however, nine (4%) subjects developed resistance versus none on darunavir/r. The resistance barrier of darunavir/r may be somewhat higher after all. Interestingly, in the second comparison, tenofovir was slightly better than AZT (92% versus 85%), which was also true for patients with tenofovir resistance. These data show that it is not always necessary to switch nukes in second-line therapy in the event of NNRTI failure. AZT can and should be omitted.
The 2SD trial enrolled 795 participants with viral suppression on a boosted PI regimen (in whom a previous first-line regimen of two NRTIs and an NNRTI had failed and for whom there were no data regarding the presence of drug-resistance mutations). A switch to dolutegravir treatment was non-inferior compared to a continued boosted PI regimen (Ombajo 2023).
The double-blind, randomized GS-4030 trial was set to evaluate the potential of Biktarvy® in 565 pre-treated PLWH. The trial explicitly allowed resistance to NRTIs, NNRTIs, and PIs (Acosta 2020). Patients on dolutegravir-containing regimens were

enrolled and randomized to Biktarvy® or dolutegravir plus TAF+FTC. Efficacy remained good despite significant baseline resistance, particularly in the NRTI drug class. Over 100 participants had NNRTI resistance but remained almost all virologically suppressed – bictegravir and dolutegravir appear to have similar potential in salvage therapy. It should be noted, however, that all patients from GS-4030 had suppressed viral loads, and the resistance was determined from proviral DNA only – so strictly speaking, it was not virologic failure.
Darunavir/r plus dolutegravir may also be considered. Two agents with a high resistance barrier may still be better than one, but adequately powered studies are lacking (Capetti 2017, Hawkins 2019, Armenia 2021). Darunavir should be preferably given as the STR Symtuza® (TAF/FTC/darunavir/c) to save pills (in some countries, darunavir/c is also available as Rezolsta®) but also to preserve a possible M184V mutation with FTC. In the case of an NNRTI failure, the combination of Symtuza® with Tivicay® remains pretty effective, but perhaps it is too much – at least in cases with limited mutations.

Virologic treatment failure with PIs. There are relevant cross-resistance mutations. First-generation PIs should be replaced by darunavir/r. Should darunavir/r fail, ART does not always need to be switched immediately. Low-level viremia on PIs is not uncommon and does not always indicate treatment failure. Even with the NRTI mutation M184V, ART can be continued. The effect of a fully active boosted PI is sufficient for virologic success; continuing cytidine analogs 3TC or FTC will preserve M184V and compromise viral fitness (Hull 2009). However, if sufficient other agents are active, it may also be appropriate to omit NRTIs (Tashima 2013). If the PI regimen fails (repeatedly viremia above 200 copies/mL, detection of resistance), switching to an INSTI-based regimen is recommended. In contrast, a new NNRTI with continuation of NRTIs alone is often insufficient (Abgrall 2007).
Dolutegravir or bictegravir should be used as INSTIs. The first-generation INSTIs raltegravir and elvitegravir/c were relatively weak in 145, a double-blind, randomized trial (Elion 2013). In the double-blinded SAILING trial in predominantly PI-pretreated individuals (n=715), dolutegravir was better than raltegravir (Cahn 2013). Rates with viral load below 50 copies/mL were 71% versus 64% at 48 weeks; moreover, there were significantly fewer resistance mutations associated with dolutegravir. The GS-4030 study showed comparable efficacy for bictegravir and dolutegravir in resistance (evaluated from proviral DNA) to NRTIs, NNRTIs, and/or PIs (Acosta 2020).
Dolutegravir plus rilpivirine, available since 2018 as the combination tablet Juluca®, could theoretically also be considered, provided there is no NNRTI resistance. However, the pivotal studies only examined individuals on first- or second-line therapy who had not yet experienced treatment failure (Llibre 2018). The combination of dolutegravir and doravirine (DoDo) may be more promising, but robust data are lacking (Denyer 2022).

Virological treatment failure with INSTIs. Fortunately, it is rare so far, expected to happen in first-line therapy with elvitegravir or raltegravir at a maximum of 1–2%. In order to not waste the whole class, action should be taken very quickly! For limited INSTI resistance against first-generation INSTIs, dolutegravir can be tried at a higher dose (see *Salvage*). However, it is better to switch to a darunavir-containing regimen, especially in cases of concurrent NRTI resistance or complex resistance settings, preferably Symtuza®. For more pronounced resistance, consideration may be given to adding another agent. NNRTIs alone may be too vulnerable in concurrent NRTI resistance but can be added. There is good etravirine data from the DUET trials (see *Salvage*), and doravirine is also an option. Maraviroc, which is often forgotten, should also be considered. Ultimately, the decision must be made individually according to the resistance.

Literature on switching in case of therapy failure

Aboud M, Kaplan R, Lombaard J, et al. Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3b trial. Lancet Inf Dis 2019, 19:253-64.

Acosta RK, Willkom M, Andreatta K, et al. Switching to Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) From Dolutegravir (DTG)+F/TAF or DTG+F/Tenofovir Disoproxil Fumarate (TDF) in the Presence of Pre-existing NRTI Resistance. J AIDS 2020, 85:363-371.

Armenia D, Bouba Y, Gagliardini R, et al. Virological response and resistance profile in highly treatment-experienced HIV-1-infected patients switching to dolutegravir plus boosted darunavir in clinical practice. HIV Med 2021, 22:519-525.

Cahn P, Pozniak AL, Mingrone H, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet 2013, 382:700-8.

Capetti AF, Cossu MV, Orofino G, et al. A dual regimen of ritonavir/darunavir plus dolutegravir for rescue or simplification of rescue therapy: 48 weeks' observational data. BMC Infect Dis 2017, 17:658.

De Meyer S, Hill A, Picchio G, et al. Influence of baseline protease inhibitor resistance on the efficacy of darunavir/ritonavir or lopinavir/ritonavir in the TITAN trial. J AIDS 2008, 49:563-4.

Denyer R, Zemskova J, Benator DA. HIV treatment with dolutegravir and doravirine: rationale for selection and clinical outcomes in a highly treatment experienced population. Int J STD AIDS. 2022 Sep 16:9564624221116533.

Elion R, Molina JM, et al. A randomized phase 3 study comparing once-daily elvitegravir with twice-daily raltegravir in treatment-experienced subjects with HIV-1 infection: 96-week results. J AIDS 2013, 63:494-7.

Hawkins KL, Montague BT, Rowan SE, et al. Boosted darunavir and dolutegravir dual therapy among a cohort of highly treatment-experienced individuals. Antivir Ther 2019, 24:513-519.

Hull M, Moore D, Harris M, et al. A lamivudine (3TC)-based backbone in conjunction with a boosted protease inhibitor (PI) is sufficient to achieve virologic suppression in the presence of M184V mutations. Abstract H-916, 49th ICAAC 2009, San Francisco.

La Rosa AM, Harrison LJ, Taiwo B, et al. Raltegravir in second-line antiretroviral therapy in resource-limited settings (SELECT): a randomised, phase 3, non-inferiority study. Lancet HIV 2016, 3:e247-58.

Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. Lancet 2018 Jan 5.

Nasta P, Matti A, Cocca G, et al. Early vs deferred HAART switch in heavily pre-treated HIV patients with low viral load level and stable CD4 cell count. Abstract 523, 13th CROI 2006, Denver.

Ombajo LA, Penner J, Nkuranga J, et al. Second-Line Switch to Dolutegravir for Treatment of HIV Infection. N Engl J Med 2023, 388:2349-2359.

Paton NI, Kityo C, Hoppe A, et al. EARNEST Trial Team. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. N Engl J Med 2014, 371:234-47.

Paton NI, Musaazi J, Kityo C, et al. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. Lancet HIV 2022, 9:e381-e393.

Petersen ML, van der Laan MJ, Napravnik S, et al. Long-term consequences of the delay between virologic failure of highly active antiretroviral therapy and regimen modification. AIDS 2008, 22:2097-106.

SECOND-LINE Study Group, et al. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen: a randomised, open-label, non-inferiority study. Lancet 2013, 381:2091-9.

Tashima K, Smeaton L, Andrade A, et al. Omitting NRTI from ARV Regimens Is Not Inferior to Adding NRTI in Treatment-experienced HIV+ Subjects Failing a Protease Inhibitor Regimen: The ACTG OPTIONS Study, Abstract 153LB, 20th CROI 2013, Atlanta.

Tenorio AR, Jiang H, Zheng Y, et al. Delaying a treatment switch in antiretroviral-treated HIV type 1-infected patients with detectable drug-resistant viremia does not have a profound effect on immune parameters: ACTG A5115. AIDS Res Hum Retroviruses 2009, 25:135-9.

Torti C, d'Arminio-Monforte A, Pozniak AL, et al. Long-term CD4+ T-cell count evolution after switching from regimens including HIV nucleoside reverse transcriptase inhibitors (NRTI) plus protease inhibitors to regimens containing NRTI plus non-NRTI or only NRTI. BMC Infect Dis 2011, 11:23.

United Kingdom Collaborative HIV Cohort Study, Lee KJ, Dunn D, et al. Treatment switches after viral rebound in HIV-infected adults starting antiretroviral therapy: multicentre cohort study. AIDS 2008, 22: 1943-50.

Wallis C, Papathanasopoulos M, Conradie F. Early switch based on virological failure reduces complexity of HIV-1 drug resistance. Abstract 594, 17th CROI 2010, San Francisco.

5.10. Salvage therapy

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The term salvage therapy is not defined. Like in oncology, it is used in various ways in HIV. While some only speak of salvage when all drug classes have failed, for others, this applies as of second line of therapy. As well, the term HTE ("heavily" or "highly treatment-experienced") has become widespread. It is not defined, is vague, excludes those people with transmitted resistance, and should be avoided. Today, salvage is usually referred to when there is at least triple class resistance (TCR) or at least triple class failure (TCF). Classes in this context are usually NRTIs, NNRTIs, PIs, and INSTIs. Viruses with even more extensive resistance are also called MDR viruses ("multi-drug resistant"), as in MDR tuberculosis.

The number of "salvage patients" is decreasing. Mainly people with mono- or dual therapy from the 90s are affected. In the Swiss cohort, the prevalence of viruses with TCR decreased from 9.0% to 4.4% between 1996 and 2013. Among individuals who started their ART after 2006, the rate was below 0.4% (Scherrer 2016). Only 14 cases of four-class resistance (QCR) were seen in the cohort. In EuroResist, an analysis of nearly 40,000 patients from 7 European countries, QCR prevalence was recently well below 1% (Dewandre 2021). Transmission of multidrug-resistant viral strains also remains a rare event to date. However, local outbreaks have been described in recent years (Viciana 2016, Esashika 2019), as well as cases of superinfection (Castro 2014).

A range of still surprisingly effective agents are now available, even with multiple resistance mutations. This is encouraging – and has changed the goals of therapy: even in intensively pre-treated patients with multi-drug resistant viruses, the aim should always be to reduce the viral load to below the limit of detection. In our experience, this is successful in up to 90% with TCR and even 55–70% of those with QCR (Däumer 2018, Parisi 2019). If the viral load is not suppressed sufficiently, the risk of AIDS may increase (Parisi 2019).

However, the small number of viremic individuals with multiple viral resistances makes conducting meaningful studies difficult or impossible. For the BRIGHTE study evaluating fostemsavir, 168 centers worldwide were required for 371 patients! Homogeneous populations hardly exist; the individual therapy history and resistance situation are often very heterogeneous. The design of salvage studies is also problematic. Since the sole use of a new agent is ethically questionable, the remaining ART must always be optimized (= OBT, optimized background therapy). If OBT is too good, the effect of the new agent may be lost since too many achieve good viral suppression even with OBT alone. On the other hand, if OBT is poor, the effect of the new compound is often transient or weak – the window in which the effect of a new compound can be shown is small. It has become difficult to bring new agents to market. The fact that three new drugs – ibalizumab, fostemsavir, and lenacapavir – have recently been successfully launched is a great success. Fosamprenavir and lenacapavir may revolutionize salvage therapy.

General

First, it should not be forgotten to encourage patients with resistance problems, who often look back on a long therapy and now find themselves supposedly on the edge of a precipice. There is no "beyond treatment"; this misnomer is even more misplaced in HIV medicine than in other specialties. Moreover, it usually takes years for virological therapy failure to be followed by immunological and, finally, clinical therapy failure. Fortunately, those affected – part of the furniture of every outpatient clinic, who have usually been treated for 25 years or more and have suffered through much

Table 10.1: Case study of what has become possible in salvage therapy today.

Date	(HA)ART	CD4 T-cells	Viral load
Jun 95	AZT (later ddC, ddI)	0	n.a.
Jun 96	"HAART": AZT+ddC+RTV	25	62,000
Oct 96	d4T+3TC+IDV	10	167,000
Jul 97	d4T+ddI+3TC+NVP+IDV	173	69,000
Jan 99	d4T+ddI+ABC+3TC+SQV/r	212	106,000
Sep 99	d4T+ABC+3TC+DLV+LPV/r	231	74,000
Dec 01	TDF+ddI+DLV+HU	174	84,000
Oct 03	TDF+3TC+DDI+TPV/r	77	733,000
May 04	AZT+3TC+TDF+LPV/r+T-20+DLV	43	123,000
Dec 04	AZT+3TC+TDF	32	204,000
Dec 07	AZT+3TC+TDF+DRV/r+RAL+T-20	7	> 1,000,000
Jan 08		54	< 50
Apr 09	AZT+3TC+TDF+DRV/r+RAL+ETV	83	< 50
Feb 20	TAF+FTC+DRV/c+DOL	192	< 50
Dec 21		236	< 50

Comment: Not all therapy switches are listed. The 2007 switch was done when darunavir and raltegravir were both available so that they could be used simultaneously. T-20 was initially "recycled" because it remained unclear after the resistance situation whether darunavir was still active. Notably, viral load was permanently suppressed after many years at high ranges. The current ART consists of 2 tablets daily and is well-tolerated.

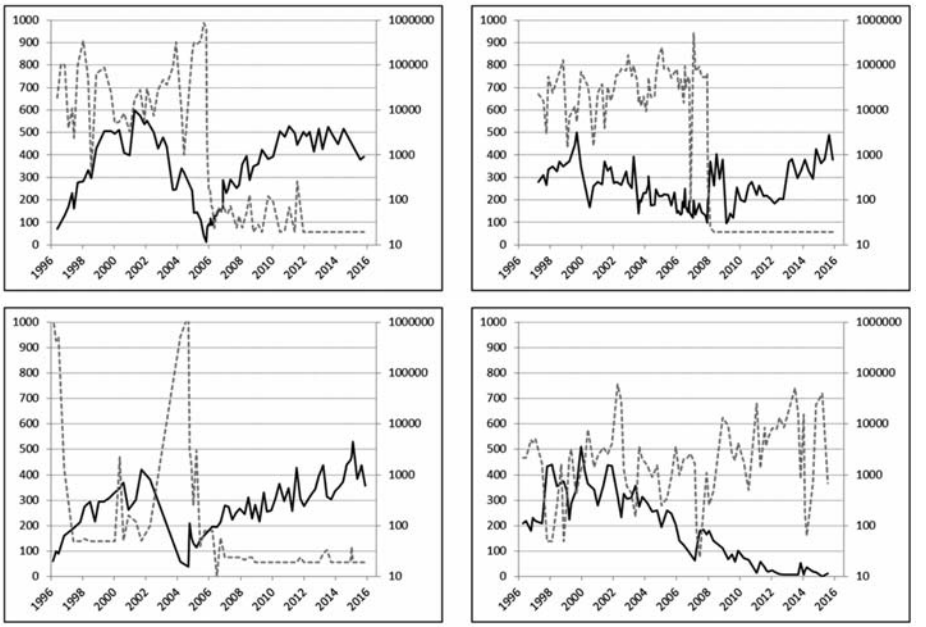

Figure 10.1: Long-term trends of CD4 T-cells/µl (dark, primary axis on the left) and HIV RNA copies/mL (gray, secondary axis on the right) in four patients with three-class resistance. Top and bottom left, three patients in whom INSTI-based regimens (mostly raltegravir) achieved sustained viral suppression between 2005 and 2008. Bottom right, a patient with multidrug-resistant virus in whom no single effective substance was available in 2016 – continuous drop in CD4 T-cells, now severe immunodeficiency.

– are often less nervous than their younger HIV doctors! They have learned that there is always a way. Many resistance mutations from the old days are also becoming less important: no one uses AZT, efavirenz, and lopinavir today. People with multidrug-resistant viruses also have a right to well-tolerated therapies! The case in the table Table 10.1 above illustrates the history of someone on antiretroviral therapy. Although the latest knowledge was consistently applied, virus suppression was unsuccessful for years. This could only be achieved by new agents (raltegravir, T-20) at the end of 2007, after more than 12 years of virological failure.

Individuals with multiple resistance may have a somewhat less favorable prognosis, especially if viral load cannot be reduced. For example, in the Italian PRESTIGIO cohort of 148 QCR individuals, the risk of AIDS was doubled with viremia at 48 months (Parisi 2019). However, multidrug-resistant viruses have lower replication fitness and are presumably less aggressive. Individuals with MDR viruses should still be closely monitored and have regular physical examinations, something often neglected today. Weight loss, B-symptoms, oral thrush, an OHL, or cognitive deterioration are early signs of disease progression that should not be overlooked. Affected individuals should also be co-managed in larger centers where new options are more readily available and experience with complex salvage regimens exists. A single new drug should not always be used up immediately – several active agents should be used if possible!

Strategies with conventional drug classes

Many agents have proven effective for PLWH with limited options over the past 20 years: the PIs darunavir and tipranavir, the NNRTI etravirine, the CCR5 antagonist maraviroc, and the INSTIs.

Some were tested in large placebo-controlled trials enrolling patients with confirmed virologic failure and multi-class resistance. Such study designs are now hardly practical given the rarity of viremia, but also for ethical reasons. As shown in Table 10.2, inclusion criteria varied significantly: in some cases, they were linked to resistance mutations; in others, three-class failure was sufficient. The definition of treatment failure differed significantly in some cases, as did the background therapy.

Not surprisingly, given the different inclusion criteria and the changing options for optimized background therapy, success rates varied considerably even in the placebo arms. For example, the proportion with a viral load below 50 copies/mL after 48 weeks ranged from 10% to 40% (and 11% to 62% when T-20 was added). The success rates of patients with a maximum of one active substance according to resistance status and who received a placebo ranged from 1% to 24%, indicating different potent background regimens.

INSTIs were also randomly tested against each other in patients with treatment failure. In BENCHMRK, raltegravir with 0–1 additional active agent still managed a rate of 48% below 50 copies/mL (see table). The effect of elvitegravir was comparable to that of raltegravir in the 145 study (Elion 2014). In SAILING, dolutegravir showed a clear advantage over raltegravir, with 71% versus 64% achieving an undetectable viral load (Cahn 2014). Here, resistance to at least two classes was a prerequisite, in addition to a viral load of at least 400 copies/mL. Participants had to have at least one fully active additional agent as an option. In the VIKING trials, dolutegravir was effective even in the presence of INSTI resistance. Of 183 PLWH, as many as 69% achieved viral loads below 50 copies/mL at 24 weeks in VIKING III (Castagna 2014). Moreover, higher doses of dolutegravir can help overcome resistance in the case of raltegravir and elvitegravir (Castagna 2014, Akil 2015). Bictegravir has never really been tested in the salvage setting but appears to have a very similar resistance profile to dolutegravir.

Table 10.2: Large randomized trials in salvage therapy.

Reference	Study (agent)	Main inclusion criteria
Lalezari 2003, Lazzarin 2003	TORO 1+2 (T-20)	TCF or TCR or both, VL > 5,000
Hicks 2006	RESIST 1+2 (Tipranavir)	TCF and 1-2 primary PI resistance, VL > 1,000
Clotet 2007	POWER 1+2 (Darunavir)	TCF and ≥ 1 primary PI resistance, VL > 1,000
Lazzarin 2007, Katlama 2009	DUET 1+2 (Etravirine)	≥ 1 NNRTI resistance and ≥ 3 primary PI resistances, VL > 5,000
Gulick 2008, Fätkenheuer 2008	MOTIVATE 1+2 (Maraviroc)	TCR or TCF or both, VL > 5,000 (interruption at baseline allowed), R5 tropism only
Cooper 2008, Steigbigl 2008	BENCHMRK 1+2 (Raltegravir)	TCR, VL >1000

TCR/TCF = Triple Class Resistance/Failure, VL = Viral Load (HIV RNA copies/mL).

Table 10.3: Large randomized trials, essential data.

	POWER	RESIST	MOTIVATE	BENCHMRK	DUET
Study drug	DRV	TPV	MVC	RAL	ETV
n total	245	1,509	1,049	701	612
Baseline characteristics					
Median VL, log RNA/mL	4.5–4.6	4.7	4.9	4.5–4.7	4.8
Median CD4/µl	153–163	195–196	187–195	102–140	99–109
0–1 active* substance, %	49–55	43–45	38–44	48–51	54
Background therapy					
with *de novo* T-20, %	29–33	18–23	40–44	20	25
with darunavir, %	100	0	0	25–50	100
with tipranavir, %	0	100	14–16	19–23	0
Response n. 48 Wo**					
total, %	45 vs. 10	23 vs. 10	44 vs. 17	64 vs. 34	61 vs. 40
with *de novo* T-20, %	58 vs. 11	28 vs. 14	61 vs. 27	84 vs. 62	71 vs. 59
0–1 active ingredient, %	37 vs. 1	n.a.	37 vs. 6***	48 vs. 12	57 vs. 24

* The definition of an active agent was inconsistent (different resistance scores)
** Viral load < 50 copies/mL *** Data at week 24. n.a. = not stated.

The "three new ones": ibalizumab, fostemsavir, lenacapavir

The progress continues. Very recently, three new compounds have entered the scene. Ibalizumab in 2020, fostemsavir in 2021, and lenacapavir in the summer of 2022. Especially with the introduction of fostemsavir and lenacapavir, many other strategies and concepts are no longer necessary. It should be noted that the indication is still very narrow for all three. It is limited to "multidrug-resistant HIV for whom no other suppressive regimen can be composed."

Fostemsavir (Rukobia®) inhibits attachment to the CD4 receptor by binding directly to the gp120 glycoprotein. Fostemsavir was given to 371 intensively pre-treated patients with three-class failure and treatment failure (> 400 copies/mL) in combination with optimized background ART in a Phase III trial (BRIGHTE). Less than half

of the participants still had more than one active agent. After 96 weeks (Lataillade 2020), 60% achieved a viral load below 40 copies/mL (37% in those without active drugs. The response rates were not only dependent on the number of active agents in the optimized adjuvant ART but also on viral load and CD4 T-cells. The higher the viremia, the lower the CD4 T-cells the lower the response rates (Ackerman 2021). Overall tolerability was good; side effects above grade 1 were rare and predominantly gastrointestinal.

Lenacapavir (Sunlenca®) is a first-in-class capsid inhibitor. Sufficient levels can be achieved for six months with a single subcutaneous administration. In CAPELLA, 72 patients on failing ART were also treated with lenacapavir subcutaneously or placebo every six months (Segal Maurer 2022). Two weeks after the first injection, viral load had fallen by at least 0.5 log levels in 88% compared with 17% on placebo. Despite limited options in background therapy, up to 81% achieved viral loads below 50 copies/mL, including 4/6 individuals in whom lenacapavir was the only active agent. The effects were seen over 52 weeks (Ogbuagu 2023). Reactions at the injection sites were the most common problems but have rarely led to discontinuation. Resistance does not appear to be entirely uncommon and has been observed even in treatment-naive individuals (Gupta 2022) – possibly indicating that the resistance barrier is not very high. In August 2022, the EMA approved lenacapavir based on the CAPELLA data. The tablets are intended as a "lead-in" before depot injection.

Ibalizumab (Trogarzo®) is a monoclonal antibody that binds directly to the CD4 receptor, preventing HIV entry. It must be infused at two-week intervals for 30–60 minutes each. In a Phase IIb study, ibalizumab was given every 2 or 4 weeks in 113 intensively pre-treated patients. At week 24, 59% and 31%, respectively, had achieved viral loads below 50 copies/mL (Khanlou 2011). In another study, 43% of 40 intensively pretreated individuals achieved a viral load below 50 copies/mL at 24 weeks – with biweekly infusions. The effect mainly persisted until 48 weeks (Emu 2018). Tolerability was good. In early 2022, Theratechnologies announced that it would market ibalizumab only in North America. In cases where ibalizumab is necessary in Europe, there is the possibility of importation in some countries. It is crucial to clarify the coverage of costs by the health insurance.

A practical procedure for multi-class resistance

Guidelines cannot be relied upon in the most complex cases. Opinions differ even on how many effective agents should be used: As a rule, however, at least two, preferably including one with a high resistance barrier. In some guidelines, such as those of EACS, three active agents are "preferably" recommended, although there is actually no data for this.

In any case, a current resistance test should be available, preferably not done during a therapy break. All old resistance tests should also be considered; the resistance situation should always be assessed cumulatively. It can be assumed that previously detected resistance mutations are still present, even if they are undetectable. These resistances are also likely to persist over time (Nishizawa 2015). It is also essential to consider previous intolerances so that people are spared unnecessary side effects or dangerous re-exposures. Good documentation of therapy history saves time and efforts.

In complex resistance settings, it is advisable to first go through all drug classes and examine possible options in each case before putting together a regimen. Previously widely used agents such as AZT, tipranavir, or T-20 (enfuvirtide) are generally no longer necessary. Raltegravir, still a life-saving salvage drug in 2007, is no longer useful because there are now INSTIs with a higher resistance barrier. This is prima-

rily also true for maraviroc, with which there is a risk of dual-topic viruses (and thus loss of efficacy), especially with low CD4 T-cell nadir. Ibalizumab, now only available outside the US as an import, is unnecessary in most cases.

If possible, complex cases and decisions should be discussed as a team with experienced HIV care providers and virologists. The resistance situation must be examined and discussed, as well as the individual situation. What can be expected of those affected? As in other cases, many factors also play a role in the treatment decision in the case of multidrug resistance:

- Co-morbidities (hepatitis B/C, renal insufficiency, cardiovascular problems)
- Concurrent medication (interactions!)
- Intolerances (weight gain with INSTIs or TAF?)
- Preferences (dietary restrictions, number of pills, desire for children)
- Current situation (virologic failure or suppression? Immune status?)

NRTIs: Because the M184V mutation reduces replication fitness (Campbell 2005, Castagna 2006), it has long been recommended to continue with 3TC or FTC despite its presence. HIV is forced to conserve M184V at the expense of fitness. However, randomized trials such as ACTG 5241 (OPTIONS) or NUKE OUT showed that ineffective NRTIs can be discontinued if other effective agents are still available – treatment success is not compromised (Tashima 2015, Llibre 2016, Gandhi 2020). Even in the VERITAS study, there was no virological rebound due to discontinuation of ineffective NRTIs (Trottier 2015). Nevertheless, many virologists continue to adhere to this strategy. The strategy often followed in the past of "recycling" AZT and combining it with TDF due to divergent resistance pathways (Stephan 2010) is no longer useful. AZT is too toxic.

Table 10.4: Strategies in salvage settings, for different drugs classes salvage settings.

Medication	Strategies, remarks
NRTIs	Attempts can be made to conserve replication fitness-reducing resistance, such as M184V with 3TC or FTC. TAF or TDF can also be considered
NNRTIs	If < 3 NNRTI resistances, use etravirine (only approved with boosted PI/r), possibly also doravirine; otherwise, discontinue NNRTIs
PIs	If there are not many PI resistance mutations, consider darunavir/c as STR along with TAF+FTC, otherwise twice daily (or consider PI omission)
INSTIs	Prefer dolutegravir and bictegravir, both also effective for some INSTI resistances
Fostemsavir	No cross-resistance to other agents but very limited approval; twice-daily administration required
Lenacapavir	No cross-resistance to other agents but very limited approval; resistance barrier may not be very high, no oral administration (six-monthly injections).

NNRTIs: For fewer than 3 NNRTI resistance mutations, etravirine is best considered, but it is only approved in combination with boosted PIs (darunavir preferred). Doravirine may still work for single NNRTI resistance mutations. Otherwise, NNRTIs should be discontinued. Resistance, once generated or detected, is likely to persist. However, among pregnant women who had received nevirapine once for transmission prophylaxis at birth, no increased rate of virologic treatment failure was observed on subsequent nevirapine-containing ART when ART was started later than six months after birth seems possible that NNRTI resistance may disappear or not interfere with subsequent therapy if there is a longer wait (Lockman 2007). However, there is no data on the possible recycling of NNRTIs.

PIs: Only darunavir/r should be considered; tipranavir/r is too toxic and offers no benefits. In cases of multiple resistance, twice-daily administration of darunavir/r is preferred. A double-PI strategy is no longer appropriate. All other PIs usually do not make sense.

INIs: Dolutegravir and bictegravir are preferred due to their higher resistance barrier. The VIKING studies showed that in the case of raltegravir resistance, higher doses of dolutegravir (50 mg BID instead of OD) could help overcome this (Castagna 2014+2017). Dolutegravir at the twice-daily dose has thus become an essential component of salvage therapy – it should always be considered in complex cases, possibly in combination with darunavir (Capetti 2017). The resistance profiles of dolutegravir and bictegravir largely overlap.

Maraviroc: An up-to-date, valid tropism test should always be available. Unfortunately, tropism correlates closely with the CD4 T-cell nadir. The lower the nadir, the more frequently non-R5 tropism is present, and maraviroc will not be effective. Especially in those who have been pre-treated for decades, a very low nadir is often present. In most cases, therefore, it is to be expected that maraviroc will not be effective. On the other hand, it may well be a highly effective substance that is also excellently tolerated. It should be considered.

Fostemsavir and lenacapavir: If at least one agent is still effective among NRTIs, NNRTIs, and PIs, an INSTI is often sufficient to reduce the viral load below the detection limit. Even in this situation, the new options would still be preserved. When INSTIs are questionable, fostemsavir or lenacapavir can be considered at the latest. Combination is also an option. Although there is virtually no data to date, these two fully effective agents are possible because of the lack of cross-resistance.

Is simplification possible?

Simplification can also be considered in the salvage setting. Although multidrug-resistant viruses can be expected to persist for life, de-escalation can be considered, especially in "historically grown" regimens that have been intensified over the years. Smaller studies show this is possible in selected patients (Valantin 2019, Vizcarra 2019). However, given the limited options, special care must be taken to maintain viral suppression. At least two fully effective agents, including one with a high resistance barrier, should remain. Often, creative use of existing STRs can noticeably reduce the number of tablets.

Especially when INSTIs are fully effective, some things are possible: for the combination elvitegravir/c+TAF+FTC (Genvoya®) plus darunavir (Prezista®), there are good data in carefully selected individuals (Chicken 2022). Darunavir is boosted here by cobicistat and does not require ritonavir.

For the very similar combination of darunavir/c+TAF+FTC (Symtuza®) plus dolutegravir (Tivicay®), there are only data from uncontrolled trials (Capetti 2017, Hawkins 2019, Armenia 2021). However, the resistance barrier is likely to be even higher with dolutegravir replacing elvitegravir; emerging resistance with both darunavir plus dolutegravir is very rare (Armenia 2021). We would, therefore, favor this combination.

Other STRs like Juluca®, but also Delstrigo® or Biktarvy® can be considered and often cleverly incorporated into creative regimens. What is combined and how depends, of course, on the individual resistance situation and your perhaps off-label creativity. Of course, ensure that the backbone dose is not accidentally doubled (i.e., do not combine Biktarvy® and Symtuza®!).

Salvage therapy, practical tips

- Clarify in advance. Which previous therapies were given for how long, and how successful were they? Test current resistance situation (not during therapy breaks)!
- Choose two to three new (active) agents if possible; try not to use only one active agent when possible.
- Do not wait too long and thus allow the virus to generate further resistance mutations; the higher the viral load at the switch, the poorer the chances of success.
- Refer patients to larger centers, if possible, as they have more experience with salvage therapies.
- Encourage the person! There is no longer such a thing as "beyond treatment"!
- Don't give the wild type a chance – in the absence of options, it may make sense to continue a "failing" therapy.
- Consider clinical trials (islatravir? bNAbs?).

Other salvage strategies

Here, some salvage strategies will be discussed. Some were tried a lot in the past and are partly obsolete today; others can still be promising in individual cases, possibly in combination.

Treatment interruptions have been evaluated in the hope that possible resistance might disappear due to "overgrowth" by the wild type. After initial positive data from GIGHAART (Katlama 2004), studies with negative results predominate. In CPRC064, four months were paused before salvage therapy in each case. There were no differences in virological response with or without the pause (Lawrence 2003). Pauses resulted in lower CD4 T-cells and more frequently severe clinical events. Many other randomized studies found no virological benefit (Benson 2006, Walmsley 2007, Holodny 2011), so strategic treatment interruptions are not recommended.

Exploit NNRTI "hypersusceptibility": This occurs when the 50% inhibitory concentration in phenotypic resistance assays for NNRTIs is lower than that of wild-type. This phenomenon, first described more than 20 years ago, is rare with NRTIs but common with NNRTIs – interestingly, especially for viruses with NRTI resistance mutations (Haubrich 2002). In more than 17,000 blood samples, the prevalence in NRTI-naive individuals was 9% and 11% for efavirenz and nevirapine and 26% and 21% for NRTI-pretreated individuals (Whitcomb 2002). In particular, NRTI mutations at codons 215, 208, and 118 render viruses hypersensitive. Some evidence suggests that NNRTI hypersusceptibility improves response (Haubrich 2002, Clark 2006). Although the significance and molecular correlation of NNRTI hypersusceptibility remain obscure: NNRTIs should be considered in the presence of NRTI mutations and the absence of NNRTI resistance.

Partial interruption means that ineffective ART is partially continued based on the consideration that multidrug-resistant viruses are somewhat less aggressive than wild types, at least for some time. Thus, 3TC still positively affects viral load in M184V resistance (Campbell 2005). In a randomized trial (Castagna 2006, Gianotti 2008) of 50 individuals with an M184V mutation and a viral load greater than 1,000 copies/mL on a 3TC-containing regimen, ART was either paused completely or 3TC alone was continued. The rationale again was that the M184V decreases the replicative fitness of HIV. Indeed, with 3TC, the viral load increased by only 0.6 logs instead of 1.2 logs, and CD4 T-cells did not fall as rapidly. In all subjects on 3TC, the M184V mutation persisted, and no accumulation of new mutations occurred. In contrast, without 3TC, a shift to wild-type virus was always observed. The beneficial effect

was observed over 144 weeks (Castagna 2007) when 3TC was continued. Also, daily FTC (not weekly) seems effective (Soria 2010). However, this concept is obsolete in the era of lenacapavir and fostemsavir.

Other: Other agents beyond ART may also have a moderate antiviral effect. Acyclovir is one of them, but also foscavir or interferon. A meta-analysis showed an average decrease in HIV viral load of 0.33 logs by acyclovir or valaciclovir (Ludema 2011). The effect can be further increased by higher doses of valaciclovir (Perti 2013). For interferon, the antiviral effect is 0.5 to 1 log (Hatzakis 2001, Rivero-Juárez 2016). For foscavir, there are single case reports (Delory 2016). In individual cases, one can consider integrating these drugs into a salvage regimen. However, this is hardly necessary (provided that there is access to fostemsavir and/or lenacapavir).

Literature on Salvage Therapies

Ackerman P, Thompson M, Molina JM, et al. Long-term efficacy and safety of fostemsavir among subgroups of heavily treatment-experienced adults with HIV-1. AIDS 2021, 35:1061-1072.

Akil B, Blick G, Hagins DP, et al. Dolutegravir versus placebo in subjects harbouring HIV-1 with integrase inhibitor resistance associated substitutions: 48-week results from VIKING-4, a randomized study. Antivir Ther 2015; 20:343-8.

Armenia D, Bouba Y, Gagliardini R, et al. Virological response and resistance profile in highly treatment-experienced HIV-1-infected patients switching to dolutegravir plus boosted darunavir in clinical practice. HIV Med 2021, 22:519-525.

Benson CA, Vaida F, Havlir DV, et al. A randomized trial of treatment interruption before optimized antiretroviral therapy for persons with drug-resistant HIV: 48-week virologic results of ACTG A5086. J Infect Dis 2006; 194: 1309-18.

Cahn P, Pozniak AL, Mingrone H, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet 2013, 382:700-8.

Campbell TB, Shulman NS, Johnson SC, et al. Antiviral activity of lamivudine in salvage therapy for multidrug-resistant HIV-1 infection. Clin Infect Dis 2005, 41:236-42.

Capetti AF, Cossu MV, Orofino G, et al. A dual regimen of ritonavir/darunavir plus dolutegravir for rescue or simplification of rescue therapy: 48 weeks' observational data. BMC Infect Dis 2017, 17:658.

Capetti AF, Cossu MV, Orofino G, et al. A dual regimen of ritonavir/darunavir plus dolutegravir for rescue or simplification of rescue therapy: 48 weeks' observational data. BMC Infect Dis 2017, 17:658.

Castagna A, Danise A, Menzo S, et al. Lamivudine monotherapy in HIV-1-infected patients harbouring a lamivudine-resistant virus: a randomized pilot study (E-184V study). AIDS 2006;20:795-803.

Castagna A, Ferrara M, Galli L, et al. Long-term efficacy of dolutegravir in treatment-experienced subjects failing therapy with HIV-1 integrase strand inhibitor-resistant virus. J Antimicrob Chemother. 2017 Oct 24.

Castagna A, Maggiolo F, Penco G, et al. VIKING-3 Study Group. Dolutegravir in Antiretroviral-Experienced Patients With Raltegravir- and/or Elvitegravir-Resistant HIV-1: 24-Week Results of the Phase III VIKING-3 Study. J Infect Dis 2014, 210:354-62.

Castro E, Zhao H, Cavassini M, Mullins JI, Pantaleo G, Bart PA. HIV-1 superinfection with a triple-class drug-resistant strain in a patient successfully controlled with antiretroviral treatment. AIDS 2014, 28:1840-4.

Clark SA, Shulman NS, Bosch RJ, Mellors JW. Reverse transcriptase mutations 118I, 208Y, and 215Y cause HIV-1 hypersusceptibility to non-nucleoside reverse transcriptase inhibitors. AIDS 2006;20:981-4.

Clotet B, Bellos N, Molina JM, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2. Lancet 2007;369:1169-78.

Cooper DA, Steigbigel RT, Gatell JM, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. NEJM 2008, 359:355-65.

Däumer M, Wolf E, Bickel M, et al. Clinical Characteristics of HIV-1-infected Patients with Multi-drug Resistance to Antiretroviral Therapy – First Results from the LOWER Study. Abstract TUPEB053, 22nd IAS 2018, Amsterdam.

Delory T, Papot E, Rioux C, et al. Foscarnet, zidovudine and dolutegravir combination efficacy and tolerability for late stage HIV salvage therapy: A case-series experience. J Med Virol 2016, 88:1204-10.

Dewandre J, Vercauteren J, Vandamme AM, et al. Declining incidence of HIV multidrug resistance in Europe. 18th European AIDS Conference, EACS 2021, October 27-30, 2021, London. Abstract BPD1/1.

Elion R, Molina JM, et al; Study 145 Team. A randomized phase 3 study comparing once-daily elvitegravir with twice-daily raltegravir in treatment-experienced subjects with HIV-1 infection: 96-week results. J Acquir Immune Defic Syndr 2013, 63:494-7.

Emu B, Fessel J, Schrader S, et al. Phase 3 Study of Ibalizumab for Multidrug-Resistant HIV-1. N Engl J Med 2018, 379:645-654.

Esashika Crispim MA, da Guarda Reis MN, Fraiji N, et al. Detection of human immunodeficiency virus Type 1 phylogenetic clusters with multidrug resistance mutations among 2011 to 2017 blood donors from the highly endemic Northern Brazilian Amazon. Transfusion 2019, 59:2593-2601.

Fätkenheuer G, Nelson M, Lazzarin A. Subgroup analysis of maraviroc in previously treated R5 HIV-1 infection. N Engl J Med 2008, 359:1442-1455.

Gandhi RT, Tashima KT, Smeaton LM, et al. Long-term Outcomes in a Large Randomized Trial of HIV-1 Salvage Therapy: 96-Week Results of AIDS Clinical Trials Group A5241 (OPTIONS). J Infect Dis 2020, 221:1407-1415.

Gianotti N, Tiberi S, Menzo S, et al. HIV-1 replication capacity and genotype changes in patients undergoing treatment interruption or lamivudine monotherapy. J Med Virol 2008;80:201-8.

Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously untreated patients with R5 HIV-1 infection. N Engl J Med 2008, 359:1429-1441.

Gupta SK, Sims J, Brinson C, et al. Lenacapavir as part of a Combination Regimen in Treatment-Naïve People with HIV: Week 54 Results. Abstract 138, CROI 2022.

Hatzakis A, Gargalianos P, Kiosses V, et al. Low-dose IFN-alpha monotherapy in treatment-naive individuals with HIV-1 infection: evidence of potent suppression of viral replication. J Interferon Cytokine Res 2001;21:861-9.

Haubrich RH, Kemper CA, Hellmann NS, et al. The clinical relevance of non-nucleoside reverse transcriptase inhibitor hypersusceptibility: a prospective cohort analysis. AIDS 2002, 16:F33-40.

Hawkins KL, Montague BT, Rowan SE, et al. Boosted darunavir and dolutegravir dual therapy among a cohort of highly treatment-experienced individuals. Antivir Ther 2019, 24:513-519.

Hicks CB, Cahn P, Cooper DA, et al. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the RESIST studies: an analysis of combined data from two randomised open-label trials. Lancet 2006, 368:466-475.

Holodniy M, Brown ST, Cameron DW, Results of Antiretroviral Treatment Interruption and Intensification in Advanced Multi-Drug Resistant HIV Infection from the OPTIMA Trial. PLoS One 2011, 6:e14764.

Huhn GD, Tebas P, Gallant J, et al. A Randomized, Open-label Trial to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide plus Darunavir in Treatment-Experienced HIV-1 Infected Adults. J AIDS 2017, 74:193-200

Katlama C, Dominguez S, Gourlain K, et al. Benefit of treatment interruption in HIV-infected patients with multiple therapeutic failures: a randomized controlled trial (ANRS 097). AIDS 2004, 18:217-26.

Katlama C, Haubrich R, Lalezari J, et al. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. AIDS 2009, 23:2289-300.

Khanlou H, Gathe G, Schrader S, et al. Safety, efficacy, and pharmacokinetics of ibalizumab in treatment-experienced HIV-1 infected patients: A phase 2b study. Abstract H2-794b, ICAAC 2011. Chicago.

Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Engl J Med 2003, 348:2175-85.

Lataillade M, Lalezari JP, Kozal M, et al. Safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced individuals: week 96 results of the phase 3 BRIGHTE study. Lancet HIV 2020, 7:e740-e751.

Lawrence J, Mayers DL, Hullsiek KH, et al. Structured treatment interruption in patients with multidrug-resistant HIV. N Engl J Med 2003, 349:837-46.

Lazzarin A, Campbell T, Clotet B, et al. DUET-2 study group. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet 2007; 370:39-48.

Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. N Engl J Med 2003, 348:2186-95.

Llibre JM, Alvarez H, Antela A, et al. Withdrawing inactive NRTIs in HIV-1 subjects with suppressed viraemia: a randomized trial. J Antimicrob Chemother 2016, 71:1346-51.

Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. N Engl J Med 2007;356:135-47.

Ludema C, Cole SR, Poole C, Chu H, Eron JJ. Meta-analysis of randomized trials on the association of prophylactic acyclovir and HIV-1 viral load in individuals coinfected with herpes simplex virus-2. AIDS 2011, 25:1265-9.

Nishizawa M, Matsuda M, Hattori J, et al. Longitudinal Detection and Persistence of Minority Drug-Resistant Populations and Their Effect on Salvage Therapy. PLoS One 2015, 10:e0135941.

Ogbuagu O, Segal-Maurer S, Ratanasuwan W, et al. Efficacy and safety of the novel capsid inhibitor lenacapavir to treat multidrug-resistant HIV: week 52 results of a phase 2/3 trial. Lancet HIV 2023, S2352-3018(23)00113-3.

Parisi MR, Poli A, Menozzi, et al. Burden of disease in PLWH harboring a 4-class drug-resistant virus: data from PRESTIGIO Registry. PE20/11, 17th EACS 2019, Basel.

Perti T, Saracino M, Baeten JM, et al. High-dose Valacyclovir Decreases Plasma HIV-1 RNA More Than Standard-dose Acyclovir in HIV-1, HSV-2 Positive Persons: a Randomized, Crossover Trial. J Acquir Immune Defic Syndr. 2013 Mar 28. [Epub ahead of print].

Rivero-Juárez A, Frias M, Rivero A. Current views on interferon therapy for HIV. Expert Opin Biol Ther. 2016 Jun 13:1-8.

Scherrer AU, von Wyl V, Yang WL, et al. Emergence of Acquired HIV-1 Drug Resistance Almost Stopped in Switzerland: A 15-Year Prospective Cohort Analysis. Clin Infect Dis 2016, 62:1310-17.

Segal-Maurer S, DeJesus E, Stellbrink HJ, et al. Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection. N Engl J Med 2022, 386:1793-1803.

Soria A, Danise A, Galli L, et al. Viro-immunological dynamics in HIV-1-infected subjects receiving once-a-week emtricitabine to delay treatment change after failure: a pilot randomised trial. J Clin Virol 2010, 47:253-7.

Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. NEJM 2008, 359:339-354.

Stephan C, Dauer B, Bickel M, et al. Intensification of a failing regimen with zidovudine may cause sustained virologic suppression in the presence of resensitising mutations including K65R. J Infect 2010, 61:346-50.

Tashima KT, Smeaton LM, Fichtenbaum CJ, et al. HIV Salvage Therapy Does Not Require Nucleoside Reverse Transcriptase Inhibitors: A Randomized, Controlled Trial. Ann Intern Med 2015, 163:908-17.

Trottier B, Galanakis C, Longpré D, et al. Removing inactive NRTIs in a salvage regimen is safe, maintains virological suppression and reduces treatment costs: results from the VERITAS study (TMC114HIV4054). HIV Clin Trials 2015; 16:111-6.

Valantin MA, Durand L, Wirden M, et al. Antiretroviral drug reduction in highly experienced HIV-infected patients receiving a multidrug regimen: the ECOVIR study. J Antimicrob Chemother 2019, 74:2716-2722.

Viciana I, González-Domenech CM, Palacios R, et al. Clinical, virological and phylogenetic characterization of a multiresistant HIV-1 strain outbreak in naive patients in southern Spain. J Antimicrob Chemother 2016, 71:357-61.

Vizcarra P, Fontecha M, Monsalvo M, et al. Efficacy and safety of dolutegravir plus boosted-darunavir dual therapy among highly treatment-experienced patients. Antivir Ther 2019;24:467-471.

Walmsley SL, Thorne A, Loutfy MR, et al. A prospective randomized controlled trial of structured treatment interruption in HIV-infected patients failing HAART (Canadian HIV Trials Network Study 164). J AIDS 2007;45:418-25.

Whitcomb JM, Huang W, Limoli K, et al. Hypersusceptibility to non-nucleoside reverse transcriptase inhibitors in HIV-1: clinical, phenotypic and genotypic correlates. AIDS 2002, 16:F41-7.

5.11. Treatment interruptions

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Therapy breaks are not uncommon. Although there is actually hardly any rational argument for them anymore, they are part of antiretroviral therapy. Adherence problems and treatment fatigue often exist, usually in combination. In the ART Collaboration Cohort (21,801 individuals from 18 cohorts from Europe/North America 2002–2009), the probability of treatment discontinuation was about 12% after three years of ART (Abgrall 2013). The likelihood is about threefold higher among drug users. Younger people (under 30 years) were also more likely to drop out of treatment.

In addition to the wishes of the patients, there are also situations in which ART must be interrupted. These can be illnesses that preclude oral intake, such as severe gastroenteritis or pancreatitis, or an accident or surgical intervention. Sometimes, only access to ART is interrupted (left on the plane and now in Bolivia, etc.). Interruptions of a few days are usually without consequences. Nevertheless, attempts should be made to keep therapeutic breaks as short as possible.

A particular case is "analytic" treatment interruptions (ATIs), where a possible rebound is investigated, usually after an experimental intervention (see *Cure*). If ATIs are planned, there are important ethical issues to consider. There are now recommendations on how to proceed and inform participants in such studies (Julg 2019). This chapter provides an up-to-date overview of therapy pauses in *chronically* infected PLWH. For therapy pauses in *acutely* infected PLWH, see *Acute HIV Infection*.

Viral load and CD4 T-cells during treatment interruptions

Almost all patients who stop their therapy experience a rebound of the viral load within a few weeks – even if it had been below the detection limit for years. In most cases, the viral load is detectable again after only 10–20 days; the doubling time in the blood is about 1.6–2.0 days (Chun 1999, Davey 1999). Since viral load parallels in compartments such as the CNS but also semen and vaginal fluid (Garcia 1999) and can also be detected very rapidly in semen within a few weeks (Ananworanich 2011), patients should be made aware of the increased risk of infection during treatment interruptions (Burman 2008). Swiss data suggest that approximately 14% of new infections are caused by individuals who have taken a break from therapy (Marzel 2016). There may also be an increased risk of maternofetal transmission, even if ART was interrupted only during the first trimester (Galli 2009). An exuberant rebound is often observed during a break (De Jong 1997), and only after weeks does the viral load settle at the pre-therapeutic level (Hatano 2000). The virus apparently does not come from latent reservoirs – other cell populations must exist from which new virus is produced so rapidly (Chun 2000, Ho 2000). The duration to rebound varies widely, and recent attempts have been made to predict rebound with biomarkers (Hurst 2015, Giron 2022).

Immunologically, pauses in therapy can have considerable consequences. Often, CD4 T-cells drop back to their pre-therapy level within a short period. The ground gained on ART can be quickly lost. The decline is biphasic and most severe in the first months (Fagard 2005). CD4 losses of 200 or 300 cells/µl within a few weeks are possible, but the range is wide. The higher the CD4 T-cells and the faster they rose on ART, the faster they fall (Tebas 2002). Other factors such as CD4 nadir, thymus size, and age also play a role. The lower the nadir, the smaller the thymus; the older the individual, the faster CD4 T-cells fall (Maggiolo 2004, Skiest 2006). An association probably also exists with the level of proviral DNA before therapy interruption (Piketty 2010).

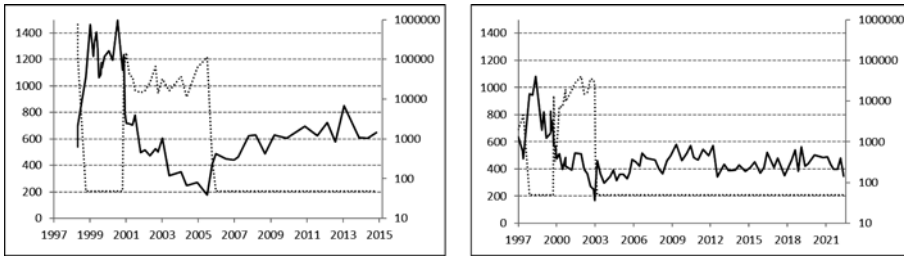

Figure 11.1: Trajectories of CD4 T-cells and viral load in two asymptomatic individuals illustrate treatment interruptions' long-term consequences. On the left, the patient started ART during acute HIV infection; on the right, ART was started during chronic infection. The dark line shows absolute CD4 T-cells/µl (primary axis on the left), and the dashed line shows viral load in RNA copies (secondary axis on the right, logarithmic). Despite years of viral suppression (almost 20 years on the right!), the former CD4 T-cell levels seen before the treatment interruptions were never again reached. In both cases, there seems to be a plateau below the initial values.

The CD4 T-cell drop due to a pause is not recovered as quickly. In a prospective study, we saw a significant disadvantage for treatment interruptions. After 18 months, CD4 T-cells were more than 120/µl lower compared to matched individuals who had continued therapy without a break (Wolf 2005). This was also seen in the SMART study (see below). Figure 11.1 illustrates that this can remain so for years.

The risks: Resistance, clinical problems, AIDS

Viral resistance always has to be anticipated whenever replication occurs in the presence of suboptimal drug levels, and thereby, resistant mutants gain a selection advantage over wild-type viruses. As a result, there are concerns that resistance may occur both during the drug washout phase (still low levels in the blood but already increasing replication) and when therapy is resumed (still replicating despite optimal levels). In the case of a single treatment interruption, the probability of this does not seem exceptionally high (Neumann 1999). However, no one can say whether resistant isolates may ultimately emerge during treatment interruption, requiring only a certain amount of time to become established against the wild-type virus. Mathematical models say that the risk is at least theoretically not low, especially if the viral load rises to high levels (Dorman 2000, Bonhoeffer 2000).

The risk of resistance is higher with repeated treatment interruptions. In several studies, it was mainly resistance to NNRTIs or 3TC that occurred (Martinez-Picado 2002, Schweighardt 2002, Ruiz 2007). There is a high risk if ART is discontinued and started at fixed intervals (see below). It seems advisable to use only agents with a high resistance barrier if a treatment interruption is necessary.

The sharp increase in viral load during treatment interruption may present as an acute retroviral syndrome. The symptoms are similar to acute HIV infection, with swelling of the lymph nodes, fever, asthenia, and malaise. Thrombocytopenia also occurs in up to 25%, especially in patients with a history of low platelets (Ananworanich 2003, Bouldouyre 2009). The blood count should, therefore, be monitored. Finally, attention should be paid to patients with hepatitis B coinfection. If HBV-active therapy with 3TC, FTC, or tenofovir is discontinued, life-threatening HBV rebounds with fulminant hepatitis may occur (Sellier 2004, Dore 2010). Monitoring these patients carefully and checking the liver enzymes at least every two weeks is advisable.

The risk of AIDS is likely low, provided the immunodeficiency is only moderate. In the Swiss Cohort, the risk of progression was not increased (Taffe 2002). In 133

patients who interrupted treatment, we observed no increased risk of AIDS after 24 months compared to 262 matched controls (Wolf 2005). However, almost all patients in this study were immunologically stable throughout. The risk is probably higher in patients with severe immunodeficiency (Deeks 2001, Lawrence 2003). The CPRC064 Study in which 270 patients with MDR virus and severe immunodeficiency (median 144 CD4 T-cells/µl) were randomized before a salvage regimen either to a four-month treatment interruption or not was stopped because of high risk of progression. Compared with the control group, a significantly higher progression to AIDS (17 versus 5) occurred in the group interrupting therapy. In a multivariate analysis, two factors predicted death or progression: treatment interruption and the CD4 T-cell count at the time of interruption. The risk increased by 1.4 with every drop of 50 CD4 T-cells. This study demonstrates that severely immunocompromised patients are particularly at risk of developing AIDS during treatment interruptions of several months. Treatment interruptions should be avoided in such patients. Data from the SMART Study show that even with higher CD4 T-cells, treatment interruptions can lead to the development of AIDS (see below).

Interruptions for immunological reasons: obsolete!

Individual cases such as the "Berlin patient", who, acutely infected, received temporary ART in a Berlin practice more than 20 years ago and later remained below the limit of detection for years without therapy (Lisziewicz 1999) raised hopes. While there are currently still attempts, at least in acutely infected individuals, to use interruptions to improve the HIV-specific immune response in the sense of "endogenous vaccination," these attempts are obsolete in chronic infection. In the Spanish-Swiss SSITT study, 133 individuals undertook four ten-week cycles of therapy, each with eight weeks of ART and two weeks off (Oxenius 2002). Subsequently, ART was discontinued. None of the 32 subjects with a pre-ART viral load above 60,000 copies/mL was subsequently able to reduce the viral load to below 5,000 copies/mL. Thus, despite repeated interruptions, the viral setpoint is reduced in very few people (with mostly previously low viral loads). If at all. Improvement in HIV-specific immune response is unlikely. Treatment breaks based on immunological considerations are, therefore, not justified. Strategies to prolong the duration with immunomodulatory agents such as hydroxyurea, mycophenolate, steroids, or interleukin-2 also failed and are obsolete.

Interruptions as a strategy for MDR viruses: obsolete

In most individuals with multi-drug-resistant viruses, treatment interruptions lead to a gradual shift back to the wild-type. Resistance testing during treatment interruptions is often useless since the mutations may disappear from the blood after only two weeks (Devereux 1999). In advanced and long-treated HIV, it often takes longer (Miller 2000). PI mutations disappear first; NNRTI mutations take longer because they have little effect on viral fitness (Deeks 2001). It can be assumed that the wild type only overgrows the resistant mutants. With special PCRs, small amounts of resistant viruses could still be detected during therapy breaks, and when ART is resumed, the viral resistances quickly dominate again (Delaugerre 2001). There are only isolated cases in which resistance was "washed out". For example, a patient from Erlangen (Walter 2002) was described who did not achieve sufficient viral suppression despite intensive ART and subsequently interrupted his therapy. During the seven-month therapy break, reversion to wild type occurred. Virus suppression was achieved for several years after the resumption of ART (which should not have been effective at all, according to the previous resistance tests).

Can patients with MDR viruses improve the effectiveness of salvage therapy if they take a break from therapy beforehand? While two early studies suggested an advantage (Miller 2000, Katlama 2004), this hypothesis is now contradicted by many studies that found no virological advantage and, in some cases, even an increased risk of AIDS (Lawrence 2003+2006, Holodny 2011). Given the AIDS risk and the questionable benefits, interruptions are not justified as a salvage strategy.

Interruptions to reduce toxicity: questionable

Can treatment side effects be reduced? Although elevated transaminases or lipids may decrease relatively quickly after discontinuation (Hatano 2000, Wolf 2005), it is questionable whether the risk of cardiovascular disease decreases. In SMART (see below), the risk of cardiovascular and metabolic complications was increased during STIs; in contrast to other studies, lipids barely improved (Lampe 2010). In SMART, increased biomarkers for cardiovascular events were observed during treatment interruptions (Olmo 2012). It is highly questionable that treatment interruptions have a favorable effect on the cardiovascular risk profile – adverse effects are more likely.

What about lipodystrophy and mitochondrial toxicity? Some studies have shown that mitochondrial DNA can regenerate during treatment interruptions (Cote 2002, Kim 2007), but only after several months. In contrast, another study found no effect (Negredo 2006). Whether clinically manifest lipodystrophy improves has also not been proven. Short breaks in therapy had no effect (Hatano 2000). In another study, however, functional parameters of the adipose tissue improved after a six-month therapy break, but again, no macroscopic benefit was visible (Kim 2007). However, a sub-study of SMART showed a moderate benefit on peripheral fat and lipids by CD4-guided treatment interruptions (Martinez 2010).

Though the data are not convincing overall, the following pages will outline some relevant data on treatment interruptions. It is essential to distinguish between structured intermittent treatment with fixed intervals and individualized interruptions based on CD4 T-cell count, in which case the interruption period depends on the patient's immunological situation.

Structured intermittent therapy with short breaks (4-on-3-off): ART on weekdays only? In pilot studies such as FOTO (Cohen 2007) or ANRS 162-4D (de Truchis 2017), short treatment interruptions of 2–3 days hardly led to resistance. In the largest study to date, the French QUATUOR trial (ANRS 170), 647 successfully pre-treated patients were randomized to continue taking their ART daily or only on 4 of 7 days. ART consisted primarily of INSTIs (48%) and NNRTIs (46%), with TDF+FTC (56%) primarily used in the backbone. After 48 weeks, 96% remained below the detection limit in the experimental arm. Within 96 weeks, resistance occurred in only 7/621 participants (Landman 2022). All 7 cases had received regimens with NNRTIs or first-generation INSTIs. Renal function improved minimally with this strategy; otherwise, there were no differences in side effects. According to the authors, the study demonstrated non-inferiority. Although one can disagree about the ethical aspects of this study – it shows that repeated treatment interruptions mostly remained without consequences, even over longer periods. Nevertheless, we would still strongly advise against this strategy. Seven cases of resistance are seven too many, and nothing got better. Moreover, some patients are only confused by such concepts.

Longer treatment interruptions of 7 days (week-on-week-off, "WOWO") increased blips and induced virologic failure (Cardiello 2005). Longer, fixed breaks are even less favorable. In a randomized NIH trial, treatment failure and resistance to NNRTIs and 3TC occurred significantly more often in the interruption arm (one month pause, two months ART), which is why the trial was stopped (Dybul 2003). There was also

some resistance in SSITT (two-week break, two months of ART) (Yerly 2003). In an African study (three-month breaks), there was even an increased risk of AIDS (DART 2008).

CD4-driven treatment interruption: A CD4-driven, individualized strategy must be distinguished from rigid intervals. ART is interrupted in patients with good immune status until the CD4 T-cell count drops to a pre-defined immunological cut-off, and only then is it resumed. Many non-randomized studies with different designs and populations concluded that this approach is safe and that a substantial amount of medication can be saved (Maggiolo 2004, Skiest 2004, Fernandez 2005). Some randomized trials now compare CD4-guided treatment interruption with continuously continued ART (Table 11.1). The results differed considerably. While TIBET, Staccato, or ACTG 5170 concluded that CD4-guided treatment interruptions are at least clinically safe, two studies, Trivacan and SMART, drew different conclusions.

Table 11.1: Randomized trials. Continuous therapy versus CD4-guided treatment interruptions.

Study, source	n	BL-CD4	CD4 T-cells at restart	Significant outcomes in the interruption arm vs. continuous therapy
TIBET Ruiz 2007	201	>500 >6 mo	<350	More complaints due to ARS, more NNRTI resistance, but otherwise clinically safe (not a single AIDS case)
SMART El Sadr 2006	5,472	>350	<250	Morbidity and mortality risk are low but significantly increased! See Table 11.2
Trivacan Danel 2006	326	>350	<250	Morbidity significantly increased (doubled) due to invasive bacterial infections
Staccato Ananworanich 2006	430	>350	<350	Clinically safe (slightly more AE in the ART arm, more candidiasis in the pause arm), no evidence of resistance
ACTG 5170 Skiest 2007	167	>350	<250	Overall safe, risk increased only with low CD4 nadir
LOTTI Maggiolo 2009	329	>700	<350	Clinically safe: more pneumonias, but fewer cardiovascular events, no increased risk of resistance

ARS = acute retroviral syndrome. FU = Follow-up. BL = baseline. AE = adverse events.

In particular, the results of SMART caused a sensation. In this trial (one of the largest randomized trials in HIV medicine ever), the CD4 cut-offs for interruption were 350 and 250 CD4 T-cells/µl for resumption. The trial, independent of the pharmaceutical industry, was highly successful worldwide – in terms of participation. In total, 318 centers from 33 countries recruited 5,472 of the planned 6,000 subjects. As expected, the baseline data of both groups did not differ, given the enormous number of cases. The Data Safety Monitoring Board concluded in January 2006 that treatment interruptions led to an excessively increased risk of mortality and morbidity – within only 17 months, about twice as many AIDS cases were observed in the intervention arm compared to continuous treatment. This was true for both severe OI and malignancies. Although the overall risk was low, the risk was so clearly increased that the decision was made to stop the trial prematurely. In addition, cardiovascular events were not (as hoped) less frequent in the intervention arm but more frequent (see Table 11.2). Quality of life also did not improve under treatment interruptions – it worsened (Burman 2008). Recent studies showed that clinical and immunological disadvantages persist even when ART is resumed (El Sadr 2008).

However, even after SMART, some questions remain unanswered. For example, the high incidence of clinical events was striking compared to Staccato, a study that was not small either, with 430 patients. Presuming the same AIDS/death rates observed in SMART, there should have been at least 17 cases in Staccato – instead, there was not a single case. Also, the suggestion that the risk of AIDS-defining malignancy was significantly increased during treatment interruptions (Silverberg 2007) is put into perspective because most patients who developed Kaposi's sarcoma or lymphoma in SMART had previously suffered from these AIDS-related conditions. Why had these individuals been enrolled in the SMART study in the first place?

Table 11.2: Events in SMART, per 100 patient-years (El Sadr 2006).

	Treatment interruptions	Continuous ART	Hazard Ratio**
Disease progression or death	3.7 (120)	1.3 (47)	2.6 (1.9–3.7)*
Death	1.5 (55)	0.8 (30)	1.8 (1.2–2.9)*
Cardiovascular, renal, and hepatic events	1.8 (65)	1.1 (39)	1.7 (1.1–2.5)*
Grade IV toxicity	5.0 (173)	4.2 (148)	1.2 (1.0–1.5)

*Significant difference **95% confidence interval in parentheses

We can also only speculate about the increased cardiovascular events during the breaks. However, some studies have shown that inflammatory or coagulatory parameters increase (Calmy 2009, Olmo 2012). Cystatin C, a measure of renal dysfunction, also increases (Mocroft 2009).
Nevertheless, the conclusion remains: According to SMART, there is no argument for treatment interruptions. Even the quality of life decreases. Patients should be encouraged to continue ART. In 2023, side effects appear less or are better managed. However, if a break in therapy is still absolutely desired, this should be respected. The break will usually be taken anyway. A supervised interruption is better than one done behind the physician's back. Under strict surveillance, the risk of clinical complications is relatively low.

Practical tips for treatment interruptions

- It is better to avoid treatment interruptions! But the wish for a break should be respected. A supervised treatment interruption is better than an unsupervised one.
- Treatment interruptions as a strategy (regression of resistance or for immunological considerations) are not useful.
- A positive effect on cardiovascular events or lipodystrophy has not been proven; according to the SMART study, it is at least questionable.
- Patients should be informed about clinical (retroviral syndrome, AIDS), immunologic (CD4 drop), and virologic (resistance) consequences.
- Patients need to know that infectivity increases – even after prolonged suppression, the viral load returns to the old level after 4–6 weeks.
- Caution in case of HBV co-infection (risk of hepatitis flare-up)!
- CD4 T-cells (also percentage), viral load, and blood count (platelets!) should be checked monthly during breaks.
- The risk of resistance is higher with NNRTIs (it is better to choose more robust regimens and discontinue NNRTIs a few days before, given their long half-life).
- Resistance testing is not helpful during treatment interruptions; it usually detects wild-type viruses.
- Do not restart ART too late!

Literature

Abgrall S, Ingle SM, May MT, et al. Durability of first ART regimen and risk factors for modification, interruption or death in HIV-positive patients starting ART in Europe and North America 2002-2009. AIDS 2013, 27:803-13.
Ananworanich J, Kerr SJ, Vernazza P, et al. Genital shedding of HIV after scheduled treatment interruption. Int J STD AIDS 2011, 22:61-6.
Ananworanich J, Phanuphak N, Nuesch R, et al. Recurring thrombocytopenia associated with structured treatment interruption in patients with HIV infection. Clin Infect Dis 2003; 37:723-5.
Bouldouyre MA, Charreau I, Marchou B, et al. Incidence and risk factors of thrombocytopenia in patients receiving intermittent antiretroviral therapy: a substudy of the ANRS 106-window trial. J AIDS 2009, 52:531-7.
Burman W, Grund B, Neuhaus J, et al. Episodic antiretroviral therapy increases HIV transmission risk compared with continuous therapy: results of a randomized controlled trial. J AIDS 2008, 49:142-50.
Burman WJ, Grund B, Roediger MP, et al. The impact of episodic CD4 cell count-guided antiretroviral therapy on quality of life. J AIDS 2008;47:185-93.
Calmy A, Gayet-Ageron A, Montecucco F, et al. HIV increases cardiovascular risk markers: results from a randomized, treatment interruption trial. AIDS 2009, 23:929-39.
Cardiello PG, Hassink E, Ananworanich J, et al. A prospective, randomized trial of structured treatment interruption for patients with chronic HIV type 1 infection. Clin Infect Dis 2005, 40:594-600.
Chun TW, Davey RT Jr, Engel D, Lane HC, Fauci AS. Re-emergence of HIV after stopping therapy. Nature 1999, 401:874-5.
Chun TW, Davey RT Jr, Ostrowski M, et al. Relationship between pre-existing viral reservoirs and the re-emergence of plasma viremia after discontinuation of HAART. Nat Med 2000, 6:757-761.
Cohen CJ, Colson AE, Sheble-Hall AG, McLaughlin KA, Morse GD. Pilot study of a novel short-cycle antiretroviral treatment interruption strategy: 48-week results of the five-days-on, two-days-off (FOTO) study. HIV Clin Trials 2007;8:19-23. Abstract MOPEB063, 5th IAS 2009, Cape Town.
Cote HC, Brumme ZL, Craib KJ, et al. Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. NEJM 2002, 346:811-20.
Danel C, Moh R, Minga A, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. Lancet 2006; 367: 1981-9.
DART. Fixed duration interruptions are inferior to continuous treatment in African adults starting therapy with CD4 cell counts <200 cells/microl. AIDS 2008;22:237-47.
Davey RT Jr, Bhat N, Yoder C, et al. HIV-1 and T cell dynamics after interruption of HAART in patients with a history of sustained viral suppression. PNAS 1999, 96:15109-14.
De Jong MD, de Boer RJ, de Wolf F, et al. Transient overshoot of HIV-1 viraemia after early discontinuation of antiretroviral treatment: role of target cell availability. AIDS 1997, 11:F79-84.
de Truchis P, Assoumou L, Landman R, et al. Four-days-a-week antiretroviral maintenance therapy in virologically controlled HIV-1-infected adults: the ANRS 162-4D trial. J Antimicrob Chemother. 2017 Nov 25.
Deeks SG, Wrin T, Liegler T, et al. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. N Engl J Med 2001, 344: 472-80.
Delaugerre C, Valantin MA, Mouroux M, et al. Re-occurrence of HIV-1 drug mutations after treatment re-initiation following interruption in patients with multiple treatment failure. AIDS 2001, 15: 2189-91.
Devereux HL, Youle M, Johnson MA, Loveday C. Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. AIDS 1999, 13: F123-7.
Dore GJ, Soriano V, Rockstroh J, et al. Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfected patients following antiretroviral therapy interruption. AIDS 2010, 24:857-65.
Dorman KS, Kaplan AH, Lange K, Sinsheimer JS. Mutation takes no vacation: can structured treatment interruptions increase the risk of drug-resistant HIV-1? J AIDS 2000, 25: 398-402.
Dybul M, Nies-Kraske E, Daucher M, et al. Long-cycle structured intermittent versus continuous HAART for the treatment of chronic infection with HIV: effects on drug toxicity and on immunologic and virologic parameters. J Infect Dis 2003, 188:388-96.
El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med 2006; 355: 2283-96.
Fagard C, Bandelier CY, Ananworanich J, et al. Biphasic decline of CD4 cell count during scheduled treatment interruptions. AIDS 2005, 19:439-41.
Fernandez Guerrero ML, Rivas P, et al. Long-term follow-up of asymptomatic HIV-infected patients who discontinued antiretroviral therapy. Clin Infect Dis 2005, 41:390-4.
Galli L, Puliti D, Chiappini E, et al. Is the interruption of antiretroviral treatment during pregnancy an additional major risk factor for mother-to-child transmission of HIV type 1? Clin Infect Dis 2009, 48:1310-7.
Garcia F, Plana M, Vidal C, et al. Dynamics of viral load rebound and immunological changes after stopping effective antiretroviral therapy. AIDS 1999, 13: F79-86.
Giron LB, Abdel-Mohsen M. Viral and Host Biomarkers of HIV Remission Post Treatment Interruption. Curr HIV/AIDS Rep 2022, 19:217-233.
Hatano H, Miller KD, Yoder CP, et al. Metabolic and anthropometric consequences of interruption of HAART. AIDS 2000, 14: 1935-42.
Hatano H, Vogel S, Yoder C, et al. Pre-HAART HIV burden approximates post-HAART viral levels following interruption of therapy in patients with sustained viral suppression. AIDS 2000, 14: 1357-63.
Ho DD, Zhang L. HIV-1 rebound after anti-retroviral therapy. Nat Med 2000, 6:736-737.
Holodniy M, Brown ST, Cameron DW, et al. Results of Antiretroviral Treatment Interruption and Intensification in Advanced Multi-Drug Resistant HIV Infection from the OPTIMA Trial. PLoS One 2011, 6:e14764.
Hurst J, Hoffmann M, Pace M, et al. Immunological biomarkers predict HIV-1 viral rebound after treatment interruption. Nat Commun 2015 Oct 9;6:8495.
Julg B, Dee L, Ananworanich J, et al. Recommendations for analytical antiretroviral treatment interruptions in HIV research trials-report of a consensus meeting. Lancet HIV 2019, 6:e259-e268.

Katlama C, Dominguez S, Gourlain K, et al. Benefit of treatment interruption in HIV-infected patients with multiple therapeutic failures: a randomized controlled trial (ANRS 097). AIDS 2004, 18:217-26.
Kim MJ, Leclercq P, Lanoy E, et al. A 6-month interruption of antiretroviral therapy improves adipose tissue function in HIV-infected patients: the ANRS EP29 Lipostop Study. Antivir Ther 2007;12:1273-83.
Lampe FC, Duprez DA, Kuller LH, et al. Changes in lipids and lipoprotein particle concentrations after interruption of antiretroviral therapy. J AIDS 2010, 54:275-84.
Landman R, de Truchis P, Assoumou L, et al. A 4-days-on and 3-days-off maintenance treatment strategy for adults with HIV-1 (ANRS 170 QUATUOR): a randomised, open-label, multicentre, parallel, non-inferiority trial. Lancet HIV 2022, 9:e79-e90.
Landman R, de Truchis P, Assoumou L, et al. ANRS 170 QUATUOR 4/7 days maintenance strategy in antiretroviral treated adults with HIV-1 infection: an open randomised parallel non-inferiority phase III trial. Abstract WEAB0406LB, IAS 2019, Mexico.
Lawrence J, Hullsiek KH, Thackeray LM, et al. Disadvantages of structured treatment interruption persist in patients with multidrug-resistant HIV-1: final results of the CPCRA 064 study. J AIDS 2006; 43: 169-78.
Lawrence J, Mayers DL, Hullsiek KH, et al. Structured treatment interruption in patients with multidrug-resistant HIV. NEJM 2003; 349: 837-46.
Lisziewicz J, Rosenberg E; Lieberman J, et al. Control of HIV despite the discontinuation of antiretroviral therapy. NEJM 1999, 340:1683-4.
Maggiolo F, Airoldi M, Callegaro A, et al. CD4 cell-guided scheduled treatment interruptions in HIV-infected patients with sustained immunologic response to HAART. AIDS AIDS 2009, 23:799-807.2008 Dec 24.
Maggiolo F, Ripamonti D, Gregis G, Quinzan G, et al. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. AIDS 2004, 18:439-46.
Martinez E, Visnegarwala F, Grund B, et al. The effects of intermittent, CD4-guided antiretroviral therapy on body composition and metabolic parameters. AIDS 2010, 24:353-63.
Martinez-Picado J, Morales-Lopetegi K, Wrin T, et al. Selection of drug-resistant HIV-1 mutants in response to repeated structured treatment interruptions. AIDS 2002, 16:895-9.
Marzel A, Shilaih M, Yang WL, et al. HIV-1 Transmission During Recent Infection and During Treatment Interruptions as Major Drivers of New Infections in the Swiss HIV Cohort Study. Clin Infect Dis 2016, 62:115-22.
Miller V, Sabin C, Hertogs K, et al. Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. AIDS 2000, 14: 2857-67.
Mocroft A, Wyatt C, Szczech L, et al. Interruption of antiretroviral therapy is associated with increased plasma cystatin C. AIDS 2009, 23:71-82.
Negredo E, Rodriguez-Santiago B, Puig J, et al. Effect of prolonged interruption of ART on mitochondrial toxicity. Abstract 758, 13th CROI 2006, Denver.
Neumann AU, Tubiana R, Calvez V, et al. HIV-1 rebound during interruption of HAART has no deleterious effect on reinitiated treatment. AIDS 1999, 13: 677-83.
Olmo M, Saumoy M, Alonso-Villaverde C, et al. Impact of antiretroviral therapy interruption on plasma biomarkers of cardiovascular risk and lipids: 144-week final data from the STOPAR study. HIV Med 2012, 13:488-98.
Oxenius A, Price DA, Gunthard HF, et al. Stimulation of HIV-specific cellular immunity by structured treatment interruption fails to enhance viral control in chronic HIV infection. PNAS 2002, 99:13747-52.
Piketty C, Weiss L, Assoumou L, et al. A high HIV DNA level in PBMCs at antiretroviral treatment interruption predicts a shorter time to treatment resumption, independently of the CD4 nadir. J Med Virol 2010, 82:1819-28.
Ruiz L, Paredes R, Gomez G, et al. Antiretroviral therapy interruption guided by CD4 cell counts and plasma HIV-1 RNA levels in chronically HIV-1-infected patients. AIDS 2007; 21: 169-78.
Schweighardt B, Ortiz GM, Grant RM, et al. Emergence of drug-resistant HIV-1 variants in patients undergoing structured treatment interruptions. AIDS 2002, 16:2342-2344.
Sellier P, Clevenbergh P, Mazeron MC, et al. Fatal interruption of a 3TC-containing regimen in a HIV-infected patient due to re-activation of chronic hepatitis B virus infection. Scand J Infect Dis 2004, 36:533-5.
Silverberg MJ, Neuhaus J, Bower M, et al. Risk of cancers during interrupted antiretroviral therapy in the SMART study. AIDS 2007;21:1957-63.
Skiest DJ, Morrow P, Allen B, et al. It is safe to stop antiretroviral therapy in patients with preantiretroviral CD4 cell counts >250 cells/microL. J AIDS 2004, 37:1351-7.
Skiest DJ, Su Z, Havlir DV, et al. Interruption of antiretroviral treatment in HIV-infected patients with preserved immune function is associated with a low rate of clinical progression: a prospective study by AIDS Clinical Trials Group 5170. J Infect Dis 2007;195:1426-36.
Taffe P, Rickenbach M, Hirschel B, et al. Impact of occasional short interruptions of HAART on the progression of HIV infection: results from a cohort study. AIDS 2002, 16: 747-55.
Tebas P, Henry K, Mondy K, et al. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4+ T cell decline in HIV-infected patients: implications for intermittent therapeutic strategies. J Infect Dis 2002, 186:851-4.
Walter H, Low P, Harrer T, et al. No evidence for persistence of multidrug-resistant viral strains after a 7-month treatment interruption in an HIV-1-Infected Individual. J AIDS 2002, 31:137-46.
Wolf E, Hoffmann C, Procaccianti M, et al. Long-term consequences of treatment interruptions in chronically HIV-1-infected patients. Eur J Med Res 2005, 10:56-62.
Yerly S, Fagard C, Gunthard HF, et al. Drug resistance mutations during structured treatment interruptions. Antivir Ther 2003, 8:411-5.

5.12. Monitoring ART

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Which parameters should be included in routine laboratory monitoring of PLWH? What results can be expected? This section deals with viral load, CD4 T-cells, routine checks, and plasma levels. Resistance and tropism tests are the subject of a separate chapter (see *HIV Resistance Testing*). For the tests to be performed on the initial presentation, see *The New Patient*.

Viral load

Viral load is the amount of HIV RNA in the blood. Alongside the CD4 T-cell count, viral load is the most important surrogate marker of HIV infection (Hughes 1997, Mellors 1997, Lyles 2000, Ghani 2001, Phillips 2004). It provides information on how high the risk is for disease progression. Above all, however, it is the critical value in determining the success of therapy. Viral load assays measure the amount of HIV RNA (viral genetic material), which correlates directly with the number of virions. It is expressed in HIV RNA copies/mL (or genome equivalents) and is reported as either a natural, integer, or logarithmic number. A change of one or more logs occurs when the viral load increases or decreases by one or more decimal powers. Thus, a decrease from 100,000 (5.0 logs) to 100 (2.0 log) copies/mL corresponds to a decrease of three logs. Changes of less than 0.5 logs are not considered significant. This means that a decrease from, for example, 4.3 to 3.9 log/mL (equivalent to approximately 20,000 to 8,000 viral copies/mL) does not indicate a relevant decrease in viral load. Many laboratories report both values, i.e., the whole number and the logarithm. Unlike HCV or HBV, the standardized specification of the viral load in International units/mL has not yet been established.

Assessment

The higher the viral load, the higher the risk of CD4 T-cell decrease, with subsequent progression or occurrence of AIDS-related illnesses (Mellors 1997, Lyles 2000, Phillips 2004). A viral load above 100,000 copies/mL (sometimes above 50,000 copies/mL) or 5.0 log is considered high. In contrast, a viral load below 10,000 copies/mL (occasionally below 5,000 copies/mL) is considered low. However, the thresholds are not absolute and only provide points of reference.

The effects of plasma viremia on immune status can vary greatly between individuals. There are some patients whose CD4 T-cells remain stable for relatively long periods despite having a high viral load, while others experience a rapid drop. However, the viral load is relatively low. Even in the so-called elite controllers where the viral load is undetectable without ART, a slow but constant drop in the CD4 T-cells can be observed (Stellbrink 2008). Viral load is probably lower in women than in men. In a meta-analysis, the difference was 41% or 0.23 logs (95% CI 0.16–0.31 logs) (Napravnik 2002). The reason for this phenomenon remains unclear, and whether it should impact the indication for treatment is still the subject of debate.

Methods

Usually, nucleic acid amplification tests (NAT) such as the polymerase chain reaction (PCR) and related techniques are used for viral load measuring. Briefly, after extraction of the blood sample, the viral RNA is first transcribed into DNA in several enzymatic steps and then amplified. Detection and quantification are performed using fluorescently labeled DNA fragments. An overview of the most commonly used commercial test systems is listed in Table 11.1. The testing systems differ in their detection limits and the linear range within which measurement is reliable or

reproducible. The formerly widely used branched DNA (b-DNA) method is no longer available. The test system market has been very dynamic in recent years. New test systems and instrument platforms have become available, and existing ones have been further developed and improved. In addition to the established companies, new manufacturers such as Qiagen, Hologic, or Cepheid have also entered the market. A real advance that significantly increases the reliability of diagnostics is the so-called "dual-target detection". In this process, not one section of the viral RNA is amplified – as was previously the case – but two sections simultaneously. If amplification fails in one section due to the high variability of the HIV genome (the result would be falsely negative), amplification in the other section takes effect.
Current developments also focus on reducing the detection limit, which is currently 20 copies/mL for the most sensitive test. However, the clinical relevance of a viral load below 50 copies/mL is questionable due to a lack of validated data. Higher sensitivity may lead to uncertainty or more frequent (and unnecessary) controls. In principle, the intra-assay variance of the test systems is good, but the measurement-related fluctuations should be considered, especially in low viremic ranges (see above). The same applies to an increase. Changes of almost threefold are usually not relevant! This fact should be pointed out to the patients, who are often unnecessarily frightened or euphoric with such numbers.
The results of the different techniques can diverge considerably. The laboratory should also have experience or make a sufficiently large number of measurements. The following rule applies: use one method, one laboratory. In addition, specific subtypes are detected differently (Alvarez 2015, Ndiaye 2015). Particularly in PLWH from Africa and Asia with non-B subtypes, clinicians should be vigilant if a viral load appears disproportionately low at initial determination. In such cases, it may then be prudent to change the methods on an exceptional basis. However, newer versions can usually sensitively measure even unusual HIV subtypes due to improved primers. It should also be noted that all techniques have a linear range outside of which it is impossible to give an exact figure.

Table 12.1: Comparison of the most important test systems for viral load determination.

Manufacturer	Test	Tech-nology	Detection limit (copies/mL)	Linear range (copies/mL)
Roche Diagnostics	cobas HIV-1	RT-PCR	14	20–10,000,000
Abbott Molecular	RealTime HIV-1	RT-PCR	40	40–10,000,000
Hologic	Aptima HIV-1 Quant Dx	TMA	12	30–1,000,000
Cepheid	Xpert HIV-1 Viral Load	RT-PCR	18	40–10,000,000

Plasma for viral load determination should be separated from whole blood within 24 hours after collection. The samples should reach the laboratory quickly. Alternatively, the whole blood can be centrifuged on-site, frozen, and refrigerated. Otherwise, excessively high values may be measured (Portman 2012). Viral load determination is also vulnerable to contamination.

Influencing factors

Apart from methodological variability, a host of other factors may influence the viral load level. These include vaccinations and intercurrent infections. During active opportunistic infections, the viral load is often remarkably high. One study showed an increase of 5 to 160-fold elevated viral load during active tuberculosis (Goletti 1996). The viral load can also increase significantly during syphilis, at least in

untreated individuals, and declines again after successful syphilis therapy (Buchacz 2004, Palacios 2007). In an extensive retrospective analysis, intercurrent infections were the cause of transient viremia in 26% of the cases (Easterbrook 2002). In these situations, determining the viral load is of limited use.
Following vaccination against influenza (O'Brien 1995) or pneumococcus (Farber 1996), but also with other vaccines, the viral load may also be transiently elevated (Kolber 2002). Since the peak is one to three weeks after vaccination, routine viral load measurements should be avoided until four weeks after vaccination.
It should be noted that not every increase must indicate virological therapy failure. Temporary, slight increases in viral load ("blips") are usually of no significance (see *Therapy Goals*). Last, one should always consider the possibility of sample mix-ups. Implausible values should first be discussed with the laboratory and then checked if no cause is apparent there – people make mistakes. Should there be any doubt about an individual result, the laboratory should be asked to repeat the test or to send part of the sample to a cooperating laboratory that uses a different test system.

Virus kinetics on ART

The introduction of viral load measurement in 1996–1997 fundamentally changed HIV therapy. The breakthrough studies by David Ho and his group showed that HIV infection has significant *in vivo* dynamics (Ho 1995, Perelson 1996). The changes in viral load on antiretroviral therapy clearly reflect the dynamics of the viral production and elimination process. The concentration of HIV-1 in plasma is usually reduced by 99% as early as two weeks after ART initiation (Perelson 1997). In one large cohort, the viral load in 84% of patients was already below 1,000 copies/mL after four weeks. The decrease in viral load follows biphasic kinetics. In the first phase, i.e., within the first three to six weeks, an extremely rapid drop occurs, followed by a more extended phase during which the viral load gradually decreases further (Wu 1999). The higher the viral load at the initiation of therapy, the longer it takes to drop below the detection level. In one study, the range was between 15 days with a baseline viral load of 1000 and 113 days with a baseline of 1 million viral copies/mL (Rizzardi 2000). Typical viral load decay curves in individuals with and without resistance can be found in the *ART Therapy Targets*.
Many studies have addressed whether durable treatment success becomes apparent early on (Thiebaut 2000, Demeter 2001, Kitchen 2001, Lepri 2001). In one study of 124 individuals, a drop of less than 0.72 log levels after one week predicted virologic treatment failure in more than 99% of cases (Polis 2001). Similarly, in another prospective study, virologic response at 48 weeks could be predicted at seven days (Haubrich 2011). However, these observations are of little practical relevance. From our point of view, it makes no sense to measure the viral load after only one or two weeks.
According to the German-Austrian guidelines, the viral load should be measured at four-week intervals during the first months after the start of therapy until it has fallen below the detection limit of 20–50 copies/mL. Thereafter, measurement every three to four months is sufficient. Eventually, longer intervals are possible (Chaiwarith 2010). In case of rebound or after a switch in therapy, closer monitoring becomes necessary. Within the first four weeks of treatment initiation, the viral load should be reduced by a factor of 100; after 3–4 months (after six months in the case of a high initial viral load), it should be below the detection limit.
Viral load can also be measured in bodily fluids other than blood or plasma (for example, cerebrospinal, vaginal, or seminal). However, such tests are usually performed for scientific purposes and are not officially licensed for other reasons.

Practical tips for dealing with viral load (see also chapter 5.4.)

- Use only one assay whenever possible.
- Use only one experienced laboratory, if possible, no home-brewed assays.
- Watch for assay variability (up to half a log) and explain this to the patient.
- Monitor viral load every four weeks with new ART until the viral load is below the detection level (50 copies/mL).
- Measure viral load sparingly – on successful ART, every three months is sufficient.
- Not on ART; measurement every three months is usually sufficient.
- Do not measure shortly after vaccinations or with concurrent infections.
- Implausible results should be rechecked after 2–4 weeks.
- Consider differences between subtypes (in some cases, it may be helpful to use another method).

CD4 T-cells

CD4 T-cells are T lymphocytes that express the CD4 receptor on their surface. This lymphocyte subpopulation is also referred to as T helper cells. Alongside viral load, measurement of the CD4 T-cell level is the most critical parameter or surrogate marker in HIV medicine. It allows for a reliable estimate of the individual risk of developing AIDS. Two reference values are generally accepted: above 400–500 CD4 T-cells/µl, severe AIDS-related diseases are very rare; below 200 CD4 T-cells/µl, the risk of AIDS-related morbidity increases significantly with increased duration of immunosuppression. Most AIDS-related illnesses occur below 100 CD4 T-cells/µl.

Several points should be considered when measuring CD4 T-cells (usually by flow cytometry). Blood samples should be processed within 18 hours. Depending on the laboratory, the lower average values are between 400 and 500 cells/µl. Samples should always be sent to the same (experienced) laboratory. The same applies to viral load for CD4 T-cells: the higher the level, the greater the variability. Differences of 50–100 cells/µl are not unusual. In one study, the 95% confidence intervals with an absolute value of 500 cells/µl were between 297 and 841 cells/µl. At 200 CD4 T cells/µl, the 95% confidence interval was between 118 and 337 cells/µl (Hoover 1993).

The measurement of CD4 T-cells should be repeated in case of highly implausible values. As long as the viral load remains below the detection limit, there is no need to be concerned, even with larger decreases in the CD4 T-cells. In such cases, the relative values (CD4 percentages) and the CD4/CD8 ratio (CD4 to CD8 T-cells) should be referred to; these are usually more robust and less prone to fluctuation. As a general point of reference, with values above 500 CD4 T-cells/µl, more than 29% fluctuations are expected, with less than 200 CD4 T-cells/µl fluctuations of up to 14%. Individual laboratories may define the normal ranges for the relative values and the ratio differently. If there are considerable discrepancies between absolute and relative CD4 T-cells, any treatment decisions should be carefully considered – if in doubt, it is better to recheck the values. The remaining differential blood count should also be scrutinized carefully – is leucopenia or leukocytosis present?

Today, clinicians sometimes forget that the result of the CD4 T-cell count is still of existential importance for many patients. To go to the doctor and discuss the test results can involve a great deal of stress for many patients. Insensitively informing the patient of a supposedly lousy result can lead to further negative results. A drop from 1,200 to 900 cells/µl is usually insignificant! From the start, patients must be

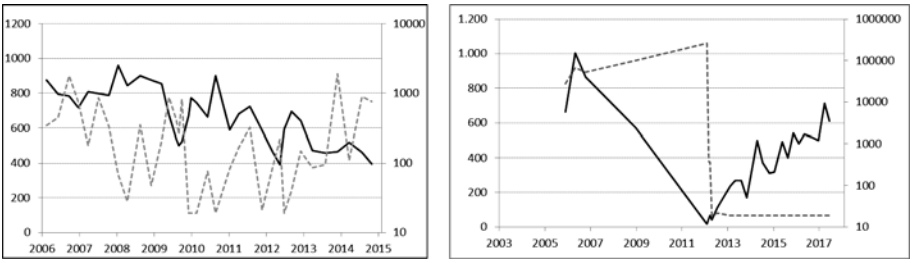

Figure 12.1: Untreated patients: drop in absolute CD4 T-cells/µl (dashed: viral load copies/mL, secondary axis on the right). On the left, an untreated patient with a course over almost ten years – note the considerable variability. On the right, a patient who experienced a massive drop from 1,000 CD4 T-cells to below 50 within only four years (during which no controls were performed). The patient developed AIDS (PCP, Kaposi's sarcoma), which could have been prevented with regular controls and timely ART initiation. Since the beginning of 2012, viral suppression and immune reconstitution.

informed about laboratory tests' possible physiological and method-related variability. In the long run, this saves time and discussions, and the patient is spared unnecessary ups and downs. We do not consider it advisable for non-physician personnel (without extensive HIV experience) to inform patients of results.

Once CD4 T-cells within the normal range are reached, in addition to adequate viral suppression, measurement every six months should suffice, in our opinion. The likelihood of CD4 T-cells dropping again to ranges below 350/µl is low in such cases (Phillips 2003). Individuals with HIV RNA below 200 copies/mL and CD4 counts above 300 cells//µl had a 97.1% probability of maintaining CD4 T-cells above 200/µl for four years. When non-HIV causes of CD4 lymphopenia were excluded, the probability rose to 99.2% (Gale 2013).

Therefore, In the US, measurement is considered optional in patients with stable viral suppression (Whitlock 2013). Patients who sometimes insist on more frequent monitoring of immune status can be assured that there are usually no detrimental changes in the CD4 T-cell count as long as HIV remains suppressed.

Influencing factors

Several other factors can influence CD4 T-cell counts apart from laboratory-related variables. These include concurrent infections, leucopenia of varying etiology, and steroids or other immunosuppressive therapies. During opportunistic infections, but also syphilis, CD4 T-cells are decreased (Kofoed 2006, Palacios 2007). Extreme exertion (marathon running), surgical procedures, or pregnancy also lead to temporarily lower levels. Even diurnal variation occurs. CD4 T-cells are low at noon and highest in the evening around 8 p.m. (Malone 1990). On the other hand, psychological stress plays a minor role at best, even though patients often assume otherwise.

Kinetics of CD4 T-cells

Most patients see a continuous CD4 T-cell decline if untreated. However, there are discontinuous cases where the decline may be rapid after a long, stable period. In an observational cohort collaboration study on 34,384 ART-naive individuals, the mean CD4 T-cell decline was -78 (95% CI, -80 to -76) cells/µl per year. The decline was strongly associated with a higher current viral load: for every 1 $\log_{10}$ copies/mL higher, CD4 T-cells declined by an additional 37.6 cells/µl per year (COHERE 2014). Of note, neither sex, race, nor transmission by injecting drug use was associated with a change in the viral load or the CD4 T-cell count.

In contrast, the increase in CD4 T-cells under ART is often biphasic (Renaud 1999, Le Moing 2002): after a rapid increase in the first three to four months, the CD4 T-cell gain is subsequently lower. In a study of almost 1,000 patients, CD4 T-cells increased by 21/µl per month during the first three months. In the following 21 months, it was only 5.5/µl per month (Le Moing 2002). The initial rapid increase in CD4 T-cells is possibly caused by redistribution. It is followed by new production of naïve T cells (Pakker 1998). Initially, reduced apoptosis may also play a role (Roger 2002).
It is debated whether the immune system steadily continues its recovery even after a long period of viral suppression or whether a plateau is reached after three to four years, beyond which there is less improvement (Smith 2004, Viard 2004). Several factors can influence the extent of immune reconstitution during ART. The degree of viral suppression is crucial – the lower the viral load, the more pronounced the effect (Le Moing 2002). Also, the absolute increase is higher if CD4 T-cell counts were high at the start of ART (Kaufmann 2000). Naïve T cells still present at the initiation of therapy also help determine long-term immune reconstitution (Notermans 1999). Age is also essential (Grabar 2004). The larger the thymus and the more active the process of thymopoiesis, the more pronounced the rise (Kolte 2002). Due to age-related thymic degeneration, CD4 T-cells do not increase as much in older people as in younger ones (Viard 2001). However, we have seen 20-year-old patients with very poor recovery and 60-year-old patients with excellent, above-average increases. The regenerative capacity of the human immune system seems to vary considerably, and no method to date has been capable of reliably predicting this capacity.
In the past, there were antiretroviral therapies, such as ddI+tenofovir, for which

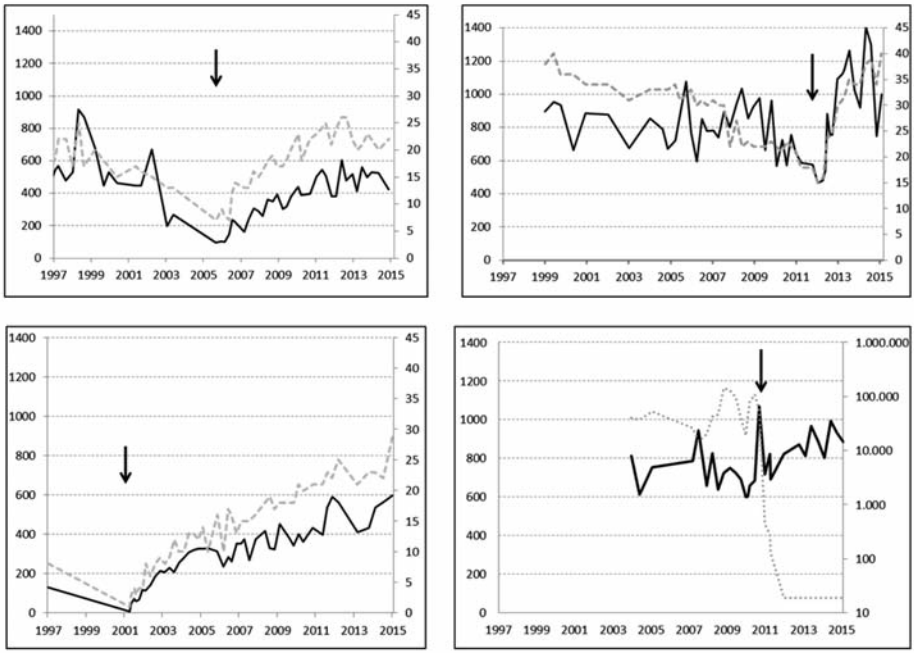

Figure 12.2: Increase in absolute (solid) and relative (dashed) CD4 T-cells in four patients on ART (arrows mark the ART initiation). Substantial variability with 200 CD4 T-cells or more in some cases. Patients should be advised that a single count is of little value. Bottom right: a patient who developed Kaposi's sarcoma with consistently high values (viral load in gray here).

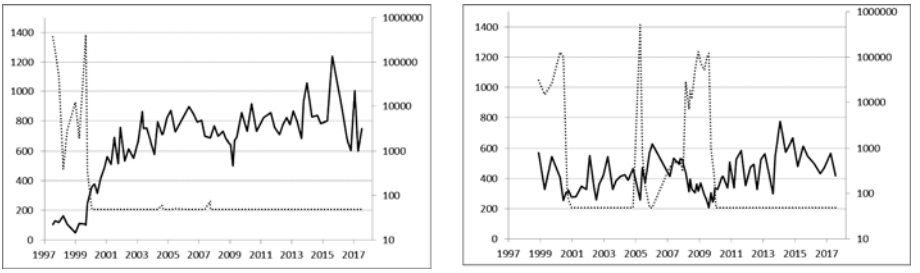

Figure 12.3: The course of viral load (dashed, right axis, logarithmic) and absolute (solid) CD4 T-cells under long-term ART. The patient on the left had considerable adherence problems until 1999. After the onset of two AIDS-related diseases (TBC, NHL), consistent use of ART with rapid and good immune reconstitution plateau in the last ten years. One can ask here how much CD4 T-cells still need to be measured. On the right, an older patient (> 60 years) with two breaks in therapy and only moderate immune reconstitution.

immune reconstitution was less good than for others. Whether current antiretroviral agents differ has not been demonstrated. Concomitant immunosuppressive medications must also be considered; they may impair immune reconstitution.
Further typical courses of CD4 T-cells can be found in chapter 5.4. Beyond CD4 T-cells, some assays test the qualitative capacity of the immune system to specific antigens (Telenti 2002). However, these methods are unnecessary in routine diagnostics, and their usefulness is questionable. They may one day help identify those (few) people at risk of opportunistic infections when their CD4 T-cells are supposedly good. In the following, two more examples of long-term treatments from practice, here with immune status and viral load.

Practical tips for dealing with CD4 T-cells

- As with viral load, use only one (experienced) laboratory.
- The higher the values, the greater the variability (consider numerous factors) – compare the relative (percentage) values and CD4/CD8 ratio with previous results.
- Do not worry the patient if there are decreases – if viral suppression is sufficient, the drop is usually not HIV-related. Highly implausible measurements can be repeated!
- If the viral load is below the detection level, three-monthly measurements are sufficient.
- In good viral suppression and normal immune status, CD4 T-cells (not viral load) may also be checked less frequently. The value as a surrogate marker is limited in these patients.
- In untreated patients, they remain an essential surrogate!
- The patient should have time to discuss the CD4 count and viral load with the physician.

Routine checks – what else should be monitored?

Besides the CD4 T-cell count and viral load, several other parameters should be monitored in the HIV-positive patient. The following recommendations apply to clinically asymptomatic patients with normal results on routine laboratory evaluation

who have been on stable treatment for several months or are not taking antiretroviral therapy. Of course, if treatment is started or changed or if the patient develops complaints, more frequent monitoring is required. Depending on the problem, additional tests may be necessary. On the other hand, the rate of new lab abnormalities decreases as more time elapses post-ART initiation (Taiwo 2012). This suggests that monitoring frequency may be reduced in subgroups without early abnormalities as time on initial ART increases.

A complete physical examination should be performed regularly, and this often leads to the discovery of important findings such as Kaposi's lesions or mycoses (thrush). The lower the CD4 T-cells, the more frequently patients should be examined.

In patients with less than 200/µl, we usually perform fundoscopies every three to six months to exclude CMV retinitis. Close cooperation with an HIV-experienced ophthalmologist is essential. The better the CD4 T-cells, the less often fundoscopies are necessary – in our opinion, when CD4 counts have normalized, these can be stopped completely. In contrast, regular gynecological examinations with PAP smears are recommended regardless of CD4 count. Many experts now also recommend rectal examination (including proctoscopy) to detect precancerous lesions and anal cancer early.

Table 12.2: Minimal evaluations per year in stable asymptomatic patients.

	Patient on ART per year	Not on ART, per year
Blood count, LDH, GPT, Crea, Bili, lipase, γGT, Glucose	4 x	2–4 x
Viral load	4 x	2–4 x
CD4 T-cells	2–4 x	4 x
Lipids	1–2 x	1 x
Physical examination, urine status	2 x	1–2 x
Gynecological examination	1 x	1 x
Fundoscopy for CD4 T-cells < 200/µl	1–2 x	4 x

However, such guidelines or recommendations can be interpreted very differently. In our opinion, in cases of good immune status, unless there is a specific suspicion, routine X-rays or ultrasound examinations (exception: patients with chronic hepatitis – hepatocellular carcinoma is not rare in such cases), multiple serologies or lactate measurements are not necessary. An annual ECG is only indicated in our view in patients with a specific risk profile (see *HIV and Cardiac Disease*). The tuberculin test (the Mendel-Mantoux skin test with 5 IE once a year) should only be repeated if it is negative initially.

Finally, it is essential not to forget cancer screening. In many countries, for example, colonoscopy is recommended for early detection of colorectal cancer for every individual older than 50–55 years (colonoscopy should be performed every ten years). For further information, see the WHO website, http://www.who.int/cancer/detection/en/.

Therapeutic Drug Monitoring (TDM)

Plasma levels of many antiretroviral drugs may vary considerably for diverse reasons (e.g., adherence, metabolism, absorption). Measurement of drug concentrations in serum or plasma is also referred to as therapeutic drug monitoring (TDM).

Adequate plasma levels are essential for the success of virologic treatment (Acosta 2000). In the VIRADAPT study, adequate PI levels were even more important than knowledge of resistance mutations (Durant 2000). However, these data are from the early years of ART.

Whether TDM with subsequent dose adjustments can improve virologic response today has not been proven (Kredo 2009). Only a few large randomized studies have provided data regarding this question. In one randomized trial, TDM showed no virologic benefit in 183 patients with treatment failure who switched to a new PI and subsequently, if levels were too low, adjusted the dose of the PI. A positive trend in viral load was merely restricted to the subgroup with only a partial PI effect (Albrecht 2011). Another randomized trial found no positive effect on viral suppression (Best 2007). The favorable effects of TDM continue to remain questionable, and the method is still regarded as experimental (review: Liu 2010).

On the other hand, very high levels also correlate with a higher rate of side effects. Hepatotoxicity under nevirapine (Gonzalez 2002) or CNS problems under efavirenz (Marzolini 2001) were associated with very high plasma levels. TDM will remain a tool for therapy observation. Not every interaction between antiretroviral agents or with concomitant drugs has been investigated. Measurement of plasma levels of NNRTIs or PIs may currently be reasonable in the following situations:

- Complex drug combinations, including boosted PIs
- Patients with very high or low body weight
- Side effects
- Treatment failure (resistance?)
- Suspected absorption or adherence problems
- Severe liver or renal diseases
- ART in children, pregnancy
- Use of new drugs (unknown interactions)

Nevertheless, several problems with TDM limit its broader use. For example, TDM makes little sense with NRTIs since these are only converted into their active metabolites intracellularly. Intracellular measurement is not available in routine clinical practice. Valid data are also still lacking for integrase inhibitors.

Measuring NNRTIs or PIs may determine levels of only one component of a failing combination. Further problems include viral strains with different levels of resistance, different inhibitory concentrations, variable protein binding, time-dependent variability of plasma levels, methodological problems with the assays, and lack of clearly defined limits. Many uncertainties remain in the assessment of therapeutic drug plasma levels. Until data from randomized studies is available, proving the clinical value of TDM, the measurement, and interpretation of results should be left to specialized centers.

Before performing TDM, it is essential to consider what the question is to answer. If the efficacy of ART is under evaluation, trough levels are essential – trough levels should be measured just before administering the next dose. If toxicity is the issue, peak levels 1–3 hours after intake are of interest.

Literature

Acosta EP, Kakuda TN, Brundage RC, Anderson PL, Fletcher CV. Pharmacodynamics of HIV type 1 protease inhibitors. Clin Infect Dis 2000, Suppl 2:S151-9.

Albrecht M, Mukherjee AL, Tierney C, et al. A randomized clinical trial evaluating therapeutic drug monitoring (TDM) for protease inhibitor-based regimens in antiretroviral-experienced HIV-infected individuals: week 48 results of the A5146 study. HIV Clin Trials 2011, 12:201-14.

Alvarez P, Martin L, Prieto L, et al. HIV-1 variability and viral load technique could lead to false positive HIV-1 detection and erroneous viral quantification in infected specimens. J Infect 2015, doi: 10.1016/j.jinf.2015.05.011.

Best BM, Goicoechea M, Witt MD, et al. A randomized controlled trial of therapeutic drug monitoring in treatment-naive and -experienced HIV-1-infected patients. J AIDS 2007;46:433-42.

Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. AIDS 2004, 18:2075-2079.

Chaiwarith R, Praparattanapan J, Salee P, et al. Frequency of HIV-RNA Monitoring: impact on outcome of antiretroviral therapy. Abstract 500, 17th CROI 2010, San Francisco.

Clevenbergh P, Mouly S, Sellier P, et al. Improving HIV infection management using antiretroviral plasma drug levels monitoring: a clinician's point of view. Curr HIV Res 2004, 2:309-21.

COHERE. Factors associated with short-term changes in HIV viral load and CD4(+) cell count in antiretroviral-naive individuals. AIDS 2014, 28:1351-6.

Demeter LM, Hughes MD, Coombs RW, et al. Predictors of virologic and clinical outcomes in HIV-1-infected patients receiving concurrent treatment with indinavir, zidovudine, and lamivudine. ACTG Protocol 320. Ann Intern Med 2001, 135: 954-64.

Durant J, Clevenbergh P, Garraffo R, et al. Importance of protease inhibitor plasma levels in HIV-infected patients treated with genotypic-guided therapy: pharmacological data from the Viradapt Study. AIDS 2000, 14:1333-9.

Easterbrook PJ, Ives N, Waters A, et al. The natural history and clinical significance of intermittent viraemia in patients with initial viral suppression to <400 copies/mL. AIDS 2002; 16:1521-7.

Farber CM, Barath AA, Dieye T. The effects of immunization in HIV type 1 infection. N Engl J Med 1996, 335:817; discussion 818-9.

Gale HB, Gitterman SR, Hoffman HJ, et al. Editor's choice: Is Frequent CD4+ T-Lymphocyte Count Monitoring Necessary for Persons With Counts ≥300 Cells/μL and HIV-1 Suppression? Clin Infect Dis, 56: 1340-1343.

Ghani AC, de Wolf F, Ferguson NM, et al. Surrogate markers for disease progression in treated HIV infection. J Acquir Immune Defic Syndr 2001; 28: 226-31.

Goletti D, Weissman D, Jackson RW, et al. Effect of Mycobacterium tuberculosis on HIV replication. Role of immune activation. J Immunol 1996, 157:1271-8.

Gonzalez de Requena D, Nunez M, Jimenez-Nacher I, Soriano V. Liver toxicity caused by nevirapine. AIDS 2002, 16:290-1.

Grabar S, Kousignian I, Sobel A, et al. Immunologic and clinical responses to highly active antiretroviral therapy over 50 years of age. Results from the French Hospital Database on HIV. AIDS 2004, 18:2029-2038.

Haubrich RH, Riddler SA, Ribaudo H, et al. Initial viral decay to assess the relative antiretroviral potency of protease inhibitor-sparing, nonnucleoside reverse transcriptase inhibitor-sparing, and nucleoside reverse transcriptase inhibitor-sparing regimens for first-line therapy of HIV infection. AIDS 2011, 25:2269-78.

Ho DD, Neumann AU, Perelson AS, et al. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 1995, 373:123-6.

Hoover DR. Would confirmatory retesting of CD4+ cells to verify AIDS status be too expensive? J Acquir Immune Defic Syndr 1993, 6:537-9.

Hughes MD, Johnson VA, Hirsch MS, et al. Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. ACTG 241 Protocol Virology Substudy Team. Ann Intern Med 1997; 126: 929-38.

Kaufmann GR, Bloch M, Zaunders JJ, Smith D, Cooper DA. Long-term immunological response in HIV-1-infected subjects receiving potent antiretroviral therapy. AIDS 2000, 14: 959-69.

Kitchen CM, Kitchen SG, Dubin JA, Gottlieb MS. Initial virological and immunologic response to HAART predicts long-term clinical outcome. Clin Infect Dis 2001; 33: 466-72.

Kolber MA, Gabr AH, De La Rosa A, et al. Genotypic analysis of plasma HIV-1 RNA after influenza vaccination of patients with previously undetectable viral loads. AIDS 2002, 16: 537-42.

Kolte L, Dreves AM, Ersboll AK, et al. Association between larger thymic size and higher thymic output in HIV-infected patients receiving HAART. J Infect Dis 2002, 185:1578-85.

Kredo T, Van der Walt JS, Siegfried N, Cohen K. Therapeutic drug monitoring of antiretrovirals for people with HIV. Cochrane Database Syst Rev 2009, 8;(3):CD007268.

Le Moing V, Thiebaut R, Chene G, et al. Predictors of long-term increase in CD4(+) cell counts in HIV-infected patients receiving a protease inhibitor-containing antiretroviral regimen. J Infect Dis 2002, 185: 471-80.

Lepri AC, Miller V, Phillips AN, et al. The virological response to HAART over the first 24 weeks of therapy according to the pre-therapy viral load and the weeks 4-8 viral load. AIDS 2001, 15: 47-54.

Liu X, Ma Q, Zhang F. Therapeutic drug monitoring in highly active antiretroviral therapy. Expert Opin Drug Saf 2010, 9:743-58.

Lyles RH, Munoz A, Yamashita TE, et al. Natural history of HIV type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men. J Infect Dis 2000, 181:872-880.

Maggiolo F, Migliorino M, Pirali A. Duration of viral suppression in patients on stable therapy for HIV-1 infection is predicted by plasma HIV RNA level after 1 month of treatment. J Acquir Immune Defic Syndr 2000, 25:36-43.

Malone JL, Simms TE, Gray GC, et al. Sources of variability in repeated T-helper lymphocyte counts from HIV type 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J Acquir Immune Defic Syndr 1990, 3:144-51.

Mellors JW, Munoz AM, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med 1997, 126:946-954.

Napravnik S, Poole C, Thomas JC, Eron JJ Jr. Gender difference in HIV RNA levels: a meta-analysis of published studies. J Acquir Immune Defic Syndr 2002, 31:11-9.

Ndiaye O, Diop-Ndiaye H, Quedraogo AS, et al. Comparison of four commercial viral load techniques in an area of non-B HIV-1 subtypes circulation. J Virol Methods 2015, doi: 10.1016/j.jviromet.2015.06.002.

Notermans DW, Pakker NG, Hamann D, et al. Immune reconstitution after 2 years of successful potent ART in previously untreated HIV type 1-infected adults. J Infect Dis 1999, 180: 1050-6.

O'Brien WA, Grovit-Ferbas K, Namazi A, et al. HIV-type 1 replication can be increased in peripheral blood of seropositive patients after influenza vaccination. Blood 1995, 86:1082-9.

Pakker NG, Notermans DW, de Boer RJ, et al. Biphasic kinetics of peripheral blood T cells after triple combination therapy in HIV-1 infection: a composite of redistribution and proliferation. Nat Med 1998, 4: 208-14.

Palacios R, Jimenez-Onate F, Aguilar M, et al. Impact of syphilis infection on HIV viral load and CD4 cell counts in HIV-infected patients. J Acquir Immune Defic Syndr 2007;44:356-9.

Perelson AS, Essunger P, Cao Y, et al. Decay characteristics of HIV-1-infected compartments during combination therapy. Nature 1997, 387:188-91.

Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. Science 1996, 271:1582-6.

Phillips A, CASCADE Collaboration. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. AIDS 2004, 18:51-8.

Phillips AN, Youle M, Lampe F, et al. CD4 cell count changes in individuals with counts above 500 cells/mm and viral loads below 50 copies/mL on antiretroviral therapy. AIDS 2002; 16: 1073-5.

Polis MA, Sidorov IA, Yoder C, et al. Correlation between reduction in plasma HIV-1 RNA concentration 1 week after start of antiretroviral treatment and longer-term efficacy. Lancet 2001, 358: 1760-5.

Portman MD, Lacey CJ. Apparent low-level HIV RNA viraemia related to sample processing time. HIV Med 2012, 13:578-9.

Renaud M, Katlama C, Mallet A, et al. Determinants of paradoxical CD4 cell reconstitution after protease inhibitor-containing antiretroviral regimen. AIDS 1999, 13:669-76.

Rizzardi GP, DeBoer RJ, Hoover S, et al. Predicting the duration of antiretroviral treatment needed to suppress plasma HIV-1 RNA. J Clin Invest 2000, 105:777-782.

Roger PM, Breittmayer JP, Durant J, et al. Early CD4(+) T cell recovery in HIV-infected patients receiving effective therapy is related to a down-regulation of apoptosis and not to proliferation. J Infect Dis 2002, 185: 463-70.

Smith CJ, Sabin CA, Youle MS, et al. Factors influencing increases in CD4 cell counts of HIV-positive persons receiving long-term highly active antiretroviral therapy. J Infect Dis 2004, 190:1860-8.

Smith CJ, Staszewski S, Sabin CA, et al. Use of viral load measured after 4 weeks of highly active antiretroviral therapy to predict virologic outcome at 24 weeks for HIV-1-positive individuals. J AIDS 2004, 37:1155-1159.

Stellbrink HJ, Schewe CK, Hoffmann C, Wolf E. Is there a harmless level of plasma viremia in untreated HIV infection? CD4+ T cells in the long-term follow-up of elite controllers and controls. Abstract 351, 14th CROI 2008, Boston.

Taiwo B, Yanik E, Napravnik S, et al. Laboratory Abnormalities Following Initiation of Modern ART in the US, 2000–2010 among the CNICS Cohort. Abstract 633, 19th CROI 2012, Seattle.

Telenti A. New developments in laboratory monitoring of HIV-1 infection. Clin Microbiol Infect 2002, 8:137-43.

Thiebaut R, Morlat P, Jacqmin-Gadda H, et al. Clinical progression of HIV-1 infection according to the viral response during the first year of antiretroviral treatment. AIDS 2000, 14: 971-8.

Viard JP, Burgard M, Hubert JB, et al. Impact of 5 years of maximally successful highly active antiretroviral therapy on CD4 cell count and HIV-1 DNA level. AIDS 2004, 18:45-9.

Viard JP, Mocroft A, Chiesi A, et al. Influence of age on CD4 cell recovery in HIV-infected patients receiving HAART: evidence from the EuroSIDA study. J Infect Dis 2001, 183: 1290-4.

Walter EA, Gilliam B, Delmar JA, et al. Clinical implications of identifying non-B subtypes of HIV type 1 infection. Clin Infect Dis 2000, 31:798-802.

Whitlock GG, Ahmed N, Benn P, Edwards S, Waters L. Stop routine CD4 monitoring in HIV-infected patients with fully suppressed virus and CD4> = 350 cells/mL. Clin Infect Dis 2013, 57: 327–328.

Wu H, Kuritzkes DR, McClernon DR, et al. Characterization of viral dynamics in HIV type 1-infected patients treated with combination antiretroviral therapy: relationships to host factors, cellular restoration, and virologic end points. J Infect Dis 1999, 179: 799-807.

5.13. Global Access to HIV Treatment

ROB CAMP

The data has changed significantly and positively since the last report:

- Some 3,550 people become infected with HIV every day, 46% of whom are women and girls, 30% under 25.
- There are some 39 million people infected, 1.3 million newly infected in 2022, **a drop of 38% since 2010**. 630,000 people died of AIDS-related causes in 2022, **a drop of 51% since 2010**.
- Approximately 29.8 million people are currently receiving ART, and while that is more than laudable, too many are not on optimal regimens – UNAIDS now recommends DLG first line. The rest (approx. 10 million) are waiting or do not know they have HIV.

Access to drugs depends not only on financial and human resources. It depends also on people being aware of their HIV status, knowledgeable about treatment, and empowered to seek it. Public information and education are important elements in widening access and therapeutic maintenance, alongside efforts to build or strengthen health services.

Stigma has been and remains a major stumbling block in wanting, seeking, and taking the treatment regimen correctly. The campaign for universal access to life-saving drugs for HIV and AIDS, started originally by grassroots AIDS activists, is today a major focus of attention of UN agencies and most all influential organizations.

The Declaration of Commitment on HIV/AIDS, unanimously endorsed by the UN General Assembly in 2001, embraced equitable access to care and treatment as a fundamental component of a comprehensive and effective global HIV response. Access to treatment has helped mobilize communities in response to HIV, preserved the health and viability of people and households vulnerable to HIV, and strengthened HIV prevention efforts in many parts of the world. The UN underscored this goal in 2011, upholding their belief in TRIPS flexibility regarding public health drugs and global trade agreements.

In the goal to reach universal access to HIV prevention, treatment, care, and support, leadership at a national level is required to establish policies that support treatment scale-up, and is now a very central part of being able to achieve the new funding levels needed to eradicate HIV:

- increasing the number of people who choose to know their HIV status;
- reducing HIV stigma;
- building human capacity to sustain treatment through education and training and better use of human resources;
- improving supply management and integrating HIV care with other health services.

Major Players

PEPFAR Update

The President's Emergency Plan for AIDS Relief (PEPFAR) was launched in 2003 to combat global HIV/AIDS. PEPFAR is the largest commitment by any nation to address these three diseases in the world; to date, its funding has totaled more than $110 billion, including contributions to the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), to which the US government is the largest donor. PEPFAR is the cornerstone of the US Global Health Initiative, which has helped countries improve and expand access to health services. PEPFAR focuses on sustainability (see below) and serves as a platform for expanded responses to a broad range of global health needs. PEPFAR partnerships in more than 70 countries have directly supported care for millions of people affected by HIV/AIDS.

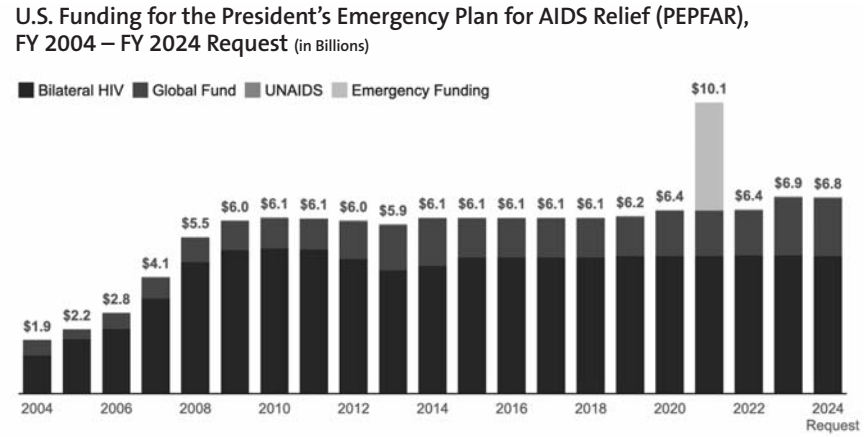

Figure 1: PEPFAR has also provided ARV treatment support for 20.1 million people as of 2022 (see TOTALS in references).

The program goals are:

1. Reach global 95-95-95 targets for all ages, gender, and population groups.
2. Reduce new HIV infections dramatically through effective prevention and treatment, in support of UNAIDS targets.
3. Close equity gaps for priority populations, including adolescent girls and young women, key populations, and children.
4. Transform the PEPFAR program towards sustaining HIV impact and long-term sustainability by strengthening the capabilities of government to lead and manage the program, in collaboration with communities, the private sector, and local partners.
5. Make measurable and sustainable gains in partner country public health systems and health security strengthen public health prevention, data, and response capabilities for HIV and other health threats.

The latest PEPFAR reports supported the prevention of mother-to-child transmission programs, preventing millions of babies from being born with HIV. It has also provided care for over 7 million orphans and vulnerable children (OVC). PEPFAR has also directly supported HIV counseling and testing for millions of people, including community-based services and rapid tests.

In late 2022, PEPFAR released its new five-year strategy *Fulfilling America's Promise to End the HIV/AIDS Pandemic by 2030,* which outlines its approach to contributing to and supporting global efforts to reach the UN Sustainable Development Goal 3 (SDG 3) target of ending the global AIDS pandemic as a public health threat by 2030, while also strengthening public health systems. Complemented by three "enablers" (community partnerships, innovation, and leading with data), the strategy focuses on five strategic pillars:

- ensuring health equity for priority populations,
- achieving long-term sustainability in the HIV/AIDS response,
- leveraging public health systems to respond to health threats,
- strengthening partnerships, and
- ensuring programs are guided by science.

The strategy is intended to align with the UNAIDS Global AIDS Strategy 2021–2026, and one of PEPFAR's goals is to reach the 95-95-95 targets and the Global Fund Strategy for 2023–2028 (PEPFAR 2022). PEPFAR activities include the provision of

antiretroviral treatment, pre-exposure prophylaxis, voluntary male circumcision, condoms, and other commodities related to HIV services (see Figure 1) (PEPFAR 2023, KFF 2023). In addition, PEPFAR has launched specific initiatives in key strategic areas. For example, PEPFAR offers DREAMS, a public-private partnership that aims to reduce HIV infections in adolescent girls and young women by offering them education and employment.

Recently, in 2023, PEPFAR has run into problems.It has had wide political support all along since its inception, but some members of the US Congress may now halt its moving forward in 2023 for indirectly supporting abortion programs. PEPFAR's reauthorization discussions are underway, which, despite a push from advocates and administration leaders for a "clean reauthorization" (one in which there are no policy changes to the existing legislation), may encounter challenges as more divisive issues, including abortion and other issues, arise. As PEPFAR enters its next phase, there are several key challenges facing the program that will likely have implications for its future, including:

- addressing the short- and long-term impacts of COVID-19 on the HIV response;
- accelerating progress toward epidemic control in the context of flat funding;
- achieving the optimal mix of services provided, populations served, and geographies targeted;
- supporting and strengthening community-led responses and sustainability;
- defining PEPFAR's role in pandemic preparedness and broader health systems strengthening efforts while ensuring synergies with other US global health and development programs; and
- continuing to coordinate with other donors and entities in the HIV ecosystem, especially the Global Fund.

As a recent Perspective article in The New England Journal states, "…(a full) reauthorization is critical not only to the global AIDS response but also to responses to future pandemics and threats to global security."

The Global Fund

The Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM) is an international financing institution that invests the world's money to save lives. It supports large-scale prevention, treatment, and care programs against the three diseases. It dedicates resources to drug procurement, human resources, program management, training, infrastructure, monitoring, and evaluation. For 2023–2025, The Global Fund will allocate $ 13.1 billion to 126 countries. The Gates Foundation and the EC are the only two in the top 10 contributors, not sovereign countries. In August 2023, through its competitive tenders, the Global Fund, together with its partners and generic pharmaceutical manufacturers, will be able to offer tenofovir disoproxil fumarate, lamivudine, and dolutegravir (TLD), a first-line HIV treatment for under US$45 per person, per year for the first time. This pricing – a 25% reduction – will allow governments in resource-limited settings to expand access to HIV services.

The Global Fund uses its Pooled Procurement Mechanism to aggregate order volumes on behalf of participating grant implementers to negotiate prices and delivery conditions with manufacturers. In 2021, the Pooled Procurement Mechanism managed approximately US$1.5 billion in orders, serving grant implementers in 90 countries. Health products available include antiretroviral, antimalarial, and essential medicines, antimalarial medicines, essential medicines, insecticide-treated mosquito nets for preventing malaria, and tests for monitoring disease progression.

In the near future (2024–2026), GFATM projects resource needs of $ 29.3 billion, of which they have raised 78%.

UNAIDS

The Joint United Nations Programme on HIV/AIDS (UNAIDS) leads and inspires the world to achieve its shared vision of zero new HIV infections, zero discrimination, and zero AIDS-related deaths. UNAIDS works closely with global and national partners towards ending the AIDS epidemic by 2030.

UNAIDS provides technical support to countries, assisting them with expertise and planning for national AIDS programs to help 'make the money work' for the people on the ground. UNAIDS tracks, evaluates, and projects the financial resource requirements at global, regional, and country levels to generate reliable and timely information on the epidemic and the response. Based on these evaluations, UNAIDS produces guidelines and progress reports. .

They are making a good effort on tackling major social issues like homophobia, financial sustainability, and gender equality. "Together we will end AIDS", whose title is annoyingly cheerleader-ish, offers some critical information, like the fact that low- and middle-income countries now invest significantly in their HIV/AIDS response, while donor countries have not increased much.

Another promising approach would be to expand innovative mechanisms like indirect taxation (airline tickets, mobile phone usage, exchange rate transactions) to support global health initiatives, including HIV (see below). The larger international community must continue to support and strengthen existing financial mechanisms, including the Global Fund and relevant UN organizations.

In 2013, UNAIDS launched the 90/90/90 program under the banner "Treatment for all", of having 90% of those with HIV tested, 90% of those tested starting treatment, and 90% of those on treatment undetectable was not hit in 2020 (81/67/?) and then upgraded to 95/95/95 in 2021, which **has** been met by a number of countries. The 95/95/95 program is underway for 2030; we must understand **why** the 90/90/90 program was not achieved – it is at 86/76/71 today, although, by sub-group, women have achieved 90/90/90!

The Bill and Melinda Gates Foundation

The largest private philanthropic organization is located in Seattle, US, "focusing on improving people's health and giving them the chance" to emerge from "hunger and extreme poverty." They have 1,818 employees with an endowment of $67.3 billion. They have committed in 2022 grants to the tune of $7 billion in 141 countries. Much of these moneys are for non-AIDS-specific works, including development (reducing poverty and hunger). In health (58% of the total spending), they fight and prevent enteric and diarrheal diseases, malaria, pneumonia, TB, neglected and infectious diseases, working on integrated health solutions, improving the delivery of existing tools, and supporting research and development in new interventions (http://www.gatesfoundation.org). They also have adopted an Open Access policy that enables the unrestricted access and reuse of all peer-reviewed published research funded, in whole or in part, by the foundation, including any underlying data sets.

Drugs available from whom and where

FDA's qualification of generics

Generic drugs are important options that allow greater access to health care. They have the same high quality, strength, purity, and stability as brand-name drugs. Generic manufacturing, packaging, and testing sites must pass the same quality standards as those of brand-name drugs.

For PEPFAR use, all drugs need FDA approval. As of 13 Sep 2023, the FDA had approved

197 generic drugs for use in the PEPFAR program that are approved in a time as six weeks. While quality, strength, purity, and stability are guaranteed, administration, delivery, and correct use are up to local use.

A note: although REMS programs from the FDA or EMA would accept information on side effects from the Global South (which has up to 6 times the amount of people on drugs), they probably contribute little to the overall numbers and therefore safety of these drugs. Mentioned below is VigiAccess from WHO.

FDA inspectors, along with EMA, will continue to perform manufacturer-related inspections to maintain quality and safety. Enforcement actions from suspension to licensing closures can be considered.

WHO

HIV, viral hepatitis, and STIs

WHO works on diagnostics (testing) and prevention as well as vaccines and treatments for these diseases. WHO's 2022–2030 global health sector strategy on HIV aims to reduce HIV infections from 1.5 million in 2020 to 335,000 by 2030 and deaths from 680,000 in 2020 to under 240,000 in 2030.

Pre-qualification and quality assurance of antiretroviral products – a fundamental human right

WHO's Prequalification Programme conducts evaluation and inspection activities and builds national capacity for manufacturing and monitoring high-quality medicines. They have now opened a pharmacovigilance website called VigiAccess where adverse events due to medicinal products collected by 110 national drug authorities are housed.

Invitations to manufacturers to submit an expression of interest (EOI) for product evaluation are issued not only for HIV/AIDS-related products but also for anti-malarial medicines, anti-tuberculosis medicines, influenza-specific antiviral medicines, and reproductive health products. The WHO List of Prequalified Medicinal Products is made by both originator and generics companies. Prequalification may be better described as pre-, ongoing, and post-qualification, as they do inspections at all these time points. On the list are many drugs for OIs (acyclovir, ceftriaxone, ciprofloxacin, amongst others). WHO also approves medicines quality control laboratories (QCLs): 57 QCLs are currently prequalified worldwide.

A bridge

Improved treatment in line with scientific evidence and international standards of care

Médecins Sans Frontières (MSF, Doctors without Borders) are on the front lines in clinics and health centers in more than 70 countries; their advocacy is not ivory tower type. On the ground, they work on innovative approaches to tackling the major health challenges posed by HIV, TB, malaria, flu, neglected tropical diseases, and emerging pathogens like COVID. They recommend:

- Supporting initiation of ART for all people with HIV. No CD4 count level.
- Dolutegravir over efavirenz, for tolerance as well as prevention.
- Providing access to viral load testing to support adherence and detect treatment failure earlier, thereby preventing resistance and needless switching to expensive sub-optimal second-line treatment.
- TPP must not impose restrictive IP protections.
- The World Trade Organization must extend its TRIPS waiver for least developed countries.
- TB and HCV testing and treatment programs must be better integrated with HIV.

How to ensure that the prices of drugs and diagnostics remain reasonable?

The international community has supported policies that will enable funds to stretch as far as possible to meet needs and contain costs in the short- and long-term by, amongst other measures, ensuring a continuing supply of drugs.
In accordance with the Doha Declaration on TRIPS and Public Health, governments can authorize governmental use or compulsory licenses to ensure the generic production of patented products (as in Brazil and Thailand).
Companies and governments can support the Medicines Patent Pool for antiretroviral medicines. This mechanism brings together patents held by different owners and makes them available to others for generic production and further development for people in LMIC.

Prices of first-line regimens in low-income countries

The decline in drug prices since 2008 can be attributed to the scaling up of treatment programs, increased competition between a growing number of products prequalified by WHO, new pricing policies by pharmaceutical companies, and successful negotiations between foundations like the William J. Clinton Foundation (CHAI) and major generic manufacturers.

Second-line regimens

Second-line regimens are more expensive than first-line regimens in low- and middle-income countries. Also, prices paid for second-line regimens can vary significantly between countries. For people who need to move to a new regimen, whether the current one is failing or not (after 10+ years on efavirenz), the new recommended first line of dolutegravir at less than 45$ is a good option. NNRTIs fail at a rate almost three times higher than the rate of PIs. MSF previously estimated that regimen failure is "largely under-diagnosed" due to limited lab facilities for viral load testing. This can only lead to resistance and harder-to-construct post-first-line regimens.

Future Funding

According to KFF, "While donor government contributions to multilateral organizations reached the highest level in 2020, rising by almost US$500 million compared to the 2019 level (US$2.1 billion), the increase was due to a small set of donors. Only 4 of 14 donors (Germany, Japan, the UK, and the US) increased their multilateral contributions, while eight (Australia, Canada, Denmark, France, the Netherlands, Norway, Sweden, and the European Commission) decreased, and two remained flat (Ireland and Italy). These trends were the same after adjusting for inflation."
New strategies have to be developed – (RED) is a fund-raising mechanism tied to the Global Fund that coordinates profits from business sales and has contributed $750 M to GFATM since 2006. Other proposals have languished – small taxes on currency transactions (Oxfam's Robin Hood tax died in 2017), an airline ticket tax (implemented in France and other countries in 2012, but no Unitaid reports since 2013…), a Global Health charge on alcohol and tobacco consumption (Hill 2012), etc.
It is perhaps more important than ever that we all contribute, whether economically or advocacy-based, to be able to help end AIDS via prevention as well as by optimally treating everyone.

Europe

The European Union impacts access to medicines for developing countries through its policies, legislation, and bilateral and regional trade agreements. The EU adopts measures to improve access to existing medical tools as well as stimulate the research in resource-limited countries. According to its data, the EC was the 5th largest contributor to WHO in 2020/2021.

Eastern Europe & Central Asia: while the disease is becoming better controlled in most parts of the world, that does not seem to be the case in Eastern Europe. Convincing political leadership in these countries (esp. Russia) is important since so few resources are allocated to fighting HIV. The number of people on treatment in EECA in 2022 is 51%, the lowest in the world, matched only by MENA. There is NO DATA on kids on treatment (under 15). How is this even possible?

How do we get there? From rhetoric to reality

Successes in controlling the epidemic can be attributed to a comprehensive response and commitment from all sectors of society, according to on-the-ground experts in sub-Saharan Africa. Buy-in from the highest political offices is important in creating policies that place HIV on all national agendas.

At the International AIDS Conference 2023, there was an effort to demonstrate the importance of including patients and their broader communities in the delivery of services. We saw, among other things, pediatric/youth testing, mobile phone messaging, accelerating PrEP services, understanding reasons for disengagement, social media support, client-initiated appointments (!), local analyses of what works (incl. community partnerships), national strategic actions for actions to Mpox prevention, long-lasting, and country-led HIV response through strengthening health systems, and informed consent processes.

The last 10 million

This is not one epidemic with a straightforward answer. There may be some basic ingredients for "getting there":

- Cascading implementation structures from national to grassroots level
- Ensuring increasing national government budget allocation to HIV responses while donors support ongoing gaps (i.e., country ownership)
- Mobilizing all sectors of society to play their part in HIV
- Integrating principles of good governance from the outset to ensure accountability at all levels.

The number of people needing access to ART is clear – 10 million, give or take. While amazing strides have happened in the last eight years, do we need to do something radically different to get the last ten million on therapy and break the never-ending chain? The most current and useful prevention and treatment strategies are key to stopping transmission to the most at-risk populations. The pipeline of novel long-acting and rapid-onset PrEP agents appears robust, including implants, vaginal rings, and topical inserts (Liu 2023). It is not the 30 million people on treatment who are transmitting. How to convince these last 10 million? Is there another message, meme, or TikTok video to convince them? Or another 10 million personalized TikTok videos? Is CAB-LA the solution? It has been under-implemented, as has the existing PrEP (TDF/FTC) for years. Is it the lack of political will? Can we bring the condom back? Raphael Landovitz at CROI 2023, presented on PrEP at the workshop for new investigators, and reminded us of other methods and possibilities – douches, inserts, patches, long-acting pills and every-6-months injections. He also reminded us of the cultural and structural barriers that are parts of this problem, and working with the end user, what do people *want* to use? We cannot sit idly by and hope for the best – we must continue to push that boulder up the hill for as long as it takes so everyone who needs it has access to prevention including PrEP, treatment, and care as early and for as long as necessary.

Literature

Collaborative Group on HIV Drug Resistance and UK CHIC Study Group. Long-term probability of detecting drug-resistant HIV in treatment-naïve patients initiating combination antiretroviral therapy. CID 2010, 50: 1275-85.
Gostin L. The unconscionable health gap: a global plan for justice. Lancet 2010, 375:1504-5.
Harrigan RP. HIV drug resistance over the long haul. Clin Infect Dis 2010, 50: 1286-87.
Hill A, Sawyer W. Funding universal access to antiretroviral treatment through a 'Global Health Charge' on alcohol and tobacco consumption: feasibility in the 20 countries with the largest HIV epidemics, International AIDS Conference, MOAE0306, July 22-27, 2012, Washington DC, USA.
Karim SSA, Barre-Sinoussi F, et al. Threatening the Global AIDS Response – Obstacles to PEPFAR's Reauthorization. NEJM DOI: 10.1056/NEJMp2310330 | September 9, 2023.
Landowitz RA. Advances in Biomedical Prevention of HIV. Scott Hammer Workshop for New Investigators and Trainees. 19 Feb 2023. https://www.croiwebcasts.org/console/player/51506?mediaType=slideVideo&
Liu A, Buchbinder S. CROI 2023: Epidemiologic Trends and Prevention for HIV and Other Sexually Transmitted Infections, Top Antivir Med. 2023 May; 31(3): 468–492, Published online 2023 May 1. PMC10266866, PMID: 37315512.
Ooms G, Hammonds R. Correcting globalization in health: transnational entitlements versus the ethical imperative of reducing aid-dependency. Public Health Ethics 2008; 1: 154-170.
Ravishankar N, Gubbins P, Cooley RJ, et al. Financing of global health: tracking development assistance for health from 1990 to 2007. Lancet 2009; 373: 2113-2124.
Resch S et al., Funding AIDS programs in the era of shared responsibility: an analysis of domestic spending in 12 low-income and middle-income countries, The Lancet Global Health, 3:e52 – e61.
https://www.statnews.com/2023/03/07/pepfar-legacy-lessons-global-health-planning/, accessed 11 Sep 2023.
https://www.statnews.com/2023/09/12/pepfar-path-forward/, accessed 12 Sep 2023.
https://www.statnews.com/2023/09/13/pepfar-hiv-aids-womens-health-africa/, accessed 13 Sep 2023.
http://vancouverconsensus.org/.
Untangling the web of antiretroviral price reductions, 17th edition, Medecins Sans Frontieres, July 2014, http://www.msfaccess.org/content/untangling-web-antiretroviral-price-reductions.
Global HIV/AIDS response. Progress Report 2014. WHO, UNICEF, UNAIDS.
Mellors S, Dybul M, Binagwaho A, et al. How Do We Get There? Country Planning for Maximum Impact, International AIDS Conference, MOSS01, July 22-27, 2012, Washington DC, USA.

Links (because global access is a moving target, the following are updated regularly and web-based)

https://www.state.gov/where-we-work-pepfar/
https://www.state.gov/reimagining-pepfar-at-20-to-end-the-hiv-aids-pandemic-by-2030/
https://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2021/june/20210614_PR_HLM_closes
UNAIDS, How AIDS changed everything
DREAMS, https://www.state.gov/pepfar-dreams-partnership/
http://utw.msfaccess.org/, accessed 14 Sep 2023.
TOTALS represent funding specified by Congress in annual appropriations bills and/or identified by agencies for the Department of State, USAID, CDC, and DoD. In addition, international HIV research activities are supported by the NIH Office of AIDS Research (OAR) through its annual appropriated budget, but these amounts are not considered part of PEPFAR. See KFF's "Breaking Down the U.S. Global Health Budget by Program Area" for additional information.
https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf
https://www.kff.org/global-health-policy/fact-sheet/the-u-s-presidents-emergency-plan-for-aids-relief-pepfar/
PEPFAR, Fulfilling America's Promise to End the HIV/AIDS Pandemic by 2030, December 2022.
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=pepfar.page
Figure 1 categorization is based on interventions laid out in the PEPFAR Financial Classification Reference Guide, used for program budgeting. PEPFAR Financial Classifications Reference Guide, March 2023.
KFF. Funding for Key HIV Commodities in PEPFAR Countries; July 2021.
https://www.theglobalfund.org/en/seventh-replenishment/, accessed 13 Sep 2023.
https://www.unaids.org/en/resources/fact-sheet
https://www.unaids.org/en/resources/presscentre/featurestories/2021/october/20211018_hiv-medicines-price-reductions-can-be-achieved
https://www.who.int/about/funding/contributors/european-union

6. Viral Resistance and Tropism

EVA WOLF AND PATRICK BRAUN

Consideration of individual resistance data in treatment decisions contributes to virologic treatment success, both in pretreated and treatment-naïve patients. In recent years, the prevalence of transmitted resistance-associated mutations (RAMs) in newly diagnosed PLWH (people living with HIV) has been relatively constant at 10%. The following chapter explains the basics of resistance and tropism testing, the mechanisms of resistance development, and the resistance profiles of available antiretroviral substances.

Blips, low-level viremia, and resistance development

Even on successful ART, viral loads above 50 copies/mL may be sporadically observed, called viral blips. Blips may reflect biological or statistical variations or maybe assay-related. Low-level viremia (LLV) is more problematic, i.e., low viral loads between 50 and 200 or 500 HIV RNA copies/mL that occur repeatedly or continuously. LLV is not rare. According to one review, approximately 4–8% of previously successfully treated patients develop LLV of 50–200 copies/mL (Ryscavage 2014). Repeated episodes of detectable viremia suggest ongoing viral replication rather than viral release from latent reservoirs secondary to immune activation. PLWH with LLV are at increased risk for developing drug resistance. Between 50 and 100 HIV RNA copies/mL, the risk of selecting resistant viral variants is about 1–3% and increases as viral load increases (Prosperi 2011, Braun 2016). The resistance barrier of the substances used also plays a role.

Resistance development

The rapid emergence of resistant viral variants is caused by the high turnover of HIV – approximately 10 billion new viral particles are generated daily in untreated patients – and by the high error rate in reverse transcription of the viral genome (Perelson 2002). Other mechanisms also contribute to the development of resistance or mutations: insufficient (*viral infectivity factor*-mediated) inhibition of the cellular HIV restriction factor APOBEC3G can lead to increased G-to-A hypermutation during reverse transcription, i.e., the transcription of RNA into DNA (Yang 2020). A correspondingly hypermutated proviral DNA usually shows a typical amino acid exchange at specific resistance positions, such as the mutations E138K, M184I, or M230I in the RT gene. Hypermutations of TGG to TGA/TAA/TAG can also result in stop codons leading to replication-incompetent viruses (Fourati 2012).

Although new viral variants ("quasispecies") are constantly emerging even without ART, resistance-relevant mutations are selected only in the presence of antiretroviral drugs. Resistant variants have a selection advantage over wild-type viruses due to reduced susceptibility and are a major cause of virologic failure. From a virological point of view, an early start of therapy, as recommended in treatment guidelines (EACS 2022), reduces the development of viral variants and the emergence of resistance under ART.

Methods of resistance testing

In the early 2000s, genotypic and phenotypic resistance testing have been established for treatment monitoring (Wilson 2003). With genotypic assays, mutations in the HIV genome (in comparison to a consensus reference sequence) are detected, and the resulting resistance profile is interpreted using algorithms based on literature and

expertise. Phenotypic resistance assays directly quantify the susceptibility of the viral population to specific drugs. Analogous to resistance analysis, the tropism testing of the viral population, which can change during HIV infection (from CCRR5 to CXCR4), can be performed genotypically or phenotypically. The methods and specific features of tropism testing are described separately in this chapter.

In **genotypic resistance determination**, a distinction is made between conventional genotyping (population sequencing), which generally only detects virus strains comprising at least 10 to 20% of the total population, and ultrasensitive sequencing methods detecting minor virus variants down to ≤1–2% (next generation sequencing, resp. NGS, or ultradeep sequencing). The clinical relevance of minor viral variants is discussed below.

Phenotypic resistance analyses are mainly needed during the development of new drugs. They are used to quantify viral resistance and interpret emerging new mutations in clinical trials. In routine care, they are rarely performed due to the high technical and time expenditure and associated costs. Moreover, phenotyping is often not possible at low viremia levels.

Phenotyping basics

Replication capacity is measured in cell culture under the selection pressure of antiretroviral substances in increasing concentrations and compared with the wild-type virus. The drug concentration necessary to inhibit replication of a virus isolate by 50% in cell culture is called IC_{50} (50% inhibitory concentration). Sensitivity is expressed as the quotient of measured IC_{50} and IC_{50} of a wild-type reference virus. For interpretation, this quotient – also called resistance factor (RF) or "fold-change" – is compared with a so-called cut-off value. The cut-off ideally indicates the value up to which the resistance factor of the HIV isolate can be increased compared to the wild-type virus without a clinically relevant loss of efficacy.

Table 1: Characteristics of the phenotypic resistance analysis.

Advantages	Disadvantages
• Direct, quantifiable measure of the virus' drug susceptibility • Valid and quantifiable result even in case of unknown resistance mutations (e.g., with new substances) • Valid result also for complex mutation patterns with, e.g., resensitization effects	• Clinical cut-off not available for all drugs • Time consuming (several weeks) • Expensive (not covered by health insurance in Germany) • HIV-1 subtype identification not possible • Intermediate steps on the way to resistance formation are not detected • Resistant populations may remain undetected due to co-existing, rapidly replicating wild-type viruses

Technical, biological, and clinical cut-offs (thresholds)

A distinction is made between three thresholds regarding drug susceptibility. The *technical* cut-off is a measure of the *methodological* range of variation. The *biological cut-off* measures the natural range of variation in the sensitivity of wild-type virus isolates. The *clinical cut-off* indicates the IC_{50} increase (fold-change) up to which unrestricted efficacy can still be expected. It is, therefore, the clinically relevant threshold. Complete resistance to a drug often does not arise abruptly but evolves gradually by acquiring several amino acid exchanges (especially in the case of drugs

with a high resistance barrier). Ideally, an upper and a lower clinical cut-off are specified. Above the lower cut-off, the virological response is already reduced; above the upper cut-off, no virological response is expected. These cut-offs are often missing for newer drugs due to a lack of data; in these cases, the biological cut-off is used. Mutations that do not themselves confer drug resistance but provide evidence of transmitted, evolving, or reverting resistance escape detection by phenotyping.

Basics of genotyping

The HIV genome generally consists of two RNA (ribonucleic acid) strands that contain the genetic information of the virus. Within the nucleotide sequences of the HIV genome, three nucleotides (codons) code for a particular amino acid in the protein sequence. Resistance mutations are described with a number indicating the position of the respective codon within the genome and two letters. The letter *before* the number indicates the amino acid for which this codon encodes in the wild-type virus at this position. The letter *following the number designates the* amino acid encoded by the mutated codon. A change in the nucleotide sequence of a codon, i.e., a mutation, can result in the incorporation of a different amino acid, impairing protein function and leading to loss of efficacy. For example, the mutation M184V at codon 184 of the RT gene results in an exchange of the amino acid methionine (M) for valine (V) in the RT enzyme, rendering the virus resistant to RT inhibition by 3TC or FTC.
So-called "silent mutations" do not result in an amino acid exchange. Only mutations causing an amino acid exchange that also leads to a change in the protein structure are clinically relevant because this can contribute to the formation of resistance. Beyond that, "lethal" mutations lead to defective protein structures and thereby interrupt the replication cycle of the virus.

Table 2: Characteristics of genotypic resistance analysis (population sequencing).

Advantages	Disadvantages
• Quick to perform (within days) • Widely used (no S3 lab required) • Detection of all changes in the nucleotide sequence and deviations from the reference wild-type virus • Detection of any mutation with either evidence of resistance, emerging resistance or reverting resistance • HIV-1 subtyping possible • In general, reimbursement by health insurance	• Indirect measurement of resistance • Detection of variants comprising ≥10–20% (minor variants with NGS up to 0.1% depending on viral load) • Complex mutation patterns are often difficult to interpret • Unknown mutations are not considered in the interpretation • Interpretation systems must be continuously updated

Resistance-associated mutations are detected by direct sequencing of the amplified HIV genome. Therapeutically relevant is the sequencing of the HIV *pol* region, which encodes the viral enzymes protease, reverse transcriptase, and integrase, and the *env* region, which encodes the envelope proteins gp41 and gp120. Other gene regions, such as RNAse H and the *gag* region, are also relevant to resistance but are not described further here; they are usually analyzed as part of research projects rather than routinely. The basis for interpretation is the correlation between genotype, phenotype, and virologic response. Data are derived from *in vitro* selection studies, clinical studies and observations, and numerous duplicate measurements in which mutations were examined for phenotypic resistance.

Viral versus proviral resistance testing

The gold standard of resistance analysis in the presence of detectable viral load in plasma is the use of HIV RNA of free virions obtained from EDTA plasma. Resistance testing is also possible from proviral DNA. Although many proviral DNA sequences are not replication competent (Bruner 2019), proviral DNA testing can be helpful when viral load is low or undetectable, particularly before a change, e.g., toxicity reasons or treatment simplification (Allavena 2018). Historically or currently, resistant viral populations can be integrated into cells as provirus. They can be detectable for years, depending on the duration of treatment failure, the level of viral load, and other factors such as clonal expansion of cells (Boukli 2015, De La Cruz 2019, Wagner 2012). The agreement between cumulative historical resistance data from viral RNA in plasma and resistance data from proviral DNA sequencing under suppressive therapy is approximately 50–60% (Däumer 2019). In a sub-analysis of the LOWER II study, sequences from the proviral DNA of 96 individuals with multiclass resistance under continuous suppressive therapy were compared intra-individually at three-year intervals. In only 27% of individuals, a 100% concordance between the two proviral measurements was observed (Hoffmann 2022). Accordingly, in analyses from proviral DNA, the negative predictive value is of limited value. Treatment decisions or de-escalation strategies should not be based on proviral resistance data alone.

Rules-based interpretation systems

Genotypic interpretation systems are often based on rules derived by experts from literature data and revised once or twice a year. In Germany, the algorithm of HIV-Grade e.V. is primarily used to interpret resistance mutations (Obermeier 2012). In addition to an algorithm, the Stanford HIV Drug Resistance Database (HIVdb) provides a comprehensive database explaining resistance-associated mutations (Table 3). Commercial resistance test vendors have often implemented interpretation rules into their systems.

Data-based interpretation systems and virtual phenotype

In contrast to knowledge-based rule systems created by teams of experts, data-based interpretation systems such as geno2pheno (Beerenwinkel 2003) use machine-learning techniques such as support vector machines or regression models. The goal is to predict the phenotype or virological response from genetic information. In this "virtual phenotype", a phenotype is assigned to the individual genotypic resistance pattern without phenotyping. It is based on databases of paired genotyping and phenotyping.

Table 3: Overview of the most important resistance interpretation systems.

System (version)	Interpretation	Free Access	Internet: http://
HIV-GRADE (01/2023), Germany	Rule-based	yes	www.hiv-grade.de/grade_new/
HIV-GRADE HIV-2 (08/2015)	Rule-based	yes	hiv-grade.de/HIV2EU/deployed/grade.pl?program=hivalg
HIVdb Version 9.4.1 (06.2023), USA	Rule-based	yes	hivdb.stanford.edu/hivdb/by-mutations/
ANRS HIV-1 (V32), HIV-2 (V33) (10/2022), France	Rule-based	yes	hivfrenchresistance.org

Table 3: Continuation

System (version)	Interpretation	Free Access	Internet: http://
MGRM GeneSure® MG (Monogram Bioscience)	Rule- and data-based	no	https://monograbio.labcorp.com
geno2pheno Version 3.4 Germany	Data-based (Virt. Phenotype)	yes	geno2pheno.org

Methods of Tropism Determination

To enter the target cell, HIV needs a so-called co-receptor in addition to the CD4 receptor, namely one of the two chemokine receptors, CCR5 or CXCR4. Depending on the use of these receptors ("tropism"), viruses are divided into CCR5- or R5-tropic and CXCR4- or X4-tropic viruses. Viral strains that can use both receptors are called "dual-tropic". Since these cannot be distinguished in the tropism test from a mixture of R5- and X4-tropic viruses, this group is called "dual/mixed" (D/M)-tropic.
Tropism determination is only useful before a planned use of a CCR5 antagonist: to ensure its effectiveness, the presence of X4-tropic viruses must be excluded. This does not only apply to viremic patients: Even in cases of prolonged viral suppression and historically proven CCR5 tropism, a tropism test from proviral DNA may be useful before switching (even though in these cases, a change in tropism from CCR5 to CXCR4 is rather unlikely). X4-tropic viruses tend to be detected in proviral DNA rather than RNA (Verhofstede 2009). In contrast, if X4-tropism has been historically detected, repeating the test is of little help. Since maraviroc is the only CCR5 antagonist used relatively rarely, tropism testing plays a minor role. However, other compounds are in clinical development, such as the humanized antibody Leronlimab (Jacobson 2010, Dhody 2018), discussed below. As resistance, tropism can be determined genotypically or phenotypically (Braun 2007, Vandekerckhove 2011).

Phenotypic Tropism Test

Monogram's Trofile® is the best-known phenotypic tropism test due to its use in maraviroc pivotal studies. Trofile® ES (Trofile® with enhanced sensitivity) detects minor virus populations with a sensitivity of 1%. The test is also offered for proviral DNA at low viral loads <1,000 HIV RNA copies/mL. Another commercial phenotypic test is Phenoscript® ENV (EuroFins/ VIRalliance). The agreement is 85% (Skrabal 2007). Phenotypic assays are mainly used in the context of studies.

Genotypic tropism test

As with genotypic resistance analysis, advantages include the broad availability and the rapid results. For subtype B viruses, genotypic and phenotypic analyses were comparably well associated with virologic response to maraviroc-based therapy (Poveda 2012, McGovern 2012). Larger discordances were described for non-B subtypes, particularly for CRF01_AE, CRF02_AG, A, and F. Geno2Pheno and WebPSSM appear to somewhat overestimate CXCR4 use (Delgado 2011, Mulinge 2013).
Only the V3 region of the gp120 gene, which is crucial for binding, is sequenced. This determines the viral tropism, even if other gp120 regions, such as V1/V2 and C4, or substitutions in gp41 are involved. The preferred method at viral loads up to 200 copies/mL is sequencing the V3 loop from proviral DNA. Based on the nucleotide sequence, tropism is predicted using bioinformatics tools (Garrido 2008).
The coreceptor tool from geno2pheno (https://coreceptor.geno2pheno.org/) is widely used, shows good agreement with Trofile® ES, and is primarily used in Europe

(Prosperi 2010). In contrast to phenotypic determination, genotypic prediction does not distinguish between X4-tropic, dual- or mixed-tropic. The result determined with geno2pheno is the so-called false positive rate (FPR), which indicates the probability that an X4 prediction is false. An FPR of 0.1% means X4 tropism and an FPR of 90% means R5 tropism, since the X4 result would be false with a 90% probability. An FPR of less than 5% is assumed to predict an X4-tropic virus strain and an FPR of 15% or more is assumed to predict R5-tropic virus (DAIG 2014). These thresholds also apply to testing from proviral DNA. Maraviroc can be considered at an FPR of 5% to 15%, although residual uncertainty remains. In a study of samples from 101 individuals, a (costly) triple measurement at an FPR of 10% showed a discordance in tropism prediction in 10 samples. It resulted in reclassification from R5 to X4 in 4 cases (Symons 2012). Of note, single testing is sufficient at an FPR of 20% (Vandekerckhove 2011).

Mechanisms of action and resistance

NRTIs (nucleos(t)ide reverse transcriptase inhibitors) are administered as prodrugs and are only effective as triphosphates. Two phosphorylation steps are required for nucleotide analogs and three for nucleoside analogs. Phosphorylated NRTIs are incorporated competitively with natural deoxynucleotide triphosphates (dNTPs) into proviral DNA. They inhibit further synthesis by the enzyme reverse transcriptase (RT), thus blocking the extension of proviral DNA and leading to chain termination. There are two essential biochemical resistance mechanisms (De Mendoza 2002):
Steric inhibition is mediated by mutations that enable the RT enzyme to recognize structural differences between NRTIs and dNTPs. The incorporation of NRTIs is prevented in favor of dNTPs, for example, in the case of mutations M184V, Q151M, L74V, and K65R (Naeger 2001, Clavel 2004).
During ATP (adenosine triphosphate)- or pyrophosphate-mediated *phosphorylysis,* NRTIs that have already been incorporated are excised from the growing DNA chain. This is the case with the thymidine analog mutations M41L, D67N, K70R, L210W, T215Y, and K219Q (Meyer 2000).
The mutation K65R counteracts the excision of already incorporated NRTIs. The balance of both mechanisms – reduced incorporation by K65R on the one hand and inhibition of excision by K65R on the other – leads to reduced sensitivity for most NRTIs but increased sensitivity for AZT (White 2005) and thus resensitization.

NNRTIs (non-nucleos(t)ide reverse transcriptase inhibitors) also inhibit RT but chemically differ from NRTIs. As small molecules, they bind to a hydrophobic pocket close to the catalytic center of RT. Mutations at the NNRTI binding site of the RT reduce the affinity of the inhibitors and result in loss of efficacy. While one mutation is often sufficient for complete resistance in first-generation NNRTIs, mutation patterns are more complex for the less rigid second-generation NNRTIs (Vingerhoets 2010, Molina 2008).

NRTTIs, so-called nucleoside reverse transcriptase translocation inhibitors, block RT by multiple mechanisms. Islatravir is the first NRTTI in clinical development. RT uses EFdA triphosphate (TP) and other NRTI-TPs for DNA synthesis in the same way as dNTP substrates. However, traditional NRTIs lack a 3'-OH group required for DNA polymerization. Therefore, they act as immediate (obligate) chain terminators after being incorporated into the nascent DNA chain. On the one hand, since EFdA has a 3'-OH group, chain termination can still occur. On the other hand, interactions of the NRTTI at the dNTP binding site itself – even after its incorporation – inhibit translocation, which in turn inhibits the binding and incorporation of subsequent

nucleotides. Another mechanism of inhibition involves efficient misincorporation of EFdA by the RT that cannot be removed by excision, thus preventing DNA elongation (Markowitz 2018).

PIs prevent the cleavage of the viral gag-pol precursor protein by the enzyme HIV protease. This produces virus particles that are not infectious. PI resistance usually develops slowly, as several mutations usually have to accumulate. A distinction is made between major and minor mutations.
Major mutations are associated with phenotypic resistance. They include mutations that are the first to appear under the selection pressure of a drug, as well as mutations (sometimes also called "primary" mutations) that are located in the active site of the HIV protease and reduce the binding ability of the PI to this enzyme. In some cases, these mutations also lead to a loss of protease activity.
Minor mutations ("secondary" mutations) are located outside the active site and usually occur after major mutations. Sometimes, they can compensate for the loss of viral fitness caused by major mutations (Nijhuis 1999, Wensing 2022).

Integrase strand transfer inhibitors (INSTIs) prevent the integration of the viral genome, the proviral DNA (after transcription), into the host cell genome. First, the viral integrase binds to the 3'ends of the proviral DNA in the cytoplasm and forms the pre-integration complex. Then, the integrase cuts out a dinucleotide at both ends of the viral DNA, creating new 3'-hydroxyl groups (3'-processing). Strand transfer occurs in the nucleus, where the integrase joins the end segments of viral DNA to cellular DNA. Integrase inhibitors prevent strand transfer (therefore also abbreviated INSTI). They bind to the integrase and migrate into the nucleus along with the pre-integration complex. In their presence, the integrase molecules can no longer catalyze the integration of proviral DNA into cellular DNA. Resistance arises by selecting certain (key) mutations in the integrase gene. Both strand transfer and 3' processing can be affected. Different resistance profiles have been described. Accumulation of additional mutations leads to a further decrease in susceptibility (Jegede 2008).

Entry inhibitors prevent the virus from entering the target cell. HIV binds to the CD4 receptor with its surface protein gp120 (docking or attachment), which leads to conformational changes in gp120 and allows the binding of the V3 loop of gp120 with the chemokine receptors of the target cell, CCR5 or CXCR4, respectively. Interactions of the two heptad repeat regions, HR1 and HR2, and the viral transmembrane protein, gp41, result in a conformational change in gp41 that allows the insertion of gp41 into the cell membrane. The **attachment inhibitor (AI)** fostemsavir blocks the HIV envelope protein gp120 after metabolization to temsavir, preventing binding to CD4. Because AIs intervene before binding to the coreceptor, they can be used regardless of tropism (Li 2013). Ibalizumab, a monoclonal antibody, prevents cell entry by binding to the second extracellular domain of the CD4 receptor (Lewis 2017). **CCR5 antagonists** bind to the CCR5 coreceptor, preventing interaction with gp120 and, thus, entry into the cell. Tropism determination is required before use. Resistance mutations can increase the affinity of gp120 to the CCR5 molecule already bound to the CCR5 antagonist (Woollard 2015). The humanized IgG4 monoclonal antibody Leronlimab (PRO-140) also binds to the CCR5 receptor. Unlike maraviroc, which inactivates CCR5 by distorting the molecule's structure, Leronlimab binds only at the HIV-binding site but does not interfere with the function of CCR5 itself. It is also effective with maraviroc-resistant strains but not with X4-tropic viruses (Jacobsen 2010).

Fusion inhibitors prevent the fusion of the viral membrane with the cell membrane. T-20 (enfuvirtide) is a synthetic peptide corresponding to the C-terminal HR2 domain of gp41 and interacts (competitively with HR2) with HR1. This prevents the neces-

sary conformational change in gp41 and fusion. Even a single amino acid exchange in HR1 can significantly limit efficacy.

Capsid inhibitors: The mode of action of capsid inhibitors (including inhibiting various steps in the replication cycle) is only partially understood. As the first-in-class capsid inhibitor, lenacapavir binds specifically at the interface between capsid protein subunits, inhibiting the replication cycle in both the early and late phases by interfering with capsid assembly or disassembly (Zhuang 2021).

A crucial step takes place in the early phase of replication. Only a few years ago, it was thought that the capsid destabilizes and dissolves in the cytoplasm. Now it is known that the capsid is transported in an intact state along the microtubule network and then imported into the nucleus through the cell pores, followed by complete uncoating of the capsid, i.e., the capsid envelope breaks into pieces in the nucleus (Zila 2021). On the one hand, it is postulated that capsid inhibitors hinder the binding of nuclear import proteins to the capsid, and thus, the transport into the nucleus is disrupted (Link 2020). On the other hand, the binding of capsid inhibitors is assumed to impair capsid flexibility. Depending on the capsid inhibitor used, this may lead to early rupture or stabilization of the capsid, achieved by lenacapavir via binding to the capsid and converting the nuclear envelope into a rigid but stabilizing form. However, this disrupts the integrity of the capsid. It is still unclear how and when the nuclear envelope breakdown occurs after binding the capsid inhibitor in the nucleus (Li 2021, Selyutina 2022, Li 2023). At a later stage, virus assembly and release are disrupted. The production of capsid subunits is reduced by interfering with the gag/gag-pol process (Link 2020).

In the final step of maturation, the binding of capsid inhibitors results in malformed capsids in the form of tube-like sheaths without integrated pentameric capsomeres (Kvaratskhelia 2023). However, the antiviral efficacy is 10 times higher in the early phase than in the late phase of the replication cycle (EC50: 25 pM versus 439 pM) (Link 2020).

Transmission of resistant strains of HIV

The prevalence of resistance mutations present before therapy varies considerably from region to region. The standardization of a list of so-called Surveillance Drug Resistance Mutations (SDRMs) by an international research group made cross-regional or cross-national comparisons of the transmission of resistance possible (Bennett 2009). Since then, the prevalence and incidence of individual mutations have changed. New mutations in the relevant gene regions have emerged, which should be considered in any list revision (Rhee 2021).

As shown in Figure 1, a trend for an increase in NNRTI resistance and a decrease in PI resistance can be observed. There is a significant decrease in NRTI resistance. Transmitted mutations primarily affected NNRTI susceptibility (6.5–6.9%, based on nevirapine, efavirenz, rilpivirine, and etravirine), whereas <3% of guideline-recommended NRTIs and PIs were affected. For darunavir, the only PI recommended for first-line therapy, it was only 0.4% (Machnowska 2019). Two- and three-class resistance remained rare, at 1.3% and 0.2%, respectively. Among chronically infected individuals from the RESINA cohort, the proportion of primary resistance was relatively stable at approximately 10.7% between 2001 and 2016 (Böhm 2017). NRTIs, PIs, and NNRTIs were affected in 5.9%, 3.2%, and 3.7%, respectively.

Outside Europe and the US, the prevalence of primary resistance (mainly NRTI and NNRTI resistance) is much higher. In many countries in Africa, South America, and Southeast Asia, the proportion of primary NNRTI-resistant viruses (efavirenz or nevirapine) has been well over 10%. The WHO considers primary resistance a major

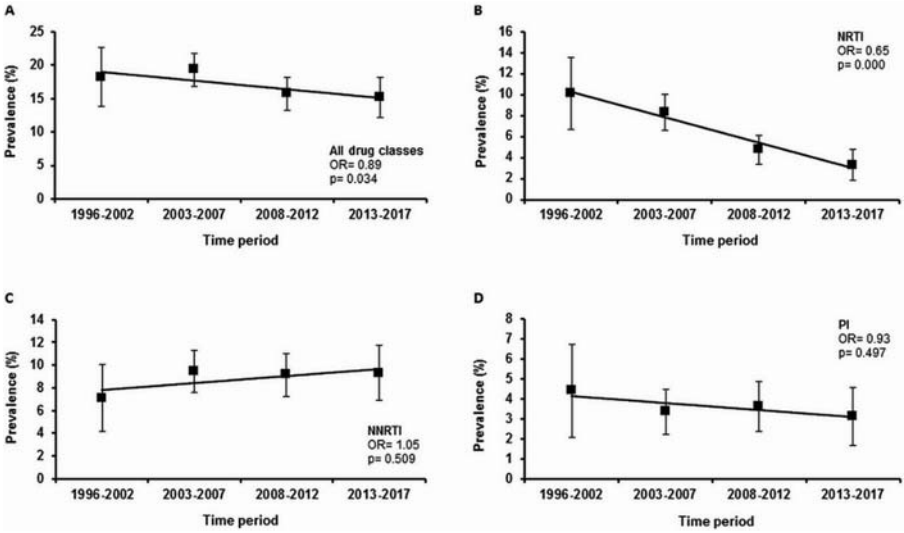

Figure 1: Prevalence of transmitted drug resistance (TDR) in the German seroconverter study over time (Machnowska 2019).

Table 4: Prevalence of primary resistance (%) in untreated patients (selection).

Reference	Country/region (study)	Period	Collective	N	Prevalence (%)
Machnowska 2019	Germany	1996–2017	Seroconverter	2,715	17.2
Hauser 2017	Germany	2013–2016	ART-naïve	881	10.8
Boehm 2017	Germany (RESINA)	2001–2016	Chronic infected	3,739	10.7
Visseaux 2019	France	2014–2016	New diagnosed	1,121	10.8
Olsen 2018	Europe/USA/ Canada (CASCADE)	1996–2012	ART-naïve	4,717	11.0
Margot 2017	Mainly USA and Europe (9 clinical studies)	2000–2013	ART-naïve	6,704	Initial: 5.2 Last: 11.4

worldwide problem (HIV drug resistance report 2021). The pattern of primary resistance may change over time due to the introduction of 2nd generation INSTIs (dolutegravir) as part of first-line ART in treatment guidelines (WHO 2021). Primary INSTI resistance has rarely been observed in Africa, especially resistance against second-generation INSTIs such as dolutegravir or bictegravir. Exceptions are HIV subtype F viruses (e.g., in Uruguay) with the frequently occurring resistance-relevant polymorphism G163R/K. In the Swiss cohort, only viruses with secondary INSTI mutations were detected in 1,319 treatment-naive individuals between 2008 and 2014, with one exception (T66I). The proportion of secondary mutations was 2.9%, with 80% occurring in non-B infections (Scherrer 2016b). Only secondary mutations were detected in a German cohort, in which 839 isolates from 2013–2016 were examined (prevalence 2.1%). The L74M and T97A mutations detected were also observed as polymorphisms before the introduction of INSTI (Hauser 2017). The major INSTI

mutation R263K was described in a French cohort of therapy-naïve individuals (Chaix 2016). In the MeditRes HIV cohort (France, Spain, Portugal, Greece, and Italy), the RT and integrase gene regions of 2,705 therapy-naive individuals between 2018 and 2021 were analyzed. The prevalence of INSTI mutations was 0.23%: T66A, T66I, E92Q, E138K, E138T, and R263K were each detected once (as a single mutation). In contrast, the RT mutation M184V/I was detected with a prevalence of 1.03% (De Salazar 2022).

Despite the currently low transmission of INSTI-resistant viruses, analyzing the integrase gene in therapy-naïve patients may be useful. This applies to patients with resistance mutations in the RT or protease gene, particularly if the index person has experienced a treatment failure on an INSTI-containing regimen.

Ultrasensitive methods such as ultradeep sequencing usually detect more resistance mutations than conventional sequencing methods (Buckton 2011). Clinical relevance, especially when detecting minor resistant viruses in the range of 1–5%, should always be evaluated in the context of treatment history (Porter 2015).

Transmitted primary resistance can remain detectable for a long time (Pao 2004). In the German seroconverter cohort, according to population-based Sanger sequencing, primary NRTI mutations persisted in the plasma of ART-naive PLWH on average 1.0–6.4 years. NNRTI mutations persisted for 1.5–8.0 years and PI mutations for 1.0–4.3 years. Mutations such as M184V that cause loss of fitness are usually the first to be replaced by wild-type viruses – others, such as K103N, remain detectable for a longer time in the plasma (Machnowska 2019).

Clinical relevance and guidelines for resistance testing

The clinical relevance of genotypic resistance testing before treatment change was demonstrated about 20 years ago in prospective studies such as Havana (Tural 2002). This is also true for phenotypic resistance testing (Cohen 2002). For ethical reasons, no more studies were designed in subsequent years to investigate the utility of resistance analysis. Resistance analysis before ART initiation is part of routine diagnostics.

A retrospective analysis of 10,056 patients who started ART after 1997 showed that taking resistance into account is essential for sustained treatment success. Patients who were not treated in accordance with resistance had a 3.1-fold higher risk of treatment failure in the first year. The difference between patients with and without primary resistance disappeared if all drugs used were fully active (Wittkop 2011). Data from the Swiss cohort confirm that the relative proportion of individuals with resistance mutations continues to decrease with new therapies that consider resistance data. Whereas in 2003, resistant viruses were detected in one in three ART-experienced individuals, this was the case in only one in four in 2013. Monotherapy or dual therapy mainly was started in the 1990s (Scherrer 2016a).

Resistance testing: When and for whom?

Resistance testing and tropism testing (when a CCR5 antagonist is used) are an integral part of the European and German guidelines, both in untreated and treated patients (see Table 5). Resistance testing should be performed if there is a viral load of >200 HIV-1 RNA copies/mL under ART. With lower viral loads, it may be considered.

The relevance of minor variants

The clinical value of detected minorities is unclear. A meta-analysis (10 studies, n=985) showed significantly poorer virologic response rates to NNRTI-containing first-line therapy in the presence of minor resistant viral variants, particularly those

Table 5: German-Austrian Guidelines on HIV Resistance Testing (DAIG 2020).

	Recommendation for resistance testing	Comments
Previously untreated persons		
Primary/recent infection	Recommended	
Chronic infection, before ART initiation	Recommended	If not done before
Treated persons		
In case of first therapy failure	Generally recommended (additional tropism testing if necessary)	Clarification of the causes of the therapy failure!
Treatment failure with extensive ART pretreatment	Generally recommended before ART switch (additional tropism testing may be required, phenotypic testing may be necessary).	Clarification of the causes of the therapy failure!
During or after treatment interruption	Possibly useful but not mandatory	Detection of reversion to wild-type

with NNRTI resistance (Li 2011). However, NGS data should be interpreted with caution even for NNRTIs, a class with a lower resistance barrier: In retained baseline samples from the STaR trial (rilpivirine versus efavirenz in treatment-naïve individuals, each plus TDF+FTC), minor variants were not predictive of treatment failure (Porter 2015). Another research group investigated whether minor resistant viral variants also exist more frequently in other gene regions in NNRTI-resistant than in wild-type viruses; this was not the case (Clutter 2017). Detection of minor variants is only reproducible above a frequency of 2% (Lee 2020). At low viral load levels of less than 500 to 1,000 HIV RNA copies/mL, NGS loses its sensitivity advantage concerning the detection of minor virus populations.

Risk of resistance with pre-exposure prophylaxis (PrEP)?

Before and during PrEP (see chapter *Prevention*), HIV antibody/antigen tests of the 4th generation must be performed regularly. If HIV infection remains undetected while on PrEP (with TDF/FTC), development of resistance is otherwise likely. The overall rate of new infection in PrEP trials was 0.18%, based on all exposed study participants (Grant 2015, Spinner 2016). In addition, there is also the risk of transmitting resistant viruses. As of early 2017, three cases of confirmed HIV infection on PrEP with TDF/FTC have been described outside of trials. In two, infection with a multidrug-resistant virus occurred, and in the third case, a wild-type virus was transmitted despite adequate TDF levels. The cause is unclear. Despite the increasing use of PrEP with TDF/FTC, resistance development remains a minor problem in clinical practice (Gibas 2019). In PrEP trials with the long-acting INSTI cabotegravir (see also chapter *ART*), the incidence of HIV infection was more frequently associated with the development of resistance mutations despite higher prevention efficacy compared with daily TDF/FTC (Landovitz 2021).

Interpretation of genotypic resistance profiles

The resistance profiles cited below are only indicative. One of the resistance interpretation systems mentioned in Table 3, such as HIV-GRADE (www.hiv-grade.de/grade_new/), should be used for treatment decisions.

NRTIs

3TC/FTC resistance: inhibition of replication capacity

FTC and 3TC have an almost identical resistance profile – treatment failure is associated with the M184V mutation (Borroto-Esoda 2007). This reduces viral replication capacity by 40–60% (Deval 2004). Under 3TC monotherapy, viral load was still 0.5 log levels below baseline after 52 weeks despite the early appearance of M184V (Eron 1995). Compared with treatment interruptions, 3TC monotherapy delays virologic and immunologic deterioration (Castagna 2006). The M184I mutation is often detected first, which may then be replaced by M184V (Schuurmann 1995) or persist, depending on concomitant medication (see rilpivirine). In the retrospective Italian ARCA cohort, the therapeutic success of dual therapies with 3TC was not affected by the detection of M184V and was better than monotherapy. This implies that 3TC or probably FTC administration is reasonable despite complete resistance (Gagliardini 2017).

Relevance of historical and newly selected mutations

Thymidine analog mutations ("**TAMs**") include the **M41L**, **D67N**, **K70R**, **L210W**, **T215Y/F**, and **K219Q/E** mutation. TAMs are selected under AZT and d4T (Larder 1989) and cause gradual cross-resistance to ABC and TDF (Harrigan 2000). Detection of primary resistant viruses with certain TAMs does not appear to affect first-line therapy with TDF (Geretti 2016). For ABC and TDF, TAMs are only "re-selected" but do not emerge.

Under failing ABC-containing therapy, the mutations **L74V/I** and, less frequently, the mutation **K65R** usually occur. **Y115F** is a specific resistance-associated ABC mutation, but it also affects the efficacy of TDF.

Under TDF, the **K65R** mutation is primarily selected. It causes intermediate resistance to TDF, ABC, 3TC, and FTC (Miller 2004). In HIV-1 subtype C infection, K65R is three to four times more likely to be detected under failing TDF-containing therapy than in other subtypes (White 2016). K65R increases sensitivity to AZT or causes resensitization to AZT in the case of (few) TAMs (White 2005). Conversely, TAMs reduce the selection of K65R under regimens with TDF and ABC (Parikh 2007).

Like M184V, K65R (unlike TAMs or L74V/I) reduces viral fitness. Replication capacity decreases to 29% in the simultaneous presence of K65R and M184V (Deval 2004).

Less frequently than K65R, the mutations **K70E** or **K70G** have been observed under failing therapy with tenofovir, especially in combinations with ABC and 3TC (Delaugerre 2008).

The mutations **M184V** and **L74V**, as well as the NNRTI-specific mutations L100I and Y181C, may exert an antagonistic effect on developing resistance to NRTIs. **M184V** causes an IC_{50} reduction of approximately 50% for AZT. L74V/I results in IC_{50} reduction of approximately 70% for AZT and TDF (Underwood 2005). In contrast, M184V, together with multiple TAMs, can enhance resistance to ABC (Harrigan 2000).

So-called **multi-drug resistance (MDR)** to all nucleoside analogs is present upon detection of mutation T69S and an insertion of two or more amino acids (SS, SG, or SA) between positions 69 and 70. The MDR mutation **Q151M** causes intermediate resistance to AZT and ABC, resulting in only a minor loss of TDF, 3TC, and FTC activity. In combination with mutations at positions 75, 77, and 116, high-level resistance to AZT and ABC and intermediate resistance to TDF arise (Masquelier 2001, Miller 2004). New emergence of these mutations is rarely observed today, yet these mutations are found virally and/or provirally in long-term treated individuals with a history of treatment failure.

Like TDF, TAF is a tenofovir pro-drug. *In vitro* data suggest that TAF can overcome NRTI-resistant viral variants with the K65R mutation or up to three TAMs. This effect may be due to the intracellularly approximately 5-fold higher levels of the active substance (Margot 2013). However, this effect has not yet been confirmed in *vivo*. In two large studies in treatment-naïve patients, the resistance rate under TAF versus TDF (both plus FTC+elvitegravir/c) was similar, at 1.2% versus 0.9% (Callebaut 2016). Quantitative sensitivity measurements in large cohorts showed that in NRTI-pretreated patients, hypersusceptibility to the first-generation NRTIs is present in up to 29%: the inhibitory concentration is lowered by a factor of 0.3–0.6. In particular, mutations at positions 215, 208, and 118 play a role (Shulman 2004). However, these results have not led to new therapeutic strategies.

NNRTIs

First-generation NNRTIs (efavirenz, nevirapine)

Numerous mutations have been described for first-generation NNRTIs. These mutations can occur alone or in combination. Even a single mutation can result in high-level resistance to **nevirapine (NVP)** or **efavirenz (EFV)**. For nevirapine, these are the mutations K101P, K103N/S, V106A/M, Y181C/I/V, Y188C/L, and G190A/E/Q/S. For efavirenz, these are L100I, K101P, K103N, V106M, Y188C/L, and G190A/E/Q/S (Melikian 2014). In contrast to V106A, V106M occurs more frequently in subtype C than B viruses (Grossmann 2004). First-generation NNRTIs should be discontinued if any of these mutations are detected, to prevent the selection of further mutations that may affect the efficacy of second-generation NNRTIs such as etravirine or doravirine.

Second-generation NNRTIs

Compared to first-generation NNRTIs, **etravirine (ETR)** has a higher resistance barrier, likely due to flexible binding to the reverse transcriptase. Etravirine is active against viruses with single NNRTI mutations, such as K103N or G190A. It remains the only NNRTI that shows efficacy in the presence of Y188L, which indicates doravirine resistance (Vingerhoets 2010).

In the DUET studies, a total of 17 mutations were found to be relevant. Y181I/V received the highest resistance score of 3, followed by L100I, K101P, Y181C, and M230L with 2.5. E138A, V106I, G190S, and V179F were assigned a score of 1.5, and the remaining mutations of 1. A total score of 0–2 points was associated with a virologic response rate of 74% (best response), 2.5–3.5 points with 52% (intermediate), and ≥4 points with 38% (reduced response) (Vingerhoets 2010). If the mutations L100I, K101P, and Y181C/I/V are detected alone, the efficacy of etravirine is already impaired (Haddad 2010).

Rilpivirine (RPV) is unaffected or barely affected in efficacy by certain NNRTI mutations such as K103N, V106A, or G190A. *In vitro, the* following mutations were selected: V90I, L100I, K101E, V106A/I, V108I, E138G/K/Q/R, V179F/I, Y181C/I, V189I, G190E, H221Y, F227C, and M230I/L (Azijn 2009). In a study of treatment-naïve individuals without known NNRTI mutations, most were confirmed in *vitro* (Molina 2008). There is high cross-resistance between rilpivirine and etravirine (Melikian 2014).

In the phase 3 ECHO and THRIVE trials, virologic failure was more common in treatment-naïve individuals on rilpivirine than on efavirenz (10.5% vs. 5.7%), particularly with high viremia above 100,000 copies/mL (17% vs. 7%). Resistance mutations were detected more frequently in treatment failure than with efavirenz (63 vs. 54%). The most common mutations with rilpivirine were E138K (45%), K101E (13%), H221Y (10%), V189I (8%), Y181C (8%), and V90I (8%) (Rimsky 2012).

In the STaR study, NNRTI and/or NRTI resistance developed in 4.3% within one year on rilpivirine+TDF+FTC, compared with 0.8% on efavirenz+TDF+FTC. The most common mutations with rilpivirine were Y181C/I, followed by E138K/Q and V90I (Porter 2014). NRTI mutations in treatment failure were also observed more frequently with rilpivirine than with efavirenz (68% versus 32%). Under rilpivirine, this was primarily M184I, and under efavirenz, M184V (Eron 2010, Rimsky 2012). Resistance testing should also be performed before use due to the naturally occurring E138A polymorphism. E138A occurs in up to 5–7% depending on HIV subtype and decreases RPV susceptibility by approximately a factor of 2 – comparable to other mutations at position 138, the effect of which is slightly increased by the M184I mutation (Xu 2013, Hauser 2018).
In the ATLAS and FLAIR studies on long-acting RPV and cabotegravir, the following NNRTI mutations were primarily detected in treatment failure: E138A/K/G, K101E, and M230L (Orkin 2020, Overton 2022). Proviral resistance testing of retained baseline samples showed that NNRTI mutations were often already detectable at therapy initiation (Overton 2020). In a pooled analysis of 48-week data from ATLAS, FLAIR, and ATLAS-2M, HIV-1 subtype A1/A6 and RPV-associated resistance mutations in the provirus were associated with virologic failure (Cutrell 2021, see cabotegravir). This underscores the high relevance of considering treatment history with all resistance data before switching therapy. In case of an incomplete treatment history, a proviral resistance test can be helpful, but its limitations should be considered (see proviral resistance testing).

Doravirine (DOR) has a different resistance profile than previous NNRTIs. It remains active in the presence of singular NNRTI mutations such as K103N, E138K, Y181C, and G190A. However, some combinations of these mutations can lead to resistance. For example, the combination of K103N, Y181C, and V179F led to a resistance factor of 22 (Saladini 2019). *In vitro,* resistance development emerges via codon changes at position 106. An exchange of valine for alanine (V106A) was observed in HIV-1 subtype B, followed by other mutations such as F227L or L234I. In subtype A and C, both the V106A and V106M pathways were selected. Other mutations, such as V108I, F227C/I/L, and L234I, were detected with a time lag. The greatest efficacy loss was seen with Y188L (Feng 2015+2016).
In the Phase 3 DRIVE-FORWARD and -AHEAD studies, the following resistance mutations were detected in 12 individuals (1.6%) by week 144: V75I, A98G, V106I/A/M V108I, Y188L, H221Y, P225H, F227C, Y318F. The mutations occurred in 10 cases in combination with V106I/A/M. The following NRTI mutations were detected in 8 individuals: M184V (n=5), M184I (n=1), K65R (n=2), and M41L (n=1). Treatment failure occurred mainly within the first two years (Martin 2020, Molina 2020+2021a, Orkin 2021).

Protease inhibitors (PIs)

PIs have a high resistance barrier. In most cases, only several resistance mutations result in a complete loss of efficacy. The spectrum of mutations is very broad. As with other antiviral agents, continuation of a failing PI regimen selects additional mutations that may result in moderate to high cross-resistance. Under classical first-line therapy with boosted PI and 2 NRTIs, PI mutations are extremely rare, even in the case of virologic failure. Mutations are more likely to affect NRTIs. Primary resistance to boosted PIs has also been rarely detected (Eron 2006, Molina 2008). Currently, only darunavir is included in the guidelines for first-line therapy (DAIG 2020).

First-generation PIs

Lopinavir/r (**LPV/r**; boosted with ritonavir): Under failure, mutations at positions 46, 54, and 82 are primarily selected, but also I50V or V32I in combination with I47A/V/I (Kempf 2001, Mo 2005). The L76V mutation, which is selected by lopinavir, fosamprenavir, and darunavir, can lead to resensitization to atazanavir, saquinavir, or tipranavir (Müller 2004). Viruses with this mutation can be successfully controlled by the combination of lopinavir (to preserve L76V) and saquinavir (resensitized PI) despite additional PI mutations (Wiesmann 2011).

Atazanavir/r/c (**ATV/r, c**; boosted with ritonavir or cobicistat) has a partially unique resistance profile. In ART-naive patients, unboosted atazanavir mainly selected for I50L (Colonno 2004). This mutation increases sensitivity to other first-generation PIs (Weinheimer 2005). With PI pretreatment, I50L emerged in one-third of cases. The resistance barrier of boosted atazanavir is significantly higher (Gianotti 2005). Among other mutations, particularly I84V leads to an efficacy loss (Colonno 2004). In the CASTLE study in therapy-naïve patients, only two cases of PI-resistant virus were detected, namely M46M/I+N88N/S and V32I+M46I+L90M (Lataillade 2008).

Second-generation PIs

Darunavir/r/c (**DRV/r,c**; boosted with ritonavir or cobicistat) has a high resistance barrier and good activity against a broad spectrum of PI-resistant viruses. *In vitro* resistance develops more slowly than against lopinavir (De Meyer 2005). The presence of at least 3/11 resistance-associated mutations (DRV-RAMs) at 10 positions was associated with a decreased response rate: V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, and L89V (Wensing 2017). Sensitivity is affected to varying degrees: I50V is in the first place, followed by I54M, L76V, and I84V. This is followed by V32I and I47V.

Emerging mutations upon treatment failure were V32I, L33F, I47V, I54L, and L89V. Approximately 50% of these isolates remained sensitive to tipranavir. Detection of the V82A mutation was positively correlated with treatment response, based on the POWER/DUET studies, as was E35D (Descamps 2009). A study of approximately 55,000 sequences of PI-naive and 10,500 sequences of PI-experienced individuals showed a slight increase in accessory DRV-RAMs such as L10F, T74P, and L89V after 2009 (Rhee 2021).

Switch studies, including DRV/r monotherapy studies, have confirmed that boosted darunavir has a very high resistance barrier. During an observation period of 144 weeks, resistance mutations were detected in only one patient on darunavir monotherapy in MONET, which did not result in phenotypic resistance (Arribas 2012). The results of the MONET study were confirmed in the PROTEA study. During a 96-week observation period, there was no treatment failure with the development of resistance. However, the virologic response was worse, particularly with low CD4 T-cell counts (Girard 2017). Monotherapies are generally not recommended so far.

In the African NADIA trial, patients who had failed first-line NNRTI therapy were randomized to two NRTIs plus either darunavir/r or dolutegravir. During darunavir, unlike dolutegravir, there was not a single failure with emerging resistance after two years (Paton 2022). These data suggest that boosted darunavir has the highest resistance barrier of all approved HIV drugs.

Tipranavir (TPV) is effective against numerous viruses with multiple PI resistances but is hardly used anymore. *In vitro,* L33F and I84V were the first mutations to appear, but they were associated with only a 2-fold decrease in sensitivity (Doyon 2005). A "weighted" score based on the RESIST data (Scherer 2007) included mutations of an unweighted score (Baxter 2006) plus five mutations (24I, 30N, 50L/V, 54L, 76V)

conferring increased susceptibility. Positive and negative weighting points were assigned to the mutations, the sum of which results in a weighted tipranavir score. Of note, the major mutations I47V, I54A/M/V, Q58E, T74P, V82L/T, N83D significantly contribute to resistance.

Integrase inhibitors (INSTIs)

Given the increasing use of INSTI-containing regimens, virologic treatment failure among INSTIs is also becoming more frequent. Nevertheless, transmission of INSTI-resistant viruses remains rare (see above). Sequence analysis of viruses from therapy-naïve individuals showed that the integrase gene is highly polymorphic, but the resistance-relevant positions 143, 148, and 155 are conserved (Rhee 2008).

Raltegravir (RAL): In the STARTMRK study of treatment-naïve patients, the following integrase mutations were detected after 156 weeks in 4/23 with evaluable resistance testing in virologic failure: Q148H+G140S, Q148R+G140S, Y143Y/H+L74L/M+E92Q+T97A, and Y143R (Rockstroh 2013). Three key mutations or resistance pathways have been described in pretreated patients with treatment failure on a raltegravir-containing regimen: N155H, Q148K/R/H, and Y143R/C. Other mutations observed along with N155H were T97A, L74M, E92A/Q, T97A, V151I, G163K/R, S230R.

In combination with Q148K/R/H, the following mutations were detected: L74M, E138A/K, G140A/S, and G163R, with mutations prevailing at position 140 (Anstett 2017). The mutations Q148K/R/H and E92Q do not co-occur on the same viral genome. The occurrence of additional mutations to the key mutations N155H or Q148K/R/H causes an increase in resistance and, depending on the mutation pattern, increases the previously reduced viral fitness. This is particularly true for the Q148H pathway (Hatano 2010). Viruses with N155H plus other secondary mutations are often replaced by a more resistant and more fit viral population harboring the mutations Q148H+G140S. Therefore, raltegravir should be discontinued once a first key resistance-associated mutation is detected to avoid compromising the efficacy of second-generation INSTIs.

The Y143 resistance pathway is specific, with this position interacting directly with the oxadiazole ring of raltegravir. The most common substitutions at this position are Y143C and Y143R (Huang 2013). Selection of other mutations, such as L74M, T97A, E138A, G163R, or S230R, cause an increase in resistance, which may include substitutions such as Y143K and S (Anstett 2017). More resistant viruses may replace virus populations with N155H with mutations at position 143 (da Silva 2010). In viruses with the relatively common HIV-1 subtype CRF02_AG, the G118R mutation causes raltegravir resistance with a resistance factor of 25 (Malet 2011).

In the presence of (other) resistance mutations, care should be taken not to use raltegravir as functional monotherapy: In SWITCHMRK, in which virologically successful lopinavir/r-based ART was either continued or lopinavir/r was replaced with raltegravir, virologic failure occurred more frequently with raltegravir, likely due to archived resistance mutations that compromised the efficacy of the NRTI backbone (Eron 2010). Accordingly, the resistance barrier of raltegravir is lower than that of a boosted PI or 2nd generation INSTI.

Elvitegravir (EVG): Under failing first-line therapy with elvitegravir/c+TDF+FTC, the NRTI mutations M184V or M184I occur first, followed by INSTI resistance mutations. In two phase III studies, the following resistance mutations were detected alone or in combination within the three-year observation period: T66I, T97A, E92Q, N155H, and Q148R (White 2015). Other mutations such as E138A/K, G140A/C/S/Q

Q148H/K, G163R were observed in cell culture as well as in ART-naïve patients (Anstett 2017). Given marked cross-resistance between elvitegravir and raltegravir (White 2015), mutual replacement of these drugs is not recommended in the setting of treatment failure. Although Y143R is most likely to emerge under raltegravir (Métifiot 2011), it causes cross-resistance to elvitegravir, particularly with secondary mutations (Huang 2013). There are sometimes different resistance patterns in virologic failure under raltegravir and elvitegravir. In a phase 3 study, T66I/A (12%) and E92Q (8%) were the most common under elvitegravir (Molina 2012). T66I phenotypically causes resistance to elvitegravir but not to raltegravir. When combined with E92Q, resistance increases for both; the resistance factor was 18 for raltegravir and 190 for elvitegravir (Van Wesenbeck 2011, Margot 2012). A pilot study evaluated the switch from successful treatment to TAF/FTC/elvitegravir/c in case of historical evidence of the M184V/I mutation. Despite initial positive data over 24 weeks (Perez-Valero 2018), long-term data in a larger collective are lacking. Detection of T97A alone has no negative impact (Kulkami 2017).

Dolutegravir (DTG) has a higher resistance barrier than raltegravir and elvitegravir. Resistance mutations emerge in cell culture only after several months, particularly R263K. In isolates of subtype CRF02_AG, the R263K or G118R mutation was selected. The latter mutation was also detectable in a subtype C isolate (Canducci 2011, Quashie 2012). The G118R mutation, which was also detected on raltegravir in subtype CRF02_AG, causes a threefold reduction in dolutegravir susceptibility. When reporting resistance factors, it should be noted that the clinical threshold for dolutegravir has not been conclusively determined. Monogram gives 4 as the lower clinical cut-off. Although R263K causes only weak resistance (resistance factor 1.5–2.1), it is considered specific and may even define its own resistance pathway (Mesplede 2013, Underwood 2013b).

Analyses of *in vitro* mutagenesis showed no influence of single primary and secondary INSTI mutations on the susceptibility of dolutegravir. Susceptibility is only affected by combinations of mutations. The highest resistance factors were obtained with Q148 combinations, depending on the substituted amino acid at the Q148 position. The combination E138K plus Q148K causes high-level resistance with a resistance factor of 19±8, which was only 2 to 5 for other dual Q148 combinations. Although the N155H mutation alone does not affect susceptibility, the resistance factor increases to 2.5±1.2 compared with wild-type virus when E92Q is concomitantly present (Kobayashi 2011).

In ART-naive patients treated with two NRTIs and dolutegravir in each of the phase 3 studies SPRING-2, SINGLE, and FLAMINGO, not a single resistance mutation was detected (Molina 2014, Raffi 2013), neither against INSTIs nor against the NRTIs used. In contrast, in a direct comparison between dolutegravir and raltegravir (SPRING-2), INSTI resistance and NRTI resistance were observed in single cases on raltegravir-based ART (Raffi 2013). These data demonstrate the high resistance barrier of dolutegravir-based regimens. However, various monotherapy studies showed that the resistance barrier of the single substance is not as high as postulated according to *in vitro* data. In these studies, early treatment failure occurred in 11/122 individuals. There was no consistent resistance pathway. Subsequent mutations were detected in 9/11 individuals with virologic failure: 118R and 148H (twice each), 92Q/155H, 97A/155H, 155H/148R, 148K, and 148R once each (Blanco 2017). In the Domono trial, treatment failure occurred in 8/77 cases after switching to dolutegravir. Different mutations were detected in three cases of drug resistance: 155H, 263K, and 230R (Wijting 2017).

In the phase 3 GEMINI (Cahn 2019) trials, in which treatment-naïve patients received either dolutegravir/3TC or dolutegravir plus TDF/FTC, there was only one treatment

failure with development of resistance under dolutegravir/3TC by week 144. Compliance was questionable in this patient. The mutation M184V was detected first (week 132), followed by R263R/K (week 144) (Cahn 2020).

More timely than ever is the question of whether dolutegravir/3TC efficacy is compromised when M184V is detected. Because a historical or currently documented M184V/I mutation was an exclusion criterion in the phase 2/3 studies, archived samples were re-analyzed to detect proviral M184V/I mutations with NGS. In the ART-PRO study, the presence of M184V did not affect treatment response or blip rates in 21 individuals (Rial-Crestelo 2021). In the phase 3 SALSA and TANGO trials, retrospective proviral detection of M184V – albeit low in number – also had no impact (Ndashimye 2021, Underwood 2022). The prospective SOLAR 3D study has provided more data regarding the impact of a historical M184V/I mutation. In this study, 100 individuals on suppressive therapy with a history of treatment failure (50 with historical M184V/I and 50 without) were switched to dolutegravir/3TC. No treatment failure was documented in either group until week 48 (Blick 2021). However, these data do not imply that dolutegravir/3TC can be recommended in successfully long-term treated patients with proviral or historically proven M184V/I. Its use remains off-label and is, at best, an option to be discussed in exceptional situations. In the case of viremia, i.e., when replicative virus with M184V is present, dolutegravir/3TC should never be given alone from a virologic perspective.

In INSTI-naïve patients of the SAILING study with a history of prior treatment failure, the mutation R263K was detected in two patients with virologic failure in the first year (once in HIV subtype B and once in subtype C). The DTG resistance factor was 1.9 (Cahn 2013). Some research groups evaluate R263K as a "dead-end" mutation because it severely impairs viral fitness. However, this loss of fitness can be reversed by the E157Q mutation – with a concomitant increase in the resistance level (Anstett 2016). Other *in vitro* experiments showed that in viruses with R263K, the development of NRTI and NNRTI resistance mutations is delayed compared to wild-type viruses (Oliveira 2014). In SAILING, other resistant viruses were identified between weeks 48 and 96, including those with the mutations R263K and N155H (Underwood 2015).

The VIKING and SAILING studies demonstrated that dolutegravir with resistance-adapted concomitant medication can be a good option for multidrug-resistant viruses. However, the response rate is lower in the case of one or two other INSTI mutations in the presence of a Q148 mutation. The following mutations newly emerged at the time of virologic failure in the VIKING-3 trial (week 48): L74L/M/I, E92Q, T97A, E138K/A, G140S, Y143H, S147G, Q148H/K/R, N155H, and E157E/Q (Castagna 2014).

Simplified, the resistance level of viruses with Q148 and other dolutegravir RAMs can be classified as follows: Q148+G140+E138+L74 > Q148+G140+E138 > Q148+G140+L74 > Q148+G140 > Q148+E138 (Underwood 2013a). On the Q148 resistance pathway, the selection of the T97A mutation enhances resistance about 10-fold (George 2017). According to the VIKING studies, increasing the dolutegravir dose to 50 mg BID is recommended in cases of suspected or proven resistance.

As described above for darunavir, in the NADIA study, INSTI-naive patients with viremia and NRTI and/or NNRTI resistance were treated with either a dolutegravir- or darunavir-based follow-up regimen. In contrast to darunavir, dolutegravir resulted in the development of resistance in 9 cases, with the patterns differing according to the concurrent agents. Under AZT/3TC, complex INSTI mutation patterns, including G118R and E138K, were primarily detectable, whereas under TDF/3TC, only the combination M50I and R263K was observed. Data on the HIV subtype that may influence the resistance pathway are lacking (Paton 2022). These data demonstrate

that in case of detectable viral load and NRTI resistance, viral load should be closely monitored before switching to DTG + 2 NRTI.
Currently, it is discussed whether other gene regions show changes in therapy failure without detectable mutations in the integrase gene. For example, in *vitro,* phenotypic INSTI resistance is also seen with alterations in highly conserved regions of the nef gene (Malet 2017). Whether this is therapeutically relevant remains to be seen.

Bictegravir (BIC), like dolutegravir, has a high resistance barrier. In phase 3 clinical trials, no resistance mutations were detected in treatment-naïve patients during virologic failure (Gallant 2017, Sax 2017). In the studies GS-1489/1490, no bictegravir resistance was observed even after five years (Wohl 2022). In rare cases, especially with comorbidities and adherence problems, resistance mutations such as R263K may be selected under bictegravir (Stoll 2020).
Since no study data exist on patients with prior INSTI failure, the resistance profile is currently characterized based solely on *in vitro data.* A clinical threshold for the resistance factor has not yet been defined. Data to date show high cross-resistance to dolutegravir, mediated mainly through the Q148 resistance pathway. In cell culture, resistance development for elvitegravir, dolutegravir, and bictegravir proceeded via selection of the R263K mutation, first for elvitegravir, then with a time lag for bictegravir, and finally for dolutegravir. The mutation M50I was subsequently selected under bictegravir, T66I under elvitegravir, and S151Y, S119R, and M50I under dolutegravir. In targeted mutagenesis, phenotypic resistance for bictegravir and dolutegravir changed slightly or moderately by the mutations above, with an increase in EC_{50} by a factor of approximately 3 to 8 (Tsiang 2016). Pre-existing resistance mutations such as M184V do not appear to affect the efficacy of bictegravir plus FTC+TAF, based on retrospective analyses of pre-selected study populations (Acosta 2019, Andreatta 2019).
The impact of archived INSTI mutations on bictegravir efficacy was investigated in a reanalysis of 7 phase 3 studies. One percent of baseline samples had archived proviral INSTI mutations – specifically E92G, Y143C/H, S147G, Q148H/K/R, N155S, or R263K +/- secondary substitutions. All 20 cases showed treatment response to bictegravir (d'Antoni 2022). Again, it should be noted that in these studies, the detection of INSTI mutations was a priori an exclusion criterion, the observation period was only one year, and 19 of 20 patients were successfully treated at baseline. Furthermore, it is unclear whether the detected proviruses were capable of replication.

Cabotegravir (CAB) is biochemically very similar to dolutegravir. *In vitro,* the following resistance mutations were selected alone or in combination: H51Y, L74M, E138K, G140S, S147G, S157V, G163R, Q148K/R, and R263K. Resistance selection occurs more rapidly in *vitro* under elvitegravir and cabotegravir than under dolutegravir and bictegravir, indicating a lower resistance barrier (Oliveira 2018).
In the phase 3 switch studies ATLAS, FLAIR, and ATLAS-2M, in which long-acting (LA) cabotegravir and LA rilpivirine were administered either every 4 or 8 weeks as intramuscular injections, virologic treatment failure was associated with HIV-1 subtype A1/A6 infection. In ATLAS-2M, treatment failure with the development of resistance during 152 weeks was observed in 2% (n=11) in the 8-week study arm and 1% (n=2) in the 4-week arm. The INSTI mutations detected in combination with NNRTI resistance mutations (see rilpivirine) were T97A, E138K, N155H, and Q148R (Hunter 2021, Overton 2022).
In multivariate analysis, baseline risk factors were HIV-1 subtypes A6 and A1, archived rilpivirine resistance mutations (in the provirus), and a BMI >30 kg/m^2. Detection of at least 2 of these factors significantly increased the risk of treatment failure. HIV-1 subtype A6, predominant in Russia, differs from subtype A1 at 12 polymorphic positions, including resistance-associated positions L74I and S119P. These occur more

frequently in subtype A6. According to the label, HIV-1 subtype A1 or A6 alone is not a contraindication. However, those affected should only switch to this new regimen cautiously after extensive discussion of the risk.
In HPTN-083, in which cabotegravir i.m was administered as PrEP every 8 weeks (after a 4-week oral lead-in phase), some individuals who became infected with HIV in the study also developed resistance. In addition to the mutations detected in ATLAS, the following were detected: E138A, G140A/S, Q148K, and R263K. These were found early at low viral loads (Landovitz 2021, Marzinke 2021). In accordance with the marketing authorization restriction, LA therapy with cabotegravir plus rilpivirine should not be prescribed if INSTI or NNRTI resistance is detected.

Entry inhibitors

CCR5 antagonists such as **maraviroc (MVC)** should only be used for exclusively CCR5-tropic viruses. Therefore, a tropism test is required prior to the use of maraviroc. This therapy is not recommended for CXCR4- or dual-tropic viruses. CCR5-tropic viruses are detectable in about 80–85% of therapy-naïve patients and about 50–60% of therapy-experienced patients. Exclusively X4-tropic viruses are rare. The likelihood of X4-tropic virus populations increases with decreases in CD4 T-cell counts, both in therapy-naïve and pre-treated individuals (Hunt 2006, Simon 2010).
Two types of resistance to CCR5 antagonists can be distinguished: on the one hand, the receptor switch from R5- to X4-tropic or dual-tropic viruses, and on the other hand, the emergence of mutations that enable the virus to use CCR5 molecules for cell entry even in the presence of CCR5 antagonists. In cases of treatment failure with maraviroc, a shift from CCR5- to CXCR4-tropic virus has been described in approximately one-third of cases (Heera 2008). Retrospective studies with more sensitive methods have shown that minor X4 variants were already present in some individuals before the start of therapy. Occasionally, however, a receptor shift was also observed in the control arm without maraviroc (Lewis 2007).
Since not every minor X4 virus population necessarily leads to treatment failure, it is currently unclear when the higher sensitivity of ultradeep sequencing (UDS) has clinical relevance or at what proportion of X4-tropic viruses the risk for treatment failure becomes greater. Samples from the A0041029 and Motivate studies were reanalyzed by UDS and classified as non-R5 if at least 2% non-R5 viral variants were detected. Response rates were similarly low for 2–20% of non-R5 viruses compared to more than 20% of non-R5 viruses (Swenson 2011).
In treatment failure without tropism switch under maraviroc, different mutations were detected in the V3 loop of the envelope protein gp120 of HIV-1. The resistance patterns were not uniform; mutations outside the V3 loop were also observed. The clinical relevance of the individual *env mutations* is unclear; in some cases, they were not associated with an increase in IC_{50}. Instead, phenotypic maraviroc resistance was associated with reduced maximal possible viral inhibition in the dose-response curves (Mori 2008). This observation suggests that maraviroc-resistant viruses may also utilize the CCR5 receptor to which maraviroc has already bound (Westby 2007).

Leronlimab (PRO-140) is a **humanized CCR5 monoclonal antibody** being evaluated in multiple indications (e.g., HIV infection, metastatic triple-negative breast cancer, or severe respiratory complications associated with COVID-19). To date, the data from HIV trials is still limited, but the results are nevertheless impressive. Of 42 patients with HIV infection and CCR5-tropic virus only who were switched to PRO-140 monotherapy (once weekly subcutaneously) on suppressive ART, 16 entered the extension phase; in 9, PRO-140 therapy was successful for more than two years. A tropism switch or a significant change in IC50 or IC90 was not observed for either

PRO-140 or maraviroc (Lalezari 2017). *In vitro* and *in vivo,* leronlimab shows low potential for a receptor switch or the development of resistance (Dhody 2018). It is also effective in maraviroc-resistant strains but not in X4-tropic viruses (Jacobsen 2010, see also chapter 5.3.).

Fostemsavir (FTV) is an **attachment inhibitor** and is indicated for the treatment of multidrug-resistant HIV-1 infection. In contrast to existing entry inhibitors, the active metabolite temsavir binds directly to gp120 of HIV, preventing its binding to the CD4 receptor. In the BRIGHTE trial, 60% of patients with four-class resistance achieved durable virologic response beyond week 96 (Ackermann 2021). In particular, 4 positions with the following key mutations/polymorphisms in the gp120 domain are associated with loss of temsavir efficacy: S375N/H/M/T/I, M426L/I, M434I/K/L/T, and M475I/L/V. S375N and M426L occurred most frequently (Kozal 2020). There is no cross-resistance to other entry inhibitors.
The efficacy of temsavir is limited to HIV-1 group M. Thus, it should not be used in HIV-2 and HIV-1 groups N, O, and P. In HIV-1 group M subtype CRF01-AE, which is dominant in Southeast Asia, fostemsavir should also not be used due to naturally occurring resistance. The AE subtype virus has polymorphisms in the gp120 domain associated with severely reduced activity to temsavir.

Fusion inhibitors: This section is limited to resistance mutations emerging on **Enfuvirtide (T-20)-based treatment.** The gp41 gene, which consists of 351 codons, has positions with very high variability and highly conserved regions. Polymorphisms have been observed in all gp41 regions, with the highest variability in the HR2 region. Primary resistance is very rare (Wiese 2005). Loss of efficacy is mainly associated with mutations at the T-20 binding site – the HR1 (heptad repeat 1) region of gp41. HR1 positions 36 to 45 are particularly affected, such as G36D/E/S, V38A/M/E, Q40H/K/P/R/T, N42T/D/S, N43D/K, or L45M/L. The degree of resistance is usually higher with double mutations than with singular mutations. In addition, mutations in HR2 and changes in the viral envelope also influence resistance (Sista 2004). In the absence of selection pressure by T-20, viral replication capacity is significantly reduced in the presence of HR1 mutations compared to wild type, with the following ranking: wild type > N42T > V38A > N42T, N43K ≈ N42T, N43S > V38A, N42D ≈ V38A, N42T. Viral fitness and T-20 susceptibility are inversely correlated (Lu 2004).

Nucleoside reverse transcriptase translocation inhibitors (NRTTIs)

Islatravir (ISL) is being studied as part of antiviral therapy due to its pharmacological properties in diverse formulations and different dose intervals. Islatravir was effective *in vitro* against wild-type viruses and most NRTI-resistant viral variants. In selection studies, islatravir-resistant virus with mutations I142V/T165R/M184V (resistance factor 22) emerged *in vitro* after 58 passages, with M184V being the first mutation selected (RF 7.5) (Markowitz 2018). In a randomized dose-ranging trial in ART-naïve individuals, no resistance occurred over 144 weeks with the combination of islatravir plus doravirine, with 3TC additionally included as part of therapy over the first 24 weeks (Molina 2021b). In MK-8591A-020, a study in ART-naïve PLWH receiving either B/F/TAF or DOR/ISL, one participant in the DOR/ISL arm with a baseline viral load above 1 million copies/mL and adherence difficulties showed incomplete viral response with the selection of virus harbouring the NNRTI mutations V106A and P225Y – associated with doravirine resistance – and the NRTI mutation M184I resulting in a fourfold reduction in susceptibility to islatravir (Rockstroh 2023)

Capsid inhibitors

Lenacapavir (**LEN**) is a long-acting capsid inhibitor with picomolar potency. *In vitro, there* was no cross-resistance between lenacapavir and the other antiviral agents approved to date, including entry inhibitors (Link 2020, Margot 2022a). Viral load is reduced rapidly (similar to INSTIs), as shown in the CALIBRATE study (Gupta 2022).

In vitro, resistance mutations were identified at 7 positions in the gag gene. The following mutations and combinations were selected: Q67H (resistance factor, RF 6), N74D (RF 22), K70N (RF 24), Q67H+N74S (RF 32), Q67H+T107N (RF 62), Q67H+N74D (RF 1,099), L56I (RF 239), M66I (RF 3,200). Except for the solitary mutation Q67H, all selected mutations – alone or in combination – lead to a loss in viral fitness (link 2020), although its clinical significance is still unclear. None of the aforementioned mutations are natural polymorphisms, as shown by an analysis of 1,500 clinical samples. Accordingly, resistance analysis before the use of lenacapavir is not necessary for HIV-1 subtype B and the non-B subtypes studied (Marcelin 2020).

The resistance barrier does not appear to match that of a second-generation INSTI. In the phase 1b dose-finding study 4072, 29 HIV patients were treated with lenacapavir as monotherapy. At day 10, resistant virus with the Q67H capsid mutation in the gag gene was isolated in 2 patients at the lowest doses (Margot 2022b). In the phase 2 CALIBRATE study, resistance development with the following mutations was observed by week 54 in two patients with presumed poor adherence to oral treatment: Q67H+K70R (RF 20, week 10) and Q67H (RF 7, week 54), respectively (Gupta 2022).

As a representative of a new class of compounds, lenacapavir is an important new option, especially in patients with resistant viruses. In the CAPELLA study, 83% achieved viral loads below 50 copies/mL after 52 weeks with lenacapavir and optimized concomitant therapy (n=36). Viruses with gag-associated resistance mutations were detected in 4 cases during the first 26 weeks: M66I (n=4) in combination with Q67H/K/N (n=1), K70H/N/R/S (n=1), N74D/H/S (n=3), A105S/T (n=3), or T107A/C/N (n=1). Functional lenacapavir monotherapy and/or poor adherence were suspected as reasons for viremia and resistance development (Ogbuaga 2022).

Summary

Sequencing of specific regions of the HIV genome to determine resistance and tropism is part of the diagnostic standard. Resistance-associated mutations are detected in about one in ten new HIV infections. Natural polymorphisms also play a role in some cases. Resistance testing before ART initiation leads to significantly better virologic response rates, and follow-up therapies can be optimized in case of treatment failure. Professional societies recommend sequencing of the reverse transcriptase, protease, integrase, and gp41 gene regions, as well as genotypic tropism testing. Resistance profiles and their interpretation are sometimes very complex. Algorithms must be continuously updated, and new drug classes must be implemented upon availability. Phenotypic resistance analysis is used to interpret genotypic resistance mutations in clinical studies. Defining the cut-offs of resistance factors associated with clinically relevant resistance is crucial for a valid interpretation of phenotypic results. A genotypic resistance test from proviral DNA can be a supportive tool in treatment decision-making, notably in case of therapy changes at low or undetectable plasma viral load levels and unknown treatment history. However, not all historically detected mutations are re-detected in the provirus. The clinical relevance of potential discordances is still unclear.

Increasingly, more sensitive resistance methods such as NGS are being used, which enable the detection of even minor viral variants. However, the significance of minor variants concerning individual drugs and drug combinations is still difficult to assess and should be interpreted in light of the treatment history. Specific thresholds for the presence of minor variants still need to be defined.
Finally, it should be emphasized that antiretroviral therapy should be started, paused, or switched only by or in consultation with an experienced HIV care provider.

Substance-specific resistance-associated mutations

The following tables provide a selection of mutations associated with resistance alone or in combination. The mutation lists do not replace the resistance algorithms used in clinical practice, such as HIV-GRADE or HIVdb (see Table 3), but serves only as a guide. They are based on data from the HIV GRADE algorithm (www.hiv-grade.de/grade_new/), the Stanford HIV Drug Resistance Database (https://hivdb.stanford.edu), and the IAS-USA Drug Resistance Mutations List (Wensing 2022).
Key mutations with the greatest impact in loss of susceptibility are printed in bold; other mutations (not printed in bold) reduce susceptibility usually in combination with other mutations.
Further information on the significance and degree of resistance of major and minor mutations can be found on the website of the HIV Drug Resistance Database (http://hivdb.stanford.edu (2023, version 9.5.0). However, despite good resistance algorithms and databases, the advice of experts often remains irreplaceable for individual treatment decisions.

Table 6a: Mutations associated with NRTI resistance.

	M 41	**K 65**	**D 67**	**H 69**	**K 70**	**L 74**	**Y 115**	**Q 151**	**M 184**	**L 210**	**T 215**	**K 219**
AZT	L		N	**Insertion**	R			**M**		W	**YF**	QE
ABC	L	**REN**		**Insertion**		**V**	**F**	**M**	V	W	YF	QE
TDF TAF	L	**REN**		**Insertion**	**E**		F			W	YF	QE
3TC FTC		REN		**Insertion**				M	**VIT**			

Table 6b: Mutations associated with NNRTI resistance.

	L 100	**K 101**	**K 103**	**V 106**	**V 108**	**E 138**	**V 179**	**Y 181**	**Y 188**	**V 189**	**G 190**	**H 221**	**P 225**	**F 227**	**M 230**	**L 234**	**Y 318**
DOR				**A**MIT	I				CLH		S**E**	Y	H	**C**LRVI	**L**	I	F
EFV	I	**P**	**HNST**	**M**	I			**CIV**	**CLH**		**ACEQS**		H	CL	**IL**		
ETR	I	EH**P**		I		AGKQR	DFTL	**CIV**			SAE			C	L		
NVP	I	**P**	**HNST**	**AM**	I			**CIV**	**CLH**		**ACEQS**				**L**		
RPV	**I**	E**P**		I		**AGKQRS**	DIL	**CIV**	**L**	I	E	Y			**ILV**		

Table 6c: Mutations associated with PI resistance.

	L 10	V 11	K 20	L 24	V 32	L 33	M 46	I 47	G 48	I 50	F 53	I 54	A 71	G 73	T 74	L 76	V 82	I 84	N 88	L 89	L 90
ATV/r	IF		RMITV	I	**I**	I**F**V	I		**V**	**L**	LY	**VMTA**	V	CSTA			ATFI	**V**	S		M
DRV/r		I			I	F		**V**		**V**		LM		S	P	**V**		**V**		V	
LPV/r	FIRV		MR	I	**I**	F	**I**	V**A**		**V**	L	**V**LAMTS	V	S		**V**	**AFTS**	VA			M

Table 6d: Mutations associated with INSTI resistance.

	T 66	L 74	E 92	T 97	G 118	F 121	E 138	G 140	Y 143	S 147	Q 148	S 153	N 155	S 230	V 260	R 263
BIC*	I		Q		**R**		AK	ACSR			**HKR**	FY	H	R		**K**
CAB	IK	I***	Q	A	**R**		AKT	ACSR	R		**HKR**	FRY	**H**	R	I	**K**
DTG**			Q		**R**		AKT	ACSR			**HKR**	FY	H	R		**K**
EVG	I**A**K		**GQ**	**A**	R	Y	K	AS	**C**R	**G**	**HKR**		**H**	R	**I**	**K**
RAL	I	M	**GQIV**	A	R	Y	AK	ACS	**CR**H		**HKR**		**HST**			K

*Based only on *in vitro* selection data, *in vitro* mutagenesis resistance data, and phenotypic analyses of patient samples with INSTI resistance-associated virus populations. **QD; ***in HIV subtype A6

Table 6e: Resistance-associated mutations in the use of entry inhibitors (CCR5 and attachment inhibitors, respectively).

Medication class	Substance	Mutations/Comments
CCR5-I	**MVC**	Virological failure associated with an increase in CXCR4-tropic viruses from minor variants. Isolated mutations are described in the V3 loop of HIV-1 gp120.
AI	**FTR**	In particular, key positions in gp120 are associated with loss of efficacy: S375N/H/M/T/I, M426L/I, M434I/K/L/T, M475I/L/V; not recommended for HIV-1 subtype CRF01_AE

Table 6f: Mutations in the capsid gene associated with resistance to capsid inhibitors.

	L 56	M 66	Q 67	K 70	N 74	A 105	T 107
LEN	I	**I**	**H**KN	HNSR	DHS	ST	ACN

Literature

Ackerman P, Melanie T, Molina JM, et al. Long-term efficacy and safety of fostemsavir among subgroups of heavily treatment-experienced adults with HIV-1. AIDS 2021, 35:1061-1072.

Acosta RK, Willkom M, Martin R, et al. Resistance analysis of Bictegravir-Emtricitabine-Tenofovir Alafenamide in HIV-1 treatment-naïve patients through 48 weeks. Antimicrob Agents Chemother 2019, 63. pii: e02533-18.

Allavena C, Rodallec A, Leplat A, et al. Interest of proviral HIV-1 DNA genotypic resistance testing in virologically suppressed patients candidate for maintenance therapy. J Virol Methods 2018, 251:106-110.

Andreatta K, Willkom M, Martin R, et al. Switching to bictegravir/emtricitabine/tenofovir alafenamide maintained HIV-1 RNA suppression in participants with archived antiretroviral resistance including M184V/I. J Antimicrob Chemother 2019, 74:3555-64.

Anstett K, Cutillas V, Fusco R, et al. The Effect of E157Q in HIV-1 Integrase on R263K-Mediated Dolutegravir Resistance. Abstract 507, CROI 2016.

Anstett K, Brenner B, Mesplede T, et al. HIV drug resistance against strand transfer integrase inhibitors. Retrovirology 2017, 14: 36.

Arribas JR, Clumeck N, Nelson M, et al. The MONET trial: week 144 analysis of the efficacy of darunavir/ritonavir (DRV/r) monotherapy versus DRV/r plus two nucleoside reverse transcriptase inhibitors, for patients with viral load < 50 HIV-1 RNA copies/mL at baseline. HIV Med 2013, 7:398-405.

Azijn H, Tirry I, Vingerhoets J, et al. TMC278, a next-generation nonnucleoside reverse transcriptase inhibitor (NNRTI), active against wild-type and NNRTI-resistant HIV-1. Antimicrob Agents Chemother 2010, 54:718-27.

Bacheler L, Winters B, Harrigan R, et al. Estimation of phenotypic clinical cut-offs for virco®Type HIV-1 through meta-analyses of clinical trial and cohort data. Antiviral Therapy 2004, 9:S154. http://www.aegis.com/conferences/hivdrw/2004/Session_6.pdf

Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. AIDS 2000, 14:F83-93.

Baxter JD, Schapiro JM, Boucher CA, et al. Genotypic changes in human immunodeficiency virus type 1 protease associated with reduced susceptibility and virologic response to the protease inhibitor tipranavir. J Virol 2006, 80: 10794-801.

Beerenwinkel N, Däumer M, Oette M, et al. Geno2pheno: estimating phenotypic drug resistance from HIV-1 genotypes. Nucleic Acids Research 2003, 13: 3850-3855.

Bennet DE, Camacho RJ, Ortelea D, et al. Drug resistance mutations for surveillance of transmitted HIV–1 drug resistance: 2009 update. PLoS One: e4724.

Blanco J,Oldenbuettel C, Thomas R, et al. Pathways of resistance in subjects failing dolutegravir monotherapy. Abstract #42, CROI 2017.

Blick G, Cerreta E, Mancini G, et al. SOLAR 3D: a prospective comparative study switching from 3-or 4-drug ART to DTG/3TC for maintenance of viral suppression in the setting of current and historical M184V/I and prior virologic failures: 48-week primary endpoint result. Abstract P2/65, 18th EACS 2021.

Böhm J, Müller C, Jensen B, et al. The RESINA data support the individualized therapy based on primary resistance testing. Abstract 37, 15th European Meeting on HIV & Hepatitis 2017.

Boender T, Boerma R, Sigaloff K, et al. High levels of HIV drug resistance in treatment naïve children in Lagos, Nigeria: original data and systematic review in sub-Saharan Africa. Abstract 22, 25th IHDRW 2016.

Borroto-Esoda K, Parkin N, Miller MD. A comparison of the phenotypic susceptibility profiles of emtricitabine and lamivudine. Antivir Chem Chemother 2007,18:297-300.

Boukli N, Boyd A, Collot M, et al. Predictive value of peripheral blood mononuclear cells HIV-1 genotype in detecting treatment resistance among patients with low or undetectable viral load. Global antiviral journal 2015; 11 Suppl 1:8 (Abstract 4).

Braun P, Wiesmann F. Phenotypic assays for the determination of coreceptor tropism in HIV-1 infected individuals. Eur J Med Res 2007, 12: 463-472.

Braun P, Wiesmann F, Naeth G, et al. Analysis of HIV resistance development in long-term low viremic patients. Abstract 48, 25th IHDRW.

Bruner KM, Wang Z, Simonetti FR, et al. A quantitative approach for measuring the reservoir of latent HIV-1 proviruses. Nature 2019, 566:120–125.

Buckton AJ, Prabhu D, Motamed C, et al. Increased detection of the HIV-1 reverse transcriptase M184V mutation using mutation-specific minority assays in a UK surveillance study suggests evidence of unrecognized transmitted drug resistance. HIV Med 2011, 12:250-4.

Cahn P, Pozniak AL, Mingrone H, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, noninferiority SAILING study. Lancet 2013; 382:700-708.

Callebaut C, Margot N, Das M, et al. Resistance Emergence in Treatment-Naive Patients Receiving E/C/F/TAF for 96 Weeks. Abstract 32, 25th IHDRW, 2016.

Canducci F, Ceresola ER, Boeri E, et al. Cross-resistance profile of the novel integrase inhibitor Dolutegravir (S/GSK1349572) using clonal viral variants selected in patients failing raltegravir. J Infect Dis 2011, 204:1811-5.

Cahn P, Sierra Madero J, Arribas JR, et al. Durable efficacy of dolutegravir (DTG) plus lamivudine (3TC) in antiretroviral treatment-naïve adults with HIV-1 infection—3-year results from the GEMINI studies. Poster P018, HIV Glasgow 2020.

Cahn P, Sierra Madero J, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naïve adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet 2019, 393:143-155.

Cane P, Chrystie I, Dunn D, et al. Time trends in primary resistance to HIV drugs in the UK: multicentre observational study. BMJ 2005; 331: 1368.

Castagna A, Danise A, Menzo S, et al. Lamivudine monotherapy in HIV-1-infected patients harbouring a lamivudine-resistant virus: a randomized pilot study (E-184V study). AIDS 2006, 20: 795-803.

Castagna A, Maggiolo F, Penco G, et al. Dolutegravir in antiretroviral-experienced patients with Raltegravir- and/or Elvitegravir-resistant HIV-1: 24-week results of the Phase III VIKING-3 study. J Infect Dis 2014, 210:354-62.

Chaix M, Fichou J, Deveau C, et al. Stable frequency of HIV-1 transmitted drug resistance over a decade (1996–2006) in France is likely explained by the increase of chronically treated patients in virological success? Antiviral Therapy 2007, 12:S49 (Abstract 42).

Chaix M, Assoumou L, Mahjoub N, et al. Polymorphic Mutations Increase NNRTI and II Resistance in Primary HIV-1 Infected Patients. Abstract 67, 25th IHDRW 2016.

Chapman TM, Plosker GL, Perry CM. Fosamprenavir: A review of its use in the management of antiretroviral therapy-naive patients with HIV infection. Drugs 2004, 64: 2101-24.

Clavel F, Hance AJ. HIV drug resistance. N Engl J Med 2004, 350: 1023-35.

Clutter D, Zhou S, Varghese V, et al. Prevalence of drug-resistant minority variants in untreated HIV-1–infected individuals with and those without transmitted drug resistance detected by Sanger sequencing. Journal of Infectious Diseases 2017, 216: 387-391.

Cohen CJ, Hunt S, Sension M, et al. A randomized trial assessing the impact of phenotypic resistance testing on ART. AIDS 2002,16: 579-88.

Colonno R, Rose R, McLaren C, et al. Identification of I50L as the signature atazanavir-resistance mutation in treatment-naive HIV-1-infected patients receiving ATV-containing regimens. J Infect Dis 2004, 189:1802-10.

Cutrell AG, Schapiro JM, Perno CF, et al. Exploring predictors of HIV-1 virologic failure to long-acting cabotegravir and rilpivirine: a multivariable analysis. AIDS 2021, 35:1333-1342.

Croom KF, Keam SJ. Tipranavir: a ritonavir-boosted protease inhibitor. Drugs 2005, 65: 1669-77.

DAIG (Deutsche AIDS Gesellschaft), ÖAG (Österreichische AIDS Gesellschaft). Deutsch-Österreichische Leitlinien zur antiretroviralen Therapie der HIV-1-Infektion, AWMF 055-001, Version 9 vom 01.09.2020. https://daignet.de/site-content/hiv-leitlinien/hiv-leitlinien

DAIG, Deutsche AIDS Gesellschaft. Empfehlungen zur Bestimmung des HIV-1-Korezeptor-Gebrauchs (Stand Mai 2014). http://www.daignet.de/site-content/hiv-therapie/leitlinien-1

D'Antoni ML, Andreatta K, Acosta R, et al. Bictegravir/Emtricitabine/Tenofovir Alafenamide Efficacy in Participants With Preexisting Primary Integrase Inhibitor Resistance Through 48 Weeks of Phase 3 Clinical Trials. JAIDS Syndr 2022, 89:433-440.

Da Silva D, Van Wesenbeeck L, Breilh D, et al. HIV-1 resistance patterns to integrase inhibitors in antiretroviral-experienced patients with virological failure on raltegravir-containing regimens. J Antimicrob Chemother 2010, 65:1262-9.

Daeumer M, Wolf E, Bickel M, et al. Detection of archived mutations in patients infected with multiclass resistant HIV-1. Abstract 544, CROI 2019.

De La Cruz J, Vardhanbhuti S, Sahoo MK, et al. Persistence of human immunodeficiency virus-1 drug resistance mutations in proviral deoxyribonucleic acid after virologic failure of efavirenz-containing antiretroviral regimens. Open Forum Infect Dis 2019, 6:ofz034.

Delaugerre C, Flandre P, Chaix ML, et al. Protease gene mutations in a trial comparing first-line lopinavir/ritonavir monotherapy to lopinavir/ritonavir + zidovudine/lamivudine (MONARK-TRIAL). Antivir Ther 2007, 12: S84 (Abstract 75).

Delaugerre C, Flandre P, Marcelin AG, et al. National survey of the prevalence and conditions of selection of HIV-1 reverse transcriptase K70E mutation. J Med Virol 2008, 80:762-765.

Delgado E, Fernández-García A, Vega Y, et al. Evaluation of genotypic tropism prediction tests compared with in vitro co-receptor usage in HIV-1 primary isolates of diverse subtypes. J Antimicrob Chemother 2012, 67:25-31.

De Mendoza C, Gallego O, Soriano V. Mechanisms of resistance to antiviral drugs – clinical implications. AIDS Rev 2002, 4: 64-82.

De Meyer S, Azijn H, Surleraux D, et al. TMC114, a novel HIV type 1 protease inhibitor active against protease inhibitor-resistant viruses, including a broad range of clinical isolates. Antimicrob Agents Chemother 2005, 49:2314-21.

De Meyer S, Vangeneugden T, van Baelen B, et al. Resistance profile of darunavir: combined 24-week results from the POWER trials. AIDS Res Hum Retroviruses 2008, 24: 379-388.

De Salazar A, Viñuela L, Fuentes A, et al. Transmitted drug resistance to integrase-based firstline treatment in Europe. Abstract 1102, virtual CROI 2022.

Descamps D, Lambert-Niclot S, Marcelin AG, et al. Mutations associated with virological response to darunavir/Ritonavir in HIV-1-infected protease inhibitor-experienced patients. J Antimicrob Chemother 2009, 63:585-92.

Deval J, White KL, Miller MD, et al. Mechanistic basis for reduced viral and enzymatic fitness of HIV-1 reverse transcriptase containing both K65R and M184V mutations. J Biol Chem 2004, 279:509-16.

Dhody K, Pourhassan N, Kazempour K, et al. PRO 140, a monoclonal antibody targeting CCR5, as a long-acting,single-agent maintenance therapy for HIV-1 infection. HIV Clin Trials 2018, 19(3):85-93.

Doyon L, Tremblay S, Bourgon L, et al. Selection and characterization of HIV-1 showing reduced susceptibility to the non-peptidic protease inhibitor tipranavir. Antiviral Res 2005, 68: 27-35.

Eron JJ, Benoit SL, Jemsek J, et al. Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. N Engl J Med 1995, 333:1662-1669.

Eron JJ, Clotet B, Durant J, et al. Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. J Infect Dis 2013, 207:740-8.

Eron J Jr, Yeni P, Gathe J Jr, et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. Lancet 2006, 368:476-482.

Eron J, Young B, Cooper D, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. Lancet 2010, 375:396-407.

Feng M, Wang D, Grobler J, et al. In Vitro Resistance Selection with Doravirine (MK-1439), a Novel Nonnucleoside Reverse Transcriptase Inhibitor with Distinct Mutation Development Pathways. Antimicrob Agents Chemother 2015, 59: 590-598.

Feng M, Sachs NA, Xu M, et al. Doravirine suppresses common nonnucleoside reverse transcriptase inhibitor-associated mutants at clinically relevant concentrations. Antimicrob Agents Chemother 2016, 60:2241-7.

Fourati S, Malet I, Lambert S, et al. E138K and M184I mutations in HIV-1 reverse transcriptase co-emerge as a result of APOBEC3 editing in the absence of drug exposure. AIDS 2012, 26:1619-24.

Gagliardini R, Ciccullo A, Borghetti A, et al. Impact of M184V resistance mutation on virological efficacy of lamivudine based maintenance dual therapies: an Italian ARCA cohort study. Abstract 13, 15th European Meeting on HIV & Hepatitis 2017.

Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet 2017, 390: 2063-72.

Garrido C, Roulet V, Chueca N, et al. Evaluation Evaluation of eight different bioinformatics tools to predict viral tropism in different human immunodeficiency virus type 1 subtypes. J Clin Microbiol 2008, 46:887-91.

George J, Kuriakose S, Dee N, et al. Emergence of high level resistance to Dolutegravir with T97A mutation in integrase in treatment experienced patients with baseline partial sensitivity to Dolutegravir. Abstract 55, 26th Int HIV Drug Res Tr Strat Workshop 2017.

Geretti A, White E, Beloukas A, et al. Impact of transmitted thymidine analogue mutations on responses to first-line ART. Abstract 482, CROI 2016.

Gibas KM, van den Berg P, Powell VE, et al. Drug resistance during HIV pre-exposure prophylaxis. Drugs 2019, 79:609-619.

Girard PM, Antinori A, Arribas JR, et al. Week 96 efficacy and safety of darunavir/ritonavir monotherapy vs. darunavir/ritonavir with two nucleoside reverse transcriptase inhibitors in the PROTEA trial. HIV Med 2017, 18:5-12.

Gupta S, Sims J, Brinson C, et al. Lenacapavir as part of a combination regimen in treatment naïve PLWH: week 54 results. Abstract 138, CROI 2022.

Grant R, Liegler T. Weighing the risk of drug resistance with the benefits of PrEP. J Inf Dis 2015, 211:1202-1204.

Grossman Z, Istomin V, Averbuch D, et al. Genetic variation at NNRTI resistance-associated positions in patients infected with HIV-1 subtype C. AIDS 2004, 18: 909-15.

Harrigan PR, Stone C, Griffin P, et al. Resistance profile of the HIV type 1 reverse transcriptase inhibitor abacavir (1592U89) after monotherapy and combination therapy. J Infect Dis 2000, 181:912-920.

Hatano H, Lampiris H, Fransen S, et al. Evolution of integrase resistance during failure of integrase inhibitor-based antiretroviral therapy. J Acquir Immune Defic Syndr 2010, 54: 389-393.

Hauser A, Hofmann A, Hanke K, et al. Trends for transmitted drug resistance and prevalence of non-B subtypes in recent HIV infections – results from the national molecular surveillance, Germany 2013 – June 2016. Abstract 07, 15th European Meeting on HIV & Hepatitis 2017.

Hauser A, Hofmann A, Meixenberger K, et al. Increasing proportions of HIV-1 non-B subtypes and of NNRTI resistance between 2013 and 2016 in Germany: Results from the national molecular surveillance of new HIV-diagnoses. PLoS One 2018,13:e0206234.

Heera J, Saag M, Ive P, et al. Virological Correlates associated with treatment failure at week 48 in the phase 3 study of maraviroc in treatment-naive patients. Abstract 40LB, CROI 2008.

Hoffmann C, Wolf E, Braun P, et al. Temporal variability of multi-class resistant HIV-1 in proviral DNA. Abstract 1512, virtual CROI 2022.

Hofstra L, Sauvageot N, Albert J, et al. Transmission of HIV drug resistance and the predicted effect on current first-line regimens in Europe. Clin Infect Dis 2016, 62:655-663.

Huang W, Frantzell A, Petropulos C. Contribution of Raltegravir selected secondary mutations to reduction in Elvitegravir susceptibility of patient-derived HIV integrase containing Y143 mutations. Antiviral Therapy 2013, 18 Suppl 1: A115 (Abstract 89).

Huang W, Frantzell A, Fransen S, et al. Multiple genetic pathways involving amino acid position 143 of HIV-1 integrase are preferentially associated with specific secondary amino acid substitutions and confer resistance to raltegravir and cross-resistance to elvitegravir. Antim Ag Chem 2013, 57:4105–13.

Hunt PW, Harrigan PR, Huang W, et al. Prevalence of CXCR4 tropism among antiretroviral-treated HIV-1-infected patients with detectable viremia. J Infect Dis 2006,194:926-930.

Jacobsen H, Yasargil K, Winslow DL, et al. Characterization of HIV type 1 mutants with decreased sensitivity to proteinase inhibitor Ro 31-8959. Virology 1995, 206:527-534.

Jacobson JM, Lalezari JP, Thompson MA, et al. Phase 2a study of the CCR5 monoclonal antibody PRO 140 administered intravenously to HIV-infected adults. Antimicrob Agents Chemother. 2010, 54:4137-4142.

Jaeger H, Overton ET, Richmond G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 96-week results: a randomized, multicentre, open-label, phase 3b, non-inferiority study. Lancet HIV 2021, 8(11):e679-e689.

Jegede O, Babu J, Di Santo R et al. HIV type 1 integrase inhibitors: from basic research to clinical implications. AIDS Rev 2008, 10:172-89

Kempf DJ, Isaacson JD, King MS, et al. Identification of genotypic changes in HIV protease that correlate with reduced susceptibility to the protease inhibitor lopinavir among viral isolates from protease inhibitor-experienced patients. J Virol 2001, 75:7462-9.

Kohlbrenner V, Hall D, Schapiro J, et al. Development of a tipranavir mutation score: analysis of protease mutations associated with phenotypic drug susceptibility and antiviral response in Phase II clinical trials. Antivir Ther 2004;9:S143 (Abstract 19).

Kozal M, Aberg J, Pialoux G, et al. Fostemsavir in adults with multidrug-resistant HIV-1 Infection. N Engl J Med 2020, 382:1232-1243.

Kulkarni R, Hodder SL, Cao H, et al. Week 48 resistance analysis of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir DF versus Atazanavir + Ritonavir + Emtricitabine/Tenofovir DF in HIV-1 infected women (WAVES study GS-US-236-0128). HIV Clin Trials 2017, 18:164-173.

Kvaratskhelia M, et al. Lenacapavir inhibits virion maturation by blocking formation of capsid pentamers. Abstract 100, CROI 2023.

Landovitz R, Donnell D, Clement M, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. N Engl J Med 2021, 385:595-608.

Larder BA, Kemp SD. Multiple mutations in HIV-1 reverse transcriptase confer high-level resistance to zidovudine (AZT). Science 1989, 246:1155-1158.

Larder BA, Bloor S. Analysis of clinical isolates and site-directed mutants reveals the genetic determinants of didanosine resistance. Antivir Ther 2001, 6:38.

Lataillade M , Molina J M, Thiry I, et al. The CASTLE study 48 week results: the impact of HIV subtypes and baseline resistance on treatment outcomes and the emergence of resistance. Antiviral Therapy 2008, 13 Suppl 3: A135 (Abstract 123).

Lalezari J, Dhody K, Kowalczyk U, et al. PRO140 Single-agent maintenance therapy for HIV-1 infection: A 2-year update. Abstract 437, CROI 2017.

Lee ER, Parkin N, Jennings C, et al. Performance comparison of next generation sequencing analysis pipelines for HIV-1 drug resistance testing. Sci Rep 2020, 10(1): 1634.

Lewis M, Simpson P, Fransen S, et al. CXCR4-using virus detected in patients receiving maraviroc in the Phase III studies MOTIVATE 1 and 2 originates from a pre-existing minority of CXCR4-using virus. Antiviral Therapy 2007, 12:S65 (Abstract 56).

Lewis S, Fessel J, Emu B, et al. Long-acting ibalizumab in patients with multi-drug resistant HIV-1: A 24-week study. Abstract 449LB, CROI 2017.

Li C, Burdick RC, Hu WS, et al. Lenacapavir disrupts HIV-1 core integrity while stabilizing the capsid lattice. Abstract 215, CROI 2023.

Li C, Burdick RC, Nagashima K, Hu WS, Pathak VK. HIV-1 cores retain their integrity until minutes before uncoating in the nucleus. Proc Natl Acad Sci USA 2021, 118:e2019467118.

Li JZ, Paredes R, Ribaudo H, et al. Minority HIV-1 drug resistance mutations and the risk of NNRTI-based antiretroviral treatment Failure: A systematic review and pooled analysis. JAMA 2011, 305:1327-1335.

Li Z, Zhou N, Sun Y, et al. Activity of the HIV-1 attachment inhibitor BMS-626529, the active component of the prodrug BMS-663068, against CD4-independent viruses and HIV-1 envelopes resistant to other entry inhibitors. Antimicrob Agents Chemother 2013, 57: 4172–80.

Link J, Rhee M, Tse WC, et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. Nature 2020, 584(7822): 614-618.

Loveday C, Devereux H, Huckett L, Johnson M. High prevalence of multiple drug resistance mutations in a UK HIV/AIDS patient population. AIDS 1999, 13: 627-628.

Lu J, Sista P, Giguel F, Greenberg M, Kuritzkes DR. Relative replicative fitness of HIV type 1 mutants resistant to enfuvirtide. J Virol 2004, 78: 4628-37.

Machnowska P, Meixenberger K, Schmidt D, et al. German HIV-1 Seroconverter Study Group. Prevalence and persistence of transmitted drug resistance mutations in the German HIV-1 Seroconverter Study Cohort. PLoS One 2019, 14: e0209605.

Malet I, Fourati S, Charpentier C, et al. The HIV-1 integrase G118R mutation confers raltegravir resistance to the CRF02_AG HIV-1 subtype. J Antimicrob Chemother 2011, 66:2827-30.

Malet A, Subra F Charpentier C, et al. Mutations located outside the integrase gene can confer resistance to HIV-1 integrase strand transfer inhibitors. mBio 2017, 8: e00922-17.

Marcelin AG et al. Mutations associated with response to boosted tipranavir in HIV-1-infected PI-experienced patients. Abstract 612, 14th CROI 2007.

Marcelin A, Charpentier C, Jary A, et al. Frequency of capsid substitutions associated with GS-6207 in vitro resistance in HIV-1 from antiretroviral-naive and -experienced patients. J Antimicrob Chemother 2020, 75:1588- 1590.

Margot N, Hluhanich R, Jones G, et al. In vitro resistance selections using elvitegravir, raltegravir, and two metabolites of elvitegravir M1 and M4. Antiviral Research 2012, 93: 288-296.

Margot N, Liu Y, Babusis D, et al. Antiviral Activity of Tenofovir Alafenamide (TAF) against Major NRTI-Resistant Viruses: Improvement over TDF/TFV is Driven by Higher TFV-DP Loading in Target cells. Antiviral Therapy 2013,18 Suppl 1: A93.

Margot NA, Wong P, Kulkarni R, et al. Reverse-Transcriptase and Protease in Antiretroviral Treatment-Naive Patients and Response to Regimens Containing Tenofovir Disoproxil Fumarate or Tenofovir Alafenamide. J Infect Dis 2017, 215:920-927.

Margot N, Vanderveen L, Naik V, et al. Phenotypic resistance to lenacapavir and monotherapy efficacy in a proof-of-concept clinical study. Journal of Antimicrobial Chemotherap 2022a, 77:989-995.

Margot N, Naik V, Rhee M, et al. Absence Of Cross-Resistance To Lenacapavir In HIV Entry Inhibitor-Resistant Isolate. Abstract 508, CROI 2022b.

Markowitz M, Sarafianos SG. 4′-Ethynyl-2-fluoro-2′-deoxyadenosine, MK-8591: a novel HIV-1 reverse transcriptase translocation inhibitor. Curr Opin HIV AIDS 2018, 3:294-299.

Martin EA, Lai MT, Ngo W, et al. Review of Doravirine Resistance Patterns Identified in Participants During Clinical Development, JAIDS 2020, 85:635-642

Marzinke M, Grinsztejn B, Fogel J, et al. Characterization of Human Immunodeficiency Virus (HIV) Infection in Cisgender Men and Transgender Women Who Have Sex With Men Receiving Injectable Cabotegravir for HIV Prevention: HPTN 083. J Infect Dis. 2021, 224(9):1581-1592.

Masquelier B, Race E, Tamalet C, et al. Genotypic and phenotypic resistance patterns of HIV type 1 variants with insertions or deletions in the reverse transcriptase (RT): multicenter study of patients treated with RT inhibitors. Antimicrob Agents Chemother 2001, 45:1836-42.

Mayers D, Leith J, Valdez H, et al. Impact of three or four protease mutations at codons 33, 82, 84 and 90 on 2 week virological responses to tipranavir, lopinavir, amprenavir and saquinavir all boosted by ritonavir in Phase 2B trial BI 1182.51. Antivir Ther 2004, 9:S163.

McGovern RA, Thielen A, Portsmouth S, et al. Population-based sequencing of the V3-loop can predict the virological response to maraviroc in treatment-naive patients of the MERIT trial. J AIDS 2012, 61:279-86.

Mesplède T, Quashie P, Osman N, et al. Viral fitness cost prevents HIV-1 from evading dolutegravir drug pressure. Retrovirology 2013, 10: 22.

Melikian GL, Rhee SY, Varghese V, et al. Non-nucleoside reverse transcriptase inhibitor (NNRTI) cross-resistance: implications for preclinical evaluation of novel NNRTIs and clinical genotypic resistance testing. J Antimicrob Chemother 2014, 69:12-20.

Métifiot M, Vandegraaff N, Maddali K, et al. Elvitegravir overcomes resistance to raltegravir induced by integrase mutation Y143. AIDS 2011, 25:1175-8.

Meyer PR, Matsuura SE, Schinazi RF, et al. Differential removal of thymidine nucleotide analogues from blocked DNA chains by HIV reverse transcriptase in the presence of physiological concentrations of 2′-deoxynucleoside triphosphates. Antimic Agents Chemother 2000, 44:3465-72.

Miller MD, Margot N, Lu B, et al. Genotypic and phenotypic predictors of the magnitude of response to tenofovir disoproxil fumarate treatment in antiretroviral-experienced patients. J Infect Dis 2004, 189:837-46.

Miller V, Ait-Khaled M, Stone C, et al. HIV-1 reverse transcriptase (RT) genotype and susceptibility to RT inhibitors during abacavir monotherapy and combination therapy. AIDS 2000, 14:163-71.

Mo H, King MS, King K, et al. Selection of resistance in protease inhibitor-experienced, HIV type 1-infected subjects failing lopinavir- and ritonavir-based therapy: Mutation patterns and baseline correlates. J Virol 2005, 79: 3329-38.

Molina J-M, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. Lancet 2008, 372: 646-655.

Molina JM, Cordes C, Ive P, et al. Efficacy and safety of TMC278 in treatment-naïve, HIV-infected patients: week 96 data from TMC278-C204. J Int AIDS Society 2008, 11(Suppl 1): P2.

Molina JM, Lamarca A, Andrade-Villanueva J, et al. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted PI: randomised, double-blind, phase 3, non-inferiority study. Lancet Inf Dis 2012, 12:27–35.

Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir is superior to once-daily darunavir/ritonavir in treatment-naïve HIV-1-positive individuals: 96 week results from FLAMINGO. Journal of the International AIDS Society 2014, 17(4Suppl 3):19490.

Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial. Lancet HIV 2020, 7:e16-e26.

Molina JM, Orkin C, Cahn P, et al. Safety and efficacy of doravirine in treatment-naïve adults with HIV-1: 4 years of experience from the DRIVE-FORWARD and DRIVE-AHEAD clinical trials. Abstract, 18th EACS 2021a.

Molina JM. Efficacy and safety of islatravir in combination with doravirine through 144 weeks for treatment-naïve adults with HIV-1 infection in a phase 2b trial. Oral Abstract OS1/5, 18th EACS 2021b.

Mori J, Lewis M, Simpson P, et al. Characterization of maraviroc resistance in patients failing treatment with CCR5-tropic virus in MOTIVATE 1 and MOTIVATE. Abstract 51, VI EHDRW 2008.

Mueller SM, Daeumer M, Kaiser R, et al. Susceptibility to saquinavir and atazanavir in highly protease inhibitor (PI) resistant HIV-1 is caused by lopinavir-induced drug resistance mutation L76V. Antiviral Therapy 2004, 9:S44.

Mulinge M, Lemaire M, Servais JY, et al. HIV-1 tropism determination using a phenotypic Env recombinant viral assay highlights overestimation of CXCR4-usage by genotypic prediction algorithms for CRF01_AE and CRF02_AG. PLoS One 2013, 8(5):e60566.

Ndashimye E, Arts EJ. Dolutegravir response in antiretroviral therapy naïve and experienced patients with M184V/I: Impact in low-and middle-income settings. Int J Infect Dis. 2021, 105:298-303.

Naeger LK, Margot NA, Miller MD. Increased drug susceptibility of HIV-1 reverse transcriptase mutants containing M184V and zidovudine-associated mutations: analysis of enzyme processivity, chain-terminator removal and viral replication. Antivir Ther 2001, 6:115-26.

Nijhuis M, Schuurman R, de Jong D, et al. Increased fitness of drug resistant HIV-1 protease as a result of acquisition of compensatory mutations during suboptimal therapy. AIDS 1999, 13:2349-59.

Obermeier M, Pironti, Berg T, et al. HIV-GRADE: A publicly available, rules-based drug resistance interpretation algorithm integrating bioinformatic knowledge. Intervirology 2012, 55:102-107.

Ogbuagu O, Segal-Maurer S, Brinson C, et al. Long-Acting Lenacapavir in people with multidrug-resistant HIV-1: Week 52 results. Abstract 491, CROI 2022.

Olsen A, Bannert N, Sönneborg A, et al. Temporal trends of transmitted HIV drug resistance in a multinational seroconversion cohort AIDS 2018, 32:161-69.

Oliveira M, Mesplède T, Quashie, et al. Resistance mutations against dolutegravir in HIV integrase impair the emergence of resistance against reverse transcriptase inhibitors. AIDS 2014, 28:813-9.

Oliveira M, Ibanescu R, Anstett K, et al. Selective resistance profiles emerging in patient-derived clinical isolates with cabotegravir, bictegravir, dolutegravir, and elvitegravir. Retrovirology 2018, 15:56.

Orkin C, Squires KE, Molina JM, et al. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (TDF) versus Efavirenz/Emtricitabine/TDF in treatment-naive adults with HIV type 1 infection: Week 96 results of the randomized, double-blind, phase 3 DRIVE-AHEAD noninferiority Trial. CID 2021, 73:33-42.

Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. N Engl J Med 2020, 382: 1124-35.

Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. Lancet 2020, 396:1994-2005.

Overton ET et al. Long-acting cabotegravir + rilpivirine every 2 months: ATLAS-2M week 152 results. Abstract 479, virtual CROI 2022.

Pao D, Andrady U, Clarke J, et al. Long-term persistence of primary genotypic resistance after HIV-1 seroconversion. J AIDS 2004, 37: 1570-3.

Parikh UM, Zelina S, Sluis-Cremer N, Mellors JW. Molecular mechanisms of bidirectional antagonism between K65R and thymidine analog mutations in HIV-1 reverse transcriptase. AIDS 2007, 21:1405-14.

Paton N, Musaazi J, Kityo C, et al. Nucleosides and darunavir/dolutegravir in Africa (NADIA) trial: outcomes at 96 weeks. Abstract 137, virtual CROI 2022.

Perelson AS. Modelling viral and immune system dynamics. Nat. Rev. Immunol. 2002, 2:28-36.

Perez-Valero I, Llibre J, Lazzarin A, et al. A phase 3b open-label pilot study to evaluate switching to E/C/F/TAF single tablet regimen in virologically-suppressed HIV-1 infected adults harboring the NRTI resistance mutation M184V and/or M184I (GS-US-292-1824): Week 24 Results. Abstract TUAB0104, 22nd IAC 2018.

Petropoulos C, Parkin N, Limoli K, et al. A novel phenotypic drug susceptibility assay for HIV type 1. Antimicrob Agents Chemother 2000, 44:920-8.

Picchio G1, Vingerhoets J, Tambuyzer L, et al. Short communication prevalence of susceptibility to etravirine by genotype and phenotype in samples received for routine HIV type 1 resistance testing in the United States. AIDS Res Hum Retroviruses 2011, 27:1271-5.

Porter DP, Däumer M, Thielen A, et al. Baseline low-frequenciey HIV-1 variants do not predict virologic failure to RPV/FTC/TDF. Global Antiviral Journal 2015, 11 Suppl 1:28 (Abstract 26).

Porter DP, Kulkarni R, Fralich T, et al. Characterization of HIV-1 drug resistance development through week 48 in antiretroviral naive subjects on rilpivirine/emtricitabine/tenofovir DF or efavirenz/emtricitabine/tenofovir DF in the STaR study (GS-US-264-0110). J AIDS 2014, 65:318-26.

Poveda E, Paredes R, Moreno S, et al. Update on clinical and methodological recommendations for genotypic determinations of HIV tropism to guide the usage of CCR5 antagonists. AIDS Rev 2012, 14:208-17.

Prosperi M, Bracciale L, Fabbiani M, et al. Comparative determination of HIV-1 co-receptor tropism by Enhanced Sensitivity Trofile, gp120 V3-loop RNA and DNA genotyping. Retrovirology 2010, 7:56.

Prosperi M, Mackie N, Giambenedetto S, et al. Detection of drug resistance mutations at low plasma HIV-1 RNA load in a European multicentre cohort study. J Antimicrob Chemother 2011, 66:1886-96.

Quashie PK, Mesplede T, Han Y, et al. Characterization of the R263K Mutation in HIV-1 Integrase That Confers Low-Level Resistance to the Second-Generation Integrase Strand Transfer Inhibitor Dolutegravir. J Virol 2012, 86:2696-2705.

Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet 2013, 13:927-935.

Rhee SY, Tzou PL, Shafer RW. Temporal Trends in HIV-1 Mutations Used for the Surveillance of Transmitted Drug Resistance. Viruses 2021, 13:879.

Rhee SY, Liu T, Kiuchi M, et al. Natural variation of HIV-1 group M integrase: Implications for a new class of antiretroviral inhibitors. Retrovirology 2008, 5:74.

Rial-Crestelo D, de Miguel R, Montejano R et al. Long-term efficacy of dolutegravir plus lamivudine for maintenance of HIV viral suppression in adults with and without historical resistance to lamivudine: Week 96 results of ART-PRO pilot study, J Antimicr Chemother 2021, 76: 738-742.

Rimsky L, Vingerhoets J, Van Eygen V, et al. Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients on rilpivirine therapy experiencing virological failure in the phase 3 ECHO and THRIVE studies: 48-week analysis. J Acquir Immune Defic Syndr 2012, 59:39-46.

Rockstroh J, DeJesus E, Lennox J, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. J Acquir Immune Defic Syndr 2013, 63:77-85.

Rockstroh JK, Paredes R, Cahn P, et al. Doravirine/islatravir (100mg/0.75mg) once daily compared to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) as initial HIV-1 treatment: 48 week results from a double-blind phase 3 trial. Abstract OALBX0102, IAS 2023.

Ryscavage P, Kelly S, Li J, et al. Significance and clinical management of persistent low-level viremia and very-low-level viremia in HIV-1-infected patients.Antimicrob Agents Chemother. 2014, 58:3585-98.

Saladini F. In vitro analysis of doravirine activity on HIV-1 clones harboring multiple NNRTI resistance mutations. Abstract #PS5/6,17th EACS 2019.

Sax P, Pozniak A, Montes M. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection: a randomised, double-blind, multicentre, phase 3, non-inferiority trial, Lancet 2017, 390: 2073-2082.

Scherrer A, von Wyl V, Yang W, et al. Emergence of acquired HIV-1 drug resistance almost stopped in Switzerland: A 15-Year prospective cohort analysis. Clin Infect Dis 2016a, 62:1310-1317.

Scherrer A, Böni J, Yang W, et al. Rate of Transmitted Integrase Inhibitor Resistance Mutations Remains Very Low in the SHCS. Abstract 72, 25th IHDRW.

Schnell T, Schmidt B, Moschik G, et al. Distinct cross-resistance profiles of the new protease inhibitors amprenavir, lopinavir, and atazanavir in a panel of clinical samples. AIDS 2003, 17:1258-61.

Schuurmann R, Nijhuis M, van Leeuwen R, et al. Rapid changes in human immunodeficiency virus type 1 RNA load and appearance of drug-resistant virus populations in persons treated with lamivudine (3TC). J Inf Dis 1995, 171: 1411-1419.

Selyutina A, Hu P, Miller S, et al. GS-CA1 and lenacapavir stabilize the HIV-1 core and modulate the core interaction with cellular factors. iScience. 2021, 25(1):103593.Shulman NS, Bosch RJ, Mellors JW, Albrecht MA, Katzenstein DA. Genetic correlates of efavirenz hypersusceptibility. AIDS 2004, 18: 1781-5.

Sista PR, Melby T, Davison D, et al. Characterization of determinants of genotypic and phenotypic resistance to enfuvirtide in baseline and on-treatment HIV-1 isolates. AIDS 2004, 18:1787-94.

Simon B, Grabmeier-Pfistershammer K, Rieger A, et al. HIV coreceptor tropism in antiretroviral treatment-naive patients newly diagnosed at a late stage of HIV-Infection. AIDS 2010, 24:2051-2058.

Skrabal K, Low AJ, Dong W, et al. Determining human immunodeficiency virus coreceptor use in a clinical setting: degree of correlation between two phenotypic assays and a bioinformatic model. J Clin Microbiol 2007, 45:279-84.

Spinner CD, Boesecke C, Zink A, et al. HIV pre-exposure prophylaxis (PrEP): A review of current knowledge of oral systemic HIV PrEP in humans. Infection 2016, 44:151-158.

Steigbigel RT, Cooper DA, Teppler H, et al.; Long-term efficacy and safety of Raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 Phase III trials. Clin Infect Dis 2010, 50:605-12.

Stoll M., Braun P., Wiesmann F, et al. Development of integrase inhibitor resistance under first-line treatment with bictegravir. Abstract P125, virtual HIV Glasgow 2020.

Swenson L, Mo T, Dong W, et al. Deep Sequencing to Infer HIV-1 Co-Receptor Usage: Application to Three Clinical Trials of Maraviroc in Treatment-Experienced Patients. JID 2011:203, 237-45.

Symons J, Vandekerckhove L, Paredes R, et al. Impact of triplicate testing on HIV genotypic tropism prediction in routine clinical practice. Clin Microbiol Infect 2012, 18:606-12.

Tsiang M, Jones G, Goldsmith J, et al. Antiviral Activity of Bictegravir (GS-9883), a Novel Potent HIV-1 Integrase Strand Transfer Inhibitor with an Improved Resistance Profile. Antimicrob Agents Chemother 2016, 60: 7086-7097.

Tural C, Ruiz L, Holtzer C, et al. Clinical utility of HIV-1 genotyping and expert advice: the Havana trial. AIDS 2002, 16:209-18.

Underwood M, St Clair M, Ross L, et al. Cross-resistance of clinical samples with K65R, L74V, and M184V Mutations. Abstract 714, 12th CROI 2005.

Underwood M, Vavro C, Haney R, et al. Epidemiology of Dolutegravir (DTG) Resistance in ~700 RAL-Resistant Isolates. Antiviral Therapy 2013a, 18 Suppl 1: A108 (Abstract 85).

Underwood M, Dudas K, Horton J, et al. Analysis and characterization of treatment-emergent resistance in ART-experienced, integrase inhibitor-naïve subjects with Dolutegravir (DTG) vs Raltegravir (RAL) in SAILING (ING111762). Antiviral Therapy 2013b, 18 Suppl 1: A29 (Abstract 21).

Underwood M, DeAnda F, Dorey D, et al. Resistance post week 48 in ART-experienced, integrase inhibitor-naïve subjects with Dolutegravir (DTG) vs. Raltegravir (RAL) in SAILING (ING111762). Reviews in Antiviral Therapy & Infectious Diseases 2015_5 (Abstract 6).

Underwood M, Osiyemi O, Rubio R, et al. Archived resistance and response to <40 c/mL and TND – DTG/3TC FDC at week 48 in SALSA. Abstract 481, virtual CROI 2022.

Vandekerckhove LPR, A M J Wensing AMJ, Kaiser R, et al. European guidelines on the clinical management of HIV-1 tropism testing. Lancet Infect Dis 2011, 11:394-407.

Van Wesenbeeck L, Rondelez E, Feyaerts M, et al. Cross-resistance profile determination of two second-generation HIV-1 integrase inhibitors using a panel of recombinant viruses derived from raltegravir-treated clinical isolates. Antimicrob Agents Chemother 2011, 55:321-5.

Verhofstede C, Vandekerckhove L, Eygen V, et al. CXCR4-using HIV type 1 variants are more commonly found in peripheral blood mononuclear cell DNA than in plasma RNA. J AIDS 2009, 50(Suppl 2):126-36.

Vingerhoets J, Tambuyzer L, Azijn H, et al. Resistance profile of etravirine: combined analysis of baseline genotypic and phenotypic data from the randomized, controlled Phase III clinical studies. AIDS 2010, 24:503–514.

Visseaux B, Assoumou L, Mahjoub N, et al. Surveillance of HIV-1 primary infections in France from 2014 to 2016: toward stable resistance, but higher diversity, clustering and virulence? J Antimicrob Chemother 2020, 75:183-193.

Wagner TA, McKernan JL, Tobin NH, Tapia KA, Mullins JI, Frenkel LM. An increasing proportion of monotypic HIV-1 DNA sequences during antiretroviral treatment suggests proliferation of HIV-infected cells. J Virol 2012, 87:1770–1778.

Weber J, Chakraborty B, Weberova J, et al. Diminished replicative fitness of primary human immunodeficiency virus type 1 isolates harboring the K65R mutation. J Clin Microbiol 2005, 43: 1395-400.

Weinheimer S, Discotto L, Friborg J, et al. Atazanavir signature I50L resistance substitution accounts for unique phenotype of increased susceptibility to other protease inhibitors in a variety of HIV type 1 genetic backbones. Antimicrob Agents Chemother 2005, 49:3816-24.

Wensing A, Calvez V, Ceccherini-Silberstein F, et al. 2022 Update of the Drug Resistance Mutations in HIV-1. Topics Antivir Med 2022, 30 (4).

Westby M, Smith-Burchnell C, Mori J, et al. Reduced maximal inhibition in phenotypic susceptibility assays indicates that viral strains resistant to the CCR5 antagonist maraviroc utilize inhibitor-bound receptor for entry. J Virol 2007, 81:2359-71.

White E, Smit E, Churchill D, et al. No Effect of HIV-1 Subtype C on Virological Failure Rate With First-Line TDF Regimens. Abstract 484, CROI 2016.

White K, Kulkarni R, Miller MD; Analysis of early resistance development at the first failure timepoint in elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate-treated patients, J. Antimicrob. Chemother 2015, 70: 2632-2638.

White K, Margot NA, Ly JK, et al. A combination of decreased NRTI incorporation and decreased excision determines the resistance profile of HIV-1 K65R RT. AIDS 2005, 19:1751-60.

WHO. HIV drug resistance report 2021. Available at https://www.who.int/publications/i/item/9789240038608)

Wiese N, Müller H, Hingst K, et al. Primary resistance mutations and polymorphisms in gp41-sequences of HIV-1 B-and non-B subtypes from Fuzeon-naïve patients. Abstract P174, 10. Deutscher und 16. Österreichischer AIDS Kongress 2005.

Wiesmann F, Vachta J, Ehret R, et al. The L76V mutation in HIV-1 protease is potentially associated with hypersusceptibility to protease inhibitors Atazanavir and Saquinavir: Is there a clinical advantage? AIDS Res Ther 2011, 8:7.

Wijting I,, Rokx C, Boucher C, et al. Dolutegravir as maintenance monotherapy for HIV-1: a randomized clinical trial. Abstract 451LB, CROI 2017.

Wilson JW. Update on antiretroviral drug resistance testing: Combining laboratory technology with patient care. AIDS Read 2003, 13:25-38.

Wittkop L, Günthard HF, de Wolf F, et al. Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): a European multicohort study. Lancet Infect Dis 2011, 11:363-71.

Wohl D, Pozniak A, Workowski K, et al. B/F/TAF Five-Year Outcomes in Treatment-Naïve Adults. Abstract 494, virtual CROI 2022.

Woollard SM, Kanmogne GD. Maraviroc: A review of its use in HIV infection and beyond. Drug Des Devel Ther 2015, 9:5447-68.

Xu HT, Colby-Germinario SP, Asahchop EL, et al. Effect of mutations at position E138 in HIV-1 reverse transcriptase and their interactions with the M184I mutation on defining patterns of resistance to nonnucleoside reverse transcriptase inhibitors rilpivirine and etravirine. Antim Ag Chemoth 2013,57:3100-9.

Xu L, Pozniak A, Wildfire A, et al. Emergence and evolution of enfuvirtide resistance following long-term therapy involves heptad repeat 2 mutations within gp41. Antimicrob Agents Chemother 2005, 49:1113-9.

Yang H, Ito F, Wolfe A, et al. Understanding the structural basis of HIV-1 restriction by the full length double-domain APOBEC3G. Nat Commun 2020, 11: 632.

Zila V, Margiotta E, Turo ová B, et al. Cone-shaped HIV-1 capsids are transported through intact nuclear pores. Cell 2021, 184:1032-1046.e18.

Zhuang S, Torbett BE. Interactions of HIV-1 Capsid with Host Factors and Their Implications for Developing Novel Therapeutics. Viruses 2021, 13:417.

SECTION 3

AIDS

7. Opportunistic infections (OI)

CHRISTIAN HOFFMANN

In Western industrialized countries, opportunistic infections (OIs) are now rare. Incidence today has declined to less than one-tenth compared to the mid-1990s (Brooks 2009, Buchacz 2017). Antiretroviral therapy has contributed to the change in the course of OIs. Whereas survival after the first AIDS-defining disease was once rarely more than three years, people now live with AIDS for thirty years or more. If the 5-year survival rate after cerebral toxoplasmosis was 7% in 1990–1993, it grew to 29% in 1994–1996. Since 1997, it has risen to 78% (Hoffmann 2007). Hardly anyone dies of AIDS anymore.

About 70–90% of people who develop AIDS today are not on antiretroviral treatment at the time of the OI, and a significant proportion are unaware of their HIV infection. Often, these people present very late and in a serious condition. AIDS remains life-threatening for this reason alone, and severe PCP does not become less threatening because the long-term prognosis has improved. The acute danger remains. It remains crucial to be well-versed in diagnosing and treating OIs.

Despite much progress, not everything has been solved. For example, some infections, such as PML or cryptosporidiosis, are still barely treatable; others have resistance problems (TB!). Even today, the mortality of PML is roughly comparable to non-Hodgkin's lymphoma (ART-CC 2009). ART does not continually improve everything immediately; some diseases remain complicated due to immune reconstitution and atypical courses. We dedicated a subchapter to the immune reconstitution syndrome (see *IRIS*).

In addition, there are always diagnostic problems with many OIs. If you don't know the germ, you can't see it! It is strongly recommended to send examination material to the reference laboratories and to seek advice in a specialized practice or an HIV center.

The first rule for almost all OIs is that the worse the immune status, the earlier invasive has to be initiated! Do not try to spare the patient unpleasant examinations. If nothing is found, diagnostics must be repeated. Therapy must be started quickly.

The second rule is that many OIs can usually excluded if the current immune status is known. Table 1 shows threshold values for CD4 T-cells.

The third rule is that in the case of an OI, ART should be started as soon as possible if it hasn't been already. Immune reconstitution is the best protection against recurrence. ART is the only hope for infections such as PML or cryptosporidia, for which no specific therapy exists. No time should be wasted. A rapid start is also crucial for PCP or toxoplasmosis.

Although OI therapy is not without toxicity and interaction issues – the choice of antiretroviral agents has increased, and side effects can be dealt with. In ACTG A5164, 282 patients with an acute OI (63% PCP) were randomized to start ART immediately or after OI therapy cessation (Zolopa 2009). After 48 weeks, significantly fewer deaths and new AIDS cases had occurred in the immediately treated group. The risk of

Table 1: CD4 thresholds above which certain AIDS diseases are unlikely. The CD4 T-cells only indicate guideline values; exceptions are possible.

Without limit	Kaposi's sarcoma, pulmonary TB, HZV, bacterial pneumonia, lymphoma.
From < 250/µl	PCP, candida esophagitis, PML, HSV
From < 100/µl	Cerebral toxoplasmosis, HAND, miliary TB
From < 50/µl	CMV retinitis, atypical mycobacteriosis, cryptococcosis

switching ART was slightly increased with immediate ART, but not the number of serious adverse events, hospitalizations, or cases of IRIS. ACTG A5164 thus provides a clear case for immediate ART initiation in PCP. But is this true for other OIs? Probably not for all (Lawn 2011). The results of two randomized clinical trials argue against it; both found unfavorable effects from early ART in cryptococcal meningitis (Makadzange 2010) and in tuberculous meningitis (Török 2011) – see also *ART* on late presenters.

A practical overview is given in the following pages. The literature references are mostly limited to high-quality reviews and randomized studies. If this is insufficient, you can download the almost 600-page, constantly updated OI guidelines of the US NIH: https://clinicalinfo.hiv.gov.

OI overviews

Antiretroviral Therapy Cohort Collaboration (ART-CC). Variable impact on mortality of AIDS-defining events diagnosed during combination antiretroviral therapy: not all conditions are created equal. Clin Infect Dis 2009, 48:1138-51.

Brodt HR, Kamps BS, Gute P, Knupp B, Staszewski S, Helm EB. Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. AIDS 1997, 11:1731-8.

Brooks JT, Kaplan JE, Holmes KK, et al. HIV-associated opportunistic infections—going, going, but not gone: the continued need for prevention and treatment guidelines. Clin Inf Dis 2009, 48:609–611.

Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-Defining Opportunistic Infections in a Multicohort Analysis of HIV-infected Persons in the United States and Canada, 2000-2010. J Infect Dis 2016, 214:862-72.

Hoffmann C, Ernst E, Meyer P, et al. Evolving characteristics of toxoplasmosis in patients infected with human immunodeficiency virus-1: clinical course and Toxoplasma gondii-specific immune responses. Clin Microbiol Infect 2007, 13:510-5.

Kirk O, Reiss P, Uberti-Foppa C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. Ann Intern Med 2002, 137:239-50.

Lawn SD, Török ME, Wood R. Optimum time to start antiretroviral therapy during HIV-associated opportunistic infections. Curr Opin Infect Dis 2011, 24:34-42.

Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. JAMA 1999, 282: 2220-6.

Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. Clin Infect Dis 2010, 50:1532-8.

McNaghten AD, Hanson DL, Jones JL, Dworkin MS, Ward JW. Effects of antiretroviral therapy and opportunistic illness primary chemoprophylaxis on survival after AIDS diagnosis. AIDS 1999, 13:1687-95.

Sepkowitz KA. Effect of HAART on natural history of AIDS-related opportunistic disorders. Lancet 1998, 351: 228-230.

Török ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)—associated tuberculous meningitis. CID 2011, 52:1374-83.

Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS 2009, 4:e5575.

Pneumocystis pneumonia (PCP)

This interstitial pneumonia, which killed a large proportion of patients in the early years of the HIV epidemic, is caused by pneumocysts. In recent years, knowledge of this pathogen has made significant progress, primarily through DNA analysis (review: Thomas 2004). Long traded as protozoa, pneumocysts are now classified as fungi (Edman 1988). In the 1990s, it became clear that each host, whether rat, monkey, or human, has its specific pneumocysts. It also became clear that *Pneumocystis carinii*, described in 1910 by the Italian Antonio Carini, occurs only in rats. Therefore, the species affecting humans was renamed from *P. carinii* to *P. jiroveci* (after the Czech parasitologist Otto Jirovec). The term "carinii" was deleted, but the abbreviation PCP remains (Stringer 2002).

PCP remains among the most common OIs worldwide (Mussini 2008, Buchacz 2016). Of 270 "late presenters" who presented to a Berlin hospital in 2009–2013, 91 (34%) had PCP (Tominski 2017). People unaware of their HIV infection are the most likely to develop it. Among those with known HIV infection, hardly anyone with PCP is on antiretroviral treatment, and adherence is often lower (Denis 2014).

PCP is dangerous. It often requires mechanical ventilation and still has a mortality rate of up to 10% (Llibre 2013). Older people have an increased mortality risk, as do patients with poor arterial blood gases and low hemoglobin (Miller 2010). Recurrences, once common, are now rare thanks to ART and prophylaxis. Scarring may leave a tendency for recurrent pneumothoraces. Rarely, PCP may also present as an immune reconstitution syndrome (see below). Extrapulmonary or disseminated *Pneumocystis* infections are now rare.

Clinic

The classic symptom triad consists of dry, irritable cough, subfebrile temperatures, and slowly progressive exertional dyspnea (ask specifically! respiratory rate?). Unlike HIV-negative patients with PCP, a subacute course is typical (review: Salzer 2018). A differentiation from bacterial pneumonia (more productive cough, less dyspnea, acute high fever, and pain!) is often possible. Often, there is an oral thrush. Weight loss in the weeks before is also common. If prophylaxis is insufficient (rare), symptoms may be even more subtle. Weeks, sometimes months, often pass before the diagnosis is made. As with all interstitial pneumonia, decompensation usually occurs more rapidly than expected. It is common for those affected to become abruptly ventilator-dependent after weeks of antibiotic therapy by their primary care physician (even broad-spectrum antibiotics do not help!). Any case with significant exertional dyspnea should be hospitalized immediately.

Diagnostics

In case of clinical suspicion (respiratory rate? Abnormal auscultation? Oral thrush?), a chest X-ray and, if possible, an HR-CT of the lungs should be performed immediately. Radiographs often show a relatively characteristic picture with butterfly-shaped (spreading bilaterally from hilars) interstitial drawing proliferation. The early stages accentuate mid and lower fields, and cystic changes occur. The usually indistinct, diffuse changes are better seen on HR-CT; other pulmonary infections can be relatively reliably differentiated (Hidalgo 2003).

However, even if nothing pathological is seen on CT, rapid initiation of therapy is justified even without a definite diagnosis – especially in the case of the classic triad of symptoms, low CD4 T-cells, and lack of prophylaxis. Almost always, there is early partial respiratory insufficiency, which an arterial blood gas analysis should objec-

tify. LDH is often elevated and is of limited use as a progression parameter – it reflects, albeit imprecisely, the severity of PCP. CRP, on the other hand, usually remains normal unless there are concurrent infections.
Sputum samples are usually of no help, so bronchoalveolar lavage (BAL) is almost always required. BAL also diagnoses co-infections (CMV, pneumococci) promptly. It should be noted that BAL can worsen respiratory insufficiency. Pathogens are still mainly detected with immunofluorescence tests, and in some laboratories now, also with very sensitive PCR (Sasso 2016). In most cases, pneumocysts remain detectable days after initiation of therapy, so do not wait for BAL results. It is recommended to send material to experienced laboratories and to explicitly inform them of the suspicion because pneumocysts are easily overlooked.
A new approach is the measurement of beta-D-glucan, a component of the cell wall in fungi. However, it has yet to be established as a diagnostic marker (Del Corpo 2020).

Therapy

General

If clinically suspected, PCP therapy should be started immediately. Mild PCP (PO2 > 70–80 mmHg) can be treated on an outpatient basis in very mild cases with oral medication. In collaboration with a competent HIV care service, this is often possible. If such monitoring is not feasible or respiratory deterioration occurs, immediate hospitalization is advisable. If ventilation is required, the prognosis is still poor today (Crothers 2005, Walzer 2008). It is possible that non-invasive techniques (CPAP) if started early, are more favorable. In particular, pneumothoraces can be prevented (Confalonieri 2002).
While ART-naïve patients usually waited until PCP was cured before starting ART, a randomized trial showed the benefits of a rapid start (Zolopa 2009, see above). No differences were seen in the IDEAL trial, but the case number was small (Schäfer 2019). A retrospective study also showed improved survival when ART was started while still in the hospital (Morris 2003). Potential cumulative toxicities and allergies that may lead to discontinuing PCP therapy and ART (Watson 2002) can usually be avoided.

Medication

The acute therapy for PCP lasts 21 days; the drug of choice is cotrimoxazole, a combination of sulfamethoxazole and trimethoprim. The dosage of 3 x 3 tablets of 960 mg is only useful in mild cases; it is often moderately tolerated gastrointestinally. There are case reports on lower doses but no controlled studies (Thomas 2009). In severe cases, therapy should be inpatient and intravenous. Because of possible deterioration, probably due to frothy bursting of pneumocysts in the alveoli, 1 mg/kg prednisone (daily, divided into 1–2 administrations) should always be given for an additional 5–10 days. Don't be afraid of steroids, especially with poor blood gases! Several reviews found a benefit (Briel 2016, Wang 2016). In severe PCP, this halves the mortality risk, with fewer cases requiring ventilation (Briel 2006). Nevertheless, clinical deterioration during the first week is not uncommon. Initial therapy should be reconsidered after one week at the earliest and only after excluding co-infections (CMV!).
Under the high cotrimoxazole doses, blood count, electrolytes, kidney values, and transaminases should be at least three times a week. In addition to myelotoxicity and liver and kidney problems, the main problem is drug exanthema, which usually occurs in the second week of therapy and is often accompanied by drug fever. The

incidence is up to 30% (Fisk 2009) – check daily for skin changes! One can try to pause for a day or two in such exanthem, then continue on antihistamines and steroids at half the dose. Otherwise, cotrimoxazole must be stopped and replaced with alternative therapies.
All alternatives to cotrimoxazole are less effective. In case of intolerance or known sulfonamide allergy, pentamidine intravenously is recommended as a second choice, initially given in a kind of induction therapy (200–300 mg in 500 mL of 5% glucose or 0.9% NaCl) during the first days, then in half dose from day 6. This therapy is very toxic; severe derailment of electrolytes and blood glucose (both hyper- and hypoglycemia) is possible, as well as pancreatitis, cardiac arrhythmias, and renal failure. Blood glucose, electrolytes, and renal values should be checked daily.
In very mild cases of PCP, purely inhaled therapy with daily pentamidine inhalations (300–600 mg daily for three weeks) may be attempted (Arasteh 1990, Montogomery 1995). However, experience has not always been positive (Conte 1990, Soo 1990), and US guidelines discourage inhalation therapy for acute PCP. Instead of pentamidine, atovaquone suspension or a combination of clindamycin and primaquine is also possible. However, data exist only for mild to moderate cases (Hughes 1993, Dohn 1994, Toma 1998). According to a meta-analysis, clindamycin plus primaquine has the best chance of success after the failure of cotrimoxazole (Benfield 2008). It appears to be better than pentamidine (Helweg-Larsen 2009), but there is a risk of hemolytic anemia (rule out G6PD deficiency first!). Caspofungin also seems to be effective against pneumocysts. Meanwhile, it remains unclear whether it should be added to initial therapy in severe cases (ventilation). A large retrospective cohort from China found clinical benefits from combining cotrimoxazole and caspofungin (Tian 2021), while another did not (Huang 2022).
In recent years, we have rarely used alternatives. Ten days of initial therapy with cotrimoxazole can almost always be managed, and things usually improve considerably by then if exanthema or toxicity force discontinuation between days 10 and 14, the third week of acute therapy is contested with daily pentamidine inhalations. However, a sufficiently powered study on this is not in view.

Prophylaxis

People with less than 200 CD4 T-cells/µl (or < 14% of total lymphocyte count) are at risk and need prophylaxis, ideally cotrimoxazole. Daily administration may be slightly more effective than thrice weekly (El Sadr 1999). Updosing 14 days is thought to prevent allergy but is cumbersome (Para 2000). Desensitization is possible for moderate allergy to cotrimoxazole (Leoung 2001); it could certainly be attempted. Although dapsone and pentamidine inhalation are almost equally effective (Bozzette 1995, Bucher 1997), cotrimoxazole prophylaxis better prevents bacterial infections such as enteritis and pneumonia (DiRienzo 2002). More importantly, cotrimoxazole also safely protects against toxoplasmosis. Cotrimoxazole suspension for children can slowly increase from 12.5, 25, 37.5, 50, and 75 to 100% of the 480 mg tablet dose over six days for desensitization. In a study of nearly 200 people, this did not result in severe allergy but did reduce fever and headache. Around three-quarters were able to "get used to" cotrimoxazole again in this way. However, eight weeks should pass before re-exposure (Leoung 2001).
Monthly pentamidine inhalations are a well-tolerated alternative. Occasionally, there is a cough, rarely an asthma attack, and very rarely, a pneumothorax may develop. Inhalation should be performed with a suitable inhalation system (e.g., Respirgard II®) and after bronchodilator administration. The loading dose used in the past (3 x 300 mg in the first five days) is no longer widely used. Inhalations are probably less effective in pulmonary disease. All other options are problematic. Dapsone is poorly

Therapy and prophylaxis of PCP (unless otherwise stated, daily dosages).

Acute therapy		Duration: Always at least three weeks
Severe to moderate PCP	Cotrimoxazole	Cotrim-ratiopharm® 3 x 5–6 amp. at 480 mg IV **plus** Decortin H® 40 – 40 – 0 mg (5–10 days, approx. 1 mg/kg)
Mild PCP	Cotrimoxazole	Cotrim forte® 3 x 3 tab. at 960 mg
Alternatives	Pentamidine	Pentacarinate® 200–300 mg IV 5 days (4 mg/kg), then half dose. Mild cases: daily inhalation with 300 mg
	Atovaquone	Wellvone® suspension 2 x 5–10 mL (2 x 750–1500 mg)
	Clindamycin + primaquine	Sobelin® 3–4 x 1 amp. at 600 mg IV **plus** primaquine 1 tab. at 30 mg
Prophylaxis		From < 200 CD4 T-cells/µl or after a PCP episode
First choice	Cotrimoxazole	Cotrim® 1 x 1 tab. at 480 mg or Cotrim forte® 3 x 1 tab. at 960 mg / week
Alternatives	Pentamidine	Pentacarinate® -inhalation 300 mg 1–2 x / month
	Dapsone	Dapsone-Fatol® 1 x 2 tab. at 50 mg
	Dapsone + pyrimethamine	Dapsone-Fatol® 1 x 1 tab. at 50 mg **plus** Daraprim® 1 x 2 tab. at 25 mg/wk **plus** Leucovorin® 1 x 2 tab. at 15 mg/week
	Atovaquone	Wellvone® suspension 2 x 5 mL (2 x 750 mg)

tolerated gastrointestinally, is relatively myelotoxic, and often leads to LDH elevations. LDH, an important diagnostic parameter, is unusable (Ioannidis 1996). Atovaquone was similarly effective to cotrimoxazole, dapsone, and pentamidine in two multicenter studies (El-Sadr 1998, Chan 1999) and has since been considered an alternative. The juice is better tolerated than the tablets (Rosenberg 2001). The main disadvantage is the high price. Atovaquone is considerably more costly in many countries than other oral agents (Germany: approx. 1000 euros/month).

PCP prophylaxis can be discontinued while on ART, provided that at least 200 CD4 T-cells/µl have been reached for at least three months (meta-analysis: Costiniuk 2011). Only occasionally have PCP cases been described after discontinuation at more than 200 CD4 T-cells/µl (Degen 2002, Mussini 2003). If viral load is well suppressed, achieving 200 CD4 T-cells/µl is probably not necessary. Also, in the large COHERE database, the risk was extremely low once the viral load was below 400 HIV RNA copies twice (Atkinson 2021), so prophylaxis can probably be discontinued in these cases. However, there are no controlled studies. Discontinuation not only reduces side effects and costs but also prevents resistance.

Resistance, current controversies

Pneumocysts have also been affected by the worldwide use of cotrimoxazole (Martin 1999). Sulfa resistance seems to be increasing (Helweg-Larsen 1999), but a negative effect on therapy remains unclear (review: Matos 2010). In Europe, resistance has been rare so far (Suárez 2017).

According to genome analyses, PCP is often a new infection, not a reactivation (Wakefield 2003). Reservoirs may be asymptomatic PLWH, in whom pneumocysts are frequently detected, but HIV-negative patients on steroids and those who manifest PCP. Many reports of nosocomial outbreaks exist (Le Gal 2012, Sassi 2012). However, isolation of PCP cases is not generally recommended (Thomas 2004).

Pneumocysts do not always cause manifest pneumonia. In many immunocompromised individuals, only "colonization" is present (Ponce 2010, Vargas 2010). This is now thought to play a role in chronic obstructive pulmonary disease (Morris 2008). It can also be a reservoir for outbreaks (Le Gal 2012).

Literature

Arasteh K, Heise W, L'age M. Treatment of mild to moderately severe pneumocystis carinii pneumonia with cotrimoxazole versus pentamidine aerosol. Med Klin 1990, 85 Suppl 2:260-3.

Atkinson A, Zwahlen M, Barger D, et al. Withholding Primary Pneumocystis Pneumonia Prophylaxis in Virologically Suppressed Patients With Human Immunodeficiency Virus: An Emulation of a Pragmatic Trial in COHERE. Clin Infect Dis 2021, 73:195-202.

Benfield T, Atzori C, Miller RF, Helweg-Larsen J. Second-Line Salvage Treatment of AIDS-Associated Pneumocystis jirovecii Pneumonia: A Case Series and Systematic Review. J AIDS 2008.

Benson CA, Kaplan JE, Masur H, et al. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the NIH, and the IDSA. MMWR Recomm Rep 2004, 53(RR-15):1-112.

Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced HIV. N Engl J Med 1995, 332:693-9.

Briel M, Bucher HC, Boscacci R, Furrer H. Adjunctive corticosteroids for Pneumocystis jiroveci pneumonia in patients with HIV-infection. Cochrane Database Syst Rev 2006, 19;3:CD006150. Review.

Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-Defining Opportunistic Infections in a Multicohort Analysis of HIV-infected Persons in the United States and Canada, 2000-2010. J Infect Dis 2016, 214:862-72.

Bucher HC, Griffith L, Guyatt GH, Opravil M. Meta-analysis of prophylactic treatments against Pneumocystis carinii pneumonia and toxoplasma encephalitis in HIV-infected patients. J AIDS Hum Retrovirol 1997, 15:104-14.

Chan C, Montaner J, Lefebvre EA, et al. Atovaquone suspension compared with aero-solized pentamidine for prevention of PCP in HIV-infected subjects intolerant of trimethoprim or sulfonamides. J Infect Dis 1999, 180:369-76.

Confalonieri M, Calderini E, Terraciano S, et al. Noninvasive ventilation for treating acute respiratory failure in AIDS patients with Pneumocystis carinii pneumonia. Intensive Care Med 2002, 28:1233-8.

Conte JE Jr., Chernoff D, Feigal DW Jr., Joseph P, McDonald C, Golden JA. Intravenous or inhaled pentamidine for treating PCP in AIDS. A randomized trial. Ann Intern Med 1990, 113:203-9.

Costiniuk CT, Fergusson DA, Doucette S, Angel JB. Discontinuation of Pneumocystis jirovecii pneumonia prophylaxis with CD4 count <200 cells/μL and virologic suppression: a systematic review. PLoS One 2011, 6:e28570.

Crothers K, Beard CB, Turner J, et al. Severity and outcome of HIV-associated Pneumocystis pneumonia containing Pneumocystis jirovecii dihydropteroate synthase gene mutations. AIDS 2005, 19:801-5.

Del Corpo O, Butler-Laporte G, Sheppard DC, et al. Diagnostic accuracy of serum (1-3)-β-D-glucan for Pneumocystis jirovecii pneumonia: a systematic review and meta-analysis. Clin Microbiol Infect 2020, 26:1137-1143.

Degen O, van Lunzen J, Horstkotte MA, Sobottka I, Stellbrink HJ. Pneumocystis carinii pneumonia after the discontinuation of secondary prophylaxis. AIDS 2002, 16:1433-4.

Denis B, Guiguet M, de Castro N, et al. Critical importance of long-term adherence to care in HIV infected patients in the cART era: new insights from Pneumocystis jirovecii pneumonia cases over 2004-2011 in the FHDH-ANRS CO4 cohort. PLoS One 2014, 9:e94183.

DiRienzo AG, van Der Horst C, Finkelstein DM, et al. Efficacy of trimethoprim-sulfamethoxazole for the prevention of bacterial infections in a randomized prophylaxis trial of patients with advanced HIV infection. AIDS Res Hum Retroviruses 2002, 18:89-94.

Dohn MN, Weinberg WG, Torres RA, et al. Oral atovaquone compared with intravenous pentamidine for Pneumocystis carinii pneumonia in patients with AIDS. Ann Intern Med 1994;121:174-80.

Edman JC, Kovacs JA, Masur H, et al. Ribosomal RNA sequence shows Pneumocystis carinii to be a member of the fungi. Nature 1988, 334:519-522.

El-Sadr WM, Luskin-Hawk R, Yurik TM, et al. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of PCP in HIV-infected persons. Clin Infect Dis 1999, 29:775-783.

El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. N Engl J Med 1998, 339:1889-95.

Fisk M, Sage EK, Edwards SG, Cartledge JD, Miller RF. Outcome from treatment of Pneumocystis jirovecii pneumonia with co-trimoxazole. Int J STD AIDS 2009, 20:652-3.

Helweg-Larsen J, Benfield T, Atzori C, Miller RF. Clinical efficacy of first- and second-line treatments for HIV-associated Pneumocystis jirovecii pneumonia: a tri-centre cohort study. J Antimicrob Chemother 2009, 64:1282-90.

Helweg-Larsen J, Benfield TL, Eugen-Olsen J, Lundgren JD, Lundgren B. Effects of mutations in Pneumocystis carinii dihydropteroate synthase gene on outcome of AIDS-associated PCP. Lancet 1999, 354:1347-51.

Hidalgo A, Falco V, Mauleon S, et al. Accuracy of high-resolution CT in distinguishing between Pneumocystis carinii pneumonia and non-Pneumocystis carinii pneumonia in AIDS patients. Eur Radiol 2003, 13:1179-84.

Huang Y, He X, Chen H, et al. No Statistically Apparent Difference in Antifungal Effectiveness Observed Among Trimethoprim/Sulfamethoxazole Plus Clindamycin or Caspofungin, and Trimethoprim/Sulfamethoxazole Monotherapy in HIV-Infected Patients with Moderate to Severe Pneumocystis Pneumonia: Results of an Observational Multicenter Cohort Study. Infect Dis Ther 2022, 11:543-557.

Hughes W, Leoung G, Kramer F, et al. Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat Pneumocystis carinii pneumonia in patients with AIDS. N Engl J Med 1993, 328:1521-7.

Ioannidis JP, Cappelleri JC, Skolnik PR, Lau J, Sacks HS. A meta-analysis of the relative efficacy and toxicity of Pneumocystis carinii prophylactic regimens. Arch Intern Med 1996, 156:177-88.

Le Gal S, Damiani C, Rouillé A, et al. A cluster of Pneumocystis infections among renal transplant recipients: molecular evidence of colonized patients as potential infectious sources of Pneumocystis jirovecii. Clin Infect Dis 2012, 54:e62-71.

Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole dose escalation versus direct rechallenge for PCP prophylaxis in HIV-infected patients with previous adverse reaction to TMP-SMZ. JID 2001, 184:992-7.

Llibre JM1, Revollo B, Vanegas S, et al. Pneumocystis jirovecii pneumonia in HIV-1-infected patients in the late-HAART era in developed countries. Scand J Infect Dis 2013, 45:635-44.

Martin JN, Rose DA, Hadley WK, et al. Emergence of trimethoprim-sulfamethoxazole resistance in the AIDS Era. J Infect Dis 1999, 180:1809-18.

Matos O, Esteves F. Epidemiology and clinical relevance of Pneumocystis jirovecii Frenkel, 1976 dihydropteroate synthase gene mutations. Parasite 2010, 17:219-32.

Miller RF, Evans HE, Copas AJ, Huggett JF, Edwards SG, Walzer PD. Seasonal variation in mortality of Pneumocystis jirovecii pneumonia in HIV-infected patients. Int J STD AIDS 2010, 21:497-503.

Montgomery AB, Feigal DW Jr., Sattler F, et al. Pentamidine aerosol versus trimethoprim-sulfamethoxazole for Pneumocystis carinii in AIDS. Am J Respir Crit Care Med 1995;151:1068-74.

Morris A, Sciurba FC, Norris KA. Pneumocystis: A novel pathogen in chronic obstructive pulmonary disease? COPD 2008;5:43-51.

Morris A, Wachter RM, Luce J, Turner J, Huang L. Improved survival with highly active antiretroviral therapy in HIV-infected patients with severe Pneumocystis carinii pneumonia. AIDS 2003, 17:73-80.

Mussini C, Manzardo C, Johnson M, et al. Patients presenting with AIDS in the HAART era: a collaborative cohort analysis. AIDS 2008, 22:2461-9.

Mussini C, Pezzotti P, Antinori A, et al. Discontinuation of secondary prophylaxis for Pneumocystis carinii pneumonia in HIV-infected patients: a randomized trial by the CIOP Study Group. Clin Infect Dis 2003, 36:645-51.

Para MF, Finkelstein D, Becker S, et al. Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for Pneumocystis carinii pneumonia. J AIDS 2000, 24:337-43.

Ponce CA, Gallo M, Bustamante R, Vargas SL. Pneumocystis colonization is highly prevalent in the autopsied lungs of the general population. Clin Infect Dis 2010, 50:347-53.

Rosenberg DM, McCarthy W, Slavinsky J, et al. Atovaquone suspension for treatment of Pneumocystis carinii pneumonia in HIV-infected patients. AIDS 2001, 15:211-4.

Salzer HJF, Schäfer G, Hoenigl M, Günther G, Hoffmann C, Kalsdorf B, Alanio A, Lange C. Clinical, Diagnostic, and Treatment Disparities between HIV-Infected and Non-HIV-Infected Immunocompromised Patients with Pneumocystis jirovecii Pneumonia. Respiration. 2018 Apr 10.

Sassi M, Ripamonti C, Mueller NJ, et al. Outbreaks of Pneumocystis Pneumonia in 2 Renal Transplant Centers Linked to a Single Strain of Pneumocystis: Implications for Transmission and Virulence. Clin Infect Dis 2012 Mar 19. [Epub ahead of print].

Sasso M, Chastang-Dumas E, Bastide S, et al. Performances of Four Real-Time PCR Assays for Diagnosis of Pneumocystis jirovecii Pneumonia. J Clin Microbiol 2016, 54:625-30.

Schäfer G, Hoffmann C, Arasteh K, et al. Immediate versus deferred antiretroviral therapy in HIV-infected patients presenting with acute AIDS-defining events (toxoplasmosis, Pneumocystis jirovecii-pneumonia): a prospective, randomized, open-label multicenter study (IDEAL-study). AIDS Res Ther 2019, 16:34.

Soo Hoo GW, Mohsenifar Z, Meyer RD. Inhaled or intravenous pentamidine therapy for Pneumocystis carinii pneumonia in AIDS. A randomized trial. Ann Intern Med 1990;113:195-202.

Stringer JR, Beard CB, Miller RF, Wakefield AE. A new name (Pneumocystis jiroveci) for Pneumocystis from humans. Emerg Infect Dis 2002, 8:891-6.

Suárez I, Roderus L, van Gumpel E, et al. Low prevalence of DHFR and DHPS mutations in Pneumocystis jirovecii strains obtained from a German cohort. Infection 2017, 45:341-347.

Thomas CF Jr, Limper AH. Pneumocystis pneumonia. NEJM 2004, 350: 2487-98.

Thomas M, Rupali P, Woodhouse A, Ellis-Pegler R. Good outcome with trimethoprim 10 mg/kg/day-sulfamethoxazole 50 mg/kg/day for Pneumocystis jirovecii pneumonia in HIV infected patients. Scand J Infect Dis 2009,17:1-7.

Tian Q, Si J, Jiang F, et al. Caspofungin combined with TMP/SMZ as a first-line therapy for moderate-to-severe PCP in patients with human immunodeficiency virus infection. HIV Med 2021, 22:307-313.

Toma E, Thorne A, Singer J, et al. Clindamycin with primaquine vs. Trimethoprim-sulfamethoxazole therapy for mild and moderately severe PCP in patients with AIDS: a multicenter, double-blind, randomized trial (CTN 004). Clin Infect Dis 1998, 27:524-30.

Tominski D, Katchanov J, Driesch D, et al. The late-presenting HIV-infected patient 30 years after the introduction of HIV testing: spectrum of opportunistic diseases and missed opportunities for early diagnosis. HIV Med 2017, 18:125-132. doi: 10.1111/hiv.12403. Epub 2016 Aug 1.

Vargas SL, Pizarro P, López-Vieyra M, et al. Pneumocystis colonization in older adults and diagnostic yield of single versus paired noninvasive respiratory sampling. Clin Infect Dis 2010, 50:e19-21.

Wakefield AE, Lindley AR, Ambrose HE, Denis CM, Miller RF. Limited asymptomatic carriage of pneumocystis jiroveci in HIV-infected patients. J Infect Dis 2003, 187: 901-8.

Wang LI, Liang H, Ye LI, Jiang J, Liang B, Huang J. Adjunctive corticosteroids for the treatment of Pneumocystis jiroveci pneumonia in patients with HIV: A meta-analysis. Exp Ther Med 2016, 11:683-687.

Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS 2009, 4:e5575.

Cerebral toxoplasmosis

Although the incidence has fallen to less than one-quarter compared with the 1990s (Abgrall 2001), toxoplasmosis encephalitis (TE) remains the most critical neurologic OI today. It almost always results from reactivating a latent infection with *Toxoplasma gondii*, an intracellular parasite that infects birds, mammals, and humans. Just over one-third of all humans have antibodies (Wang 2017). However, prevalence varies considerably, reaching up to 90% in Central Europe. Toxoplasmas have an affinity for the CNS. Extracerebral manifestations (heart, muscle, liver, intestine, lung) are rare. People who become ill today are almost always untreated "late presenters." TE is potentially life-threatening, and therapy is complicated. Residual neurologic syndromes with disability (hemiparesis!) or seizure tendencies may remain. In our cohort study, this was the case in 37% (Hoffmann 2007). It should also be noted that recurrences occur even after a long time because of intracerebral persistence. With ART, the prognosis has improved significantly. The 5-year survival rate has increased to 78% since 1997 (Hoffmann 2007) but seems to have stagnated in recent years.

Clinic

Within a few days, depending on the localization of the foci, focal neurological deficits such as paresis, speech problems, or sensory disturbances may develop. Cerebral seizure or febrile psychosyndrome with confusion may also be the first symptoms. Headache and concurrent fever are also suspicious, whereas meningism is atypical. Toxoplasma chorioretinitis is an important differential diagnosis of CMV retinitis in cases of visual disturbances and occurs without encephalitis (Rodgers 1996).

Diagnostics

Above 100 CD4 T-cells/µl, TE is rare; above 200/µl, it is a rarity (Bossi 1998). Below 100 CD4 T-cells/µl, it should always be expected. Any focal neurologic deficit or seizures in a markedly immunocompromised person should prompt immediate CCT or MRI of the head. MRI is better and almost always visualizes more foci. Either solitary, multiple (2–5) or numerous foci are found in one-third of each case. There is annular contrast enhancement and often concomitant edema in about nine out of ten cases. Occasionally, bleeding may occur.

With all focal findings on CCT or MRI, TE is the most likely diagnosis. The more foci, the more likely it becomes. Even "atypical" foci are still more common than all differential diagnoses. Bacterial abscesses or cerebral lymphomas are the most common, but PML, infarcts, tuberculomas, and cryptococcosis are less common. Especially in the case of unfavorably located foci, a trial of therapy is warranted before a brain biopsy. However, a rapid stereotactic brain biopsy cannot be avoided if symptoms do not improve within a week or worsen.

In the CSF, which does not necessarily have to be examined in the case of clear radiological findings (several foci with contrast enhancement), there is usually a moderate pleocytosis and a slightly elevated total protein. Our experience with toxoplasma PCR from CSF has been relatively poor. The specificity is high, but the sensitivity is low. A negative result does not exclude TE.

A current serology should be available. Since up to 97% of TE patients have IgG antibodies, a negative result, which should be repeated in another laboratory if there is any doubt, makes TE unlikely. Whether IgG titer level is a diagnostic aid has not been validated. IgM is rarely positive, so it does not help, nor does PCR in blood (Brittany 2003).

Treatment

Although the current combinations work quite well (resistance has not been convincingly described), they must be switched in half of the cases because of side effects – especially allergies. In combination with pyrimethamine, sulfadiazine and clindamycin are largely equivalent (Dannemann 1992), although with slight advantages for sulfadiazine (Katlama 1996). Cotrimoxazole may also be considered. There is no gold standard (Hernandez 2017).

We recommend an oral therapy with sulfadiazine and pyrimethamine. Arguments favoring clindamycin (instead of sulfadiazine) are sulfonamide allergy and severely ill patients in whom pill-taking is unsafe. However, the allergy rate with sulfadiazine is considerable, and there are also recurrent supply bottlenecks. On the other hand, clindamycin is also allergenic and problematic (pseudomembranous colitis).

A so-called "loading dose" has been advocated for pyrimethamine during the first days since the first study (Leport 1988). Whether it is necessary is not proven. In Germany, 100 mg is usually given over three days, followed by 50 mg. Unlike clindamycin, pyrimethamine is effective even when the blood-brain barrier is intact. Because of the myelotoxicity of pyrimethamine, which inhibits the conversion of folic acid to folinic acid, substitution with folinic acid (expensive) is recommended from the beginning. Folic acid (cheap) is useless because it cannot be converted in the presence of pyrimethamine (Luft 2000).

Good experience is also reported with intravenous cotrimoxazole, which is dosed like in PCP (Béraud 2009). In two randomized studies of ocular and cerebral toxoplasmosis, respectively, cotrimoxazole was as effective as sulfadiazine/pyrimethamine (Torre 1998, Soheilian 2005).

If there are intolerances to sulfonamides and clindamycin, atovaquone plus pyrimethamine is an alternative (Chirgwin 2002). The data are less robust for azithromycin plus pyrimethamine (Bosch-Driessen 2002).

Acute therapy lasts four to six weeks, possibly longer with alternative therapies. Improvement is often seen within a few days – cases that have not improved at least a little clinically after two weeks of adequate therapy are probably not TE (were the pills taken?). Diagnosis should be in these cases, and a brain biopsy should be quickly performed. Changing TE therapy makes little sense and only costs time.

ART (no allergenic substances such as abacavir, darunavir/r, NNRTIs) should be started quickly. A control MRI is useful in stable cases after two weeks at the earliest; regressions are often only recognizable after four weeks. In case of increased intracranial pressure or edema, steroids are used (3–4 x 8 mg fortecortin, only short period, caveat: aspergillosis!). Maintenance therapy should only be started when the lesions have regressed by 75%.

Prophylaxis

Exposure prophylaxis: Although it has not been proven that one can be infected by mere contact with cats, the definitive host of *Toxoplasma gondii* (Wallace 1993), cat owners should pay attention to hygiene (gloves in the litter box!). IgG-negative persons should also avoid eating raw or only briefly roasted meat (especially pork, beef, and sheep!).

Primary prophylaxis: IgG-positive individuals with less than 100 CD4 T-cells/µl are recommended cotrimoxazole. Desensitization is possible if an allergy is present (see PCP). Alternatives such as dapsone plus pyrimethamine are comparably effective but less tolerated. Primary prophylaxis can be discontinued on ART if CD4 T-cells exceed 200/µl for at least three months.

Therapy/prophylaxis of cerebral toxoplasmosis
(unless otherwise stated, daily dosages)

Acute therapy		Duration: Always at least four weeks
Therapy of choice	Sulfadiazine + Pyrimethamine	Sulfadiazin-Heyl® 4 x 2–3 tab. at 500 mg **plus** Daraprim® 2 x 2 tab. of 25 mg (for 3 days, then halve dose) **plus** leucovorin® 3 x 1 tab. of 15 mg/wk
Therapy of choice	Clindamycin + Pyrimethamine	Clinda-saar® 4 x 1 amp. at 600 mg IV or 4 x 1 tab. à 600 mg **plus** Daraprim® 2 x 2 tab. of 25 mg (for 3 days, then halve dose) **plus** leucovorin® 3 x 1 tab. of 15 mg/wk
Alternative	Atovaquone + Pyrimethamine	Wellvone® suspension 2 x 10 mL (2 x 1500 mg) **plus** Daraprim® 2 x 2 tab. of 25 mg (for 3 days, then halve dose) **plus** leucovorin® 3 x 1 tab. of 15 mg/wk
Maintenance therapy		
	Like acute therapy	Like acute therapy, but half dosages Discontinuation from > 200 CD4 T-cells/µl > 6 months (if MRT normal or no contrast enhancement)
Possibly possible	Cotrimoxazole	Cotrim forte® 1 x 1 tab. at 960 mg
Primary prophylaxis		
Standard	Cotrimoxazole	Cotrim® 1 x 1 tab. at 480 mg
Alternative	Dapsone	Dapsone-Fatol® 1 x 2 tab. at 50 mg
Alternative	Dapsone + pyrimethamine	Dapsone-Fatol® 1 x 1 tab. at 50 mg **plus** Daraprim® 1 x 2 tab. at 25 mg/wk plus Leucovorin® 1 x 2 tab. at 15 mg/wk

Secondary prophylaxis: In the absence of immune reconstitution, lifelong maintenance therapy is required; otherwise, relapse almost always occurs. It usually consists of halved doses of acute therapy (Podzamczer 2000). Clindamycin, which does not cross the intact blood-brain barrier, is probably less suitable than sulfadiazine (Luft 2000). Cotrimoxazole also does not seem as effective as secondary prophylaxis, but it should be considered because of its simplicity. In any case, higher doses than for PCP should be used (Ribera 1999, Duval 2004).
Secondary prophylaxis can be discontinued if there is sufficient immune reconstitution (at least three months more than 200 CD4 T-cells/µl) (Benson 2004, Miro 2006). However, a recent MRI should be available. Caution should be exercised in foci with enhancement, where a tendency to recur persists even after years. Good CD4 T-cells do not always reflect the quality of the toxoplasma-specific immune response (Stout 2002, Furco 2008, Lejeune 2011).

Literature

Abgrall S, Rabaud C, Costagliola D. Incidence and risk factors for toxoplasmic encephalitis in HIV-infected patients before and during the HAART era. Clin Infect Dis 2001, 33: 1747-55.

Benson CA, Kaplan JE, Masur H, et al. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the NIH, and the IDSA. MMWR Recomm Rep 2004, 53(RR-15):1-112.

Béraud G, Pierre-François S, Foltzer A, et al. Cotrimoxazole for treatment of cerebral toxoplasmosis: an observational cohort study during 1994-2006. Am J Trop Med Hyg 2009, 80:583-7.

Bosch-Driessen LH, Verbraak FD, Suttorp-Schulten MS. A prospective, randomized trial of pyrimethamine and azithromycin vs pyrimethamine and sulfadiazine for the treatment of ocular toxoplasmosis. Am J Ophthalmol 2002, 134:34-40.

Bossi P, Caumes E, Astagneau P, et al. Epidemiologic characteristics of cerebral toxoplasmosis in 399 HIV-infected patients followed between 1983 and 1994. Rev Med Interne 1998, 19:313-7.

Bretagne S. Molecular diagnostics in clinical parasitology and mycology: limits of the current polymerase chain reaction (PCR) assays and interest of the real-time PCR assays. Clin Microbiol Infect 2003, 9:505-11.

Bucher HC, Griffith L, Guyatt GH, Opravil M. Meta-analysis of prophylactic treatments against PCP and toxoplasma encephalitis in HIV-infected patients. J Acquir Immune Defic Syndr Hum Retrovirol 1997,15:104-14.

Chirgwin K, Hafner R, Leport C, et al. Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with AIDS: ACTG 237/ANRS 039 Study. Clin Infect Dis 2002, 34:1243-50.

Dannemann B, McCutchan JA, Israelski D, et al. Treatment of toxoplasmic encephalitis in patients with AIDS. A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. Ann Intern Med 1992, 116:33-43.

Duval X, Pajot O, Le Moing V, et al. Maintenance therapy with cotrimoxazole for toxoplasmic encephalitis in the era of highly active antiretroviral therapy. AIDS 2004, 18:1342-4.

Furco A, Carmagnat M, Chevret S, et al. Restoration of Toxoplasma gondii-specific immune responses in patients with AIDS starting HAART. AIDS 2008, 22:2087-96.

Girard PM, Landman R, Gaudebout C, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis in HIV infection. N Engl J Med 1993, 328:1514-20.

Hernandez AV, Thota P, Pellegrino D, et al. A systematic review and meta-analysis of the relative efficacy and safety of treatment regimens for HIV-associated cerebral toxoplasmosis: Is trimethoprim-sulfamethoxazole a real option? HIV Med. 2017, 18:115-124.

Hoffmann C, Ernst M, Meyer P, et al. Evolving characteristics of toxoplasmosis in patients infected with HIV-1: clinical course and Toxoplasma gondii-specific immune responses. Clin Microbiol Infect 2007;13:510-5.

Jones JL, Hanson DL, Chu SY, et al. Toxoplasmic encephalitis in HIV-infected persons: risk factors and trends. AIDS 1996, 10:1393-9.

Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. Clin Infect Dis 1996, 22:268-75.

Lejeune M, Miró JM, De Lazzari E, et al. Restoration of T cell responses to Toxoplasma gondii after successful combined antiretroviral therapy in patients with AIDS with previous toxoplasmic encephalitis.Clin Infect Dis 2011, 52:662-70.

Leport C, Raffi F, Matheron S, et al. Treatment of central nervous system toxoplasmosis with pyrimethamine/sulfadiazine combination in 35 patients with the AIDS. Efficacy of long-term continuous therapy. Am J Med 1988, 84:94-100.

Luft BJ, Chua A. Central Nervous System Toxoplasmosis in HIV. Pathogenesis, diagnosis, and therapy. Curr Infect Dis Rep 2000, 2:358-362.

Miro JM, Lopez JC, Podzamczer D, et al. Discontinuation of primary and secondary Toxoplasma gondii prophylaxis is safe in HIV-infected patients after immunological restoration with highly active antiretroviral therapy: results of an open, randomized, multicenter clinical trial. Clin Infect Dis 2006;43:79-89.

Podzamczer D, Miro JM, Ferrer E, et al. Thrice-weekly sulfadiazine-pyrimethamine for maintenance therapy of toxoplasmic encephalitis in HIV-infected patients. Eur J Clin Microbiol Infect Dis 2000, 19:89-95.

Ribera E, Fernandez-Sola A, Juste C, et al. Comparison of high and low doses of Trimethoprim-Sulfamethoxazole for primary prevention of toxoplasmic encephalitis in HIV-infected patients. Clin Infect Dis 1999, 29:1461-6.

Rodgers CA, Harris JR. Ocular toxoplasmosis in HIV infection. Int J STD AIDS 1996, 7:307-9.

Ruf B, Schurmann D, Bergmann F, et al. Efficacy of pyrimethamine/sulfadoxine in the prevention of toxoplasmic encephalitis relapses and PCP in HIV-infected patients. Eur J Clin Microbiol Infect Dis 1993, 12:325-9.

Soheilian M, Sadoughi MM, Ghajarnia M, et al. Prospective randomized trial of trimethoprim/sulfamethoxazole versus pyrimethamine and sulfadiazine in the treatment of ocular toxoplasmosis. Ophthalmology 2005, 112:1876-82.

Stout JE, Lai JC, Giner J, Hamilton CD. Reactivation of retinal toxoplasmosis despite evidence of immune response to highly active antiretroviral therapy. Clin Infect Dis 2002, 35:37-39.

Torre D, Casari S, Speranza F, et al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Antimicrob Agents Chemother 1998, 42:1346-9.

Torres RA, Barr M, Thorn M, et al. Randomized trial of dapsone and aerosolized pentamidine for the prophylaxis of pneumocystis carinii pneumonia and toxoplasmic encephalitis. Am J Med 1993, 95:573-83.

Wallace MR, Rossetti RJ, Olson PE. Cats and toxoplasmosis risk in HIV-infected adults. JAMA 1993, 269:76-7.

Wang ZD, Wang SC, Liu HH, et al. Prevalence and burden of Toxoplasma gondii infection in HIV-infected people: a systematic review and meta-analysis. Lancet HIV 2017, 4:e177-e188.

Weigel HM, de Vries E, Regez RM, et al. Cotrimoxazole is effective as primary prophylaxis for toxoplasmic encephalitis in HIV-infected patients: a case control study. Scand J Infect Dis 1997, 29:499-502.

CMV retinitis

Infections with cytomegaloviruses (CMV) are widespread. In many Western countries, the infection rates are around 50–70%, in homosexual men even over 90%. In cases of significant immunodeficiency (below 50 CD4 T-cells/µl), reactivated CMV infection can lead to retina inflammation (retinitis). CMV retinitis was a common AIDS disease, causing blindness in up to 30% of affected individuals. Today, it is rare and seen almost exclusively in late presenters (Jacobson 2000). Inflammatory CMV retinitis with severe vitritis as IRIS is also possible (see IRIS chapter). In visual disturbances, lesions are almost always already present and are not reversible, even with adequate therapy. Thus, CMV retinitis remains a dangerous disease even today, although the prognosis has improved with ART (Salzberger 2005, Thorne 2006).
Other manifestations of disseminated CMV infection are relatively rare (about 15%). They can affect any organ. Pneumonias, esophageal ulcers, colitides, and encephalitides are the most common, but sinusitis also occurs (Jutte 2000). The clinic depends on the organ affected; the diagnosis can only be made histologically. In the absence of studies, systemic therapies analogous to CMV retinitis are usually chosen (Whitley 1998).
CMV infection also plays a role in the development of atherosclerosis and immune activation or immune reconstitution deficiency (reviews: Gianelli 2016, Moss 2019) – the importance of CMV co-infection is only beginning to be understood.

Clinic

Any peracute or acute visual disturbance such as blurred vision ("snow drift"), shadows, or spots – especially unilateral – should be a reason to send the patient immediately to ophthalmology. Today, and not tomorrow. Already symptomatic CMV retinitis is an emergency – once there is a black spot in the visual field, there remains a black spot. It is often retinal detachment and macular edema, less commonly cataractous changes (Thorne 2006). CMV therapies can usually only stop progression and cannot reverse anything. Pain in the eye, burning, increased tearing, and conjunctival irritation are not typical. Many suffer systemic symptoms such as fever and weight loss.

Diagnostics

The diagnosis of retinitis is made by fundoscopy. The examiner's experience is crucial in evaluating the predominantly peripherally located, whitish exudates. Unfortunately, misdiagnosis, which wastes valuable time (and retina), is not an exception. If necessary, start with oral valganciclovir and transport the patient to a center with more experience!
With CD4 T-cells below 100/µl, chorioretinitis due to *Toxoplasma gondii* is the most important differential diagnosis. With CD4 T-cells above 100/µl, CMV retinitis is almost excluded, and other viral infections (HSV, VZV) or even neurosyphilis are more likely. Sometimes, CMV lesions are confused with cotton wool foci, which are not uncommon with high HIV viral load. Many small foci without bleeding or exudates are almost always cotton-wool foci and rarely CMV retinitis. Bilateral infestations also tend to be the exception. Vitritis beyond an immune reconstitution syndrome is also rare.
CMV serologies (IgG almost always positive, IgM alternating) do not help. A CMV PCR (formerly also pp65 antigen) in the blood, on the other hand, makes perfect sense: a negative PCR makes CMV retinitis at least less likely, and the risk of CMV disease and overall mortality increases with the level of CMV viremia. Positive PCR is associated with unfavorable prognoses (Nokta 2002, Jabs 2005, El Amari 2011).

Treatment

Every CMV therapy should be started quickly and monitored very closely by fundoscopy (once a week, photo documentation!). In the beginning, there is an intensive induction therapy of two to three weeks, usually with valganciclovir (see below), until the lesions are scarred. This is followed by reduced-dose maintenance therapy. All patients should also be started on ART expeditiously. The specific CMV immune response is thus restorable (Komanduri 1998), and CMV viremia usually disappears after a few weeks (Deayton 1999, O'Sullivan 1999). In the absence of symptoms, we would tend not to treat isolated CMV viremia specifically. However, a (non-randomized) Japanese study showed that "preventive" CMV therapy can prevent organ manifestations in the presence of low CD4 T-cells and CMV viremia (Mizushima 2013). Treating only a positive IgM serology (without further diagnostics or clinic) is expensive and usually an unnecessary risk.

Systemic therapy

The drug of choice is valganciclovir, an orally well absorbable prodrug of ganciclovir. In a randomized trial, it was as effective as intravenous ganciclovir but also as myelotoxic (Martin 2002). Regular blood count checks are vital. Ganciclovir resistance is rare (Martin 2007).

However, intravenous therapy is usually still favored for acute vision-threatening lesions. In addition to intravenous ganciclovir, foscarnet can also be used, which should also be used if valganciclovir is not tolerated. However, foscarnet is nephrotoxic and can cause very painful penile ulcers. Intensive hydration is necessary. There are no comparative studies for cidofovir, which is rarely used. The advantage of its long half-life (given once a week) is offset by its significant nephrotoxicity (Plosker 1999). We saw creatinine increases every second case despite a meticulous infusion regimen (see *Drugs*).

A new option could be letermovir (Prevymis®), which targets CMV terminase and was approved in 2018 in HIV-negative transplant patients (reviews: Chen 2019, El-Helou 2019). However, there are no data for HIV to date.

Local therapy

Various local therapies have been tested in CMV retinitis (Smith 1998). Although their use rarely causes complications (infections, bleeding), some drawbacks remain. For example, intravitreal injections of ganciclovir or foscarnet or implantation of pellets (Vitrasert®) do not protect against infection in the contralateral eye or extraocular manifestations (Martin 1999). This is also true for fomivirsen (Vitravene®), an antisense oligonucleotide to be injected intravitreally, which is also effective against multidrug-resistant CMV strains (Perry 1999). Local therapies hardly play a role today.

Prophylaxis

Primary prophylaxis: In prospective studies, no primary prophylaxis has been convincing. There is also no effective vaccination. Therefore, the three-monthly fundoscopy is the most crucial prophylaxis with less than 200 CD4 T-cells/µl. If the immune reconstitution is good, the intervals can be extended. If immune status is poor, fundoscopy should be performed before ART initiation. Smaller lesions, which may present as very pronounced inflammatory during immune reconstitution, can thus be detected in time.

Therapy/prophylaxis of CMV retinitis (unless otherwise indicated, daily doses)

Acute therapy		Duration: Always at least three weeks
Therapy of choice	Valganciclovir	Valcyte® 2 x 2 tab. of 450 mg (for acute vision-threatening lesions, choose intravenous alternatives)
Alternative	Ganciclovir	Cymeven® 2 x 5 mg/kg IV
Alternative	Foscarnet	Foscavir® 2 x 90 mg/kg IV
Alternative	Ganciclovir + Foscavir	Half dosages each as above
Maintenance therapy		Discontinuation from > 100–150 CD4 T-cells/µl > 6 months
Therapy of choice	Valganciclovir	Valcyte® 2 x 1 tab. of 450 mg
Alternative	Foscarnet	Foscavir® 1 x 120 mg/kg IV on 5 days/week
Alternative	Cidofovir	Vistide® 1 x 5 mg/kg IV every 14 days (plus probenecid and hydration as scheduled; see also medication section)
Primary prophylaxis		Not recommended

Secondary prophylaxis: After about three weeks of acute therapy, but at the earliest when the lesions scar, dose-reduced secondary prophylaxis (maintenance therapy) should be started, preferably with oral valganciclovir (Lalezari 2002). However, valganciclovir is not only expensive (in Germany, two tablets per day cost about 2000 euros / month) but also as myelotoxic as ganciclovir infusions. Therefore, discontinuing secondary prophylaxis as soon as possible is desirable and practical (Jouan 2001). It is recommended by the US guidelines at the earliest after six months of maintenance therapy and immune reconstitution to above 100–150 CD4 T-cells/µl. However, we have successfully discontinued valganciclovir even at fewer values, provided both HIV and CMV PCR in blood were below the detection limit. One study showed that discontinuation after 18 months of ART/maintenance therapy was safe at levels as low as 75 CD4 T-cells/µl (Jouan 2001). After discontinuation, ophthalmologic monitoring should be performed at least once monthly during the initial period. Fortunately, the daily infusions of ganciclovir or foscarnet, which used to be administered via port, pumps, and nursing service for the rest of the patient's life, are now history. If recurrences occur under oral valganciclovir, we recommend re-induction and maintenance therapy with foscarnet.

Literature

Chen SJ, Wang SC, Chen YC. Antiviral Agents as Therapeutic Strategies Against Cytomegalovirus Infections. Viruses 2019, 12(1). pii: E21.

Deayton J, Mocroft A, Wilson P, et al. Loss of cytomegalovirus viremia following HAART in the absence of specific anti-CMV therapy. AIDS 1999, 13:1203-6.

Deayton JR, Prof Sabin CA, Johnson MA, et al. Importance of cytomegalovirus viremia in risk of disease progression and death in HIV-infected patients receiving HAART. Lancet 2004, 363:2116-21.

El Amari EB, Combescure C, Yerly S, et al. Clinical relevance of cytomegalovirus viraemia. HIV Med 2011, 12:394-402.

El Helou G, Razonable RR. Letermovir for the prevention of cytomegalovirus infection and disease in transplant recipients: an evidence-based review. Infect Drug Resist 2019, 12:1481-1491.

Gianella S, Letendre S. Cytomegalovirus and HIV: A Dangerous Pas de Deux. J Infect Dis 2016, 214 Suppl 2:S67-74.

Jabs DA, Martin BK, Forman MS, et al. Cytomegalovirus (CMV) blood DNA load, CMV retinitis progression, and occurrence of resistant CMV in patients with CMV retinitis. J Infect Dis 2005, 192:640-9.

Jabs DA, Martin BK, Ricks MO, Forman MS. Detection of ganciclovir resistance in patients with AIDS and cytomegalovirus retinitis: correlation of genotypic methods with viral phenotype and clinical outcome. J Infect Dis 2006, 193:1728-37.

Jacobson MA, Maecker HT, Orr PL, et al. Results of a cytomegalovirus (CMV)-specific CD8+/interferon- gamma+ cytokine flow cytometry assay correlate with clinical evidence of protective immunity in patients with AIDS with CMV retinitis. J Infect Dis 2004, 189:1362-73.

Jacobson MA, Stanley H, Holtzer C, et al. Natural history and outcome of new AIDS-related cytomegalovirus retinitis in the era of HAART. Clin Inf Dis 2000, 30:231-3.

Jouan M, Saves M, Tubiana R, et al. Discontinuation of maintenance therapy for cytomegalovirus retinitis in HIV-infected patients receiving HAART. AIDS 2001, 15: 23-31.

Jutte A, Fätkenheuer G, Hell K, Salzberger B. CMV sinusitis as the initial manifestation of AIDS. HIV Med 2000, 1:123-4.

Komanduri KV, Viswanathan MH, Wieder ED, et al. Restoration of cytomegalovirus-specific CD4+ T-lymphocyte responses after ganciclovir and HAART in individuals infected with HIV-1. Nature Med 1998, 8:953-6.

Lalezari J, Lindley J, Walmsley S, et al. A safety study of oral valganciclovir maintenance treatment of cytomegalovirus retinitis. J Acquir Immune Defic Syndr 2002, 30:392-400.

Martin BK, Ricks MO, Forman MS, Jabs DA. Change over time in incidence of ganciclovir resistance in patients with cytomegalovirus retinitis. Clin Infect Dis 2007;44:1001-8.

Martin DF, Kuppermann BD, Wolitz RA, et al. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. N Engl J Med 1999, 340: 1063-70.

Martin DF, Sierra-Madero J, Walmsley S, et al. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. N Engl J Med 2002, 346:1119-26.

Mizushima D, Nishijima T, Gatanaga H, et al. Preemptive Therapy Prevents Cytomegalovirus End-Organ Disease in Treatment-Naïve Patients with Advanced HIV-1 Infection in the HAART Era. PLoS One 2013, 8:e65348.

Moss P. From immunosenescence to immune modulation': a re-appraisal of the role of cytomegalovirus as major regulator of human immune function. Med Microbiol Immunol 2019, 208:271-280.

No authors listed. Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial: 5. Clinical features of cytomegalovirus retinitis at diagnosis. Studies of ocular complications of AIDS Research Group in collaboration with the ACTG. Am J Ophthalmol 1997,124:141-57.

Nokta MA, Holland F, De Gruttola V, et al. Cytomegalovirus polymerase chain reaction profiles in individuals with advanced HIV infection: relationship to CMV disease. J Infect Dis 2002, 185:1717-22.

O'Sullivan CE, Drew WL, McMullen DJ, et al. Decrease of cytomegalovirus replication in HIV infected-patients after treatment with HAART. J Infect Dis 1999, 180:847-9.

Perry CM, Balfour JA. Fomivirsen. Drugs 1999, 57:375-80.

Plosker GL, Noble S. Cidofovir: a review of its use in cytomegalovirus retinitis in patients with AIDS. Drugs 1999, 58:325-45.

Salzberger B, Hartmann P, Hanses F, et al. Incidence and prognosis of CMV disease in HIV-infected patients before and after introduction of combination antiretroviral therapy. Infection 2005, 33:345-9.

Smith CL. Local therapy for cytomegalovirus retinitis. Ann Pharmacother 1998, 32:248-55.

Thorne JE, Jabs DA, Kempen JH, et al. Causes of visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. Ophthalmology 2006, 113:1441-5.

Thorne JE, Jabs DA, Kempen JH, et al. Incidence of and risk factors for visual acuity loss among patients with AIDS and cytomegalovirus retinitis in the era of highly active antiretroviral therapy. Ophthalmology 2006, 113:1432-40.

Whitley RJ, Jacobson MA, Friedberg DN, et al. Guidelines for the treatment of cytomegalovirus diseases in patients with AIDS in the era of potent antiretroviral therapy: recommendations of an international panel. Arch Intern Med 1998, 158:957-69.

Candidiasis

Candidoses are infections with yeast-forming fungi. Of the 150 *Candida* species known to date, only about 20 cause disease. The most common strain is *C. albicans*, accounting for 60–90% (Review: Patil 2018). Other strains, such as *C. tropicalis*, *C. glabrata*, and *C. krusei,* are rare, but some respond worse to -azoles. Any candidiasis is an important indicator of immunodeficiency and often occurs in the wake of other OIs. Thus, it provides crucial clues not only to HIV infection but also to other more serious infections such as PCP – one should be very vigilant, especially in the presence of fever (not part of candidiasis). Candida esophagitis is AIDS-defining. With good immune status, other causes of thrush should be considered – alcoholism and steroid therapy are just two of many. In addition to candidiasis of the oropharynx and esophagus, vaginitis (although quite common in healthy individuals) is a common problem in women. Candidemia, on the other hand, rarely occurs in PLWH, even in those with massive immunodeficiency.

Clinic

The oropharynx is usually affected. Taste disturbances, sometimes a burning sensation, and whitish, strippable deposits on the buccal mucosa, pharyngeal ring, and tongue allow visual diagnosis. The tongue alone is rarely affected. Occasionally, there is atrophic candidiasis with only reddened mucosa.
Thrush esophagitis usually occurs with oropharyngeal involvement but in about 30% without oral thrush. An inconspicuous pharynx, therefore, does not necessarily exclude esophagitis. It is often manifested by dysphagia ("food does not slide down") and retrosternal pain. Occasionally, there is also nausea, but vomiting rarely occurs.

Diagnostics

In the throat, visual diagnosis is sufficient. A smear is usually not necessary, and the determination of antibodies or antigens in serum is almost always superfluous. Typing with culture or even resistance determination (caveat: laboratory uncertainties!) will only cause unnecessary costs and only make sense if a therapy attempt with fluconazole and itraconazole, respectively, has failed.
Oral candidiasis should not be confused with oral hairy leukoplakia (OHL). Unlike candidiasis, these whitish, hairy coatings on the lateral margins of the tongue cannot be scraped off. OHL is not induced by mycoses but by EBV and, although harmless and not in need of therapy, is an important disease marker for HIV.
Thrush esophagitis can also often be diagnosed clinically. Dysphagia, retrosternal pain, and an oral thrush make it very likely. Empiric fluconazole therapy saves costs (Wilcox 1996). Esophagogastroduodenoscopy (EGD) becomes necessary only when symptoms persist with fluconazole. To differentiate fluconazole-refractory thrush esophagitis from herpes or CMV esophagitis, specimens should be obtained.

Treatment

If the immune status is still good and the first episode has occurred, topical treatment with suspensions or lozenges (nystatin, amphomoronal) can be tried first. However, these are usually not particularly pleasant; systemic therapy is also more effective and protects against recurrences for longer (Pons 1997).
Fluconazole is the drug of choice; in oral thrush, a one-week oral therapy is sufficient (Sangeorzan 1994), possibly even a single dose of 750 mg (Hamza 2008). In *C. albicans,* -azole resistance has been rare (Sanglard 2002). If thrush persists despite therapy, a smear should be taken, and the fluconazole dose should be increased to 800 mg

in a second attempt. If thrush esophagitis is present, treatment should be given immediately for 14 days. Itraconazole, which is still effective in about two-thirds of cases (Saag 1999), is only considered if another attempt fails and/or non-albicans strains are detected. Itraconazole suspension is as effective as fluconazole (Graybill 1998) but is burdened by unreliable plasma levels and numerous interactions. We do not use itraconazole primarily.

Many new antifungal agents have been developed in recent years. However, they should only be used in cases of apparent fluconazole resistance. There is no evidence for the superiority of any particular antifungal (Pienaar 2006). Voriconazole is likely as effective as fluconazole but may not be tolerated well (Ruhnke 1997, Ally 2001). Posaconazole is also about as effective as fluconazole (Vaszquez 2006). These new azoles, like amphotericin B, may be considered primarily for multi-azole-resistant mycoses.

An alternative is mucosal adhesive miconazole tablets (Loramyc®), approved in Europe (Lalla 2011). However, no comparative studies for PLWH with oral candidiasis (Vazquez 2010).

The new antifungal class of echinocandins is also effective against most *Candida* strains. Substances such as caspofungin, micafungin, or anidulafungin, which can, however, only be given intravenously, were as effective and tolerable as fluconazole in randomized trials for thrush esophagitis or invasive candidiasis (Villanueva 2001, de Wet 2004, Reboli 2007). However, given their cumbersome application, their use is limited to -azole-resistant strains.

ART should be started if mycosis is present, but at the latest, if there are resistance problems, since multidrug-resistant strains usually disappear with sufficient immune reconstitution (Ruhnke 2000).

Therapy/prophylaxis of candidiasis (daily doses)

Acute therapy		Duration: 5–10 days
In mild cases	Topical	Ampho-Moronal® lozenges 4 x 1 or Nystaderm® Suspension 4 x 1 mL (4 x 1 Pip)
Therapy of choice	Fluconazole	Diflucan® or Fluconazole CT/Stada® 1 x 1 cap. at 100 mg for oral candidiasis Diflucan® or Fluconazole CT/Stada® 1 x 1 cap. at 200 mg for candida esophagitis (double dose on the first day)
Alternative	Itraconazole	Sempera® 2 x 1–2 cap. at 100 mg or Sempera liquid® 2 x 10–20 mL (1 mL = 10 mg)
Prophylaxis		Not recommended

Prophylaxis

A survival benefit has not yet been shown for any *Candida* prophylaxis (McKinsey 1999, Rex 2000, Goldman 2005). However, in the largest randomized trial, continuous prophylaxis reduced both oral thrush episodes and invasive candidiasis (Goldman 2005). Incidentally, this study did not confirm the hypothesis that continuous therapy selects resistant nonalbicans strains (Vazquez 2001). In any case, azole-resistant candidiasis was not more frequent in the continuous therapy arm. But every immunosuppressed person should have his or her mouth checked at every presentation!

Patients should be urged to change their toothbrushes frequently and carefully clean dentures. Disinfecting mouth rinses with chlorhexidine 0.12% 1–2 x daily may also be useful.

Literature

Ally R, Schurmann D, Kreisel W, et al. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. Clin Infect Dis 2001, 33:1447-54.

De Wet N, Llanos-Cuentas A, Suleiman J, et al. A randomized, double-blind, parallel-group, dose-response study of micafungin compared with fluconazole for the treatment of esophageal candidiasis in HIV-positive patients. Clin Infect Dis 2004, 39:842-9.

Graybill JR, Vazquez J, Darouiche RO, et al. Randomized trial of itraconazole oral solution for oropharyngeal candidiasis in HIV/AIDS patients. Am J Med 1998, 104:33-9.

Hamza OJ, Matee MI, Brüggemann RJ, et al. Single-dose fluconazole versus standard 2-week therapy for oropharyngeal candidiasis in HIV-infected patients: a randomized, double-blind, double-dummy trial. Clin Infect Dis 2008, 47:1270-6.

Lalla RV, Bensadoun RJ. Miconazole mucoadhesive tablet for oropharyngeal candidiasis. Expert Rev Anti Infect Ther 2011, 9:13-7.

McKinsey DS, Wheat LJ, Cloud GA, et al. Itraconazole prophylaxis for fungal infections in patients with advanced HIV infection: randomized, placebo-controlled, double-blind study. Clin Infect Dis 1999, 28:1049-56.

Pienaar ED, Young T, Holmes H. Interventions for the prevention and management of oropharyngeal candidiasis associated with HIV infection in adults and children. Cochrane Database Syst Rev 2006, 3:CD003940. Review.

Patil S, Majumdar B, Sarode SC, et al. Oropharyngeal Candidosis in HIV-Infected Patients-An Update. Front Microbiol. 2018 May 15;9:980.

Pons V, Greenspan D, Lozada-Nur F, et al. Oropharyngeal candidiasis in patients with AIDS: randomized comparison of fluconazole versus nystatin oral suspensions. Clin Infect Dis 1997, 24:1204-7.

Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. N Engl J Med 2007;356:2472-82.

Rex JH, Walsh TJ, Sobel JD, et al. Practice guidelines for the treatment of candidiasis. Clin Infect Dis 2000, 30:662-78.

Ruhnke M, Adler A, Muller FM. Clearance of a fluconazole-resistant Candida albicans strain after switching antifungal therapy and initiation of triple therapy for HIV infection. Clin Microbiol Infect 2000, 6:220-3.

Ruhnke M, Schmidt-Westhausen A, Trautmann M. In vitro activities of voriconazole (UK-109,496) against fluconazole-susceptible and -resistant Candida albicans isolates from oral cavities of patients with HIV infection. Antimicrob Agents Chemother 1997, 41:575-7.

Saag MS, Fessel WJ, Kaufman CA, et al. Treatment of fluconazole-refractory oropharyngeal candidiasis with itraconazole oral solution in HIV-positive patients. AIDS Res Hum Retroviruses 1999, 15:1413-7.

Sangeorzan JA, Bradley SF, He X, et al. Epidemiology of oral candidiasis in HIV-infected patients: colonization, infection, treatment, and emergence of fluconazole resistance. Am J Med 1994, 97:339-46.

Sanglard D, Odds FC. Resistance of Candida species to antifungal agents: molecular mechanisms and clinical consequences. Lancet Infect Dis 2002, 2:73-85.

Vazquez JA, Peng G, Sobel JD, et al. Evolution of antifungal susceptibility among Candida species isolates recovered from HIV-infected women receiving fluconazole prophylaxis. Clin Infect Dis 2001, 33:1069-75.

Vazquez JA, Skiest DJ, Nieto L, A multicenter randomized trial evaluating posaconazole versus fluconazole for the treatment of oropharyngeal candidiasis in subjects with HIV/AIDS. Clin Infect Dis 2006, 42:1179-86.

Vazquez JA, Patton LL, Epstein JB, et al. Randomized, comparative, double-blind, double-dummy, multicenter trial of miconazole buccal tablet and clotrimazole troches for the treatment of oropharyngeal candidiasis: study of miconazole Lauriad® efficacy and safety (SMiLES). HIV Clin Trials 2010, 11:186-96.

Villanueva A, Arathoon EG, Gotuzzo E, et al. A randomized double-blind study of caspofungin versus amphotericin for the treatment of candidal esophagitis. Clin Infect Dis 2001, 33:1529-35.

Walsh TJ, Gonzalez CE, Piscitelli S, et al. Correlation between in vitro and in vivo antifungal activities in experimental fluconazole-resistant oropharyngeal and esophageal candidiasis. J Clin Microbiol 2000, 38:2369-73.

Wilcox CM, Alexander LN, Clark WS, Thompson SE 3rd. Fluconazole compared with endoscopy for HIV-infected patients with esophageal symptoms. Gastroenterology 1996, 110:1803-9.

Tuberculosis

CHRISTIAN HERZMANN, GUNAR GÜNTHER

Background

Tuberculosis (TB) is one of the most common life-threatening infectious diseases worldwide. In 2020, approximately 10.6 million people fell ill. About 1.59 million people died, including 187,000 PLWH (WHO 2022a). The incidence and prevalence of the disease varies globally but was affected almost universally by the COVID-19 pandemic, as surveillance, diagnostic, and therapeutic services were massively impaired. Globally reported cases declined significantly in 2020 (5.9 million) and rebounded modestly in 2021 (6.7 million). The global decline in the incidence of TB slowed significantly, whereas mortality increased (Figure 1). A global increase in TB disease is expected in the post-pandemic years (WHO 2022a).

For European countries with low incidence rates, it can be assumed that the refugee movement from Ukraine will contribute to an increase in incidence in the coming years. For example, the incidence in 2020 in Ukraine was 70/100,000, compared with 4.8/100,000 in Germany and 8.8/100,000 in Poland. Mainly due to the high rate of multidrug-resistant tuberculosis in Ukraine (MDR-TB, 33% of all cases), increased surveillance efforts and diagnostic vigilance are required when tuberculosis is suspected.

About 6.7% of all new TB cases occurred among PLWH. In Africa and some European countries, the HIV prevalence among TB patients is exceptionally high. There is a significantly increased risk of TB disease, especially in those with advanced immunodeficiency and ongoing viral replication (Lange 2016). Approximately 76% of reported TB cases worldwide were tested for HIV in 2021, and 89% of reported cases with coinfection received antiretroviral therapy (WHO 2022a).

The therapy of PLWH with TB is significantly complicated by its long duration, frequent side effects, interactions, and poor adherence due to the large number of drugs. For therapy-naïve individuals without risk of drug resistance (see below), a combination of rifampicin, isoniazid, pyrazinamide, and ethambutol along with ART of TDF/3TC or TDF/FTC plus efavirenz, TDF/FTC/efavirenz, or TDF/3TC or TDF/FTC plus an INSTI at adjusted doses is initially recommended (EACS 2021). If these

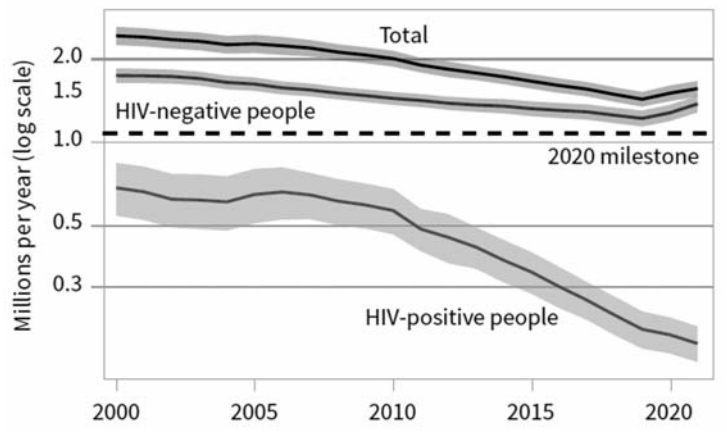

Figure 1: Estimated global number of TB deaths with or without HIV infection since 2000. A pandemic-related increase since 2019. Dashed: WHO target for 2020 (WHO 2022a).

regimens are not an option, a PI-based regimen such as TDF/3TC(FTC) plus darunavir/r, atazanavir/r, or lopinavir/r in adjusted dose may also be considered in combination with rifabutin. Therapy must be adjusted to the results of genotypic (TB and HIV) and phenotypic (TB) drug sensitivity testing (DST). EACS offers an online course on HIV and co-infections at *eacsociety.org*.

Interrelationship of HIV and *M. tuberculosis*

Infections by HIV and *Mycobacterium tuberculosis* (MTB) synergistically affect the human immune response. This occurs with continued viral replication (usually in the absence of effective ART) through reduction of CD4 T-cells or functional loss of immunocompetence. Even under ART and despite numerically normal numbers, immune reconstitution remains incomplete in correlation to the CD4 T-cell nadir (Lange 2003, Lundgren 2015). The pathogenic effect of HIV infection is not limited to CD4 T-cell function. Even in the early stages of HIV infection, the risk of developing TB is significantly increased (Sonnenberg 2005).
PLWH have a 21- to 37-fold risk of developing active TB compared with HIV-negative individuals (Getahun 2010). In addition to low CD4 T-cells, low body mass index, anemia, diabetes mellitus, and existing viral replication are risk factors. TB can also lead to immune paralysis and exacerbate the effect of HIV-associated immunodeficiency (Toossi 2003).

Clinical manifestation

In the early stages of HIV infection, TB manifests no differently than in HIV-negative individuals. Cough, fatigue, fever, night sweats, and weight loss are the most common symptoms. As immunodeficiency progresses, extrapulmonary (e.g., pleurisy, lymphadenopathy, osteomyelitis) and disseminated manifestations such as meningitis and miliary TB occur (Elliott 1993).

Pulmonary TB is the most common organ manifestation with infiltrations and/or cavity formation. The upper lobes are most commonly affected. Enlarged hilar lymph nodes are often a manifestation of HIV infection.

Extrapulmonary TB: The most common manifestation is cervical lymphadenopathy with enlarged and painful cervical lymph nodes. The lymph nodes may liquify and form spontaneous fistulae on the cutaneous surface. Smaller abscesses may heal without surgical intervention; larger abscesses should be drained surgically. Other forms include pleurisy, pericarditis, abdominal TB, and meningitis. Osteoarticular, spinal, urogenital, or cutaneous forms of TB also occur; virtually any organ can be affected.

Miliar-TB (lat. *Milium effusum* = millet): The chest X-ray shows a nodular pattern reminiscent of millet grains, which is radiologically indistinguishable from cryptococcosis. Radiological changes can often be seen in the meninges, liver, and spleen.

Diagnosis of active tuberculosis and drug sensitivity testing

Suspicion of active TB is based on clinical symptoms and radiological findings (Lange 2004). The gold standard is the cultural detection of MTB from sputum or other specimens, and nucleic acid amplification techniques (NAAT) have become the standard of initial diagnosis. Blood tests cannot detect active TB (IGRA; see below). Differential diagnoses include diseases caused by non-tuberculous mycobacteria, solid tumors, lymphomas, lung abscesses, and sarcoidosis. Less common differential diagnoses include granulomatosis with polyangiitis, nocardiosis, actinomycosis, rhodococcosis, aspergillosis, histoplasmosis, and cryptococcosis.

Radiology: Radiological changes may vary widely, mimic other pneumological pathologies, or be absent. The more severe the immunodeficiency, the fewer pathologic changes are usually found on conventional radiographic thorax (Chamie 2010). Blurred, streaked infiltrations with cavities, especially in the upper lobes, are typical; fine-spotted, disseminated (miliary) infiltrates are found in miliary tuberculosis. In advanced immunodeficiency, pleural effusion without pulmonary infiltrates may occur early. A CT of the chest should be obtained if in doubt. Pulmonary imaging is also recommended in cases of extrapulmonary TB. In addition, an ultrasound should be performed to look for intra-abdominal abscesses, lymphadenopathy, bowel wall thickening, renal and bladder pathology, and ascites. MRI is superior to CT for meningitis, radiculitis, and osteomyelitis.

Sputum examination and microscopy: If pulmonary TB is clinically suspected, 2–3 morning sputum samples taken immediately and on the following morning should be examined. If sputum production is not possible, it can be augmented by inhalation of hypertonic saline (3%). Microscopic detection of alcohol- and acid-fast bacilli (AAFB) in sputum is successful in only about 30% of PLWH with pulmonary tuberculosis – at least 5,000–10,000 mycobacteria/mL must be present for detection. The specificity of microscopy is also low; they cannot be told apart from non-tuberculous mycobacteria (NTM). However, microscopy is still necessary for diagnosing atypical mycobacterial disease if MTB-specific NAAT remains negative and as a monitoring tool during therapy.

Nucleic acid amplification: Methods for the detection of MTB DNA by nucleic acid amplification (Xpert® MTB/RIF, Xpert® MTB/RIF Ultra, Truenat® MTB Plus/MTB-Rif Dx) are diagnostically clearly superior to sputum microscopy and are recommended by WHO. The time to diagnosis is approximately 2 hours. This allows rapid differentiation of MTB from other acid-fast organisms on microscopy. The sensitivity and specificity of the Xpert® MTB/RIF Ultra exceed 99% for microscopically positive sputum samples.

In people living with HIV, the Xpert MTB/RIF Ultra sensitivity is 87%. Even if no AAFB is detectable in microscopy, but the culture is positive (as is often the case with HIV), the sensitivity is 77% (Zifodya 2021). The assay is also suitable for diagnosing extrapulmonary TB, but the sensitivity is lower than for pulmonary TB (Denkinger 2014, Kohli 2021). The Xpert MTB/RIF Ultra significantly increases diagnostic sensitivity compared to the Xpert MTB/RIF, especially for the diagnosis of TB in CSF (89%) and pleural effusion (74%) (Kohli 2021). However, in the context of the improved sensitivity, the number of false positive findings unfortunately also increases, especially in former TB patients.

The Xpert MTB/RIF Ultra and Truenat MTB-Rif Dx can simultaneously detect mutations in the rpoB gene that indicate rifampicin resistance with approximately 95% sensitivity (Boehme 2010, Zifodya 2021). False-positive test results can be expected in countries where rifampicin resistance is relatively rare (e.g., Western Europe). The Xpert MTB/XDR enables rapid detection of common resistance mutations to isoniazid, fluoroquinolones, ethionamides, and amikacin.

Lipoarabinomannan assay: This urine test with lateral flow technology is a point-of-care test recommended by WHO for diagnosing TB in HIV co-infection and severe immunosuppression. The assay can improve or complement the diagnosis of active TB, especially in individuals without sputum production and few clinical signs of TB. A recent Cochrane analysis reported a sensitivity of approximately 40% (Bjerrum 2019). The Fuji company has developed a significantly improved version. However, a recent evaluation of PLWH showed highly variable results (Szekely 2022).

Line probe assays (Hain-Lifescience, AID) allow the detection of mutations within 24–48 hours in the mycobacterial genes katG, inhA, rrs, and gyrA/B and others that are associated with resistance to isoniazid, amikacin, and fluoroquinolones.

Genome sequencing for DST has been established as the new standard for drug sensitivity testing, although its use in primary biological samples like sputum remains challenging. In 2021, WHO published a catalog of known resistance mutations of MTB with a grading of clinical relevance (WHO 2021). Currently, Deeplex® Myc-TB, an assay based on "targeted next-generation sequencing," analyzes 18 gene targets for 15 drugs and allows a standardized web-based interpretation of its findings (Jouet 2021). Further assays will be available soon, based on different sequencing technologies (e.g., Oxford Nanopore Technologies).

Microbiological culture: The diagnostic gold standard is the cultural detection of *M. tuberculosis complex* in liquid media (approx. 2–4 weeks) or solid media (approx. 3–5 weeks). If microscopy is negative, a specimen should not be considered culturally negative for 6–8 weeks. NTMs often grow much faster and are usually diagnosed within two weeks in specialized laboratories. DST is always required when MTB has been detected culturally and is now available for most new TB drugs (besides carbapenems).

Bronchoscopy: If both sputum microscopy and NAAT are negative, bronchoscopy is indicated if TB is still suspected. The investigation of gastric juice is less sensitive. Bronchial secretions, bronchoalveolar lavage, and transbronchial biopsies can be analyzed by microscopy, culture, and NAAT. Detecting caseating granulomas or giant cells in the transbronchial biopsy may further back up the diagnosis of TB. In addition, MTB-specific immuno-diagnosis using Elispot (T-SPOT.TB®) from bronchoalveolar lavage can be performed at specialized centers (Jafari 2018). This procedure identifies more than 90% of all cases of active pulmonary TB. Most differential diagnoses require bronchoscopic investigation.

Extrapulmonary diagnostic: Biological samples should be obtained from the affected organ, e.g., heparin blood, urine (three morning samples), cerebrospinal fluid, pleural, peritoneal, and pericardial fluids. Biopsies of lymph nodes, pleura, peritoneum, synovium, or pericardium may also be considered. Biopsies should not be shipped in formalin but in normal saline (NaCl 0,9%) for culture and NAAT. The sensitivity of molecular tests varies widely; culture remains the gold standard. Details on the diagnostic quality of molecular tests in different body materials can be found in a recent Cochrane analysis (Kohli 2021). For lymphadenopathy, needle aspiration followed by NAAT diagnosis has a high sensitivity for the diagnosis of TB.

Latent infection and preventive therapy

Latent infection with MTB is defined as a positive immune response in the tuberculin skin test (TSTTST) or interferon–γ release assay (IGRA) in the absence of active disease (Mack 2009). Immunodiagnostics are part of TB prevention. After the active disease has been excluded, IGRA or TST should be used to identify PLWH at the highest risk of developing active disease (Getahun 2015). Immunoassays do not distinguish between active and latent disease, i.e., they are not helpful in diagnosing active TB. IGRAs are more specific than skin testing. The T-SPOT.TB® test appears to be less dependent on CD4 T-cell count (Rangaka 2007) than the IFN–γ response of the QuantiFERON®-TB Gold test (Leidl 2010). However, the higher specificity is not associated with a higher positive predictive value for the development of active TB. Few studies have evaluated progression rates to active TB in PLWH based on TST and IGRA (Aichelburg 2009, Sester 2014). Viral loads above 50 copies/mL and positive TST are the greatest risk factors for developing TB (Sester 2014). Progression from

latent to active disease is prevented by preventive therapy (Sester 2014). The "number needed to treat" to prevent one case of active TB in TST-positive HIV patients is below 10, and TST is superior to IGRAs. However, many cases that later develop TB are not detected by either TST or IGRAs (Sester 2014). New approaches are aiming for assays with higher positive predictive values. For example, transcriptome-based gene signatures (such as RISK 6/RISK 11) are currently evaluated for their predictive value, but also for triage and treatment monitoring (Hamada 2022).
To prevent TB, administration of six to nine months of INH (300 mg) plus pyridoxine (25 mg) is recommended in PLWH with positive TST or IGRA. Alternatively, rifampicin or rifabutin may be administered for four months (EACS 2022). Once-weekly administration of rifapentine 900 mg and INH 900 mg for 12 weeks was non-inferior to 600 mg INH for nine months (Sterling 2016). Rifapentine 600 mg and isoniazid 300 mg daily for one month are good alternatives. However, rifapentin is not approved by the EMA and is therefore unavailable in Europe (EACS 2022). Children living with HIV likely benefit from preventive INH administration, but this recommendation is not strong (Zunza 2017).

Infection Control

Most people fall ill a short time after infection. Therefore, infection control is vital in contact with actively ill people (Horsburgh 2010, Houben 2011). Contact isolation from the moment of diagnosis until effective treatment according to DST has been established as particularly important in HIV co-infection (Escombe 2008). Transmission of MTB appears to decrease sharply in a short time after initiation of effective treatment (Dharmadhikari 2014). However, the absence of MTB growth in culture is probably still the best indicator that patients are no longer contagious. For pulmonary TB, initial weekly sputum microscopy and evaluation of MTB growth in culture are useful (Schaberg 2022).

Treatment

Treatment of susceptible TB consists of a combination of the first-line drugs rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB). RIF is the most potent drug. Standard therapy consists of a two-month initiation phase with RIF, INH, PZA, and EMB, followed by a four-month maintenance phase with RIF and INH (WHO 2022b). Molecular DST (e.g., Xpert® MTB/Rif Ultra and Xpert® MTB/XDR) with a diagnostic interval of approximately 2 hours should rapidly provide information on the most important genotypic resistance mutations. DST for additional second-line drugs from primary material (e.g., GenoType MTBDRplus VER2.0 and MTBDRsl VER2.0, Deeplex Myc-TB) should be available within a few days to adjust therapy as needed.
Since 2022, WHO recommends the combination of rifapentine, isoniazid, moxifloxacin, and pyrazinamide for four months, which was not inferior to the previous standard regimen (WHO 2022b). As rifapentin is not approved by the EMA, this regimen is challenging to implement in European practice. Results were replicated in a subgroup of PLWH on efavirenz-based ART (Pettit 2022). Further, the rifampicin dosing should be optimized, with up to 35 mg/kg appearing safe and more effective (Boeree 2015). Dosages, side effects, and drug interactions of the major TB drugs are listed in Table 1. The duration of therapy in PLWH is the same as in non-infected persons (WHO 2022). There is insufficient evidence to justify prolonged therapy in disseminated TB, except for CNS manifestations. There is a survival benefit for TB meningitis when steroids are used in patients without HIV infection. Unfortunately, data are lacking for co-infected individuals (Prasad 2016).

Table 1: Anti-TB drugs, side effects, and interactions.

Drug	Daily dose	Common side effects	Comments
Rifampicin (RIF) oral, IV	10 mg/kg > 50 kg: 600 mg < 50 kg: 450 mg	Hepatitis, anemia, lymphopenia, fever, discoloration of urine, nephritis, rash	Numerous interactions: (see Table 2), monitoring of liver function, possibly safe up to 35 mg/kg (Boeree 2015), avoiding alcohol consumption
Isoniazid (INH) oral, IV	5 mg/kg, maximum 300 mg/day combine with vitamin B6	Hepatitis, polyneuropathy, psychosis	Avoid d4T, ddI Avoid alcohol consumption Liver failure: replacement with levofloxacin
Ethambutol (EMB) oral, IV	15 mg/kg (15–20 mg/kg)	Neuritis optica (contra-indicated in the presence of pre-existing optic nerve damage)	Monthly screening of visual acuity and color vision Antacids decrease absorption
Pyrazinamide (PZA) oral	25 mg/kg (20–30 mg/kg)	Hepatitis, hyperuricemia, gout	Treat hyperuricemia only if symptomatic
Amikacin (Am) IV/IM	15 mg/kg max 1 g/day	Ototoxicity, nephrotoxicity	Audiometry, monitoring of renal function, avoid during pregnancy
Cycloserine (CS) oral	15 mg/kg (0,75–1 g/day)	CNS side effects (in the first few weeks): Dizziness, psychosis	Enhances CNS side effects of INH and protionamide
Levofloxacin (LFX) oral, IV	750–1,500 mg/day (15 mg/kg)	CNS side effects (headache, dizziness, sleep disturbances), Achilles tendon rupture (rare), QT prolongation	Not approved for children
Linezolid (LZD) oral, IV	600 mg/day	Frequent: thrombocytopenia, anemia, polyneuropathy	Mostly 600 mg
Moxifloxacin (MFX) oral/IV	400 mg/day	See levofloxacin, acute liver failure (very rare)	Activity similar to levofloxacin, 800 mg can also be used if necessary
Prothionamide (PTO) oral	15 mg/kg (0.75–1 g/day)	Nausea, vomiting (especially with PAS), hepatotoxicity, CNS side effects	Monitoring of liver values, if necessary, gradual dosage
Rifabutin (RFB) oral	150–300 mg/day or 3 x 150 mg/week in combination with PI	Hepatitis, anemia, lympho-penia, thrombocytopenia Fever, urine discoloration, nephritis, uveitis, rash	Weaker CYP 450 inducer than RIF, therefore preferred with ART (see Table 2)
Bedaquiline (BDQ) oral	400 mg 2 x daily for 2 weeks, then 200 mg per day	Nausea, QT prolongation	Rifampicin halves plasma levels, EFV reduces plasma levels, in combination with QT-prolonging drugs, ECG monitoring, monitoring liver values

Table 1: Continuation

Drug	Daily dose	Common side effects	Comments
Delamanid (DLM) oral	100 mg 2 x daily	Nausea, vomiting, dizziness, QT prolongation	Not in combination with rifampicin
Clofazimine (CFZ) oral	100 mg/d	Skin discoloration, pruritus, photosensitivity, nausea, QT prolongation	Combination with QT-prolonging drugs: ECG monitoring Avoid direct sunlight
Meropenem/ amoxicillin-clavulanic acid (MPM; AMX-CLV)	1–2,000 mg 3 x daily i.v. plus 125 mg clavulanic acid, e.g., as amoxicillin/ clavulanic acid 875 mg+125 mg	Exanthema, nausea, leukocytopenia, thrombocytopenia	Only active in combination, data still limited
Pretomanide	Pretomanide 200 mg daily	In combination often neuropathy and anemia	Study data in combination with MXF, BDQ, and LZD (initial dose 600 mg recommended)
Paraamino-salicylic acid	4–6 g 2 x daily	Nausea, diarrhea, vomiting	

Therapy of resistant tuberculosis (MDR/XDR-TB)

Resistance to RIF and INH defines MDR-TB (multidrug resistance) and requires second-line drugs. If additional resistance to fluoroquinolones is present, pre-XDR (extensively drug-resistant) TB is present; if additional resistance to linezolid or bedaquiline is present, XDR-TB is present.

The treatment options for MDR/rifampicin-resistant TB (RR-TB) have changed considerably in recent years. Ideally, therapy based on up-to-date drug susceptibility testing should be initiated with at least four, preferably five, effective drugs. NAAT-based methods and genome sequencing gain importance in resistance testing. Experts should interpret sequencing results as there are still uncertainties about the extent to which genotypic resistance is associated with phenotypic resistance.

Two clinical trials have documented high efficacy with significantly shorter duration of therapy of only six months and reduced toxicity with new combinations: the combination of bedaquiline, linezolid, pretomanid (TB PRACTECAL) and moxifloxacin for MDR-TB and bedaquiline, linezolid and pretomanid (ZeNIX-TB) for pre-XDR/XDR-TB (Conradi 2022). Based on available data, WHO has recommended using these treatment regimens since May 2022. The recommendation also addresses PLWH despite low case numbers to date. In principle, expert advice is recommended for MDR/XDR tuberculosis, and therapy should be carried out at an experienced center.

Timing of ART and TB therapy

Three large clinical trials (SAPIT, CAMELIA, and STRIDE) have investigated the best timing for ART initiation in TB (Abdool Karim 2011, Blanc 2011, Havlir 2011). In particular, patients with low CD4 T-cell counts benefit from early initiation; those with less than 50/µl should receive antiretroviral treatment no later than two weeks after initiation of TB therapy (EACS 2022). However, in TB meningitis, even with

low CD4 T-cells, a postponement of 8 weeks is reasonable (see below). Pregnant women should also receive prompt antiretroviral treatment to avoid vertical transmission.

Combination of ART and TB therapy

Under RIF-containing therapy, ART consists of efavirenz 600 or 400 mg daily, each combined with TDF+FTC or TDF+3TC. Raltegravir 400 mg or 800 mg BID in combination with TDF/FTC or TDF/3TC is considered an alternative, as is dolutegravir. However, the latter requires a dose adjustment to 2 x 50 mg (EACS 2022). Based on the ENCORE trial, efavirenz is often given as 400 mg daily. ART must be adjusted to resistance levels. Table 2 shows the required dose adjustments for rifampicin and rifabutin. Interactions are manifold, mainly due to RIF-associated induction of cytochrome P450 3A4/5.

Table 2: Recommendations for co-administration of ART with rifampicin/rifabutin.

Drug	Dose adjustment	Comments
Lopinavir/r	Rifabutin 150 mg daily If rifabutin is unavailable, lopinavir/r 400/400 mg 2 x daily (super-boosting)	only if no alternative is available: hepatotoxicity, diarrhea TDM recommended for PIs
Darunavir/r	Rifabutin 150 mg daily	
Atazanavir/r	Rifabutin 150 mg daily	
Efavirenz	Rifampicin 600 mg 1 x daily (probably also 400 mg safe) Rifabutin 450 mg	TDM after 2 weeks
Nevirapine	No co-administration with rifampicin	
Etravirine	No co-administration with rifampicin or rifabutin	
Rilpivirine	Rifabutin 300 mg daily and double the rilpivirine dose	Rilpivirine levels drop by 80%
Raltegravir	400 or 800 mg 2 x daily	TDM for raltegravir
Elvitegravir/Cobicistat	No co-administration with rifampicin, with caution: rifabutin 150 mg daily	
Dolutegravir	Rifampicin 50 mg 2 x daily Rifabutin 300 mg daily	
Bictegravir	No co-administration with rifampicin and rifabutin	
Cabotegravir oral	Administration is possible with rifabutin, not with rifampicin/rifapentine	
Cabotegravir/ rilpivirine	No co-administration with rifampicin, rifabutin, rifapentine	
NRTIs (incl. TAF)	Standard ARV dosing for rifampicin and rifabutin	Triple NRTI is not recommended
Maraviroc	Rifampicin 600 mg every 12 h	AUC reduction 63%

Comment: There are no recommendations for dosage adjustment of rifampicin

Rifabutin (150 mg/d) can also be combined with boosted PIs after dose adjustment. However, increased neutropenias have been observed with atazanavir/r (Zhang 2011). With the recommended rifabutin dose of 150 mg daily, watch out for possible uveitis and/or neutropenia (EACS 2022). Tenofovir does not interact with RIF (Droste 2005), and TAF 25 mg daily can probably be given with rifampicin. Efavirenz (standard dose) can be combined with rifabutin (450 mg daily) (EACS 2022).
The INSPIRING trial showed good tolerability and efficacy of dolutegravir 2 x 50 mg with rifampicin (Dooley 2019). NRTI-only therapy (AZT, ABC, 3TC ± TDF) may be considered in the absence of alternatives and low viral load (< 100,000 copies/mL) until therapy with RIF is completed. Rilpivirine is not recommended with rifabutin and rifampicin. Etravirine may be given in combination with rifabutin 300 mg OD, but not with rifampicin. Bedaquiline should not be combined with CYP3A4 inhibitors or inducers (efavirenz). Lopinavir/r increases bedaquiline levels but appears to be safe. Dolutegravir and nevirapine are potential partners for bedaquiline. Delamanid has few relevant interactions with antiretroviral agents but should not be combined with rifampicin (Mallikaariun 2016), and pretomanid should not be combined with efavirenz. In any case, regular consultation of the Liverpool Drug Interactions Database (*www.hiv-druginteractions.org*) is recommended.
The key to success is good adherence, hampered by the high tablet load and numerous side effects. This is why WHO recommends DOT (directly observed therapy) for all TB patients.

Immune Reconstitution Syndrome (IRIS)

When ART and TB therapy are started simultaneously, there is a high risk of TB-IRIS (immune reconstitution inflammatory syndrome). TB-IRIS may occur in about 15% of patients with severe immunodeficiency (Meintjes 2008). A distinction is made between paradoxical and unmasking IRIS. In paradoxical IRIS, active TB initially responds well to therapy but deteriorates within the first three months after ART initiation with lymphadenopathy, pulmonary infiltrates, serous effusions, or CNS symptoms. Differential diagnosis must exclude side effects, infections, poor adherence, malignancies, and resistance. The cause is thought to be an exaggerated TH1 immune response against mycobacterial antigens (Bourgarit 2006). In unmasking IRIS, active TB develops within three months, which was previously subclinical (Meintjes 2008); symptoms are first triggered by immune reconstitution.
People with severe immunodeficiency should be monitored closely. Because of the high IRIS-associated mortality in TB meningitis, ART should not be started until eight weeks after initiating TB therapy (Török 2011). ART and TB therapy should be continued despite IRIS (EACS 2022). Steroids may be useful. In the only randomized trial of IRIS to date, 1.5 mg/kg prednisolone for two weeks followed by 0.75 mg/kg for an additional two weeks showed benefit (Meintjes 2010) in terms of inpatient treatment days and outpatient resources. In a more recent study, steroids were helpful, provided ART was started within 30 days of TB therapy initiation in case of fewer than 100 CD4 T-cells/µl: 40 mg and then 20 mg prednisolone for two weeks each reduced the incidence of TB IRIS by more than 50% (Meintjes 2019).

Side effects

For the most common side effects, see Table 1. INH should always be given with vitamin B6 (pyridoxine) to prevent peripheral polyneuropathy. Color vision should be assessed before and during therapy with EMB because of possible optic nerve damage. EMB and PZA must be dose-adjusted in renal insufficiency. Liver injury is common and usually resolves after discontinuation (drug-induced liver injury, DILI). Management can follow the South African HIV Society guidelines (Jong 2013). Liver

enzymes, creatinine, electrolytes, and blood counts should be monitored during TB therapy (initially weekly, later monthly). Hyperuricemia often occurs under PZA but usually does not require treatment. Mild polyarthralgia can be treated with allopurinol or nonsteroidal analgesics.

In the treatment of M/XDR-TB, linezolid is associated with high toxicity in a dose-dependent manner. Given peripheral neuropathies, anemias, and optic nerve neuropathies, treated patients should be screened regularly for side effects and managed in experienced centers. Arthralgias can also be induced by rifamycins. The combination of nephrotoxic substances should be avoided. Current guidelines only allow amikacin as an aminoglycoside, with close monitoring of renal function (Brust 2018). In addition, monthly audiometry should be performed.

Based on the DELIBERATE trial, the administration of bedaquiline and delamanid with dolutegravir appears relatively safe (Dooley 2019). Both can cause QTc prolongation, which requires regular ECG monitoring, especially when combined with fluoroquinolones and clofazimine (WHO 2019). Pretomanid does not cause QT time prolongation and can be administered with INSTIs. More data are needed, particularly on the toxicity of the new short regimens for MDR/XDR-TB. Affected individuals with severe side effects should be hospitalized, and TB medications should be discontinued until adverse effects have resolved.

Literature

Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. NEJM 2011; 365: 1492-1501.

Aichelburg MC, Rieger A, Breitenecker F, et al. Detection and prediction of active tuberculosis disease by a whole-blood interferon-g release assay in HIV-1–infected individuals. Clin Infect Dis 2009; 48: 954-962.

Bahr NC, Nuwagira E, Evans EE, et al. Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study. Lancet Infect Dis 2018, 18:68-75.

Bjerrum S, Schiller I, Dendukuri N, et al. Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in people living with HIV. Cochrane Database Syst Rev 2019 Oct 21;10:CD011420.

Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. NEJM 2011, 365:1471-81.

Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. NEJM 2010, 363:1005-15.

Boeree MJ, Diacon AH, Dawson R, et al. A dose-ranging trial to optimize the dose of rifampin in treating tuberculosis. Am J Respir Crit Care Med 2015, 191:1058-65.

Bourgarit A, Carcelain G, Martinez V, et al. Explosion of a tuberculin-specific TH1 immune response induces immune restoration syndrome in tuberculosis and HIV-coinfected patients. AIDS 2006; 20:F1-F7.

Brust JCM, Shah NS, Mlisana K et al. Improved Survival and Cure Rates With Concurrent Treatment for Multidrug-Resistant Tuberculosis-Human Immunodeficiency Virus Coinfection in South Africa. Clin Infect Dis 2018, 66:1246-53.

Chamie G, Luetkemeyer A, Walusimbi-Nanteza M, et al. Significant variation in presentation of pulmonary tuberculosis across a high resolution of CD4 strata. Int J Tuberc Lung Dis 2010, 14:1295-302.

Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline-Pretomanid-Linezolid Regimens for Drug-Resistant Tuberculosis. N Engl J Med. 2022 Sep 1;387(9):810-823. doi: 10.1056/NEJMoa2119430.

Denkinger CM, Schumacher SG, Boehme CC, et al. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. Eur Respir J 2014; 44:435-46.

Dharmadhikari AS, Mphahlele M, Venter K, et al. Rapid impact of effective treatment on transmission of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2014, 18

Dooley KE, Kaplan R, Mwelase N, et al. Dolutegravir-based antiretroviral therapy for patients co-infected with tuberculosis and HIV: a multicenter, noncomparative, open-label, randomized trial. Clin Infect Dis 2019.

Droste JA, Verweij-van Wissen CP, Kearney BP, et al. Pharmacokinetic study of tenofovir disoproxil fumarate combined with rifampin in healthy volunteers. Antimicrob Agents Chemother 2005;49:680-4.

Elliott AM, Halwiindi B, Hayes RJ, et al. The impact of human immunodeficiency virus on presentation and diagnosis of tuberculosis in a cohort study in Zambia. J Trop Med Hyg 1993, 96:1-11.

Escombe AR, Moore DA, Gilman RH, et al. The infectiousness of tuberculosis patients coinfected with HIV. PLoS Med. 2008, 5:e188.

EACS 2022. Version 11.1. https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf (Letzter Zugriff 30.10.2022)

EuroTB.net/UKR2022 (Letzter Zugriff: 23.10.2022)

Getahun H, Gunneberg C, Granich R, et al. HIV infection-associated tuberculosis: the epidemiology and the response. CID 2010, 50 Suppl 3:S201-7.

Getahun H, Matteelli A, Chaisson RE, et al. Latent Mycobacterium tuberculosis infection. NEJM 2015; 372:2127-35.

Hamada Y, Penn-Nicholson A, Krishnan S, et al. Are mRNA based transcriptomic signatures ready for diagnosing tuberculosis in the clinic? – A review of evidence and the technological landscape. EBioMedicine 2022, 82:104174.

Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. N Engl J Med 2011; 365: 1482-1491.

Horsburgh CR Jr, O'Donnell M, Chamblee S, et al. Revisiting rates of reactivation tuberculosis: a population-based approach. Am J Respir Crit Care Med 2010, 182:420-5.

Houben RM, Crampin AC, Ndhlovu R, et al. Human immunodeficiency virus associated tuberculosis more often due to recent infection than reactivation of latent infection. Int J Tuberc Lung Dis 2011, 15:24-31.

Jafari C., Olaru ID, Daduna F, et al. Rapid diagnosis of pulmonary tuberculosis by combined molecular and immunological methods. Eur Respir J 2018, 51(5).

Jong E, Conradie F, Berhanu R, et al. Consensus statement: Management of drug-induced liver injury in HIV-positive patients treated for TB. S Afr J HIV Med 2013,14:113-119.

Jouet A, Gaudin C, Badalato N et al. Deep amplicon sequencing for culture-free prediction of susceptibility or resistance to 13 anti-tuberculous drugs. Eur Respir J 2021, 57(3):2002338.

Kohli M, Schiller I, Dendukuri N et al. Xpert MTB/RIF Ultra and Xpert MTB/RIF assays for extrapulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev 2021, 1(1):CD012768..

Lange C, Aarnoutse RE, Alffenaar JWC, et al. Management of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2019, 23:645-62.

Lange C, Duarte R, Fréchet-Jachym M, et al. Limited benefit of the new shorter multidrug-resistant tuberculosis regimen in Europe. Am J Respir Crit Care Med 2016; 194: 1029–1031.

Lange C, Lederman MM, Medvik K, et al. Nadir CD4+ T-cell count and numbers of CD28+ CD4+ T-cells predict functional responses to immunizations in chronic HIV-1 infection. AIDS 2003; 17: 2015-23.

Lange C, Schaaf B, Dalhoff K. HIV and lung. Pneumologie 2004; 58:416-27.

Lange C, van Leth F, Sester M. Viral load and risk of tuberculosis in HIV-infection. J AIDS 2016, 71:e51-3.

Lange C, Dheda K, Chesov D, et al. Management of drug-resistant tuberculosis. Lancet 2019, 394:953-66.

Leidl L, Mayanja-Kizza H, Sotgiu G, et al. Relationship of immunodiagnostic assays for tuberculosis and numbers of circulating CD4+ T-cells in HIV infection. Eur Respir J 2010, 35:619-26.

Mack U, Migliori GB, Sester M, et al. LTBI: latent tuberculosis infection or lasting immune response to Mycobacterium tuberculosis. A TBNET consensus statement. Eur Respir J 2009; 33:956-73.

Mallikaarjun S, Wells C, Petersen C, et al. Delamanid coadministered with antiretroviral drugs or antituberculosis drugs shows no clinically relevant drug-drug interactions in healthy subjects. Antimicrob Agents Chemother 2016; 60:5976-5985.

Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis 2008, 8:516-23.

Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. AIDS 2010, 24:2381-90.

Meintjes G, Stek C, Maartens G, et al. Prednisone for Prevention of Paradoxical Tuberculosis-Associated IRIS. NEJM 2019, 380(18):1781

Pettit AC, Phillips PP, Kurbatova E, et al. Rifapentine with and without moxifloxacin for pulmonary tuberculosis in people with HIV (S31/A5349). Clin Infect Dis 2022:ciac707.

Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev 2016;4:CD002244.

Rangaka MX, Diwakar L, Seldon R, et al. Clinical, immunological, and epidemiological importance of antituberculosis T cell responses in HIV-infected Africans. Clin Infect Dis 2007, 44:1639-46.

Schaberg T, Brinkmann F, Feiterna-Sperling C, et al. Tuberkulose im Erwachsenenalter. S2k Leitlinie 2022. https://www.awmf.org/uploads/tx_szleitlinien/020-019l_S2k_Tuberkulose-im-Erwachsenenalter_2022-10.pdf

Sester M, van Leth F, Bruchfeld J, et al. The risk of tuberculosis in immunocompromized hosts. Am J Respir Crit Care Med 2014; 190:1168-76

Sonnenberg P, Glynn JR, Fielding K, et al. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. J Infect Dis 2005; 191:150-8.

Sterling TR1, Scott NA, Miro JM, et al. Three months of weekly rifapentine and isoniazid for treatment of Mycobacterium tuberculosis infection in HIV-coinfected persons. AIDS 2016, 30:1607-15.

Székely R, Sossen R, Mukoka M, et al. Multicentre accuracy trial of FUJIFILM SILVAMP TB LAM test in people with HIV reveals lot variability. medRxiv 2022.09.07.22278961

Toossi Z. Virological and immunological impact of tuberculosis on human immunodeficiency virus type 1 disease. J Infect Dis 2003, 188:1146-55.

Török ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in HIV-associated tuberculous meningitis. CID 2011; 52: 1374-1383.

WHO 2021. Catalogue of mutations in Mycobacterium tuberculosis complex and their association with drug resistance. Licence: CC BY-NC-SA 3.0 IGO.

WHO 2022a. Global Tuberculosis Report 2022. Licence: CC BY-NC-SA 3.0 IGO.

WHO 2022b. Operational handbook on tuberculosis Module 4: Treatment – drug-susceptible tuberculosis treatment. Licence: CC BY-NC-SA 3.0 IGO.

Zifodya JS, Kreniske JS, Schiller I et al. Xpert Ultra versus Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis. Cochrane Database Syst Rev 2021 Feb 22.

Zhang J, Zhu L, Stonier M, et al. Determination of rifabutin dosing regimen when administered in combination with ritonavir-boosted atazanavir. J Antimicrob Chemother 2011, 66:2075-82.

Zunza M, Gray DM, Young T, et al. Isoniazid for preventing tuberculosis in HIV-infected children. Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD006418.

Atypical mycobacteriosis (MAC)

Atypical mycobacterioses are most often understood as synonymous with *Mycobacterium avium complex* (MAC) infections. MAC is by far the most common pathogen; however, a variety of other atypical mycobacteria can cause similar clinical pictures, such as *M. celatum, M. kansasii, M. xenopi,* or *M. genavense*. MAC bacteria can be detected in diverse animal species, soil, water, and food. Exposure prophylaxis is not possible, and isolating affected patients is not advisable. At the same time, MAC may be detectable in the sputum or stool of asymptomatic individuals (colonization); almost only patients with less than 50 CD4 T-cells/µl become ill (Horsburgh 1999). Meanwhile, the infection is rare in industrialized countries (Karakousis 2004). The clinical picture has changed significantly – the formerly almost always chronic disseminated disease, found in many "wasting" cases, has become a primarily localized infection, which occurs under ART almost only in the course of an immune reconstitution syndrome. However, the disease may remain threatening and show very unusual manifestations.

Clinic

Symptoms of *disseminated* MAC infection are non-specific. Fever, weight loss, and diarrhea with less than 100 CD4 T-cells/µl should always suggest atypical mycobacteriosis. Abdominal pain also occurs. Far more common than disseminated are now *localized* MAC infections, especially in the form of lymph node abscesses. We have seen abscesses in cervical, inguinal, and abdominal lymph nodes, some forming fistulas and healing very slowly after surgical opening. Any abscess developing during ART (in severe immunodeficiency) is suspicious for MAC! Osteomyelitides are also possible as localized forms, especially in the vertebral bodies and joints (seen: knee, hand, fingers).

Diagnostics

Diagnosis is difficult in the disseminated form. Blood cultures (heparin blood) should always be sent to a reference laboratory. Although atypical mycobacteria usually grow more rapidly than TB bacteria, it may take weeks to culture and differentiate from tubercle bacilli. If anemia is present, bone marrow aspiration is often successful. If detected in stool or sputum, but also in BAL, there is usually only colonization: in the absence of general symptoms, therapy can be dispensed. This also applies to *Mycobacterium kansasii* (Kerbiriou 2003). In the laboratory, alkaline phosphatase (AP) is typically elevated – high AP in the presence of poor immune status is always suspicious for MAC. MAC infection should also be considered in the presence of anemia and constitutional symptoms. Cytopenia, especially anemia, often indicates bone marrow involvement. Sonographically, the liver and spleen are enlarged. Lymph nodes are also often enlarged but are notable less for their size than numbers (Gordin 1997). Differential diagnoses include TB or lymphoma. In the localized forms, material should always be obtained directly; detection from abscess punctate is usually successful.

Treatment

The treatment of a culturally proven MAC infection is complex. Analogous to TB, one drug alone is not sufficient. Since 1996, many have favored a combination of macrolide (clarithromycin or azithromycin), rifabutin, and ethambutol (Shafran 1996). This used to be given for life; now, it should be continued for at least six

months until the CD4 T-cell increase exceeds 100/µl on ART. After some data suggested that rifabutin could be omitted (Dunne 2000), the randomized ACTG 223 trial showed a survival benefit with the triple combination of clarithromycin, rifabutin, and ethambutol over clarithromycin and ethambutol or rifabutin, and mortality rates were halved in the triple arm (Benson 2003).

However, rifabutin should be discontinued after several weeks and clinical improvement because of its large interaction potential. For clarithromycin, the dose should not exceed 2 x 500 mg. In two randomized trials, the number of deaths was significantly increased at higher doses for unexplained reasons (Chaisson 1994, Cohn 1999). Equally effective as clarithromycin is azithromycin, which also interacts less with cytochrome p450 enzymes (Ward 1998).

Therapy should be monitored in disseminated disease by regular blood cultures, which should be negative after 8 weeks at the latest. In localized forms, the response is better assessed clinically. Any MAC therapy carries a high potential for side effects and interactions. Concomitant medications, including ART, must be closely reviewed – it is not uncommon for dose adjustments to be required, and contraindications exist (see chapter *Drug*). Reserve drugs such as amikacin or levofloxacin are needed only in exceptional cases. In all atypical mycobacterioses, the resistance situation should be investigated.

In localized MAC disease, we usually stop therapy when the abscess resolves – usually, this takes a few months. In individual cases, steroids may be helpful temporarily. However, there are no separate recommendations in localized MAC infections.

Therapy/prophylaxis of MAC infections (unless otherwise indicated, daily doses)

Acute therapy		
Therapy of choice	Clarithromycin + Ethambutol + possibly Rifabutin	Klacid retard® 2 x 1 tab. at 500 mg **plus** Myambutol® 1 x 3 tab. at 400 mg **plus** Mycobutin® 1 x 2 tab. at 150 mg
Alternative	Azithromycin + Ethambutol + possibly Rifabutin	Ultreon® 1 x 1 tab. at 600 mg **plus** Myambutol® 1 x 3 tab. at 400 mg **plus** Mycobutin® 1 x 2 caps. at 150 mg
Maintenance therapy		Like acute therapy but **without** rifabutin Discontinuation from > 100 CD4 T-cells/µl > 6 months
Primary prophylaxis		If CD4 T-cells are persistently below 50/µl, consider Discontinuation from > 100/µl > 3 months
Therapy of choice	Azithromycin	Ultreon® 1 x 2 tab. at 600 mg/week
Alternative	Clarithromycin	Klacid retard® 2 x 1 tab. at 500 mg

Prophylaxis

In the United States, for clarithromycin, azithromycin, and rifabutin, large placebo-controlled trials have shown that primary prophylaxis significantly reduces MAC mortality in severely immunocompromised individuals (Havlir 1996, Nightingale 1992, Pierce 1996, Oldfield 1998). In Europe, MAC infections are less common. Partly because of concerns about compliance and resistance developments, few individuals in Europe receive primary MAC prophylaxis for this reason. Azithromycin should be considered from below 50 cells/µl if ART options are limited. Weekly administration is patient-friendly and, according to a Cochrane analysis, the prophylaxis of choice (Uthman 2013).

Primary prophylaxis and maintenance therapies (see above) can be discontinued if CD4 T-cells exceed 100/µl (El Sadr 2000, Shafran 2002, Aberg 2003). Partial viral suppression may be sufficient for MAC-specific immune reconstitution (Havlir 2000). Cures under immune reconstitution are possible (Aberg 1998).

Literature

Aberg JA, Williams PL, Liu T, et al. A study of discontinuing maintenance therapy in human immunodeficiency virus-infected subjects with disseminated Mycobacterium avium complex: AIDS Clinical Trial Group 393 Study Team. J Infect Dis 2003; 187: 1046-52.

Aberg JA, Yajko DM, Jacobson MA. Eradication of AIDS-related disseminated mycobacterium avium complex infection after 12 months of antimycobacterial therapy combined with HAART. J Infect Dis 1998, 178:1446-9.

Benson CA, Williams PL, Currier JS, et al. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated Mycobacterium avium complex disease in persons. Clin Infect Dis 2003; 37:1234-43.

Chaisson RE, Benson CA, Dube MP, et al. Clarithromycin therapy for bacteremic Mycobacterium avium complex disease. A randomized, double-blind, dose-ranging study in patients with AIDS. Ann Intern Med 1994, 121:905-11.

Cohn DL, Fisher EJ, Peng GT, et al. A prospective randomized trial of four three-drug regimens in treating disseminated Mycobacterium avium complex disease in AIDS patients: excess mortality associated with high-dose clarithromycin. Clin Infect Dis 1999, 29:125-33.

Dunne M, Fessel J, Kumar P, et al. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated Mycobacterium avium infection in patients with HIV. Clin Infect Dis 2000, 31:1245-52.

El-Sadr WM, Burman WJ, Grant LB, et al. Discontinuation of prophylaxis for Mycobacterium avium complex disease in HIV-infected patients responding to ART. N Engl J Med 2000, 342:1085-92.

Gordin FM, Cohn DL, Sullam PM, Schoenfelder JR, Wynne BA, Horsburgh CR Jr. Early manifestations of disseminated Mycobacterium avium complex disease: a prospective evaluation. J Infect Dis 1997, 176:126-32.

Havlir DV, Dube MP, Sattler FR, et al. Prophylaxis against disseminated Mycobacterium avium complex with weekly azithromycin, daily rifabutin, or both. N Engl J Med 1996, 335:392-8.

Havlir DV, Schrier RD, Torriani FJ, et al. Effect of potent antiretroviral therapy on immune responses to Mycobacterium avium in HIV-infected subjects. J Infect Dis 2000, 182:1658-63.

Horsburgh CR Jr. The pathophysiology of disseminated Mycobacterium avium complex disease in AIDS. J Infect Dis 1999, Suppl 3:S461-5.

Karakousis PC, Moore RD, Chaisson RE. Mycobacterium avium complex in patients with HIV infection in the era of highly active antiretroviral therapy. Lancet Infect Dis 2004, 4:557-65.

Kerbiriou L, Ustianowski A, Johnson MA, Gillespie SH, Miller RF, Lipman MC. HIV type 1-related pulmonary Mycobacterium xenopi infection: a need to treat? Clin Infect Dis 2003; 37: 1250-4.

Nightingale SD, Byrd LT, Southern PM, et al. Incidence of Mycobacterium avium-intracellulare complex bacteremia in HIV-positive patients. J Infect Dis 1992, 165:1082-5.

Oldfield EC 3rd, Fessel WJ, Dunne MW, et al. Once weekly azithromycin therapy for prevention of Mycobacterium avium complex infection in patients with AIDS: a randomized, double-blind, placebo-controlled multi-center trial. Clin Infect Dis 1998, 26:611-9.

Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated Mycobacterium avium complex infection in patients with advanced AIDS. N Engl J Med 1996, 335:384-91.

Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of Mycobacterium avium complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. N Engl J Med 1996, 335:377-83.

Shafran SD, Mashinter LD, Phillips P, et al. Successful discontinuation of therapy for disseminated Mycobacterium avium complex infection after effective antiretroviral therapy. Ann Intern Med 2002;137:734-7.

Uthman MM, Uthman OA, Yahaya I. Interventions for the prevention of mycobacterium avium complex in adults and children with HIV. Cochrane Database Syst Rev 2013 Apr 30;4:CD007191.

Ward TT, Rimland D, Kauffman C, Huycke M, Evans TG, Heifets L. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for Mycobacterium avium complex bacteremia in patients with HIV infection. Clin Infect Dis 1998, 27:1278-85.

Herpes simplex

Herpes simplex virus (HSV) infections are a common problem, and chronic courses are possible, especially in cases of significant immunodeficiency (below 100 CD4 T-cells/µl). There are two viruses:
HSV-1 is transmitted through mucosal contact (kissing) and causes itchy perioral blisters on the lips, tongue, palate, or oral mucosa.
HSV-2 is sexually transmitted and causes herpetiform lesions on the penis, vagina, vulva, and anus. The lesions significantly increase the risk of transmission of HIV (Freeman 2006, see *Prevention*).
In severe cases, other organs may be affected. These include esophagus (ulcers), CNS (encephalitis), eye (keratoconjunctivitis, uveitis), and respiratory tract (pneumonitis, bronchitis). In these cases, and if persistent for more than four weeks, HSV infection is considered AIDS-defining.

Clinic, diagnostics

The vesicles itch and burn. Oral involvement may impair food intake. In genital or anal infestation (proctitis!), urination and defecation can be painful. Extensive lesions are possible in severe immunodeficiency. Regional lymph nodes are often swollen. The clinic of disseminated herpes infections depends on the organs affected.
In the case of oral, genital, or perianal infestation, visual diagnosis is often sufficient. In case of doubt, a swab can be taken, which must be transported quickly to the laboratory in a virus culture medium. Resistance testing in refractory lesions is also possible. Organ manifestations are usually diagnosed histologically. In HSV encephalitis, diagnosis is difficult because CSF often is not helpful. Serologies are only informative if negative (rare), making HSV infection unlikely.

Treatment

Any therapy is more effective the sooner it is started. If the immune status is good and the lesions are only discrete, topical administration of acyclovir may be sufficient. Penciclovir cream (Vectavir®) is probably as effective (Chen 2000) and reportedly somewhat less irritating but significantly more expensive.
Systemically, the nucleoside analog acyclovir remains the drug of choice. It inhibits the DNA polymerase of herpes viruses. Resistance is rare, even 40 years after market introduction (Levin 2004). Acyclovir is well tolerated and effective against HSV-1 and HSV-2. Intravenous treatment should be used in severe cases and organ manifestations. Because CNS levels are lower than in plasma, the dose should be increased in the presence of encephalitis. Renal values should be monitored during intravenous administration of acyclovir.
Equivalent alternatives are valaciclovir and famciclovir (Ormrod 2000, Conant 2002), which need to be taken less often with better oral availability but are more expensive and not approved in immunosuppression. They should be used only when acyclovir is not effective. We have had good experience with famciclovir, a prodrug of penciclovir (Vinh 2006). For uncomplicated genital lesions, two days of 500 mg of famciclovir may be sufficient, provided there is no immunodeficiency (Bodsworth 2008). Brivudine (approved only for HZV) should no longer be used.

Treatment/prophylaxis of HSV infection (daily doses)

Acute therapy		Duration: 7–14 days
First choice	Acyclovir	Aciclovir ratiopharm® 5 x 1 tablets of 400 mg
Severe cases		Aciclovir p.i.® 3 x ½–1 amp. of 500 mg (3 x 5–10 mg/kg) IV
Alternatives	Valaciclovir	Valtrex® 3 x 2 tablets at 500 mg
Alternatives	Famciclovir	Famvir® 3 x 1 tablet at 250 mg
Prophylaxis		Not recommended

In exceptions, especially in refractory lesions, therapy with foscarnet for several weeks may be useful. New drugs such as pitrelivir, which inhibits another enzyme of herpes viruses, helicase, were quite promising in initial larger studie, but are not yet approved (Wald 2014+2016). Phase III trials began in 2020. The same is true for therapeutic vaccines, and several companies have initiated clinical studies (Bernstein 2017).
In the case of painful mucocutaneous lesions, a local anesthetic is useful. Unfortunately, the proven tetracaine solution (Herviros®) has been withdrawn from the market, but some pharmacies can prepare something comparable.

Prophylaxis

Primary prophylaxis with HSV drugs is not usually recommended. An early meta-analysis, according to which the risk of both HSV and HZV disease decreased by more than 70% and even mortality decreased under acyclovir (Ioannidis 1998), is nowadays probably to be put into perspective. For persistent recurrences, low continuous doses of acyclovir or valaciclovir (DeJesus 2003, Warren 2004) may be useful. However, sub-clinical HSV reactivations are unlikely to be adequately prevented in this way (Johnston 2012). Vaccination studies are still in the early stages and are only partially protective (Belshe 2012).

Interactions between HIV and herpes simplex

Genital HSV infections increase the risk of contracting HIV almost threefold (Freeman 2006, see *Prevention*). In recent years, extensive randomized studies showed that HSV therapy interestingly also reduces the HIV viral load: with acyclovir by 0.33 logs (Ludema 2011), on higher doses or valacyclovir even slightly more (Mugwanya 2011, Perti 2013, Vanpouille 2015). Even the progression of HIV infection can be slowed (Reynolds 2012). Although the antiviral effect clearly cannot prevent HIV transmission, these observations have breathed new life into HSV and especially acyclovir therapy (Vanpouille 2009+2015). An “ancient drug” such as acyclovir has become interesting again: it may be possible to develop new derivatives based on it, whose antiviral potency is better with good tolerability with respect to HIV.

Literature

Belshe RB, Leone PA, Bernstein DI, et al. Efficacy results of a trial of a herpes simplex vaccine. N Engl J Med 2012, 366:34-43.

Bernstein D, Wald A, Warren T, et al. Therapeutic Vaccine for Genital Herpes Simplex Virus-2 Infection: Findings From a Randomized Trial. J Infect Dis. 2017, 215:856-64.

Bodsworth N, Bloch M, McNulty A, et al. 2-day versus 5-day famciclovir as treatment of recurrences of genital herpes: results of the FaST study. Short-Course Herpes Therapy Study Group. Sex Health 2008, 5:219-25.

Chen XS, Han GZ, Guo ZP, et al. A comparison of topical application of penciclovir 1% cream with acyclovir 3% cream for treatment of genital herpes: a randomized, double-blind, multicentre trial. Int J STD AIDS 2000, 11:568-73.

Conant MA, Schacker TW, Murphy RL, et al. Valaciclovir versus aciclovir for herpes simplex virus infection in HIV-infected individuals: two randomized trials. Int J STD AIDS 2002, 13:12-21.

DeJesus E, Wald A, Warren T, et al. Valacyclovir for the suppression of recurrent genital herpes in HIV-infected subjects. J Infect Dis 2003; 188: 1009-16.

Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus two infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. AIDS 2006, 20:73-83.

Ioannidis JP, Collier AC, Cooper DA, et al. Clinical efficacy of high-dose acyclovir in patients with HIV infection: a meta-analysis of randomized individual patient data. J Infect Dis 1998, 178:349-59.

Johnston C, Saracino M, Kuntz S, et al. Standard-dose and high-dose daily antiviral therapy for short episodes of genital HSV-2 reactivation: three randomised, open-label, cross-over trials. Lancet 2012, 379:641-7.

Levin MJ, Bacon TH, Leary JJ. Resistance of herpes simplex virus infections to nucleoside analogues in HIV-infected patients. Clin Infect Dis 2004, 39 Suppl 5:S248-57.

Ludema C, Cole SR, Poole C, Chu H, Eron JJ. Meta-analysis of randomized trials on the association of prophylactic acyclovir and HIV-1 viral load in individuals coinfected with herpes simplex virus-2. AIDS 2011, 25:1265-9.

Mugwanya K, Baeten JM, Mugo NR, et al. High-dose valacyclovir HSV-2 suppression results in greater reduction in plasma HIV-1 levels compared with standard dose acyclovir among HIV-1/HSV-2 coinfected persons: a randomized, crossover trial. J Infect Dis 2011, 204:1912-7.

Ormrod D, Scott LJ, Perry CM. Valaciclovir: A review of its long-term utility in the management of genital herpes simplex virus and cytomegalovirus infection.

Perti T, Saracino M, Baeten JM, Johnston C, Diem K, Ocbamichael N, Huang ML, Selke S, Magaret A, Corey L, Wald A. High-dose valacyclovir decreases plasma HIV-1 RNA more than standard-dose acyclovir in persons coinfected with HIV-1 and HSV-2: a randomized crossover trial. J AIDS 2013, 63:201-8.

Reynolds SJ, Makumbi F, Newell K, et al. Effect of daily aciclovir on HIV disease progression in individuals in Rakai, Uganda, co-infected with HIV-1 and herpes simplex virus type 2: a randomised, double-blind placebo-controlled trial. Lancet Infect Dis 2012, 12:441-8.

Safrin S. Treatment of acyclovir-resistant herpes simplex virus infections in patients with AIDS. J Acquir Immune Defic Syndr 1992, Suppl 1:S29-32.

Vanpouille C, Lisco A, Margolis L. Acyclovir: a new use for an old drug. Curr Opin Infect Dis 2009, 22:583-7.

Vanpouille C, Lisco A, Grivel JC, et al. Valacyclovir Decreases Plasma HIV-1 RNA in HSV-2 Seronegative Individuals: A Randomized Placebo-Controlled Crossover Trial. Clin Infect Dis 2015, 60:1708-14.

Vinh DC, Aoki FY. Famciclovir for the treatment of recurrent genital herpes: a clinical and pharmacological perspective. Expert Opin Pharmacother 2006, 7:2271-86.

Warren T, Harris J, Brennan CA. Efficacy and safety of valacyclovir for the suppression and episodic treatment of herpes simplex virus in patients with HIV. Clin Infect Dis 2004, 39 Suppl 5:S258-66.

Wald A, Corey L, Timmler B, Magaret A, et al. Helicase-primase inhibitor pritelivir for HSV-2 infection. N Engl J Med 2014, 370:201-10.

Wald A, Timmler B, Magaret A et al. Effect of Pritelivir Compared With Valacyclovir on Genital HSV-2 Shedding in Patients With Frequent Recurrences: A Randomized Clinical Trial. JAMA 2016, 316:2495-2503.

Herpes zoster

Zoster is the reactivation of a previous infection with varicella (chickenpox), which persists in the spinal ganglia for life. Zoster episodes are observed even with relatively good immune status and, despite recent declines in incidence (Moanna 2013), are still common enough to be considered an indicator disease for HIV infection. Typically, zoster presents as IRIS (Martinez 1998). With increasing immunodeficiency, the risk of generalization increases (Zou 2022). In addition to the typical involvement of one or more dermatomes, there is also complicated involvement of the eye (when the trigeminal branch is affected, "zoster ophthalmicus" with involvement of the cornea) and ear ("zoster oticus"). Necrotizing zoster retinitis is feared. Other complications include meningoencephalitis, myelitis, and involvement of other cranial nerves (Brown 2001, Zou 2022).

Clinic

There are often prodromes with headache, feeling of sickness and photophobia, which are rarely accompanied by fever. At the affected sites, there is often initially only hypersensitivity, which changes to itching and/or pain within a few hours or days. The pain may precede the skin lesions by several days. These often present as segmental (always unilateral!) redness with herpetiform blisters in the area of one or more dermatomes. The lesions are ulcerative, often hemorrhagic, and gradually dry up. They should be kept dry and clean to prevent bacterial superinfection. Unpleasant pain syndromes remain in 20%, especially when multiple dermatomes are affected. Such zoster neuralgia can be assumed if the pain persists for more than a month (Gnann 2002).

Diagnostics

In cutaneous cases, visual diagnosis is usually sufficient. However, the diagnosis may be misjudged in atypical localization (extremities!) and complicated cases. If you are unsure you can send a swab from a blister to the laboratory. An immunofluorescence assay is probably more reliable. VZV encephalitis can only be detected by CSF diagnostics or PCR. In case of peracute hearing disorders, zoster oticus should be considered, which is not necessarily recognizable from the outside – either look into the ear yourself or go to the ENT department! For visual disturbances – quickly go to the ophthalmology department!

Treatment

Monosegmental zoster can be treated on an outpatient basis with oral acyclovir. Rapid onset is essential. Systemic therapy is always required, and dosages are higher than for HSV. Drying up the lesions is accelerated by a zinc mixture, which simultaneously relieves the pain: put on gloves! Initially, the lesions are highly infectious, and unvaccinated persons without a history of chickenpox, especially pregnant women, should avoid contact with persons with herpes zoster. Analgesics (novaminsulfone, tramadol) should not be spared. Complicated, multisegmental, or facial zoster episodes are usually a case for intravenous therapy. Valaciclovir and famciclovir are alternatives to acyclovir. Whether zoster neuralgia occurs less frequently remains controversial (Li 2009, McDonald 2011). These agents have hardly been tested for HIV, are not approved for use in immunocompromised patients, and are significantly more expensive. Acyclovir resistance is rare (Saint-Leger 2001) and can

be treated with foscarnet. Brivudine (Zostex®) should no longer be used because of unclear deaths (especially in combination with chemotherapies).
The therapy of zoster neuralgia is complex. Carbamazepine or gabapentin is only partially effective, and steroids are not useful (Gnann 2002). Lidocaine patches (Versatis®), applied to the painful area, have been approved in Europe since 2007. Due to possible local skin irritation, the lesions should have resolved. The effect often takes days to appear (Garnock-Jones 2009).

Prophylaxis

Live varicella vaccination with Zostavax® has since been replaced by a likely more effective vaccine (Shingrix®). Shingrix® was approved in 2018 for HIV patients over age 50. This also applies to those with a history of zoster, although data are scarce here. Some safety interval (6 months) should be maintained from a zoster episode. Two vaccinations 2–6 months apart are necessary. Otherwise, vaccination success is compromised. Shingrix® causes relatively frequent local reactions and, although primarily moderate, myalgias, fatigue, and headache (Review: Short 2019).
In case of negative serology and varicella exposure (highly infectious!), hyperimmunoglobulin (2 mg/kg IV) can be given. Low-dose continuous therapy is only considered for persistent recurrences. In a randomized trial, zoster episodes were prevented by acyclovir (Barnabas 2016).

Treatment/prophylaxis of VZV infection (daily doses)

Acute therapy		Duration: At least 7 days
First choice	Acyclovir	Aciclostad® 5 x 1 tablets at 800 mg
Severe cases		Aciclovir p.i.® 3 x 1–2 amp. of 500 mg (3 x 10 mg/kg) IV
Alternatives	Valaciclovir	Valtrex® 3 x 2 tablets at 500 mg
Alternatives	Famciclovir	Famvir® 3 x 2 tablets at 250 mg
Prophylaxis		Not recommended

Literature

Barnabas RV, Baeten JM, Lingappa JR. Acyclovir Prophylaxis Reduces the Incidence of Herpes Zoster Among HIV Individuals. JID 2016;213:551-5.

Brown M, Scarborough M, Brink N, et al. Varicella zoster virus-associated neurological disease in HIV-infected patients. Int J STD AIDS 2001, 12:79-83.

Garnock-Jones KP, Keating GM. Lidocaine 5% medicated plaster: a review of its use in postherpetic neuralgia. Drugs 2009, 69:2149-65.

Li Q, Chen N, Yang J, et al. Antiviral treatment for preventing postherpetic neuralgia. Cochrane Database Syst Rev 2009, 2: CD006866.

Martinez E, Gatell J, Moran Y, et al. High incidence of herpes zoster in patients with AIDS soon after therapy with PIs. CID 1998, 27:1510-3.

McDonald EM, de Kock J, Ram FS. Antivirals for management of herpes zoster including ophthalmicus: a systematic review of high-quality randomized controlled trials. Antivir Ther 2012, 17:255-64.

Moanna A, Rimland D. Decreasing incidence of herpes zoster in the highly active antiretroviral therapy era. Clin Infect Dis 2013, 57:122-5.

Saint-Leger E, Caumes E, Breton G, et al. Clinical and virologic characterization of acyclovir-resistant varicella-zoster viruses isolated from 11 patients with AIDS. Clin Infect Dis 2001, 33:2061-7.

Short MD, Fergus C. Which patients should receive the herpes zoster vaccine? JAAPA 2019, 32:18-20.

Zou J, Krentz HB, Lang R, et al. Seropositivity, Risks, and Morbidity From Varicella-Zoster Virus Infections in an Adult PWH Cohort From 2000-2020. Open Forum Infect Dis 2022, 9(8):ofac395.

Progressive multifocal leukoencephalopathy

PML is a severe demyelinating disease of the central nervous system. It is caused by the JC virus (JCV), a simply constructed polyomavirus distributed worldwide. JCV was named after the initials of the patient John Cunningham, from whom it was first isolated in 1971 (Major 1992). Thus, JC has nothing to do with Jakob-Creutzfeldt syndrome, as is often erroneously assumed. Given worldwide seroprevalence rates of up to 80%, latent persistent infection with a normally apathogenic JCV archetype is assumed. Kidney and bone appear to be important reservoirs. Only when the cellular immune response is impaired, reactivation reactivation or transformation of the archetype into the JCV that ultimately triggers PML occur. The difference between archetype and PML-JCV lies in the non-coding regulatory region of the viral DNA. Since this region looks different in each PML case, it is assumed that the pathogenic JCV strains are not transmitted but evolve in the respective host – over the years – from the apathogenic variants (Pavlovic 2015).

It seems inevitable that JCV enters the CNS via leukocytes and primarily affects oligodendrocytes and, thus, the myelin sheath cells. Their destruction is macroscopically manifested as multifocal demyelination. The white matter of the cerebral hemispheres is predominantly affected, but also the cerebellum and partly the gray matter. PML is a classic opportunistic infection. It can occur in hematologic diseases and during therapy with monoclonal antibodies such as rituximab, efalizumab, and especially natalizumab (Misbah 2017). However, people living with HIV are still the most commonly affected.

Severe immunodeficiency is common but not obligatory – CD4 T-cells are below 100/µl at manifestation in about 75% but above 200 CD4 T-cells/µl in 5–10% (Gasnault 2008). The decline in incidence is not as steep as for other OIs; it is about one-third from the pre-ART era (Engsing 2009). After cerebral toxoplasmosis, PML is the second most common neurological OI in HIV (Antinori 2001).

The prognosis used to be very poor without ART – the time from first symptoms to death was between 3 and 6 months. In most cases, the patients died of secondary complications after being bedridden for weeks. Under ART, slower courses and even complete remissions are possible (Albrecht 1998). In 1,427 PML patients in France, one-year survival increased from 20% before 1996 to 54% in 1996–2004 (Gasnault 2008). However, relatively lower rates have been reported in Spain or Denmark (Falco 2008, Engsing 2009). Complete remissions are most likely to be observed in inflammatory PML in the setting of IRIS (Du Pasquier 2003, Hoffmann 2003, Tan 2009). The level of CD4 T-cells and the strength of the JCV-specific immune response are of prognostic relevance; in contrast, the level of JCV viral load does not play a role (Khanna 2009, Marzocchetti 2009). PML remains the OI with the highest mortality today (ART-CC 2009).

Clinic

The clinic offers a broad spectrum due to the differently localized demyelinating foci, but it still shows some characteristics. For example, in addition to cognitive disorders ranging from mild concentration disorders to dementia, focal neurological deficits are typical. Most common are mono- or hemiparesis, language deficits, and visual deficits – we have seen several cases of blindness. The deficits may begin as discrete coordination deficits and rapidly progress to significant disability. Epileptic seizures are possible. Sensory disturbances, fever, and headache are rare and are more suggestive of cerebral toxoplasmosis.

Diagnostics

If there is a clinical suspicion of PML, this should be objectified quickly. CCT shows the (hypodense) lesions only inadequately. MRI is much more sensitive in terms of both number and size of lesions. It reveals mostly signal-intense foci in T2 weighting and in the FLAIR sequence, which are hypointense in T1 weighting and usually remain without gadolinium enhancement or mass effect. However, inflammatory courses with sometimes marked enhancement are possible under ART (see *immune reconstitution syndrome*). Typically, the gray matter is spared – this is, after all, a "leuko"-encephalopathy. The lesions are almost always asymmetric.
Differentiation from cerebral toxoplasmosis or lymphoma is usually possible with MRI. The vast, planar lesions over an entire hemisphere often seen in textbooks are not obligate. All PML starts small – discrete, localized, solitary lesions do not preclude the diagnosis. PML can be localized anywhere in the brain without predilection sites. Foci are often parieto-occipital or periventricular, but the cerebellum may also be affected. Differentiation from HHV-6 infection (Caserta 2004) or HIV-related leukoencephalopathy (Langford 2002) is challenging.
Therefore, the clinical radiological diagnosis is not conclusive. An examination of the cerebrospinal fluid is essential. Here, the nonspecific signs of inflammation are usually absent, provided no coinfections exist. However, the total protein is usually slightly elevated. Conversely, pleocytosis is rarely present, and more than 100/3 of cells tend to argue against PML. CSF should be tested for JCV or sent to a laboratory experienced in JCV. Newer PCR techniques have a sensitivity of about 80% with a specificity of well over 90%.
The diagnosis is very likely in case of clinical radiological suspicion and positive JCV-PCR. A brain biopsy is then unnecessary. However, a negative PCR does not exclude PML with certainty. The level of JCV viral load varies widely and does not correlate with the extent of lesions (Eggers 1999, Garcia 2002, Bossolasco 2005). Many people with PML have low or undetectable JCV viral load in CSF on ART (Bossollasco 2005). Here, stereotactic brain biopsy may still be necessary in individual cases. A sophisticated diagnostic algorithm has been published (Berger 2013).

Treatment

To date, there is no effective therapy. Foscarnet, interferon, immunostimulators, steroids, and chemotherapies with camptothecin/topotecan or cytosine arabinoside (Hall 1998) are ineffective. Even the nucleotide analog cidofovir, approved for CMV retinitis and initially attributed positive effects, showed no clinical benefit in a meta-analysis of 370 patients (De Luca 2008).
The serotonergic receptor 5HT2AR is a receptor for JC viruses to infect human glial cells (Elphick 2004); thus, the blockade could be a therapeutic target. Case studies exist for neuroleptics such as risperidone and mirtazapine that block serotonergic receptors (Verma 2007, Focosi 2008, Cettomai 2009). Controlled studies are lacking. Mefloquine, which was already held in hope after *in vitro* data (Brickelmeier 2009) and positive case reports, failed to provide any evidence of an effect in a randomized trial (Clifford 2013). Another approach is pembrolizumab, which showed some effect as a checkpoint inhibitor in a small uncontrolled case series (Cortese 2019). Most case reports are published in HIV-negative cases (review: Corey 2022).
However, many experts are currently rather pessimistic about effective PML therapies in the coming years (Pavovic 2015, Du Pasquir 2019), not only because of the lack of animal models, the rarity of the disease, and the rapid progression of primarily comorbid patients, which usually make controlled trials impossible – it also remains

questionable whether systemic therapies will be able to reach concentrations to stop the extraordinarily high replication of JCV in the brain which is seen in patients with PML.

It remains an absolute priority to optimize ART in every PML. Restoration of the JCV-specific immune response is a crucial determinant of outcome (Khanna 2009, Marzocchetti 2009, Gasnault 2011). Numerous research groups have confirmed our early observation (Albrecht 1998) that prognosis improves significantly with ART) (Clifford 1999, Berenguer 2003, Khanna 2009, Gasnault 2011). In view of an in vitro demonstrated synergism of HIV and JCV, HIV should be maximally suppressed. While progressive courses are also possible, ART remains the only hope. The common opinion is that primarily antiretrovirals should be used that can penetrate CNS (see chapter *Neurology*). This has not been proven, nor has the use of intensive ART regimens (Gasnault 2011).

Therapy/prophylaxis of PML

Acute therapy	
ART	The main goal is maximum HIV suppression and immune reconstitution! Integrate substances that penetrate CNS if possible
Experimental	Nothing to recommend outside of trials, possibly risperidone, mirtazapine, possibly pembrolizumab as a clinical cure trial?
Prophylaxis	Not available. Exposure prophylaxis is also not available

Literature

Albrecht H, Hoffmann C, Degen O, et al. HAART significantly improves the prognosis of patients with HIV-associated progressive multifocal leukoencephalopathy. AIDS 1998, 12:1149-1154.

Antinori A, Ammassari A, Giancola ML, et al. Epidemiology and prognosis of AIDS-associated progressive multifocal leukoencephalopathy in the HAART era. J Neurovirol 2001, 7:323-8.

Antiretroviral Therapy Cohort Collaboration (ART-CC). Variable impact on mortality of AIDS-defining events diagnosed during combination antiretroviral therapy: not all AIDS-defining conditions are created equal. Clin Infect Dis 2009, 48:1138-51.

Berenguer J, Miralles P, Arrizabalaga J, et al. Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy. Clin Infect Dis 2003, 36: 1047-52.

Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. Neurology 2013, 80:1430-8.

Berger JR, Levy RM, Flomenhoft D, et al. Predictive factors for prolonged survival in AIDS-associated progressive multifocal leukoencephalopathy. Ann Neurol 1998, 44:341-9.

Bossolasco S, Calori G, Moretti F, et al. Prognostic significance of JC virus DNA levels in cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy. Clin Infect Dis 2005, 40:738-44.

Brickelmaier M, Lugovskoy A, Kartikeyan R, et al. Identification and characterization of mefloquine efficacy against JC virus in vitro. Antimicrob Agents Chemother 2009, 53:1840-9.

Caserta MT. Human Herpesvirus 6 Infection of the Central Nervous System. Curr Infect Dis Rep 2004, 6: 316-321.

Cettomai D, McArthur JC. Mirtazapine use in human immunodeficiency virus-infected patients with progressive multifocal leukoencephalopathy. Arch Neurol 2009, 66:255-8.

Clifford DB, Nath A, Cinque P, et al. A study of mefloquine treatment for progressive multifocal leukoencephalopathy: results and exploration of predictors of PML outcomes. J Neurovirol 2013 [Epub ahead of print].

Clifford DB, Yiannoutsos C, Glicksman M, et al. HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. Neurology 1999, 52:623-5.

Corey S, Smith BR, Cortese ICM. Promise and Challenges of Checkpoint Inhibitor Therapy for Progressive Multifocal Leukoencephalopathy in HIV. Curr HIV/AIDS Rep 2022 Oct 1.

Cortese I, Muranski P, Enose-Akahata Y, et al. Pembrolizumab Treatment for Progressive Multifocal Leukoencephalopathy. NEJM 2019, 380:1597-1605.

De Luca A, Ammassari A, Pezzotti P, et al. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. AIDS 2008, 22:1759-67.

Du Pasquier RA, Koralnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? J Neurovirol 2003; 9 Suppl 1:25-31.

Du Pasquier RA. Pembrolizumab as a treatment for PML? Waiting for Godot. Neurol Neuroimmunol Neuroinflamm 2019, 6:e629.

Eggers C, Stellbrink HJ, Buhk T, Dorries K. Quantification of JC virus DNA in the cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy – a longitudinal study. J Infect Dis 1999, 180:1690-4.

Elphick GF, Querbes W, Jordan JA, et al. The human polyomavirus, JCV, uses serotonin receptors to infect cells. Science 2004;306:1380-3.

Engsig FN, Hansen AB, Omland LH, et al. Incidence, clinical presentation, and outcome of progressive multifocal leukoencephalopathy in HIV-infected patients during the highly active antiretroviral therapy era: a nationwide cohort study. J Infect Dis 2009, 199:77-83.

Falcó V, Olmo M, del Saz SV, et al. Influence of HAART on the clinical course of HIV-1-infected patients with progressive multifocal leukoencephalopathy: results of an observational multicenter study. J AIDS 2008, 49:26-31.

Focosi D, Kast RE, Maggi F, et al. 5-HT2a inhibitors for progressive multifocal leukoencephalopathy: old drugs for an old disease. J Infect Dis 2008, 197:328.

Garcia De Viedma D, Diaz Infantes M, Miralles P, et al. JC virus load in progressive multifocal leukoencephalopathy: analysis of the correlation between the viral burden in cerebrospinal fluid, patient survival, and the volume of neurological lesions. Clin Infect Dis 2002, 34:1568-75.

Gasnault J, Costagliola D, Hendel-Chavez H, et al. Improved survival of HIV-1-infected patients with progressive multifocal leukoencephalopathy receiving early 5-drug combination antiretroviral therapy. PLoS One 2011, 6:e20967.

Hall CD, Dafni U, Simpson D, et al. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with HIV infection. N Engl J Med 1998, 338:1345-51.

Hoffmann C, Horst HA, Albrecht H, Schlote W. Progressive multifocal leucoencephalopathy with unusual inflammatory response during antiretroviral treatment. J Neurol Neurosurg Psychiatry 2003;74:1142-4.

Khanna N, Elzi L, Mueller NJ, et al. Incidence and outcome of progressive multifocal leukoencephalopathy over 20 years of the Swiss HIV Cohort Study. Clin Infect Dis 2009, 48:1459-66.

Khanna N, Wolbers M, Mueller NJ, et al. JC virus-specific immune responses in human immunodeficiency virus type 1 patients with progressive multifocal leukoencephalopathy. J Virol 2009, 83:4404-11.

Langford TD, Letendre SL, Marcotte TD, et al. Severe, demyelinating leukoencephalopathy in AIDS patients on antiretroviral therapy. AIDS 2002, 16:1019-29.

Major EO, Amemiya K, Tornatore CS, Houff SA, Berger JR. Pathogenesis and molecular biology of progressive multifocal leukoencephalopathy, the JC virus-induced demyelinating disease of the human brain. Clin Microbiol Rev 1992, 5:49-73.

Marzocchetti A, Tompkins T, Clifford DB, et al. Determinants of survival in progressive multifocal leukoencephalopathy. Neurology 2009, 73:1551-8.

Misbah SA. Progressive multi-focal leucoencephalopathy – driven from rarity to clinical mainstream by iatrogenic immunodeficiency. Clin Exp Immunol 2017, 188:342-352.

Pavlovic D, Patera AC, Nyberg F, et al. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. Ther Adv Neurol Disord 2015, 8: 255–273.

Tan K, Roda R, Ostrow L, McArthur J, Nath A. PML-IRIS in patients with HIV infection. Clinical manifestations and treatment with steroids. Neurology 2009 Jan 7. [Epub ahead of print].

Verma S, Cikurel K, Koralnik IJ, et al. Mirtazapine in progressive multifocal leukoencephalopathy associated with polycythemia vera. J Infect Dis 2007;196:709-11.

Bacterial pneumonia

Bacterial pneumonia occur even with relatively good immune status (above 200 CD4 T-cells/µl); the association with immunodeficiency is not compelling, and the decline in incidence is more moderate with ART than with other OIs. AIDS-defining conditions are exclusively repeated, radiologically (and) culturally proven acute pneumonia (more than one in the past 12 months). A distinction should be made between community-acquired and nosocomial-acquired pneumonias. For the former, a detailed history (travel? animal contacts?) should be obtained. Nosocomial pneumonias are often caused by hospital germs (Klebsiellae, Staphylococcus or Pseudomonas) (Franzetti 2006). Therapy should be adapted to the local resistance situation and experience (Gant 2000, Vogel 2000).
The local pathogen spectrum of community-acquired pneumonia does not differ significantly from that of uninfected people. The most common pathogens are pneumococci and *hemophilus influenza,* also in PLWH. In younger people, mycoplasma plays a role. Klebsiellae, *Staphylococcus aureus,* and *Pseudomonas aeroginosa* should be noted; legionella is rare. Intravenous drug users are at higher risk. Nicotine abuse, alcohol abuse, and pre-existing pulmonary disease are other risk factors (Grau 2006, De 2013); in the SMART study, treatment breaks and nicotine abuse were risk factors (Gordin 2008). Nicotine abstinence significantly reduces the risk (Bénard 2010). Low CD4 T-cells and liver cirrhosis are risk factors for severe courses (Manno 2009, Madeddu 2010).

Clinic/Diagnostics

Acute, usually high fever and cough with sputum are typical. Breathing is painful due to the accompanying pleurisy, whereas pronounced dyspnea is rare. Auscultation of the infiltrates almost always differentiates it from PCP. If you hear something, it is not PCP! The chest x-ray confirms the diagnosis. CRP is clearly elevated, LDH is usually normal. Blood cultures should be taken several times before starting therapy and at temperatures above 38.5 degrees. The main problems with blood culture are the duration of diagnosis (24–48 hours) and relatively low sensitivity. However, culture is the only method that allows resistance testing. Using a sputum sample, the etiology can be determined in about half of the cases, but its usefulness is controversial (Cordero 2002). This also applies to pneumococcal antigen detection in urine and diagnostics for other specific pathogens. S3 guidelines recommend baseline pathogen diagnostics with at least two blood culture pairs, a urine antigen test for Legionella, and sputum examination in all patients hospitalized for moderate to severe pneumonia. If processing within 2–4 hours for Gram stain and culture is not possible, sputum examination is dispensable (Ewig 2016).

Treatment

In principle, the treatment of bacterial pneumonia is similar to that of HIV-negative cases. Therapy should be started empirically and quickly; sputum and blood cultures should not be awaited. Cases with poor immune status below 200 CD4 T-cells/µl should be hospitalized (Madeddu 2010). This also applies in cases of high fever (above 39.5 degrees), poor compliance, signs of organ failure, CNS disturbances (confusion), or disturbances of vital signs (tachypnea, tachycardia, hypotension), and older age (above 65 years). The guidelines also use a simplified CRB-65 score (C = Confusion, R = Respiratory rate > 30/min, B = Blood pressure: Systolic/diastolic below 90/60 mmHg, 65 = Patient is at least 65 years old). This ranges from 0 (no factor) to

4 (all positive), and admission is recommended at a score of 1. In more recent guidelines, age is no longer a criterion; only respiratory rate, blood pressure, O_2 saturation (92% as a limit), and consciousness are factors to be taken into account.
Adequate hydration should always be ensured. Supportive therapies with mucolytics such as N-acetylcysteine or antitussives are controversial. With sufficient antibiotic therapy, improvement can be expected within 48–72 hours. With clinical response, 5–7 days is usually sufficient. The "use up the pack" paradigm is gone; the new paradigm is "as short as possible." If fever persists, especially in cases of significant immunodeficiency, reconsider therapy after 72 hours at the latest. It should be noted that the current first-line therapies are not effective against *Pseudomonas aeruginosa*.

Medication

The guidelines distinguish between mild (CRB-65= 0, O_2 saturation > 90%), moderate (1–2), and severe pneumonia (3–4, acute respiratory failure and/or severe sepsis), each of which requires different therapies (Ewig 2016). The pathogen spectrum is largely identical for moderate and severe pneumonia – the combinations for severe pneumonia (intensive care unit!) are primarily aimed at reducing possible gaps in efficacy.
For mild pneumonia, aminopenicillin is considered the first choice. Some practitioners favor those with beta-lactamase inhibitors (BLIs), such as clavulanic acid, which expands the spectrum of activity to include BL-forming *S. aureus*, *H. influenza*e, and enterobacteria. Quinolones are considered an alternative in penicillin allergy cases, but the indication has been significantly limited due to (rare) skin and liver reactions. Oral cephalosporins are no longer recommended (underdosed), as is roxithromycin.
Macrolides such as azithromycin or clarithromycin may be considered in mild cases but only in patients without co-morbidities – whether HIV infection qualifies as one (the guidelines do not list it separately, unlike heart failure, CNS disease, or COPD) remains unclear and should be decided on a case-by-case basis. Macrolides have

Empirical treatment of community-acquired bacterial pneumonia (daily doses, selection)

Outpatient (mild)		Duration: 5 days
First choice	Amoxicillin + Clavulanic acid	Augmentan® 3 x 1 tab. at 875/125 mg
Alternative	Clarithromycin	Klacid PRO® 2 x 1 tab. of 500 mg
Alternative	Azithromycin	Azithromycin® 1 x 1 tab. at 500 mg
Alternative	Moxifloxacin	Avalox® 1 x 1 tab. of 400 mg
Hospitalized		
Intermediate Severe	Amoxicillin + clavulanic acid plus macrolide 3 days	Augmentan® 3 x 1 infusion vials at 2.2 g **plus** azithromycin® 1 x 1 tab. of 500 mg **or** Klacid PRO® 2 x 1 tab. at 500 mg
Intermediate Severe	Ceftriaxone plus macrolide 3 days	Rocephin® 1 x 1 infusion vials of 2 g IV **plus** azithromycin® 1 x 1 tab. at 500 mg **or** Klacid PRO® 2 x 1 tab. of 500 mg
Severe	Piperacillin + Tazobactam + macrolide 3 days	Tazobac® 3 x 1 infusion vials of 4.5 g IV **plus** azithromycin® 1 x 1 tab. at 500 mg **or** Klacid PRO® 2 x 1 tab. of 500 mg
Prophylaxis	Vaccination (pneumococcal polysaccharide)	Sequential: first Prevenar13® and after 6 months with Pneumovax 23® IM

advantages for atypical pathogens such as mycoplasma, chlamydia, and Legionella. However, macrolide-resistant pneumococci are increasing in Europe (Germany: approximately 14%). There are gaps in effectiveness with hemophilus strains.
Moderate and severe pneumonia should be treated as an inpatient and intravenously. The combination with macrolides is recommended in principle, although the data is insufficient.

Prophylaxis

Pneumovax® vaccination is recommended above 200 CD4 T-cells/µl but is probably protective below that level (Penaranda 2007). The 13-valent conjugate vaccine Prevenar 13® is said to have better immunogenicity but has a narrower spectrum. Many guidelines recommend a sequence of first Prevenar13® and, after 6 months, Pneumovax® (see *Vaccinations*).

Literature

Barakat LA, Juthani-Mehta M, Allore H, et al. Comparing clinical outcomes in HIV-infected and uninfected older men hospitalized with community-acquired pneumonia. HIV Med 2015;16:421-30.

Bénard A, Mercié P, Alioum A, et al. Bacterial Pneumonia among HIV-infected patients: decreased risk after tobacco smoking cessation. ANRS CO3 Aquitaine Cohort, 2000-2007. PLoS One 2010, 5:e8896.

Cordero E, Pachon J, Rivero A, et al. Usefulness of sputum culture for diagnosis of bacterial pneumonia in HIV-infected patients. Eur J Clin Microbiol Infect Dis 2002, 21:362-7.

De P, Farley A, Lindson N, Aveyard P. Systematic review and meta-analysis: influence of smoking cessation on incidence of pneumonia in HIV. BMC Med 2013, 11:15.

Ewig S, Höffgen G, Kern WK et al. Behandlung von erwachsenen Patienten mit ambulant erworbener Pneumonie und Prävention – Update 2016. Pneumologie 2016; 70: 151-200.

Franzetti F, Grassini A, Piazza M, et al. Nosocomial bacterial pneumonia in HIV-infected patients: risk factors for adverse outcome and implications for rational empiric antibiotic therapy. Infection 2006;34:9-16.

Gant V, Parton S. Community-acquired pneumonia. Curr Opin Pulm Med 2000, 6:226-33.

Gordin FM, Roediger MP, Girard PM, et al. Pneumonia in HIV-infected persons: increased risk with cigarette smoking and treatment interruption. Am J Respir Crit Care Med 2008, 178:630-6.

Grau I, Pallares R, Tubau F, et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. Arch Intern Med 2005;165:1533-40.

Madeddu G, Fiori ML, Mura MS. Bacterial community-acquired pneumonia in HIV-infected patients. Curr Opin Pulm Med 2010 Feb 11.

Manno D, Puoti M, Signorini L, et al. Risk factors and clinical characteristics associated with hospitalization for community-acquired bacterial pneumonia in HIV-positive patients according to the presence of liver cirrhosis. Infection 2009, 37:334-9.

Penaranda M, Falco V, Payeras A, et al. Effectiveness of polysaccharide pneumococcal vaccine in HIV-infected patients: a case-control study. Clin Infect Dis 2007;45.

Rimland D, Navin TR, Lennox JL, et al. Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. AIDS 2002, 16:85-95.

Vogel F, Worth H, Adam D, et al. Rationale Therapie bakterieller Atemwegsinfektionen. Empfehlungen einer Expertengruppe der Paul-Ehrlich-Gesellschaft für Chemotherapie e.v. und der Deutschen Atemwegsliga. Chemotherapie Journal 2000, 1:3-23.

Cryptosporidiosis

Cryptosporidiosis is a parasitic, fecal-orally transmitted intestinal disease. *Cryptosporidium parvum* and *hominis* are the most relevant among the numerous species of these intracellular protozoa. Both immunocompetent and immunocompromised individuals may be affected (review: Checkley 2015). Since their first description in 1976, cryptosporidia have been among the most important diarrheal pathogens worldwide; in children, they are considered the second most important causative agent of severe diarrhea after rotaviruses. The primary sources of infection are animals, contaminated water, and food. The incubation period is about 10 days. While diarrhea in PLWH with more than 200 CD4 T-cells/µl usually disappears after a few days, cryptosporidiosis can become chronic, with massive water and electrolyte losses in cases of immunodeficiency below 50/µl (Colord 1996). The chronic – not acute – disease is AIDS-defining.

Clinic

The watery diarrhea can be so severe that it leads to death via electrolyte loss and dehydration. Twenty defecations per day are not uncommon. Tenesmus usually persists, often causing nausea and vomiting. However, there is great variability in symptoms. Fever is usually absent. Occasionally, there is bile duct involvement with elevated bile enzymes. Pancreatitis is also possible.

Diagnostics

The laboratory must be explicitly informed of the suspicion when the stool samples are sent. Otherwise, cryptosporidia are usually overlooked. If the laboratory has experience, a stool sample is usually sufficient for detection by immunofluorescence microscopy. Antibodies or other diagnostic methods are of no help. Differentially, all diarrheal germs can be considered.

Therapy

With good immune status, diarrhea is self-limiting; ART often leads to a cure if poor immune status is improved (Carr 1998, Miao 2000). In addition, loperamide and/or Tinctura opii simplex (opium) should be given. If this is unsuccessful, other diarrheal agents, possibly including Sandostatin®, should be tried. Care should be taken to ensure good hydration – infusions are occasionally necessary.
All specific therapies are suboptimal (review: Diptyanusa 2021). We have had some good experiences with nitazoxanide (Alinia®, Cryptaz). This anthelmintic was effective in a small randomized trial (Rossignol 2001). Nitazoxanide was approved in the United States in 2005 for cryptosporidium-associated diarrhea in immunocompetent individuals; it can be imported. There is no approval for AIDS patients, and it was without effect in HIV-positive children with cryptosporidia in a double-blind randomized trial (Amadi 2009). Rifaximin (Xifaxan®) is a non-absorbable rifampicin derivative approved as a diarrheal agent in the United States. There are case reports of people with AIDS (Gathe 2008).
Paromomycin (Humatin®), a non-absorbable aminoglycoside antibiotic, had a beneficial effect on diarrhea in small, uncontrolled studies (White 2001). However, in a double-blind randomized trial, there was no advantage over placebo (Hewitt 2000). There may, however, be some effect in combination with azithromycin (Smith 1998).

Therapy/prophylaxis of cryptosporidiosis (daily doses)

Acute therapy		
Symptomatic	Loperamide + Opium tincture	Imodium® 2–6 x 1 cap. at 2 mg **or** Imodium solution® 2–6 x 10 mL **and/or** Tinctura opii simplex 1% = 4 x 5–15 drops
Symptomatic	Octreotide	Sandostatin Injection Solution® 2–3 x 1 Amp à 50 µg SC (increase dose only slowly)
Experimental	Nitazoxanide	Cryptaz™ 2 x 1 tab. at 500 mg
Experimental	Rifaximin	Xifaxan™ 2 x 2 tab. of 200 mg
Experimental	Paromomycin + azithromycin	Humatin Pulvis® 3 x 1 tab. at 1 g **plus** Ultreon® 1 x 1 tab. of 600 mg
Prophylaxis		Exposure prophylaxis: Do not drink tap water

Prophylaxis

There is no recognized prophylaxis, although rifabutin and clarithromycin were protective in retrospective studies (Holmberg 1998). It is more important not to drink tap water in countries with hygiene problems. Contact with human and animal feces should be avoided. Cryptosporidia are resistant to most disinfectants. However, standard hygiene measures (gloves) are sufficient in the hospital. Patients do not need to be isolated, but it is better not to place them with immunocompromised persons.

Literature

Amadi B, Mwiya M, Musuku J, et al. Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial. Lancet 2002, 360:1375-1380.

Amadi B, Mwiya M, Sianongo S, et al. High dose prolonged nitazoxanide treatment is ineffective for cryptosporidiosis in HIV positive Zambian children: a randomised controlled trial. BMC Infect Dis 2009, 9:195.

Carr A, Marriott D, Field A, Vasak E, Cooper DA. Treatment of HIV-1 associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. Lancet 1998, 351:256-61.

Checkley W, White AC Jr, Jaganath D, et al. A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for cryptosporidium. Lancet Infect Dis 2015, 15:85-94.

Colford JM Jr, Tager IB, Hirozawa AM, et al. Cryptosporidiosis among patients infected with HIV. Factors related to symptomatic infection and survival. Am J Epidemiol 1996, 144:807-16.

Diptyanusa A, Puspa Sari I. Treatment of human intestinal cryptosporidiosis: A review of published clinical trials. Int J Parasitol Drugs Drug Resist 2021, 17:128-138.

Gathe JC Jr, Mayberry C, Clemmons J, Nemecek J. Resolution of severe cryptosporidial diarrhea with rifaximin in patients with AIDS. J AIDS 2008, 48:363-4.

Griffiths JK. Treatment for AIDS-associated cryptosporidiosis. J Infect Dis 1998, 178:915-6.

Hewitt RG, Yiannoutsos CT, Higgs ES, et al. Paromomycin: No more effective than placebo for treatment of cryptosporidiosis in patients with advanced HIV infection. Clin Inf Dis 2000, 31:1084-92.

Holmberg SD, Moorman AC, Von Bargen JC, et al. Possible effectiveness of clarithromycin and rifabutin for cryptosporidiosis chemoprophylaxis in HIV disease. JAMA 1998, 279:384-6.

Miao YM, Awad-El-Kariem FM, Franzen C, et al. Eradication of cryptosporidia and microsporidia following successful antiretroviral therapy. J Acquir Immune Defic Syndr 2000, 25: 124-9.

Rossignol JF, Ayoub A, Ayers MS. Treatment of diarrhea caused by Cryptosporidium parvum: a prospective randomized, double-blind, placebo-controlled study of Nitazoxanide. J Infect Dis 2001, 184:103-6.

Smith NH, Cron S, Valdez LM, Chappell CL, White AC Jr. Combination drug therapy for cryptosporidiosis in AIDS. J Infect Dis 1998, 178:900-3.

White AC, Cron SG, Chappell CL. Paromomycin in cryptosporidiosis. Clin Inf Dis 2001, 32:1516-7.

Cryptococcosis

Infections caused by the yeast *Cryptococcus neoformans* are rare in Europe. They are more common in the US, Africa, and Southeast Asia and are among the most important AIDS-defining diseases worldwide (review: Rajasingham 2017). *C. neoformans* is likely transmitted by inhalation. Bird droppings are an important reservoir of pathogens. Pulmonary infection is occasionally not apparent in immunocompetent individuals; in HIV, it is usually the onset of disseminated disease. The CNS is the leading site of manifestation besides the lungs after hematogenous dissemination. However, isolated skin manifestations and lymphadenitis also occur, and more rarely, osseous or urogenital involvement.
Cryptococcosis almost always occurs in the presence of massive immunodeficiency. Of 114 patients in Germany, 87% had fewer than 100 CD4 T-cells/µl, with a median of 30/µl (Weitzel 1999). Cryptococcosis is also relatively commonly seen in the setting of IRIS. If left untreated, it is fatal – causing approximately 15% of all AIDS deaths worldwide (Rajasingham 2017). Treatment is complicated, lengthy, and recommended only as an inpatient. Recurrences used to be common (at least 15%) but are now less frequent due to ART.

Clinic

The *CNS manifestation* with an encephalitic picture is the most frequent (approx. 80%). Headache, fever, and increasing disturbances of consciousness (confusion) within a few days are typical. Sometimes, there are also gait, hearing or visual disturbances, and paresis, especially of the cranial nerves. The intracranial pressure is almost always elevated. Meningeal irritation symptoms are usually absent. In the setting of IRIS, the clinic is often atypical and characterized by abscesses (Manfredi 1999). In *pulmonary involvement,* there are symptoms of atypical pneumonia with nonproductive cough and chest pain. *Skin lesions* may initially resemble molluscs that later confluence into ulcerative lesions.

Diagnostics

Cryptococcosis is acutely life-threatening; there is no time to lose. In case of any suspicion (positive cryptococcal antigen!), lungs (HR-CT!) and CNS (MRI head!) should be examined quickly. The spectrum in HR-CT of the lung is varied: scattered, small foci, as in TB, are possible, as are sharply demarcated infiltrates reminiscent of bronchopneumonia. Cavernous formations, even bronchiectasis, occur. An attempt should be made to identify the causative agent by BAL. MRI of the head is often unremarkable, in contrast to toxoplasmosis and cerebral lymphoma, and single or multiple mass lesions ("cryptococcomas") are rare. Nevertheless, intracranial pressure is elevated at 50–70%. Fundoscopy (papilledema?) and MRI should be quickly followed by CSF puncture. It almost always brings the diagnosis with an ink preparation. Even in the case of pulmonary or other localization, the CSF must be examined to exclude CNS involvement. cryptococcal antigen in the blood (titer > 1:8) is a suitable parameter and should always be determined, especially if CD4 T-cells are low below 100/µl (Jarvis 2011). In asymptomatic individuals with positive antigen, meningitis is already present in one-third (Wake 2017), and they should be treated promptly. Blood cultures are also often positive. In cutaneous infestations, the diagnosis is usually made only by biopsy.

Treatment

In the case of CNS involvement, several antimycotics must be combined acutely. Fluconazole alone is not sufficient, even in high doses. In large randomized trials from Africa, mortality in the first few weeks was as high as 40–60% (Longley 2008, Makadzange 2009, Beardsley 2016). Combinations prevent resistance and allow induction therapy to be shortened to two weeks.

Historically, a triple combination of amphotericin B, flucytosine, and fluconazole has often been used for several weeks in cases of CNS infection; complete remission can be achieved in about 80% (Weitzel 1999). Liposomal amphotericin (Ambisome®) is probably somewhat more effective than conventional amphotericin B – apart from lower toxicity (Leenders 1997, Hamill 1999).

Recently, the results of the large AMBITION study were published (Jarvis 2022). In this study, a single dose of high-dose liposomal amphotericin (10 mg/kg) on day 1 plus 14 days of flucytosine (100 mg/kg per day) and fluconazole (1,200 mg per day) was compared with the standard therapy recommended by the WHO since 2018. This consisted of a combination of amphotericin-B (1 mg/kg per day) plus flucytosine (100 mg/kg) for 7 days, followed by fluconazole (1200 mg per day) for an additional 7 days. Clinically, the arm with the single dose Ambisome® was not inferior, and toxicity was even reduced, so this combination has already found its way into some guidelines (Ngan 2022).

Induction therapy is followed after to weeks by at least eight weeks of maintenance therapy with high-dose fluconazole (400–800 mg per day); for subsequent secondary prophylaxis for at least one year, the dose may be reduced to 200 mg.

When amphotericin B is unavailable, the combination of flucytosine and fluconazole is better than fluconazole alone (Nussbaum 2010). Fluconazole should be given as an infusion, especially in confused individuals. Therapy is also very toxic with Ambisome® -containing combinations. Daily monitoring of renal and liver enzymes, blood counts, and electrolytes is recommended during induction therapy. Other azoles (except voriconazole, studies ongoing) have poor liquid tolerance and should be avoided.

The optimal timing of ART is challenging, due to a high risk of IRIS. Several major African studies showed that IRIS incidence and mortality decrease when waiting at least four weeks (Makadzange 2010, Bisson 2013, Boulware 2014). Thus, starting cryptococcal therapy and ART at the same time should be avoided. ART should not contain TDF (renal failure) and substances with high interaction potential (no boosting agents).

In case of isolated pulmonary involvement (CSF negative!) or other extracerebral manifestations, we treat without flucytosine. A positive cryptococcal antigen test without a clinic would be treated with fluconazole only.

The success of therapy is monitored clinically and with repeated lumbar punctures. After two weeks, the CSF is usually negative (Saag 2000). If so, the patient can be switched to maintenance therapy. The sooner the CSF is negative, the better the prognosis (Bicanic 2009, Chang 2012). If intracranial pressure is elevated, therapeutic CSF punctures may be useful (Rolfes 2014), sometimes even CSF drainage (Graybill 2000), both of which are possible (Xu 2022). Steroids are harmful and should be avoided (Beardsley 2016).

Treatment/prophylaxis of cryptococcosis (if not otherwise specified, daily doses); for application, see *Drug* chapter. Wait at least 4 weeks before starting ART!

Acute therapy		Duration: Always at least two weeks
Therapy of choice	Amphotericin B	Amphotericin B® 1 x 0.5–0.75 mg/kg **or** AmBisome® 1 x 3 mg/kg (also consider single dose 1 x 10 mg/kg) **plus**
	+ Fluconazole	Diflucan® 3 x 1 inf. vial of 400 mg IV **or** Diflucan® or Fluconazole CT/Stada 3 x 2 cap. at 200 mg **plus**
	+ Flucytosine	Ancotil® 4 x 1 inf. vial of 250 mL (2.5 g) IV (= 100–150 mg/kg distributed over 4 individual doses)
Maintenance therapy		
Therapy of choice	Fluconazole	Diflucan® or Fluconazole CT/Stada 2 x 2 cap. of 200 mg for 8 weeks, then 1 x 1 cap. at 200 mg for one year, discontinue only after > 200 CD4 T-cells/µl > 6 months and negative cryptococcal antigen
Primary prophylaxis		Not recommended

Prophylaxis

Exposure is hardly preventable. Primary prophylaxis is not recommended because there was no survival benefit, even in endemic areas such as Thailand (McKinsey 1999, Chariyalertsak 2002). In a study from Uganda of 1,519 PLWH with negative cryptococcal antigen and less than 200 CD4 T-cells, of 19 episodes, 18 occurred with placebo, and only one with fluconazole, but overall survival was not improved (Parkes-Ratanshi 2011).

Secondary prophylaxis or maintenance therapy consists of fluconazole, which is significantly more effective than itraconazole (Saag 1999). Fluconazole can be discontinued upon immune reconstitution (> 100 CD4 T-cells, viral load three months below the limit of detection) and after at least six months of maintenance therapy (Aberg 2002, Kirk 2002, Vibhagool 2003, Mussini 2004). Before this, the cryptococcal antigen should be checked (Mussini 2004). If the antigen is positive, which is associated with an increased risk of recurrence, especially with high titers (Lortholary 2006), it is better to continue therapy.

Literature

Bicanic T, Wood R, Meintjes G, Rebe K, Brouwer A, Loyse A, Bekker LG, Jaffar S, Harrison T. High-dose amphotericin B with flucytosine for the treatment of cryptococcal meningitis in HIV-infected patients: a randomized trial. Clin Infect Dis. 2008 Jul 1;47(1):123-30. doi: 10.1086/588792. PMID: 18505387.

Aberg JA, Price RW, Heeren DM, Bredt B. A pilot study of discontinuing antifungal therapy for disseminated cryptococcal disease in patients with AIDS, following immunologic response to ART. J Infect Dis 2002, 185:1179-82.

Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis. N Engl J MedEJM 2016;374:542-54.

Bicanic T, Muzoora C, Brouwer AE, et al. Independent association between rate of clearance of infection and clinical outcome of HIV-associated cryptococcal meningitis: analysis of a combined cohort of 262 patients. Clin Infect Dis 2009, 49:702-9.

Bisson GP, Molefi M, Bellamy S, et al. Early Versus Delayed Antiretroviral Therapy and Cerebrospinal Fluid Fungal Clearance in Adults With HIV and Cryptococcal Meningitis. Clin Infect Dis 2013, 56:1165-73.

Boulware DR, Meya DB, Muzoora C, COAT Trial Team. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. N Engl J Med 2014, 370:2487-98.

Chang C, Dorasamy A, Elliot J, et al. HIV+ Patients with CM Who Attain CSF Sterility Pre-cART Commencement Experience Improved Outcomes in the First 24 Weeks. Abstract 955, 19th CROI 2012, Seattle.

Chariyalertsak S, Supparatpinyo K, Sirisanthana T, et al. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced HIV infection in Thailand. Clin Infect Dis 2002, 34:277-84.

Graybill JR, Sobel J, Saag M, et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. Clin Infect Dis 2000;30:47-54.

Hamill RJ, Sobel J, El-Sadr W, et al. Randomized double blind trial of Ambisome and amphotericin B in acute cryptococcal meningitis in AIDS patients. 39th ICAAC 1999, San Francisco; Abstract 1161.

Jarvis JN, Lawrence DS, Meya DB, et al. Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis. N Engl J Med 2022, 386:1109-1120.

Jarvis JN, Percival A, Bauman S, et al. Evaluation of a novel point-of-care cryptococcal antigen test on serum, plasma, and urine from patients with HIV-associated cryptococcal meningitis. Clin Infect Dis 2011, 53:1019-23.

Kirk O, Reiss P, Uberti-Foppa C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. Ann Intern Med 2002, 137:239-50.

Leenders AC, Reiss P, Portegies P, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. AIDS 1997, 11:1463-71.

Longley N, Muzoora C, Taseera K, et al. Dose response effect of high-dose fluconazole for HIV-associated cryptococcal meningitis in southwestern Uganda. Clin Infect Dis 2008, 47:1556-61.

Lortholary O, Poizat G, Zeller V, et al. Long-term outcome of AIDS-associated cryptococcosis in the era of combination antiretroviral therapy. AIDS 2006, 20:2183-91.

Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. Clin Infect Dis 2010, 50:1532-8.

Manfredi R, Pieri F, Pileri SA, Chiodo F. The changing face of AIDS-related opportunism: cryptococcosis in the HAART era. Case reports and literature review. Mycopathologia 1999, 148:73-8.

McKinsey DS, Wheat LJ, Cloud GA, Itraconazole prophylaxis for fungal infections in patients with advanced HIV infection: randomized, placebo-controlled, double-blind study. Clin Infect Dis 1999, 28:1049-56.

Mussini C, Pezzotti P, Miro JM, et al. Discontinuation of maintenance therapy for cryptococcal meningitis in patients with AIDS treated with HAART: an international observational study. Clin Infect Dis 2004, 38:565-71.

Ngan NTT, Flower B, Day JN. Treatment of Cryptococcal Meningitis: How Have We Got Here and Where are We Going? Drugs 2022, 82:1237-1249.

Nussbaum JC, Jackson A, Namarika D, et al. Combination flucytosine and high-dose fluconazole compared with fluconazole monotherapy for the treatment of cryptococcal meningitis: a randomized trial in Malawi. Clin Infect Dis 2010, 50:338-44.

Parkes-Ratanshi R, Wakeham K, Levin J, et al. Primary prophylaxis of cryptococcal disease with fluconazole in HIV-positive Ugandan adults: a double-blind, randomised, placebo-controlled trial. Lancet Infect Dis 2011, 11:933-41.

Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis 2017,17:873-881.

Rolfes MA, Hullsiek KH, Rhein J, et al. The Effect of Therapeutic Lumbar Punctures on Acute Mortality from Cryptococcal Meningitis. Clin Infect Dis. 2014 Jul 23. pii: ciu596.

Saag MS, Cloud GA, Graybill JR, et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. Clin Infect Dis 1999, 28:291-6.

Temfack E, Rim JJB, Spijker R, et al. Cryptococcal Antigen in Serum and Cerebrospinal Fluid for Detecting Cryptococcal Meningitis in Adults Living With Human Immunodeficiency Virus: Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies. Clin Infect Dis 2021, 72:1268-1278.

Vibhagool A, Sungkanuparph S, Mootsikapun P, et al. Discontinuation of secondary prophylaxis for cryptococcal meningitis in HIV-infected patients treated with HAART: a prospective, multicenter, randomized study. Clin Infect Dis 2003, 36:1329-31.

Wake RM, Britz E, Sriruttan C, et al. High Cryptococcal Antigen Titers in Blood are Predictive of Subclinical Cryptococcal Meningitis Among HIV-Infected Patients. Clin Infect Dis. 2017 Oct 5.

Weitzel A, Arasteh K, Mertenskötter T, et al. Kryptokokkosen bei HIV-positiven Patienten in Deutschland – eine Auswertung 24 deutscher Zentren. In: Brockmeyer NH et al. HIV-Infekt, Springer-Verlag; 1999.

Xu XL, Zhao T, Huang YQ, et al. Therapeutic lumbar puncture and lumbar drainage: Which is more effective for the management of intracranial hypertension in HIV patients with cryptococcal meningitis? Results of a prospective non-randomized interventional study in China. Curr Med Res Opin 2022, 38:803-810.

Salmonella septicemia

Infection with non-typhoidal Salmonella species, which usually cause only enteritis in healthy individuals, can result in severe septicemia in immunocompromised individuals (Jacobs 1985). The most important reservoir of pathogens is food, especially poultry. Recurrent, non-typhoidal Salmonella septicemias are AIDS-defining. In central Europe, they are rare and account for less than 1% of all AIDS cases (Burckhardt 1999). In contrast, in southern Europe or Africa, salmonella species are the most common pathogens detected in blood cultures (Gordon 2008). In addition to septicemia, osteomyelitis, empyema, lung abscesses, pyelonephritis, or meningitis have been described (Albrecht 1992, Nadelman 1985). Recurrences have become less frequent with ART (Hung 2007).

Clinic/Diagnostics

The patients are often seriously ill. Chills and high fever are usually present, but diarrhea is not always present. If not treated in time, septic shock may occur. Blood cultures are primarily used to isolate the enteritis salmonella strains *S. enteritides* and *S. typhimurium*. The typhoid and paratyphoid fever pathogens, *S. typhi* and *S. paratyphi,* occur only rarely.

Treatment/Prophylaxis

Ciprofloxacin is the drug of choice. In most cases, one-week intravenous administration is sufficient. In Asia, resistance rates are sometimes as high as 30% (Hung 2007); cefotaxime or ceftriaxone can then be considered. Oral maintenance therapy for 6–8 months should not be discontinued too early (Hung 2001). Previously, lifelong relapse prophylaxis is no longer required. Primary prophylaxis is not recommended; food hygiene rules should be followed (see *Travel Medicine*). As with shigella (see Dermatology), outbreaks among MSM have not been observed.

Treatment/prophylaxis of salmonella sepsis (daily doses)

Acute therapy		7–14 days
Therapy of choice	Ciprofloxacin	Ciprofloxacin 2 x 1 infusions of 200 mg IV
Alternative	Ceftriaxone	Rocephin® 1 x 1 infusions of 2 g IV
Prophylaxis		Against recurrences
	Ciprofloxacin	Ciprofloxacin 2 x 1 tab. at 500 mg (6–8 months)

Literature

Albrecht H, Stellbrink HJ, Fenske S, Steiner P, Greten H. Salmonella typhimurium lung abscesses in an HIV-infected patient: successful treatment with oral ciprofloxacin. AIDS 1992, 6:1400-1.

Burckhardt B, Sendi P, Pfluger D, et al. Rare AIDS-defining diseases in the Swiss HIV Cohort Study. Eur J Clin Microbiol Infect Dis 1999, 18:399-402.

Forrest GN, Wagner LA, Talwani R, Gilliam BL. Lack of fluoroquinolone resistance in non-typhoidal salmonella bacteremia in HIV-infected patients in an urban US setting. J Int Assoc Physicians AIDS Care 2009, 8:338-41.

Gordon MA. Salmonella infections in immunocompromised adults. J Infect 2008, 56:413-22.

Hung CC, Hsieh SM, Hsiao CF, Chen MY, Sheng WH. Risk of recurrent non-typhoid Salmonella bacteraemia after early discontinuation of ciprofloxacin as secondary prophylaxis in AIDS patients in the era of HAART. AIDS 2001, 15:645-7.

Hung CC, Hung MN, Hsueh PR, et al. Risk of recurrent nontyphoid Salmonella bacteremia in HIV-infected patients in the era of highly active antiretroviral therapy and an increasing trend of fluoroquinolone resistance. Clin Infect Dis 2007;45.

Jacobs JL, Gold JW, Murray HW, Roberts RB, Armstrong D. Salmonella infections in patients with the AIDS. Ann Intern Med 1985, 102:186-8.

Nadelman RB, Mathur-Wagh U, Yancovitz SR, Mildvan D. Salmonella bacteremia associated with the AIDS. Arch Intern Med 1985, 145:1968-71.

Immune Reconstitution Syndrome (IRIS)

In 1997, PLWH who developed unusual CMV retinitis (Jacobsen 1997) or abscessing MAC infections (Race 1998) a few weeks after ART initiation was reported for the first time. The common feature was a pronounced inflammatory component – early on. Therefore, a syndrome was postulated in which an infection or disease already latent before therapy was more adequately fought by the restoring immune system (review: Walker 2015). This "immune reconstitution inflammatory syndrome" (IRIS) is defined as a worsening of an infectious or inflammatory event that is temporally related to ART initiation. In addition to activation of the cellular immune response, changes in the cytokine network are also involved in the pathogenesis of IRIS – but apparently, the mechanisms differ depending on the disease and genetic profile (Price 2001, Shelbourne 2005).

A viral load drop of at least one log is required as a response criterion, and the symptoms must not be explainable by side effects, therapy failure, or non-adherence. A distinction must be made between subclinical infections that are unmasked during ART ("unmasking IRIS") and infections that were already clinically evident at the start of ART, and that paradoxically worsen during therapy ("paradoxical IRIS"). IRIS is not limited to infections; the spectrum includes autoimmune diseases and malignancies. Thus, IRIS today is a panopticon of bizarre case reports with only one thing in common: unexpected, clinically usually impressive problems occurred under newly started, effective ART. The ART regimen does not matter: the hypothesis that INSTIs increase the risk of IRIS, which was repeatedly raised for a while, has not been proven true (Zhao 2022).

How common is IRIS? In the absence of a definition, the figures vary. We consider a frequency of 5–10% realistic with less than 200 CD4 T-cells/µl. Very low CD4 T-cells, a high viral load before starting therapy, a rapid decline under ART seem to be predictors, and an elevated CRP before starting ART. If only cases infected with mycobacteria or cryptococci before ART initiation are considered, IRIS rates of 30% and more are observed (Müller 2010).

Atypical mycobacterial IRIS: For MAC, the number of published cases with fistulous lymphadenitis, cutaneous or muscular abscesses, osteomyelitis, nephritides, or meningitis exceeds the citable range. Lymph node abscesses usually occur in the first few weeks. IRIS cases with *Mycobacterium xenopi* or *kansasii* have also been described (Chen 2004, Phillips 2005).

TB-IRIS: In four large randomized trials of ART-naïve patients with TB, the IRIS rate was 18% (Namale 2015). These cases initially worsen dramatically under tuberculostasis and ART-mediated immune reconstitution. Meningitis, and in some cases, excessive lymph node swelling with often nonspecific histology, complicate the course. The administration of prednisolone was very effective in a placebo-controlled study and should be considered (Meintjes 2010+2012). Mortality in TB-IRIS is then not increased, except for tuberculous meningitis (Török 2009).

CMV-IRIS: In CMV retinitis, IRIS will be expected in about one-third (Müller 2010). Inflammatory CMV retinitis with vision-threatening vitritis, papillitis, and macular edema is considered a distinct syndrome and differs significantly from classic CMV retinitis (Jacobson 1997, Karavellas 1999). Neovascularization threatens visual acuity even after healing (Wright 2003). Analogous to MAC, the CMV-specific response was also shown to improve most in cases of vitritis (Mutimer 2002, Stone 2002). Inflammatory CMV manifestations are not limited to the retina but can also affect other organs.

PML-IRIS: The clinic of "IRIS-PML" is often initially more fulminant than in classic PML. Also atypical is contrast enhancement, which gradually regresses over time. There is a more favorable prognosis, and a complete cure is possible (Hoffmann 2003, Du Pasquier 2003). There are positive case reports on steroids acutely (Nuttall 2004, Tan 2009).

Cryptococcal IRIS: Besides MAC/TBC and CMV, cryptococci are probably the most essential IRIS pathogens (Haddow 2010). In co-infected individuals, the incidence is up to 20% (Sungkanuparph 2009, Müller 2010). MRI usually shows choriomeningitis with marked enhancement into the choroid plexus. Cryptococcal antigen in CSF is positive, but culture remains negative. CSF pressure is often remarkably high (Shelburne 2005). Because cryptococcal IRIS has a high mortality rate, ART should always be delayed by several weeks and never start simultaneously (Boulware 2014).

Other infections: The IRIS panopticon also has various case examples on hand, such as leishmanioses (Badaró 2015), histoplasmoses (De Lavaissière 2008), penicillioses (Ho 2010), coccidioidomycoses (Mu 2017), pneumocysts (Mok 2014), toxoplasmoses (Martin-Blondel 2011, van Bilsen 2017), or herpes infections (Tobian 2014). Episodes of herpes zoster and relapses of hepatitis B or C also appear to occur on ART, especially in the first few weeks (Martinez 1998, Behrens 2000, Chung 2002, Manegold 2001). HHV-8-associated Kaposi's sarcoma may initially worsen significantly on ART (Bower 2005, Feller 2008). Furthermore, exacerbations of molluscum, warts, folliculitis, or dermatoses have been reported (Handa 2001, Lehloenyia 2006, Pereira 2007, Iarikov 2008). There are reports on parvoviruses and leprosy (Nolan 2003, Couppie 2004, Watanabe 2011).

Other diseases: IRIS has long been attributed not only to OI but also to autoimmune diseases such as Graves' disease, lupus erythematosus, Sweet and Reiter syndrome, Guillain-Barré syndrome, and acute porphyria, gout, sarcoidosis, to name a few (Behrens 1998, Bevilacqua 1999, Fox 1999, Mirmirani 1999, Makela 2002, Neumann 2003, Sebeny 2010, Rasul 2011). Two cases of Peyronie's disease, a penile fibromatosis, have been reported (Rogers 2004).

Consequences

Patients who start ART with less than 200 CD4 T-cells/µl (and a high viral load simultaneously) should be observed carefully during the first weeks. Vigilance is required primarily for those who refused ART for a long time but now feel physically "weak" (subfebrile?) and want to start ART "after a longer period of consideration." In this case, there is often already a latent infection. The worse the immune status and the longer it has been poor, the higher the risk of IRIS. Although studies show that inflammatory parameters such as CRP, D-dimers, or cytokines such as IL-6 or IL-7, among others, are predictive of IRIS or OI (Rodger 2009, Porter 2010, George 2017), this has not yet found its way into routine diagnostics.

X-ray thorax, abdominal ultrasonography, and fundoscopy, on the other hand, are part of the standard program before ART initiation. Prophylaxis cannot prevent MAC-IRIS (Phillips 2002+2005), nor can the administration of maraviroc (Sierra-Madero 2014). In contrast, when present, steroids should not be spared, particularly for mycobacterioses. In a randomized trial, prednisolone showed a clear clinical benefit (Meintjes 2018). In contrast, steroids are probably of no benefit in viral-induced IRIS (Meintjes 2012).

In any case, clinicians should be prepared for atypical localizations and courses of opportunistic infections. There is nothing that does not exist, and nothing is the same anymore. IRIS does not mean that ART has failed. The prognosis is usually good, and mortality is not increased (Park 2006).

Literature

Aberg JA, Chin-Hong PV, McCutchan A, et al. Localized osteomyelitis due to Mycobacterium avium complex in patients with HIV receiving HAART. Clin Infect Dis 2002, 35:E8-E13.

Badaró R, Gonçalves LO, Gois LL, et al. Leishmaniasis as a Manifestation of Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV-Infected Patients: A Literature Review. J Int Assoc Provid AIDS Care 2015, 14:402-7.

Behrens G, Knuth C, Schedel I, Mendila M, Schmidt RE. Flare of SLE following HAART. Lancet 1998, 351:1057-8.

Behrens GM, Meyer D, Stoll M, Schmidt RE. Immune reconstitution syndromes in HIV infection following effective antiretroviral therapy. Immunobiology 2000, 202:186-93.

Bevilacqua S, Hermans P, Van Laethem Y, Demaubeuge J, Clumeck N. Sweet's syndrome in an HIV-infected patient. AIDS 1999, 13: 728-9.

Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. NEJM 2014, 370:2487-98.

Bower M, Nelson M, Young AM, et al. Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. J Clin Oncol 2005, 23:5224-8.

Chen F, Sethi G, Goldin R, Wright AR, Lacey CJ. Concurrent granulomatous Pneumocystis carinii and Mycobacterium xenopi pneumonia: an unusual manifestation of HIV immune reconstitution disease. Thorax 2004, 59:997-999.

Chung RT, Evans SR, Yang Y, et al. Immune recovery is associated with persistent rise in HCV RNA, infrequent liver test flares, and is not impaired by HCV in co-infected subjects. AIDS 2002, 16:1915-1923.

Couppie P, Abel S, Voinchet H, et al. Immune reconstitution inflammatory syndrome associated with HIV and leprosy. Arch Dermatol 2004, 140:997-1000.

De Lavaissière M, Manceron V, Bourée P, et al. Reconstitution inflammatory syndrome related to histoplasmosis, with a hemophagocytic syndrome in HIV infection. J Infect 2008 Dec 16. [Epub ahead of print]

Du Pasquier RA, Koralnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? J Neurovirol 2003, 9 Suppl 1:25-31.

Feller L, Anagnostopoulos C, Wood NH, et al. Human immunodeficiency virus-associated Kaposi sarcoma as an immune reconstitution inflammatory syndrome: a literature review and case report. J Periodontol 2008;79:362-8.

Fox PA, Boag FC, Hawkins DA, Francis N. Acute porphyria following commencement of indinavir. AIDS 1999, 13: 622-3.

French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with HAART. HIV Med 2000, 1:107-15.

George V, Harrison L, Roach M, et al. Associations of Plasma Cytokine and Microbial Translocation Biomarkers With Immune Reconstitution Inflammatory Syndrome. J Infect Dis 2017, 216:1159-1163.

Ghosn J, Paris L, Ajzenberg D, et al. Atypical toxoplasmic manifestation after discontinuation of maintenance therapy in a HIV type 1-infected patient with immune recovery. Clin Infect Dis 2003; 37: E112-4.

Haddow LJ, Colebunders R, Meintjes G, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. Lancet Infect Dis 2010, 10:791-802.

Haddow LJ, Easterbrook PJ, Mosam A, et al. Defining immune reconstitution inflammatory syndrome: evaluation of expert opinion versus 2 case definitions in a South African cohort. Clin Infect Dis 2009, 49:1424-32.

Handa S, Bingham JS. Dermatological immune restoration syndrome: Does it exist? J Eur Acad Dermatol Venereol 2001, 15:430-2.

Ho A, Shankland GS, Seaton RA. Penicillium marneffei infection presenting as an immune reconstitution inflammatory syndrome in an HIV patient. Int J STD AIDS 2010, 21:780-2.

Hoffmann C, Horst HA, Albrecht H, Schlote W. Progressive multifocal leucoencephalopathy with unusual inflammatory response during antiretroviral treatment. J Neurol Neurosurg Psychiatry 2003, 74:1142-4.

Iarikov D, Duke W, Skiest D. Extensive development of flat warts as a cutaneous manifestation of immune reconstitution syndrome. AIDS Read 2008, 18:524-7.

Jacobson MA, Zegans M, Pavan PR, et al. Cytomegalovirus retinitis after initiation of HAART. Lancet 1997, 349:1443-5.

Karavellas MP, Plummer DJ, Macdonald JC, Torriani FJ, Shufelt CL, Azen SP, Freeman WR. Incidence of immune recovery vitritis in cytomegalovirus retinitis patients following institution of successful highly active antiretroviral therapy. J Infect Dis. 1999 Mar;179(3):697-700. doi: 10.1086/314639. PMID: 9952380.

Lehloenya R, Meintjes G. Dermatologic manifestations of the immune reconstitution inflammatory syndrome. Dermatol Clin 2006, 24:549-70.

Makela P, Howe L, Glover S, Ferguson I, Pinto A, Gompels M. Recurrent Guillain-Barre Syndrome as a complication of immune reconstitution in HIV. J Infect 2002, 44:47-9.

Manegold C, Hannoun C, Wywiol A, et al. Reactivation of hepatitis B virus replication accompanied by acute hepatitis in patients receiving HAART. Clin Infect Dis 2001, 32: 144-8.

Martin-Blondel G, Alvarez M, Delobel P, et al. Toxoplasmic encephalitis IRIS in HIV-infected patients: a case series and review of the literature. J Neurol Neurosurg Psychiatry 2011, 82:691-3.

Martinez E, Gatell J, Moran Y, et al. High incidence of herpes zoster in patients with AIDS soon after therapy with protease inhibitors. Clin Infect Dis 1998, 27:1510-3.

Meintjes G, Scriven J, Marais S. Management of the immune reconstitution inflammatory syndrome. Curr HIV/AIDS Rep 2012, 9:238-50.

Meintjes G, Stek C, Blumenthal L, et al. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. N Engl J Med 2018, 379:1915-1925.

Mirmirani P, Maurer TA, Herndier B, et al. Sarcoidosis in a patient with AIDS: a manifestation of immune restoration syndrome. J Am Acad Dermatol 1999, 41:285-6.

Mok HP, Hart E, Venkatesan P. Early development of immune reconstitution inflammatory syndrome related to Pneumocystis pneumonia after antiretroviral therapy. Int J STD AIDS 2014, 25:373-7.

Müller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis 2010, 10:251-61.

Mu A, Shein TT, Jayachandran P, Paul S. Immune Reconstitution Inflammatory Syndrome in Patients with AIDS and Disseminated Coccidioidomycosis: A Case Series and Review of the Literature. J Int Assoc Provid AIDS Care. 2017 Jan 1:2325957417729751.

Mutimer HP, Akatsuka Y, Manley T, et al. association between immune recovery uveitis and a diverse intraocular cytomegalovirus-specific cytotoxic T cell response. J Infect Dis 2002, 186: 701-5.

Namale PE, Abdullahi LH, Fine S, et al. Paradoxical TB-IRIS in HIV-infected adults: a systematic review and meta-analysis. Future Microbiol 2015, 10:1077-99.

Neumann S, Kreth F, Schubert S, Mossner J, Caca K. Reiter's syndrome as a manifestation of an immune reconstitution syndrome in an HIV-infected patient: successful treatment with doxycycline. Clin Infect Dis 2003; 36: 1628-9.

Nolan RC, Chidlow G, French MA. Parvovirus b19 encephalitis presenting as immune restoration disease after highly active antiretroviral therapy for HIV infection. Clin Infect Dis 2003; 36: 1191-4.

Nuttall JJ, Wilmshurst JM, Ndondo AP, et al. Progressive multifocal leukoencephalopathy after initiation of highly active antiretroviral therapy in a child with advanced HIV infection: a case of immune reconstitution inflammatory syndrome. Pediatr Infect Dis J 2004, 23:683-5.

Park WB, Choe PG, Jo JH, et al. Immune reconstitution inflammatory syndrome in the first year after HAART: influence on long-term clinical outcome. AIDS 2006, 20:2390-2.

Pereira B, Fernandes C, Nachiambo E, et al. Exuberant molluscum contagiosum as a manifestation of the immune reconstitution inflammatory syndrome. Dermatol Online J 2007;13:6.

Phillips P, Bonner S, Gataric N, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. Clin Infect Dis 2005, 41:1483-97.

Phillips P, Chan K, Hogg R, et al. Azithromycin prophylaxis for Mycobacterium avium complex during the era of HAART: evaluation of a provincial program. Clin Infect Dis 2002, 34: 371-8.

Porter BO, Ouedraogo GL, Hodge JN, et al. D-Dimer and CRP levels are elevated prior to antiretroviral treatment in patients who develop IRIS. Clin Immunol 2010, 136:42-50.

Price P, Mathiot N, Krueger R, Stone S, Keane NM, French MA. Immune dysfunction and immune restoration disease in HIV patients given HAART. J Clin Virol 2001, 22:279-87.

Race EM, Adelson-Mitty J, Kriegel GR, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. Lancet 1998, 351:252-5.

Rasul S, Delapenha R, Farhat F, Gajjala J, Zahra SM. Graves' Disease as a Manifestation of Immune Reconstitution in HIV-Infected Individuals after Initiation of Highly Active Antiretroviral Therapy. AIDS Res Treat 2011; 2011:743597.

Rodger AJ, Fox Z, Lundgren JD, et al. Activation and coagulation biomarkers are independent predictors of the development of opportunistic disease in patients with HIV infection. J Infect Dis 2009, 200:973-83.

Rogers GD, French MA. Peyronie's disease in men with HIV responding to highly active antiretroviral therapy. HIV Med 2004, 5:185-6.

Sebeny PJ, Keith MP, Love KM, Dwyer TX, Ganesan A. Refractory polyarticular gouty arthritis as a manifestation of immune reconstitution inflammatory syndrome. J Clin Rheumatol 2010, 16:40-2.

Shelburne SA, Visnegarwala F, Darcourt J, et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. AIDS 2005, 19:399-406.

Sierra-Madero JG, Ellenberg SS, Rassool MS, et al. Effect of the CCR5 antagonist maraviroc on the occurrence of immune reconstitution inflammatory syndrome in HIV (CADIRIS): a double-blind, randomised, placebo-controlled trial. Lancet HIV 2014, 1:e60-7.

Stone SF, Price P, Tay-Kearney ML, French MA. Cytomegalovirus (CMV) retinitis immune restoration disease occurs during HAART-induced restoration of CMV-specific immune responses within a predominant Th2 cytokine environment. J Infect Dis 2002, 185:1813-7.

Stout JE, Lai JC, Giner J, Hamilton CD. Reactivation of retinal toxoplasmosis despite evidence of immune response to highly active antiretroviral therapy. Clin Infect Dis 2002; 35:E37-9.

Sungkanuparph S, Filler SG, Chetchotisakd P, et al. Cryptococcal immune reconstitution inflammatory syndrome after antiretroviral therapy in AIDS patients with cryptococcal meningitis: a prospective multicenter study. Clin Infect Dis 2009, 49:931-4.

Tan K, Roda R, Ostrow L, McArthur J, Nath A. PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. Neurology 2009, 72:1458-64.

Tobian AA, Grabowski MK, Serwadda D, et al; Rakai Health Sciences Program. Reactivation of herpes simplex virus type 2 after initiation of antiretroviral therapy. J Infect Dis. 2013 Sep 1;208(5):839-46.

Török ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)—associated tuberculous meningitis. CID 2011, 52:1374-83.

Tsambiras PE, Larkin JA, Houston SH. Toxoplasma encephalitis after initiation of HAART. AIDS Read 2001, 11:608-10.

van Bilsen WPH, van den Berg CHSB, Rijnders BJA, et al. Immune reconstitution inflammatory syndrome associated with toxoplasmic encephalitis in HIV-infected patients. AIDS 2017, 31:1415-1424.

Walker NF, Scriven J, Meintjes G, Wilkinson RJ. Immune reconstitution inflammatory syndrome in HIV-infected patients. HIV AIDS (Auckl) 2015, 7:49-64.

Watanabe D, Taniguchi T, Otani N, et al. Immune reconstitution to parvovirus B19 and resolution of anemia in a patient treated with highly active antiretroviral therapy. J Infect Chemother 2011, 17:283-7.

Wright ME, Suzman DL, Csaky KG, Extensive retinal neovascularization as a late finding in human immunodeficiency virus-infected patients with immune recovery uveitis. Clin Infect Dis 2003;36:1063-6.

Zhao Y, Hohlfeld A, Namale P, et al. Risk of Immune Reconstitution Inflammatory Syndrome With Integrase Inhibitors Versus Other Classes of Antiretrovirals: A Systematic Review and Meta-analysis of Randomized Trials. J Acquir Immune Defic Syndr 2022, 90:232-239.

Wasting Syndrome

Classic wasting syndrome is defined as an involuntary weight loss of at least 10% of the original body weight that occurs concurrently with persistent diarrhea (at least two bowel movements per day for more than 30 days) or weakness and/or fever without an identifiable infectious cause. Thus, wasting syndrome is a diagnosis of exclusion. Formerly a common sight in every HIV center, classic wasting syndrome has become rare in Europe and the United States. However, weight loss remains an independent mortality factor (Tang 2002), and every person with HIV should be weighed regularly! Affected persons with classic wasting syndrome are often very debilitated. Their risk of opportunistic infections is significantly increased (Dworkin 2003). Cognitive abilities are also reduced (Dolan 2003).

Diagnostics

First, opportunistic infections (TB, MAC, crypto-, and microsporidia) should be excluded or treated. If nothing can be found, such different reasons remain, such as metabolic disorders, hypogonadism, malnutrition, and malabsorption syndromes (overview: Grinspoon 2003), which can be combined. The medical history remains vital: What is the diet, are there diets? Is there depression, drug use, eating disorders? What ART is being taken? There are often smooth transitions to antiretroviral-induced lipoatrophy (history of AZT, d4T, ddI?). Under interferon, (reversible) severe weight loss is also common (Garcia-Benayas 2002). Next, hypogonadism should be ruled out (measurement of testosterone). Several simple tests are available for malabsorption syndromes. For now, it makes sense to determine albumin, TSH, and cholesterol. Further tests, such as the D-xylose absorption test or small intestine biopsies, are only valuable for gastroenterologists. Also, tests like DEXA, densitometry, and bioelectrical impedance analysis should only be used in centers where experience with wasting syndrome in AIDS exists.

Treatment

Nutritional counseling and exercise are helpful, if possible, but successful only up to a point. Parenteral nutrition only helps in absorption disorders (Kotler 1990, Melchior 1996). An ART that avoids AZT and possibly even nucleoside analogs is essential (see *Nuke-Sparing*). Drugs have limited success and are often problematic.

Megestrol acetate, a synthetic progestogen approved in Europe as Megestat® for advanced breast cancer, also has a benefit in wasting syndrome due to its appetite-stimulating effect (Von Roenn 1994, Mulligan 2006). Due to the steroid-typical side effects (including hypogonadism), we do not consider its use to be useful.

Dronabinol (THC), the main active ingredient in marijuana, has been approved as a narcotic in several European countries since 1998. However, legislation and regulation of medicinal products containing cannabinoids vary across EU countries, leading to different accessibility to these products. In any case, the effect on wasting is moderate at best (Beal 1995, Badowski 2016) and probably even weaker than that produced by megestrol acetate (Timpone 1997).

Hypogonadism is a common problem in the wasting syndrome. When testosterone levels are depressed, substitution is effective in terms of weight gain and quality of life (Grinspoon 1998). Testosterone 250 mg IM every 3–4 weeks is given; generic drugs are available. The effect lasts even with long-term use (Grinspoon 1999). In women, one should be cautious with androgens. Other anabolic steroids such as oxandrolone or nandrolone may be more effective than testosterone (Gold 2006,

Sardar 2010) but are likely fraught with more side effects, primarily affecting the liver (Corcoran 1999). Positive effects have also been reported for the anabolic steroid oxymetholone (Hengge 2003), although significant transaminase elevations are sometimes observed.

Side effects and costs also limit the use of growth hormones, and nothing is known about long-term use (Schambelan 1996). However, according to a meta-analysis, there is evidence that growth hormones are more effective than anabolic steroids or testosterone in wasting syndrome (Moyle 2004). Major side effects are glucose elevations, arthralgias, myalgias, and peripheral edema, which respond to discontinuation or dose reductions (review: Gelato 2007).

Literature

Badowski ME, Perez SE. Clinical utility of dronabinol in the treatment of weight loss associated with HIV and AIDS. HIV AIDS (Auckl) 2016. 8:37-45.

Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage 1995;10:89-97.

Corcoran C, Grinspoon S. Treatments for wasting in patients with the acquired immunodeficiency syndrome. NEJM 1999, 340:1740-50.

Dolan S, Montagno A, Wilkie S, et al. Neurocognitive Function in HIV-Infected Patients With Low Weight and Weight Loss. JAIDS 2003; 34: 155-64.

Dworkin MS, Williamson JM. AIDS wasting syndrome: trends, influence on opportunistic infections, and survival. J AIDS 2003; 33: 267-73.

Garcia-Benayas T, Blanco F, Soriano V. Weight loss in HIV-infected patients. N Engl J Med 2002, 347: 1287-8.

Gelato M, McNurlan M, Freedland E. Role of recombinant human growth hormone in HIV-associated wasting and cachexia: pathophysiology and rationale for treatment. Clin Ther 2007; 29:2269-88.

Gold J, Batterham MJ, Rekers H, et al. Effects of nandrolone decanoate compared with placebo or testosterone on HIV-associated wasting. HIV Med 2006, 7:146-55.

Grinspoon S, Corcoran C, Anderson E, Hubbard J, Basgoz N, Klibanski A. Sustained anabolic effects of long-term androgen administration in men with AIDS wasting. Clin Infect Dis 1999, 28:634-636.

Grinspoon S, Corcoran C, Askari H, et al. Effects of androgen administration in men with the AIDS wasting syndrome: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998; 129:18-26.

Grinspoon S, Mulligan K. Weight loss and wasting in patients infected with human immunodeficiency virus. Clin Infect Dis 2003; 36: S69-78.

Hengge UR, Stocks K, Faulkner S, et al. Oxymetholone for the treatment of HIV-wasting: a double-blind, randomized, placebo-controlled phase III trial in eugonadal men and women. HIV Clin Trials 2003; 4:150-63.

Kotler DP, Tierney AR, Culpepper-Morgan JA, Wang J, Pierson RN Jr. Effect of home total parenteral nutrition on body composition in patients with AIDS. J Parenter Enteral Nutr 1990;14:454-458.

Melchior J, Chastang C, Gelas P, et al. Efficacy of 2-month total parenteral nutrition in AIDS patients: a controlled randomized prospective trial. AIDS 1996;10:379-384.

Moyle GJ, Daar ES, Gertner JM, et al. Growth hormone improves lean body mass, physical performance, and quality of life in subjects with HIV-associated weight loss or wasting on highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2004;35:367-75.

Mulligan K, Zackin R, Von Roenn JH, et al. Testosterone supplementation of megestrol therapy does not enhance lean tissue accrual in men with HIV-associated weight loss: A randomized, double-blind, placebo-controlled multicenter trial. J Clin Endocrinol Metab 2006 Nov 7.

Sardar P, Jha A, Roy D, Majumdar U, et al. Therapeutic effects of nandrolone and testosterone in adult male HIV patients with AIDS wasting syndrome (AWS): a randomized, double-blind, placebo-controlled trial. HIV Clin Trials 2010, 11:220-9.

Schambelan M, Mulligan K, Grunfeld C, et al. Recombinant human growth hormone in patients with HIV-associated wasting: a randomized, placebo-controlled trial. Ann Intern Med 1996, 125:873-882.

Tang AM, Forrester J, Spiegelman D, et al. Weight loss and survival in HIV-positive patients in the era of highly active antiretroviral therapy. J AIDS 2002, 31: 230-6.

Timpone JG, Wright DJ, Li N, et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. AIDS Res Hum Retroviruses 1997, 13:305-15.

Von Roenn JH, Armstrong D, Kotler DP, et al. Megesterol acetate in patients with AIDS-related cachexia. Ann Intern Med 1994, 121:393-399.

Wanke CA, Silva M, Knox TA, et al. Weight loss and wasting remain common complications in individuals infected with HIV in the era of highly active antiretroviral therapy. Clin Infect Dis 2000, 31:803-5.

Rare opportunistic infections (OIs)

CHRISTIAN HOFFMANN AND GERD FÄTKENHEUER

In the following, OIs that hardly occur in Central Europe or have become very rare due to ART will be described. These affect PLWH more often than immunocompetent patients, are more severe, and recur more frequently. Only three infections, namely histoplasmosis, isosporiasis, and coccidioidomycosis, are AIDS-defining.

Aspergillosis

Aspergilloses are not AIDS-defining, although the CD4 T-cell count is almost always below 50/µl (Mylonakis 1998). The primary manifestation is the lungs (pneumonia, tracheobronchitis). CNS and renal or hepatic abscesses also occur (Hunt 2000, Mylonakis 2000). Steroids and severe neutropenia are risk factors. *Aspergillus fumigatus* is the most common pathogen (> 90%).

The most severely ill complain of fever, cough, dyspnea, and chest pain. Hemoptysis is often present. The diagnosis can only be made reliably by biopsy. A serum antigen test for galactomannan may support the tentative diagnosis. Detection of *Aspergillus* in pulmonary secretions is considered circumstantial but is often colonization-related. The chest x-ray usually shows nonspecific changes or is unremarkable. The diagnostic method of choice is HR-CT, which shows pulmonary infiltrates that typically contain air pockets or are blurred (halo sign) (Ullmann 2018).

Voriconazole is the therapy of choice; it was better than conventional amphotericin B in a randomized study (Herbrecht 2002). The daily dose is 2 x 4 mg IV/kg (loading dose: 2 x 6 mg/kg day 1, switching to oral therapy with 2 x 200 mg from day 7). It has the advantage of effectively penetrating the brain parenchyma (Schwartz 2005), but visual disturbances occur in about 20% and often (reversible) liver elevations. Therapeutic monitoring with target levels 1–5,5 mg/l is recommended (Ullmann 2018).

Alternatives to voriconazole include isavuconazole (Cresemba®), at a daily dose of 3 x 200 mg i.v. for 2 days, followed by 1 x 200 mg IV or per os (Maertens 2016), liposomal amphotericin B (3 mg/kg/d), caspofungin, or posaconazole. Combinations are probably no better (Garbati 2012). Steroid therapies should be discontinued if possible, and any affected individual should receive antiretroviral therapy promptly. The duration of therapy with antimycotics depends on the clinical course; before discontinuation, no activity should be detectable in the CT thorax.

Literature

Garbati MA, Alasmari FA, Al-Tannir MA, et al. The role of combination antifungal therapy in the treatment of invasive aspergillosis: a systematic review. Int J Infect Dis 2012, 16:e76-81.

Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus vs amphotericin B for primary therapy of invasive aspergillosis. NEJM 2002, 347:408-15.

Hunt SM, Miyamoto RC, Cornelius RS, Tami TA. Invasive fungal sinusitis in the AIDS. Otolaryngol Clin North Am 2000, 33:335-47.

Maertens JA, Raad II, Marr K, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet 2016, 387(10020):760-9.

Mylonakis E, Barlam TF, Flanigan T, Rich JD. Pulmonary aspergillosis and invasive disease in AIDS: review of 342 cases. Chest 1998, 114:251-62.

Mylonakis E, Paliou M, Sax PE, et al. Central nervous system aspergillosis in patients with HIV infection. Medicine (Baltimore) 2000, 79:269-80.

Schwartz S, Ruhnke M, Ribaud P, et al. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. Blood 2005, 106:2641-5.

Ullmann AJ, Aguado JM, Arikan-Akdagli S, et al. Diagnosis and management of Aspergillus diseases. Clin Microbiol Infect 2018, 24 Suppl 1:e1-e38.

Yoganathan K. Long-term suppressive therapy for pulmonary aspergilloma in an immunocompromised man with AIDS. Is it always necessary? Int J STD AIDS 2009, 20:434-6.

Bacillary angiomatosis

Bacillary angiomatosis (BA) was already described in PLWH in the 1980s (review: Maguiña 2000). It is caused by the two species *Bartonella henselae* and *Bartonella quintana* (formerly "Rochalimaea"). Cats are the primary host for *Bartonella henselae*, and cat fleas are the vector. Various pathogen reservoirs are discussed for *Bartonella quintana*, and people from socially deprived backgrounds, especially people experiencing homelessness, frequently become ill (Gasquet 1998). In North and South America, BA is probably more common; in Brazil, antibody prevalence was 38% (Lamas 2010). In a study of 382 febrile PLWH in San Francisco, bartonella was the cause of fever in 18% (Koehler 2003).

BA is an important differential diagnosis in cases of unclear skin proliferations. The vascular skin proliferation can occur solitary but is usually multiple and is clinically (and histologically!) confused with Kaposi's sarcomas or even hemangiomas as cherry-red or purplish nodules. Dry, hyperkeratotic changes reminiscent of psoriasis also occur. In addition to the skin, the skeleton is also affected in about 25%, with osteolytic, painful foci (AP elevation!). In a case collection of 21 patients, the skin was involved in 19, bone in 5, and liver in 4 (Plettenberg 2000). Lymph nodes, muscle, CNS involvement, and eye, gingiva, and gastrointestinal tract manifestations have also been reported.

Diagnosis is difficult. The Gram-negative pathogens can only be visible from biopsy material using Warthin-Starry silver staining. If you do not do a Warthin-Starry silver stain, you will not diagnose BA! Pathologies should be advised of the suspicion as this stain is not routine. PCR is also possible.

Therapy consists of at least four weeks of erythromycin, 4 x 500 mg/die (Maguiña 2009). Recurrences are common, so some experts favor at least three months of therapy. Clarithromycin and doxycycline are also reported to be effective, the latter being considered the treatment of choice for CNS involvement.

Because cats are important carriers, US guidelines recommend not keeping them as pets. If it "has to be", the cat should be older than one year and healthy. Scratch injuries should be avoided.

Literature

Cockerell CJ, LeBoit PE. Bacillary angiomatosis: a newly characterized, pseudoneoplastic, infectious, cutaneous vascular disorder. J Am Acad Dermatol 1990, 22:501-12.

Gasquet S, Maurin M, Brouqui P, Lepidi H, Raoult D. Bacillary angiomatosis in immunocompromised patients. AIDS 1998, 12:1793-803.

Koehler JE, Sanchez MA, Garrido CS, et al. Molecular epidemiology of Bartonella infections in patients with bacillary angiomatosis-peliosis. N Engl J Med 1997, 337:1876-83.

Koehler JE, Sanchez MA, Tye S, et al. Prevalence of Bartonella infection among HIV-infected patients with fever. Clin Infect Dis 2003, 37:559-66.

Lamas CC, Mares-Guia MA, Rozental T, et al. Bartonella spp. infection in HIV positive individuals, their pets and ectoparasites in Rio de Janeiro, Brazil: serological and molecular study. Acta Trop 2010, 115:137-41.

LeBoit PE, Berger TG, Egbert BM, Beckstead JH, Yen TSB, Stoler MH. Bacillary angiomatosis: the histopathology and differential diagnosis of a pseudoneoplastic infection in patients with HIV disease. Am J Surg Pathol 1989, 13:909-920.

Maguiña C, Guerra H, Ventosilla P. Bartonellosis. Clin Dermatol 2009, 27:271-80.

Plettenberg A, Lorenzen T, Burtsche BT, et al. Bacillary angiomatosis in HIV-infected patients—an epidemiological and clinical study. Dermatology 2000, 201:326-31.

Pons I, Sanfeliu I, Nogueras MM, et al. Seroprevalence of Bartonella spp. infection in HIV patients in Catalonia, Spain. BMC Infect Dis 2008, 8:58.

Stoler MH, Bonfiglio TA, Steigbigel RB, et al. An atypical subcutaneous infection associated with AIDS. Am J Clin Pathol 1983, 80:714-718.

Histoplasmosis

Histoplasma capsulatum is a dimorphic mold that lives primarily in moist soil and, despite its name, does not have a capsule. Endemic areas include the southern and Midwestern United States, Central America, and Africa. Histoplasmosis remains a severe and important OI in these regions (Ocansey 2022) and is a rarity in Northern Europe.

If the microconidia (spores) are inhaled, they can cause granulomatous disease in the lungs of immunocompetent individuals. In PLWH (85–95% have less than 100 CD4 T-cells/µl), infection leads to a life-threatening illness with dry cough, fever, dyspnea, and feeling sick (Gutierrez 2005, Mora 2008). Miliary TB or PCP are important differential diagnoses. Disseminated courses also occur, where the pathogen can be detected in bone marrow or liver (Albrecht 1994). Skin (ulcers), oropharynx, or CNS may also be involved (Scheinfeld 2003, Wheat 2005, Antonello 2011). Hepatosplenomegaly is usually present (Mora 2008).

Histoplasmosis is an AIDS-defining disease. Analogous to cryptococci, the pathogen can be detected relatively reliably in the blood with an antigen test. In the laboratory, LDH, AP, and transaminases are sometimes significantly elevated.

Itraconazole (2–3 x 200 mg/day) can be given in milder cases, arguably better than fluconazole (Wheat 2002). In all other cases, liposomal amphotericin (3 mg Ambisome®, 3 mg/kg/day for 14 days) is recommended, which is less toxic and possibly more effective than amphotericin (Johnson 2002). It can be switched to itraconazole after 7–10 days if stabilized. Acute therapy lasts 12 weeks, after which itraconazole is given at half dose (1 x 200 mg) as secondary prophylaxis. Note interactions, especially with ritonavir and efavirenz (Andrade 2009, Hills-Nieminen 2009), which frequently require dose modifications. Analogous to other OIs, secondary prophylaxis can be discontinued if immune reconstitution is permanent (Goldman 2004). Immune reconstitution syndromes are possible (Nacher 2006).

Literature

Albrecht H, Stellbrink HJ, Petersen J, et al. Disseminated histoplasmosis in AIDS. Dtsch Med Wschr 1994, 119:657-62.

Andrade RA, Evans RT, Hamill RJ, Zerai T, Giordano TP. Clinical evidence of interaction between itraconazole and NNRTIs in HIV-infected patients with disseminated histoplasmosis. Ann Pharmacother 2009, 43:908-13.

Antonello VS, Zaltron VF, Vial M, Oliveira FM, Severo LC. Oropharyngeal histoplasmosis: report of eleven cases and review of the literature. Rev Soc Bras Med Trop 2011, 44:26-9.

Goldman M, Zackin R, Fichtenbaum CJ, et al. Safety of discontinuation of maintenance therapy for disseminated histoplasmosis after immunologic response to antiretroviral therapy. Clin Infect Dis 2004, 38:1485-9.

Gutierrez ME, Canton A, Sosa N, et al. Disseminated histoplasmosis in patients with AIDS in Panama: a review of 104 cases. Clin Infect Dis 2005;40:1199-202.

Hills-Nieminen C, Hughes CA, Houston S, Shafran SD. Drug-drug interaction between itraconazole and the protease inhibitor lopinavir/ritonavir. Ann Pharmacother 2009, 43:2117-20.

Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. Ann Intern Med 2002, 137: 105-9.

Mora DJ, dos Santos CT, Silva-Vergara ML. Disseminated histoplasmosis in AIDS patients in Uberaba, MG, Brazil. Mycoses 2008;51:136-40.

Nacher M, Sarazin F, El Guedj M, et al. Increased incidence of disseminated histoplasmosis following HAART initiation. J AIDS 2006, 41:468-70.

Ocansey BK, Kosmidis C, Agyei M, et al. Histoplasmosis in Africa: Current perspectives, knowledge gaps, and research priorities. PLoS Negl Trop Dis 2022, 16:e0010111.

Scheinfeld N. Diffuse ulcerations due to disseminated histoplasmosis in a patient with HIV. J Drugs Dermatol 2003, 2:189-91.

Wheat LJ, Connolly P, Haddad N, et al. Antigen clearance during treatment of disseminated histoplasmosis with itraconazole versus fluconazole in patients with AIDS. Antimicrob Agents Chemother 2002, 46:248-50.

Wheat LJ, Musial CE, Jenny-Avital E. Diagnosis and management of central nervous system histoplasmosis. Clin Inf Dis 2005, 40:844-52.

Isosporiasis (Cystoisosporiasis)

Isospora belli is a ubiquitous intestinal parasite. Rare in Europe and the US, isosporiasis is a major problem, especially in the tropics and subtropics – mainly affecting PLWH in Africa (Lagrange-Xelot 2008). In India, *Isospora belli* was the second most common diarrheal germ after cryptosporidia in PLWH (Kulkarni 2009). Like cryptosporidiosis, the germ occasionally causes epidemic-like outbreaks, even in immunocompetent individuals. Affected individuals suffer from (usually mild) enteritis-like symptoms, occasionally severe watery diarrhea, abdominal cramps, and nausea.

Chronic diarrhea and malnutrition may occur in immunodeficient patients (review: Goodgame 1996). Fever is rare. The median CD4 T-cell count in isosporiasis is 150/µl, slightly higher than in cryptosporidia or microsporidia.

Chronic isosporiasis with diarrhea lasting more than four weeks is considered AIDS-defining. Detection of the relatively large oocysts is successful in regular stool examinations for parasites and acid-fast stains. There is usually an eosinophilia in the blood (Certad 2003).

Cotrimoxazole (960 mg/die, one week) is suitable as therapy. Somewhat less effective is ciprofloxacin (Verdier 2000). Recurrences also occur despite ART and secondary prophylaxis with cotrimoxazole (Lagrange-Xelot 2008).

Literature

Certad G, Arenas-Pinto A, Pocaterra L, et al. Isosporiasis in Venezuelan adults infected with HIV: clinical characterization. Am J Trop Med Hyg 2003, 69:217-22.

Goodgame RW. Understanding intestinal spore-forming protozoa: cryptosporidia, microsporidia, isospora, cyclospora. Ann Int Med 1996,124:429-41.

Kulkarni SV, Kairon R, Sane SS, et al. Opportunistic parasitic infections in HIV/AIDS patients presenting with diarrhoea by the level of immunesuppression. Indian J Med Res 2009, 130:63-6.

Lagrange-Xelot M, Porcher R, Sarfati C, et al. Isosporiasis in patients with HIV infection in the HAART era in France. HIV Med 2008;9:126-30.

Verdier RI, Fitzgerald DW, Johnson WD Jr, Pape JW. Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of Isospora belli and Cyclospora cayetanensis infection in HIV-infected patients. A randomized, controlled trial. Ann Intern Med 2000, 132:885-8.

Coccidioidomycosis

The mold infection with *Coccidioides immitis* occurs endemically in the southwestern US (review: Ampel 2003, Crum 2022). The disease should be considered when visiting Arizona or New Mexico. Disseminated coccidioidomycoses beyond the lungs and hilar lymph nodes (chronic meningoencephalitides) occur almost exclusively in the presence of marked immunodeficiency of less than 250 CD4 T-cells/µl. This disease is AIDS-defining.

The spores are inhaled, primarily affecting the lungs (Pappagianis 1993). About 1–3 weeks after exposure, a pneumonia-like clinical picture develops with fever, cough, chest pain, and feeling of illness. In immunocompetent individuals, the infection, which is often asymptomatic, usually heals without sequelae. Occasionally, cavities remain, rarely requiring surgical intervention (Jaroszewski 2009). In the "pre-HAART era," prognosis was poor, with a one-year mortality of 63% in 602 patients (Jones 1995). Today, the course is usually milder with ART (Masannat 2010).

Serology is usually of little help in immunodeficient patients. The diagnosis can usually be made from cultures or histological materials (Adam 2009). Suspicion must be reported to laboratory personnel, as there is a high risk of infection.

Both amphotericin and azoles are effective (Hernandez 1997); they should possibly be combined (Ampel 2007). Detailed recommendations for different situations

(meningeal or disseminated cases must be treated more intensively) can be found in Galgiani 2005. Fluconazole should be given in high doses (400 mg) as maintenance therapy. Posaconazole may also be considered (Schein 2011). In recent years, the disease has become less common with ART. Maintenance therapy can probably be discontinued if CD4 T-cells exceed 250/µl and initial pulmonary involvement is present. However, lifelong therapy is still recommended for meningeal involvement (Woods 2000, Galgiani 2005, Ampel 2007).

Literature

Adam RD, Elliott SP, Taljanovic MS. The spectrum and presentation of disseminated coccidioidomycosis. Am J Med 2009, 122:770-7.

Ampel NM. Coccidioidomycosis in persons infected with HIV-1. Ann N Y Acad Sci 2007;1111:336-42.

Crum NF. Coccidioidomycosis: A Contemporary Review. Infect Dis Ther 2022, 11:713-742.

Hernandez JL, Echevarria S, Garcia-Valtuille A, Mazorra F, Salesa R. Atypical coccidioidomycosis in an AIDS patient successfully treated with fluconazole. Eur J Clin Microbiol Infect Dis 1997, 16:592-4.

Jaroszewski DE, Halabi WJ, Blair JE, et al. Surgery for pulmonary coccidioidomycosis: a 10-year experience. Ann Thorac Surg 2009, 88:1765-72.

Masannat FY, Ampel NM. Coccidioidomycosis in patients with HIV-1 infection in the era of potent antiretroviral therapy. Clin Infect Dis 2010, 50:1-7.

Pappagianis D. Coccidioidomycosis. Semin Dermatol 1993, 12:301-9.

Schein R, Homans J, Larsen RA, Neely M. Posaconazole for chronic refractory coccidioidal meningitis. Clin Infect Dis 2011, 53:1252-4.

Woods CW, McRill C, Plikaytis BD, et al. Coccidioidomycosis in HIV-infected persons in Arizona, 1994-1997: incidence, risk factors, and prevention. J Infect Dis 2000, 181:1428-34.

Leishmaniasis (visceral)

Leishmaniasis is the collective term for infections with protozoa of the genus Leishmania; cutaneous leishmaniasis is to be distinguished from visceral leishmaniasis (Kalar Azar); the form of manifestation depends, among other things, on the species (*L. donovani, L. infantum, L. chagasi*). According to WHO, 12 million people are infected, and 350 million live in risk areas. Leishmaniasis is thus one of the most important parasitoses of all. In Europe, the Mediterranean region is particularly affected (mostly *L. infantum*).

PLWH are more likely to develop visceral leishmaniasis than HIV-negative individuals. In Spain, one-third are HIV-infected (Gil-Prieto 2011). Although much would suggest this, leishmaniasis is not considered AIDS-defining. An evaluation of 15 cases from Germany showed significant immunosuppression (mostly below 100 CD4 T-cells/µl). Some patients had not been in the endemic areas for several years (Albrecht 1998).

The almost obligate pancytopenia, particularly pronounced in PLWH (Pintado 2001), reflects bone marrow involvement. Fever, hepatosplenomegaly, and mucocutaneous lesions are additional symptoms. Diagnosis is usually made by bone marrow aspirate.

Treatment of visceral leishmaniasis is difficult (overview: Burza 2018). Previously used antimony preparations such as stibogluconate (Pentostam®) and meglumine antimonate (Glucantime®) are toxic. Myalgias, arthralgias, gastrointestinal symptoms, pancreatitis, and cardiotoxicity often force discontinuation (Laguna 1999). Combination therapies are probably equally effective and allow a shortening of therapy – a strategy hardly used in Germany (van Griensven 2010, Sundar 2011).

According to a meta-analysis, amphotericin works better than the antimony preparations (Cota 2013). In the 2016 guidelines of the German Tropical Medicine Society, liposomal amphotericin B (AmBisome®) is considered the drug of choice for HIV:

in the total dose of 30–40 mg/kg, divided into at least 5 single doses over 10–21 days, followed by relapse prophylaxis 3 mg/kg every three weeks). However, the effect is not always optimal (Rijtmeier 2011, Sinha 2011).
An alternative – because it is tolerable, effective, and the only Leishmania drug that is orally bioavailable – is the alkylphosphocholine analog miltefosine (Impavido®), approved in Germany in 2004. How miltefosine inhibits Leishmania metabolism is still unclear, but it is effective in a large phase III study in India (Sundar 2002). However, a randomized trial in Ethiopia showed a somewhat weaker effect in PLWH than under stiboglucanate, albeit with better tolerability (Ritmeijer 2006). Higher success rates are shown with combination therapy of liposomal amphotericin B and miltefosine – versus liposomal amphotericin B alone (Diro 2019, Burza 2022). The aminoglycoside paromomycin also appears to be effective when administered intramuscularly (Sundar 2007+2011). Paromomycin (Humatin®) has only been approved as a local intestinal therapeutic in Europe.
Pentamidine may also work as secondary prophylaxis (Patel 2009), but fluconazole is probably ineffective (Rybniker 2009). Leishmania recurrences can be expected in almost half of the cases. ART seems to change this – another argument for the inclusion of visceral leishmaniasis in the AIDS classification (de La Rosa 2002, Fernandez-Cotarelo 2003).

Literature

Albrecht H, Sobottka I, Emminger C, et al. Visceral leishmaniasis is emerging as an important opportunistic infection in HIV-infected persons living in areas nonendemic for Leishmania donovani. Arch Pathol Lab Med 1996, 120:189-98.

Albrecht H. Leishmaniosis – new perspectives on an underappreciated opportunistic infection. AIDS 1998, 12:2225-6.

Burza S, Croft SL, Boelaert M. Leishmaniasis. Lancet 2018, 392:951-970.

Burza S, Mahajan R, Kazmi S, et al. AmBisome Monotherapy and Combination AmBisome-Miltefosine Therapy for the Treatment of Visceral Leishmaniasis in Patients Coinfected With Human Immunodeficiency Virus in India: A Randomized Open-Label, Parallel-Arm, Phase 3 Trial. Clin Infect Dis 2022;75:1423-1432.

Cota GF, de Sousa MR, Fereguetti TO, Rabello A. Efficacy of anti-leishmania therapy in visceral leishmaniasis among HIV infected patients: a systematic review with indirect comparison. PLoS Negl Trop Dis 2013, 7:e2195.

Diro E, Blesson S, Edwards T, et al. A randomized trial of AmBisome monotherapy and AmBisome and miltefosine combination to treat visceral leishmaniasis in HIV co-infected patients in Ethiopia. PLoS Negl Trop Dis 2019, 13(1):e0006988.

de La Rosa R, Pineda JA, Delgado J, et al. Incidence of and risk factors for symptomatic visceral leishmaniasis among HIV type 1-infected patients from Spain in the era of HAART. J Clin Microbiol 2002, 40:762-7.

Fernandez-Cotarelo MJ, Abellan Martinez J, Guerra Vales JM, et al. Effect of highly active antiretroviral therapy on the incidence and clinical manifestations of visceral leishmaniasis in human immunodeficiency virus-infected patients. Clin Infect Dis 2003, 37: 973-7.

Gil-Prieto R, Walter S, Alvar J, de Miguel AG. Epidemiology of leishmaniasis in Spain based on hospitalization records (1997-2008). Am J Trop Med Hyg 2011, 85:820-5.

Laguna F, Lopez-Velez R, Pulido F, et al. Treatment of visceral leishmaniasis in HIV-infected patients: a randomized trial comparing meglumine antimoniate with amphotericin B. AIDS 1999, 13:1063-9.

Patel TA, Lockwood DN. Pentamidine as secondary prophylaxis for visceral leishmaniasis in the immunocompromised host: report of four cases. Trop Med Int Health 2009, 14:1064-70.

Ritmeijer K, Dejenie A, Assefa Y, et al. A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. CID 2006, 43:357-64.

Ritmeijer K, ter Horst R, Chane S, et al. Limited effectiveness of high-dose liposomal amphotericin B (AmBisome) for treatment of visceral leishmaniasis in an Ethiopian population with high HIV prevalence. CID 2011, 53:e152-8.

Rybniker J, Goede V, Mertens J, et al. Treatment of visceral leishmaniasis with intravenous pentamidine and oral fluconazole in an HIV-positive patient with chronic renal failure – a case report and brief review of the literature. Int J Infect Dis. 2009 Aug 31.

Sinha PK, van Griensven J, Pandey K, et al. Liposomal amphotericin B for visceral leishmaniasis in human immunodeficiency virus-coinfected patients: 2-year treatment outcomes in Bihar, India. Clin Infect Dis 2011, 53:e91-8.

Sundar S, Jha TK, Thakur CP, et al. Oral miltefosine for Indian visceral leishmaniasis. N Engl J Med 2002, 347:1739-46.

Sundar S, Jha TK, Thakur CP, Sinha PK, Bhattacharya SK. Injectable paromomycin for Visceral leishmaniasis in India. N Engl J Med 2007;356:2571-81.

Sundar S, Sinha PK, Rai M, et al. Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. Lancet 2011, 377:477-86.

van Griensven J, Balasegaram M, Meheus F, et al. Combination therapy for visceral leishmaniasis. Lancet Infect Dis 2010, 10:184-194.

Microsporidiosis

Microsporidiosis is an important cause of diarrhea in PLWH worldwide. At least four human pathogenic genera of these obligate intracellular protozoa have been described, *Enterocytozoon bieneusi* being the most important. Microsporidia were also once among the common diarrheal pathogens in Germany (Sobottka 1998). ART has resulted in a sharp decline in incidence. The microsporidia are not AIDS-defining, although they almost exclusively affect massively immunocompromised individuals with fewer than 50 CD4 T-cells/µl.

Diarrhea is usually watery, without blood, accompanied by abdominal pain, nausea, and vomiting. Fever is almost always absent. Rarely, myositis, keratoconjunctivitis, and sinusitis have been described. Biliary tract infections are more common. The laboratory must have experience! Microsporidia are very small, and those not explicitly asked about them do not see them! Cultures are not established. Detection is best done with special stains. Special transport or preparation is not necessary.

Albendazole (Eskazole® 2 x 1–2 tab. of 400 mg/day for 4 weeks) works relatively well, but *E. bieneusi* is often resistant. Small case series on fumagillin (caveat: thrombocytopenias!) have been published (Carr 2002, Molina 2002), as well as on niazoxanide (Bicart-See 2000). However, ART-mediated immune reconstitution seems to be most effective (Carr 1998+2002, Maggi 2000).

Literature

Bicart-See A, Massip P, Linas MD, Datry A. Successful treatment with nitazoxanide of Enterocytozoon bieneusi microsporidiosis in a patient with AIDS. Antimicrob Agents Chemother 2000, 44:167-8.

Carr A, Cooper DA. Fumagillin for intestinal microsporidiosis. N Engl J Med 2002, 347:1381.

Carr A, Marriott D, Field A, Vasak E, Cooper DA. Treatment of HIV-1 associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. Lancet 1998, 351:256-61.

Maggi P, Larocca AM, Quarto M, et al. Effect of antiretroviral therapy on cryptosporidiosis and microsporidiosis in patients infected with HIV virus type 1. Eur J Clin Microbiol Infect Dis 2000, 19:213-7.

Molina JM, Tourneur M, Sarfati C, et al. Fumagillin treatment of intestinal microsporidiosis. N Engl J Med 2002, 346:1963-9.

Sobottka I, Schwartz DA, Schottelius J, et al. Prevalence and clinical significance of intestinal microsporidiosis in HIV-infected patients with and without diarrhea in Germany: a prospective coprodiagnostic study. Clin Infect Dis 1998, 26:475-80.

Nocardiosis

Nocardia are aerobic bacteria or actinomycetes that occur worldwide. They mainly cause pneumonia but also systemic diseases. In one of the largest case collections (from Florida), the lungs were affected in 21 cases in 30 PLWH (Uttamchandani 1994). Pulmonary nocardiosis is often confused with tuberculosis. Extrapulmonary sites of manifestation include skin, brain, as well as kidney, muscle, and bone.

In most cases, severe immunodeficiency is present (Javaly 1992, Uttamchandani 1994). The CD4 T-cells were about 100/µl. Therapeutically, carbapenems (imipenem) and cotrimoxazole are mainly used (Ott 2019). However, experience hardly goes beyond case reports or small case series.

Literature

Javaly K, Horowitz HW, Wormser GP. Nocardiosis in patients with HIV infection. Report of 2 cases and review of the literature. Medicine 1992,71:128-38.

Ott SR, Meier N, Kolditz M, et al. Pulmonary nocardiosis in Western Europe-Clinical evaluation of 43 patients and population-based estimates of hospitalization rates. Int J Infect Dis 2019, 81:140-148.

Pintado V, Gomez-Mampaso E, Cobo J, et al. Nocardial infection in patients infected with the HIV. Clin Microbiol Infect 2003, 9:716-20.

Uttamchandani RB, Daikos GL, Reyes RR, et al. Nocardiosis in 30 patients with advanced HIV infection: clinical features and outcome. Clin Infect Dis 1994, 18:348-53.

Rhodococcosis

Rhodococcus equi (formerly *Corynebacterium equi*) is a sporeless, Gram-positive, intracellular pathogen that is ubiquitous and occurs primarily in dry, dusty soil. *R. equi* has been found on every continent and is most significant in veterinary medicine in horses. The first case of an AIDS patient was described as early as 1986 (Samies 1986). Predominantly, individuals with less than 50 CD4 T-cells/µl are affected (Capdevila 1997). Clinically, there are severe granulomatous or abscessing pneumonia and occasionally disseminated infections. The main symptoms are fever, dyspnea, and nonproductive cough (Capdevila 1997). Radiographs often show caverns in the upper lobes (Marchiori 2005).

Rhodococci are best detected in sputum and blood cultures (Torres-Tortosa 2003). In sputum, however, the coryneform bacteria are often confused with diphtheroid germs of the oral flora.

Erythromycin, azithromycin, ciprofloxacin, rifampicin, or vancomycin are effective. The substances are also combined. However, therapy sometimes does not result in a cure despite ART (Plum 1997, Sanz-Moreno 2002, Ferretti 2011), and surgical intervention may be required for extensive cavities. However, ART improves the prognosis overall; in any case, antiretroviral treatment should be given immediately (Torres-Tortosa 2003, Gundelly 2016).

Literature

Capdevila JA, Bujan S, Gavalda J, Ferrer A, Pahissa A. Rhodococcus equi pneumonia in patients infected with HIV. Report of 2 cases and review of the literature. Scand J Infect Dis 1997, 9:535-41.

Ferretti F, Boschini A, Iabichino C, et al. Disseminated Rhodococcus equi infection in HIV infection despite highly active antiretroviral therapy. BMC Infect Dis 2011, 11:343.

Gundelly P, Suzuki Y, Ribes JA, Thornton A. Differences in Rhodococcus equi Infections Based on Immune Status and Antibiotic Susceptibility of Clinical Isolates in a Case Series of 12 Patients and Cases in the Literature. Biomed Res Int. 2016;2016:2737295.

Marchiori E, Muller NL, de Mendonca RG, et al. Rhodococcus equi pneumonia in AIDS: high-resolution CT findings in five patients. Br J Radiol 2005, 78:783-6.

Plum G, Fätkenheuer G, Hartmann P, et al. Secondary prophylaxis of Rhodococcus equi pneumonia in HIV infection: breakthrough despite rifampicin/erythromycin suppressive therapy. Clin Microbiol Infect 1997, 3:141-143.

Samies JH, Hathaway BN, Echols RM, et al. Lung abscess due to Corynebacterium equi: report of the first case in a patient with AIDS. Am J Med 1986, 80:685–688.

Sanz-Moreno J, Flores-Segovia J, Olmedilla-Arregui G, et al. Rhodococcus equi pneumonia: HAART helps but does not cure lung infection. AIDS 2002, 16:509-11.

Torres-Tortosa M, Arrizabalaga J, Villanueva JL, et al. Prognosis and clinical evaluation of infection caused by Rhodococcus equi in HIV-infected patients: a multicenter study of 67 cases. Chest 2003, 123:1970-6.

Talaromycosis (formerly penicilliosis)

*Talaromycis (*formerly *Penicillium) marneffei* is a problem relevant to Southeast Asia – especially during the rainy season (Le 2011). Rather a rarity in Germany, the disease is the most common fungal infection in PLWH in Thailand, Vietnam, and southern China, along with cryptococcosis (Review: Cao 2019). The only patient we saw had traveled through Thailand for several months (Sobottka 1996).

There is almost always a severe immunodeficiency; in the IVAP study (see below), the median CD4 T-cell count of 440 PLWH was 10/µl. Nevertheless, according to the CDC classification, the infection is not considered AIDS-defining. The only known hosts for *T. marneffei* are humans, rats, and possibly dogs. Most infections likely occur via spore inhalation.

Lungs and skin are most frequently affected, and disseminated courses are possible (Ma 2005). Clinically, there are striking parallels to histoplasmosis. The clinic consists of high, prolonged fever, lymphadenopathy, weight loss, malaise, cough, and

hemoptysis. Cutaneous lesions, present in 80%, resemble molluscs. The liver and spleen are often enlarged (see picture plates!). The culture from blood (successful in 70%), bone marrow, sputum, or biopsies is diagnostically decisive.
Amphotericin B, voriconazole, and itraconazole are effective (Cao 2019). However, in the randomized IVAP trial in 440 (!) patients in Vietnam, conventional amphotericin B was more clinically effective than itraconazole (Le 2017). Liposomal amphotericin B at the dose of 3 mg/kg IV is considered the agent of choice in the current EACS guidelines. Itraconazole is recommended only as an alternative relapse prophylaxis at 200 mg once daily (Supparatpinyo 1998, EACS 2021). Secondary prophylaxis can be discontinued when the viral load has been below the detection limit for at least six months, and CD4 T-cells have reached at least 100/µl (Tun 2020). On the other hand, primary prophylaxis is not advisable even for prolonged stays in endemic areas (Chariyalertsak 2002) but is sometimes recommended for severe immunodeficiency (Cao 2019).

Literature

Cao C, Xi L, Chaturvedi V. Talaromycosis (Penicilliosis) Due to Talaromyces (Penicillium) marneffei: Insights into the Clinical Trends of a Major Fungal Disease 60 Years After the Discovery of the Pathogen. Mycopathologia 2019, 184:709-720.

Chariyalertsak S, Supparatpinyo K, Sirisanthana T, et al. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced HIV infection in Thailand. Clin Infect Dis 2002, 34:277-84.

European AIDS Clinical Society (EACS), GUIDELINES Version October 2021; https://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html (abgerufen 5.4.2022).

Le T, Wolbers M, Chi NH, et al. Epidemiology, Seasonality, and Predictors of Outcome of AIDS-Associated Penicillium marneffei Infection in Ho Chi Minh City, Viet Nam. Clin Infect Dis 2011, 52:945-52.

Le T, Kinh NV, Cuc NTK, Tung NL. A Trial of Itraconazole or Amphotericin B for HIV-Associated Talaromycosis. NEJM 2017, 376:2329-2340.

Ma ES, Ho PL. Disseminated Penicillium marneffei infection. Br J Haematol 2005, 130:2.

Sobottka I, Albrecht H, Mack D, et al. Systemic Penicillium marneffei infection in a German AIDS patient. Eur J Clin Mic Inf Dis 1996,15:256-9.

Supparatpinyo K, Perriens J, Nelson KE, Sirisanthana T. A controlled trial of itraconazole to prevent relapse of Penicillium marneffei infection in patients infected with the HIV. N Engl J Med 1998, 339:1739-43.

Tun N, Mclean A, Deed X. Is stopping secondary prophylaxis safe in HIV-positive talaromycosis patients? Experience from Myanmar. HIV Med 2020, 21:671-673.

Trypanosomiasis

Trypanosoma cruzi is a protozoan transmissible through the infected feces of predatory bugs, found almost exclusively in the Americas. It causes Chagas disease, one of South America's most common causes of cardiomyopathy. PLWH have more frequent and higher parasitemia (Sartori 2002), and the trypanosome-specific immune response is predominantly cellular. Far more frequently than in uninfected persons, there is also a usually severe meningoencephalitis that is radiologically indistinguishable from cerebral toxoplasmosis or primary cerebral lymphoma. Reactivation is most likely (Diazgranados 2009, de Almeida 2011). In PLWH from South America, trypanosome infection should be considered (Silva 1999, Cordova 2008, Llenas-García 2012).
Diagnosis is based on serology (which can also be negative) and evidence from the cerebrospinal fluid. Although therapy with, for example, benznidazole is effective, mortality is nevertheless very high (Sartori 2007, Cordova 2008). Itraconazole or ketoconazole may also be effective (de Almeida 2009).

Literature

Cordova E, Boschi A, Ambrosioni J, Cudos C, Corti M. Reactivation of Chagas disease with central nervous system involvement in HIV-infected patients in Argentina, 1992-2007. Int J Infect Dis 2008,12:587-92.

de Almeida EA, Ramos Júnior AN, Correia D, Shikanai-Yasuda MA. Co-infection Trypanosoma cruzi/HIV: systematic review (1980-2010). Rev Soc Bras Med Trop 2011, 44:762-70.

de Almeida EA, Silva EL, Guariento ME, et al. Aetiological treatment with itraconazole or ketoconazole in individuals with Trypanosoma cruzi/HIV co-infection. Ann Trop Med Parasitol 2009, 103:471-6.

Diazgranados CA, Saavedra-Trujillo CH, Mantilla M, et al. Chagasic encephalitis in HIV patients: common presentation of an evolving epidemiological and clinical association. Lancet Infect Dis 2009, 9:324-30.

Llenas-García J, Hernando A, Fiorante S, et al. Chagas disease screening among HIV-positive Latin American immigrants: an emerging problem. Eur J Clin Microbiol Infect Dis. 2012 Jan 19.

Sartori AM, Ibrahim KY, Nunes Westphalen EV, et al. Manifestations of Chagas disease (American trypanosomiasis) in patients with HIV/AIDS. Ann Trop Med Parasitol 2007;101:31-50.

Sartori AM, Neto JE, Nunes EV, et al. Trypanosoma cruzi parasitemia in chronic Chagas disease: comparison between HIV-positive and HIV-negative patients. J Infect Dis 2002, 186:872-5.

Silva N, O'Bryan L, Medeiros E, et al. Trypanosoma cruzi meningoencephalitis in HIV-infected patients. J AIDS Hum Retrovirol 1999, 20:342-9.

8. Kaposi's sarcoma

CHRISTIAN HOFFMANN, STEFAN ESSER

Kaposi's sarcoma (KS) is the most common AIDS-defining neoplasm. In 1981, the simultaneous occurrence of *Pneumocystis pneumonia* in young MSM led to the first description of AIDS. KS is named after the Hungarian dermatologist Moritz Kaposi, who described "classic" KS more than 100 years ago – a variant not associated with HIV that occurs predominantly in older men from the Eastern European-Mediterranean region with a genetic disposition. In addition, there is also "endemic" KS in some sub-Saharan countries. Classical CS is relatively benign, often affecting only the skin of the lower extremities, and is thus clinically distinct from HIV-associated KS, which will be discussed below.

HIV-associated KS primarily affects the skin and mucous membranes. However, lymph nodes and internal organs such as the gastrointestinal tract, lungs, or liver are also frequently affected. Lymphatic or visceral involvement also occurs in isolation. The course of KS is highly variable, ranging from single lesions that remain stationary for years to markedly aggressive courses that lead to death within a few weeks. Until the 1990s, one of the most common AIDS diseases of all, the prevalence has declined significantly due to ART (Francesci 2010) and is now barely one-tenth compared to earlier years (Grabar 2006, Simard 2011). Also, the clinical course today is usually milder; in particular, the sudden and severe, disfiguring, and often fatal manifestations have become rare. In our retrospective cohort (2000–2014), KS was the probable cause of death in only 5/230 cases (Meyer 2016). KS in the setting of immune reconstitution syndrome (IRIS) is a particular case. Here, aggressive courses, often with visceral involvement, occur a few months after ART initiation, and mortality is considerable (Crane 2005, Achenbach 2012). High HHV-8 and HIV viremia are risk factors for aggressive courses (Letang 2013).

The typical KS spindle cells probably originate from lymphatic endothelial cells (Dupin 2006). Since 1994, KS has been known to be caused by an infection with the human herpesvirus 8 (HHV-8, also "Kaposi sarcoma-associated herpesvirus" KSHV). HHV-8 can always be detected in tumor tissue. HHV-8 viremia (median 6000 copies/mL) is present in approximately 40% but does not correlate with prognosis and is unlikely to correlate with progression (Laney 2007, Haq 2016). Like other herpesviruses, HHV-8 is transmitted predominantly by saliva (Pauk 2000) but also sexually, vertically, and via blood (Pica 2008). In some regions (Italy, Central Africa), HHV-8 can be detected in up to 50% of the population. However, the exact role of HHV-8 in the development is not clear. There may be a predisposition. Specific endothelial cell receptor gene variants appear to play a role (Blumenthal 2019). HHV-8 likely manipulates transcriptional regulators of endothelial cells, interfering with normal cell differentiation (Cancian 2013). Infection with HHV-8 does not necessarily lead to KS. Interactions with HIV, possibly also with HHV-6 and HSV-1, altered signal transduction chains, increased production of growth factors, and cytokine dysregulation all play a role (McCormack 2005). HHV-8 is the driver, and HIV is the trigger (Lidenge 2019).

Among PLWH in Western industrialized countries, almost exclusively homosexual men are affected; KS is rare in women, children, or hemophiliacs. An immunodeficiency or low CD4 T-cells promote development and growth but are not a condition. Thus, KS is among the few AIDS conditions that occur even with good immune status; nearly one-third have more than 300 CD4 T-cells/µl at diagnosis and a viral load below the detection limit (Krown 2008). In the START trial of early ART initiation, KS was primarily responsible for clinical differences (Borges 2016). Interestingly,

cases of HIV-negative MSM with KS have been published (Rashidghamat 2014), and KS lesions occur despite ART and suppressed viral load (Palich 2022). A low CD4/CD8 ratio appears to be a risk factor, especially with good CD4 T-cells and ART (Caby 2022). New or recurrent KS lesions are also frequently seen during treatment with rituximab.

Clinical course

Typically, KS initially presents as bright to livid red, spindle-shaped patches or nodules arranged in the direction of the skin cleavage lines. In the oral mucosa, the hard palate is often affected. However, there are no predilection sites; any localization is possible. The clinical course varies. The tumors may remain virtually unchanged for years or grow and spread rapidly in a few weeks. Rapid growth is sometimes accompanied by pain and yellow-green discoloration of the tumor surroundings (hemorrhages!). Central necrosis and exulceration with bleeding tendency are possible, as well as massive edema, especially on the extremities, genitals, and face. Healing KS often initially fades, loses size, and leaves dirty grayish-brown to light brown hyperpigmentation for months (sometimes for life). These are caused by hemosiderin deposition and increased melanocyte stimulation due to inflammation. Lymphedema can persist for years, especially on the lower legs.

Diagnostics

Although KS is usually a diagnosis by sight, histology (excision or incision) should be generously taken in all unclear cases. Especially in African patients, clinical gaze can be deceiving (Amerson 2016). This is the only way to avoid overlooking differential diagnoses such as cutaneous lymphoma, angiosarcoma, or bacillary angiomatosis. Histologically, the typical spindle-shaped KS cells are found, accompanied by lymphohistiocytic infiltrates and slit-shaped vascular neoplasms surrounded by erythrocyte extravasations. If the diagnosis is definitive, the spread should be clarified by a complete inspection (oral and genital mucosa! Look in the mouth!) and abdominal ultrasonography. If there is mucosal involvement, an EGD/colonoscopy, as is a chest x-ray, is recommended to rule out pulmonary involvement. HHV-8 viral load has no prognostic value (Haq 2016).

Treatment

In naïve and/or viremic individuals with HIV, initiation or optimization of ART is the priority. In cases of low-level KS infection, additional therapy is rarely needed. Immediate administration of etoposide had no sustained effect in a randomized trial of 190 patients from Africa and South America (Hosseinipur 2018). With the decrease in HIV viral load and onset of immune reconstitution, most mucocutaneous KS stabilize or heal completely; however, post-inflammatory hyperpigmentation often remains. In 213 cases of early-stage KS, 5-year survival with ART alone was 95%, with 77% remaining without progression (Bower 2014). ART improves the humoral response against HHV-8 (Sullivan 2010), and HHV-8 viremia decreases rapidly (Cattamanchi 2011). ART breaks should be avoided. In the SMART trial, KS was one of the most common AIDS during treatment interruptions, especially with a history of KS (Silverberg 2007).

Which ART is given does not matter: although a direct antiproliferative effect for PIs has been shown in the laboratory and also in animal studies (Sgadari 2002, Gantt 2011), PIs remained without clinical advantage over other regimens in a large randomized trial (Martin 2014). Recurrences are not more common under non-PI

regimens (Lajaunie 2022). However, "oral shedding" of HHV-8 appears to be reduced under PIs (Gantt 2014).

ART and any local therapies are not sufficient in the following situations:
- Rapid growth of multiple tumors, especially in the setting of an IRIS
- Tumors that occur despite sufficient antiretroviral therapy (for example, with comedication with rituximab or immunosuppressants) or that are progressive
- Infiltrative or exulcerative growth
- Severely affected by the tumor (facial involvement, edema, etc.)
- Therapy request (patient's wish)

Additional treatment methods required are as follows:
Chemotherapies: The pegylated, liposomal anthracycline doxorubicin (Caelyx®) at a dose of 20 mg/m² body surface area is the agent of choice (Stewart 1998, Di Trolio 2006). It has replaced the previously widely used ABV regimen, a combination of adriamycin, bleomycin, and vincristine. Up to 80% of remissions are achieved with Caelyx® (Lichterfeld 2005). Infusions for 30–60 min every 2–3 weeks are feasible on an outpatient basis and are usually well tolerated; antiemetic therapy is not required. Treatment is continued until apparent partial remission (tumors flattened to skin level, color change from livid to brownish and lighter), usually achieved after 6–8 cycles. Recurrences under Caelyx® rarely occur with concurrent ART, most likely in the first year (Martin-Carbonero 2008). If recurrence occurs later, Caelyx® is often quite successful again. If well tolerated, intensification of therapy with shortening of cycles and/or increasing the dose is also possible. Myelotoxicity and cardiotoxicity must be taken into account. Although the latter occurs only above cumulative doses of 450 mg, transthoracic echocardiography (ejection fraction?) is recommended at the beginning of therapy and after every six cycles. Another side effect of Caelyx® is "palmoplantar erythrodysesthesia", which manifests as painful macular erythema on the hands and feet (Lorusso 2007). Given the immunosuppressive effect, cotrimoxazole prophylaxis is recommended at least for the duration of therapy, even for CD4 T-cells above 200 cells/µl. An alternative in case of supply shortages is liposomal daunorubicin (DaunoXome®), which is probably somewhat less effective (Cooley 2007).

Table 1: KS therapies when ART and local therapies are not sufficient.

Therapy	Dosage	Comment
Pegylated liposomal doxorubicin (Caelyx®)	20 mg/m² intravenously every 2 weeks	Therapy of choice, cave myelo- and cardiotoxicity, hand-foot syndrome
Liposomal Daunorubicin (DaunoXome®)	40 mg/m² intravenously every 2–3 weeks	Probably somewhat weaker, considered an alternative in case of supply shortage for Caelyx®
Pegylated Interferon-α 2b* (PegIntron®)	50 µg subcutaneously 1 x / week	Like IFN-α (2a,b) but better tolerated, little data in AIDS KS! Off-label use!
Paclitaxel (Taxol®)	100 mg/m² IV every 2 weeks or 135 mg/m² IV every 3 weeks	Reserve, no first-line use Beware of neutropenia, peripheral neuropathy, allergies, alopecia Off-label use! Caution ART interactions

The taxane paclitaxel (Taxol®) is also effective (Tulpule 2002, Cianfrocca 2010). In a large randomized trial, it was better than ABV and oral etoposide (Krown 2022). However, it is more myelotoxic than Caelyx® and almost always leads to alopecia, often after the first dose (inform patients beforehand!). Paclitaxel should only be used if KS is progressive or relapses under anthracycline therapy. In addition to paclitaxel, docetaxel (Taxotere®) also appears to be effective according to uncontrolled studies (Autier 2005, Lim 2005). Interactions should be noted with taxanes; levels increase with concurrent PI administration (Cianfrocca 2011).
As recurrence treatment (after anthracycline or paclitaxel therapy), oral etoposide (Evans 2002), irinotecan (Vaccher 2005), and the ABV regimen are also suitable. Gemcitabine is also probably effective (Strother 2010, Busakhala 2018).

Immunotherapies: Good remission rates are achieved with interferon (IFN), although these are probably somewhat lower than with liposomal doxorubicin (Kreuter 2005). The mechanism of action is not precise. However, in addition to the immunomodulatory effect, interferons probably induce apoptosis in KS cells and inhibit angiogenesis. Remission rates depend on the immune status; above 400 CD4 T-cells/µl, they are above 45%; below 200, they are only 7%. Standard regimens do not exist. Interferon-α 2b (Roferon®), commonly used in the past, has been withdrawn from the market. Interferon-α 2a (Intron A®) does not have approval for KS (Krown 2002). This also applies to pegylated interferons (weekly administration possible, more tolerable). The optimal dose is unknown; there are small case series in AIDS KS (Rokx 2013) and classical KS (Di Lorenzo 2008). Following instructions, injections can be self-administered. Administration can be reduced with the onset of remission (stop of tumor growth, flattening, change from livid-red to brownish, lighter shades). In addition to regular inspection of the local findings on the skin and mucous membranes, adapted staging examinations are part of the therapy control.

Local therapies are tolerable and usually inexpensive. Single aesthetically or functionally disturbing lesions can be treated quickly and effectively with local therapy. Many things are possible: simple camouflage, local compression therapy (Brambilla 2006), but also cryosurgery, purely intralesional treatment with vinca alkaloids (Ramirez-Amador 2002), excisions, or even Imiquimod cream (Celestin Schartz 2008).
The KS is radiation sensitive (Donato 2013). Soft X-rays in single doses of 4–5 Gy (total dose 20–30 Gy, fractionation 3x/week) are sufficient for superficial macular or plaque tumors. In contrast, for extensive KS with edema, radiation should be delivered with fast electrons (5 x 2 Gy per week) up to a total target volume dose of 40 Gy.
Since KS is a multilocular systemic disease, surgery usually makes little sense. If at all, only small, cosmetically conspicuous tumors should be surgically removed. However, scar recurrences are expected in this case due to the Koebner phenomenon. These can be avoided by radiation therapy, the radiation field of which extends 0.5–1.0 cm beyond the tumor borders and also reaches the tumor cells spreading in vascular lodges.
In KS-related lymphedema, especially in the extremities, mechanical lymphatic drainage and, if necessary, adapted compression therapy should be performed early on, provided there are no contraindications (severe cardiac and/or renal insufficiency). These promote recanalization of the damaged lymphatic vessels and prevent complications such as chronic ulcers.
However, local therapies have become much less important in the ART era; they are rarely necessary.

New therapeutic approaches: Due to KS pathogenesis, new therapies are constantly being proposed, including viral statics, but also cytokines and angiogenesis inhibitors. Some of them will be mentioned here.

- Valganciclovir – decreased HHV-8 viral load in a randomized trial (Casper 2008). The effect is probably greater than under valaciclovir and famciclovir, which also have antiviral activity. However, clinical KS studies are lacking. Since HHV-8 is involved in early tumorigenesis, it remains to be seen whether there is any effect in already manifest KS. In classical KS, valganciclovir remained ineffective (Krown 2011).
- Imatinib (Gleevec®) – tyrosine kinase inhibitor used in leukemias, inhibiting relevant growth factors (PDGF) in KS. Partial remissions were found in 10/30 AIDS KS cases in a phase II study (Koon 2013). There are case reports of refractory cases (Cao 2015). In contrast, sorafenib (Nexavar®) was only moderately effective and poorly tolerated in Phase 1b (Uldrick 2017).
- Nivolumab is a checkpoint inhibitor. A pilot study found a response in 5/8 cases (Galanina 2018). Pembrolizumab also showed some efficacy in HIV-negative patients in Phase II (Delyon 2022).
- Interleukin-12 – high response rates in a phase II trial, albeit combined with liposomal doxorubicin (Little 2007). Randomized studies are lacking.
- Sirolimus (and everolimus) – immunosuppressants used in transplantation medicine. Inhibit angiogenesis by decreasing the production of vascular endothelial growth factors. In uncontrolled studies, good response rates in HIV-negative kidney transplant patients (Stallone 2005, Campistol 2007).
- Lenalidomide – this immunomodulator with anti-angiogenic properties achieved response rates between 40 and 60% in Phase II (Pourcher 2017, Reid 2022). There are also positive reports on pomalidomide from a Phase I/II trial; the most notable was the effect on lymphedema (Polizzotto 2016).
- Bevacizumab – an early study of this VEGF antibody showed moderate response rates of 31% in 17 PLWH with progression on ART (Uldrick 2012). The effects of PTC299, a post-transcriptional inhibitor of VEGF, remained only moderate in a small study (Bender 2016).
- Retinoids (all-trans-retinoic acid) inhibit KS proliferation. However, the response rates were not convincing. This approach has not gained acceptance, and the same is true for inhibitors of matrix metalloproteinases (MMPs).

Literature

Achenbach CJ, Harrington RD, Dhanireddy S, Crane HM, Casper C, Kitahata MM. Paradoxical immune reconstitution inflammatory syndrome in HIV-infected patients treated with combination antiretroviral therapy after AIDS-defining opportunistic infection. Clin Infect Dis 2012, 54:424-33.

Amerson E, Woodruff CM, Forrestel A, et al. Accuracy of Clinical Suspicion and Pathologic Diagnosis of Kaposi Sarcoma in East Africa. J AIDS 2016, 71:295-301.

Aoki Y, Tosato G. HIV-1 Tat enhances KSHV infectivity. Blood 2004; 104: 810-4

Autier J, Picard-Dahan C, Marinho E, et al. Docetaxel in anthracycline-pretreated AIDS-related Kaposi's sarcoma: a retrospective study. Br J Dermatol 2005, 152:1026-9.

Bender Ignacio RA, Lee JY, Rudek MA, Dittmer DP, Ambinder RF, Krown SE. Brief Report: A Phase 1b/Pharmacokinetic Trial of PTC299, a Novel PostTranscriptional VEGF Inhibitor, for AIDS-Related Kaposi's Sarcoma: AIDS Malignancy Consortium Trial 059. J AIDS 2016;72:52-7.

Blumenthal MJ, Schutz C, Meintjes G. EPHA2 sequence variants are associated with susceptibility to Kaposi's sarcoma-associated herpesvirus infection and Kaposi's sarcoma prevalence in HIV-infected patients. Cancer Epidemiol 2018 Oct;56:133-139.

Bower M, Dalla Pria A, Coyle C, et al. Prospective stage-stratified approach to AIDS-related Kaposi's sarcoma. J Clin Oncol 2014, 32:409-14.

Bower M, Nelson M, Young AM, et al. Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. J Clin Oncol 2005; 23: 5224-8.

Brambilla L, Tourlaki A, Ferrucci S, Brambati M, Boneschi V. Treatment of classic Kaposi's sarcoma-associated lymphedema with elastic stockings. J Dermatol 2006; 33: 451-6.

Busakhala NW, Waako PJ, et al. Randomized Phase IIA Trial of Gemcitabine Compared With Bleomycin Plus Vincristine for Treatment of Kaposi's Sarcoma in Patients on Combination Antiretroviral Therapy in Western Kenya. J Glob Oncol. 2018 Sep;4:1-9.

Caby F, Guiguet M, Weiss L, et al. CD4/CD8 Ratio and the Risk of Kaposi Sarcoma or Non-Hodgkin Lymphoma in the Context of Efficiently Treated Human Immunodeficiency Virus (HIV) Infection: A Collaborative Analysis of 20 European Cohort Studies. Clin Infect Dis 2021, 73:50-59.

Campistol JM, Schena FP. Kaposi's sarcoma in renal transplant recipients—the impact of proliferation signal inhibitors. Nephrol Dial Transplant 2007, 22 Suppl 1:i17-22.

Cancian L, Hansen A, Boshoff C. Cellular origin of Kaposi's sarcoma and Kaposi's sarcoma-associated herpesvirus-induced cell reprogramming. Trends Cell Biol 2013; 23:421-32.

Cao W, Vyboh K, Routy B. Imatinib for highly chemoresistant Kaposi sarcoma in a patient with long-term HIV control: a case report and literature review. Curr Oncol 2015, 22:e395-9.

Casper C, Krantz EM, Corey L, et al. Valganciclovir for suppression of human herpesvirus-8 replication: a randomized, double-blind, placebo-controlled, crossover trial. J Infect Dis 2008, 198:23-30.

Celestin Schartz NE, Chevret S, Paz C, et al. Imiquimod 5% cream for treatment of HIV-negative Kaposi's sarcoma skin lesions: A phase I to II, open-label trial in 17 patients. J Am Acad Dermatol 2008, 58:585-91.

Cianfrocca M, Lee S, Von Roenn J, et al. Pilot study evaluating the interaction between paclitaxel and protease inhibitors in patients with human immunodeficiency virus-associated Kaposi's sarcoma. Cancer Chemother Pharmacol 2011, 68:827-33.

Cianfrocca M, Lee S, Von Roenn J, et al. Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kaposi sarcoma: evidence of symptom palliation from chemotherapy. Cancer 2010, 116:3969-77.

Cooley T, Henry D, Tonda M, Sun S, O'Connell M, Rackoff W. A randomized, double-blind study of pegylated liposomal doxorubicin for the treatment of AIDS-related Kaposi's sarcoma. Oncologist 2007, 12:114-23.

Crane HM, Deubner H, Huang JC, Swanson PE, Harrington RD. Fatal Kaposi's sarcoma-associated immune reconstitution following HAART initiation.Int J STD AIDS 2005; 16:80-3.

Delyon J, Biard L, Renaud M, et al. PD-1 blockade with pembrolizumab in classic or endemic Kaposi's sarcoma: a multicentre, single-arm, phase 2 study. Lancet Oncol 2022, 23:491-500.

Di Lorenzo G, Di Trolio R, Montesarchio V, et al. Pegylated liposomal doxorubicin as second-line therapy in the treatment of patients with advanced classic Kaposi sarcoma: a retrospective study. Cancer 2008, 112:1147-52.

Di Trolio R, Di Lorenzo G, Delfino M, De Placido S. Role of pegylated lyposomal doxorubicin (PLD) in systemic Kaposi's sarcoma: a systematic review. Int J Immunopathol Pharmacol 2006; 19: 253-63.

Donato V, Guarnaccia R, Dognini J, et al. Radiation therapy in the treatment of HIV-related Kaposi's sarcoma. Anticancer Res 2013, 33:2153-7.

Dupin N, Grange, PA. Looking for the target cell of Kaposi's sarcoma-associated herpesvirus. J Invest Dermatol 2006, 126:545-7.

Evans SR, Krown SE, Testa MA, Cooley TP, Von Roenn JH. Phase II evaluation of low-dose oral etoposide for the treatment of relapsed or progressive AIDS-related Kaposi's sarcoma: an AIDS Clinical Trials Group clinical study. J Clin Oncol 2002, 20:3236-41.

Franceschi S, Lise M, Clifford GM, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. Br J Cancer 2010, 103:416-22.

Galanina N, Goodman AM, Cohen PR, Frampton GM, Kurzrock R. Successful Treatment of HIV-Associated Kaposi Sarcoma with Immune Checkpoint Blockade. Cancer Immunol Res 2018, 6:1129-1135.

Gantt S, Carlsson J, Ikoma M, et al. The HIV protease inhibitor nelfinavir inhibits Kaposi sarcoma-associated herpesvirus replication in vitro. Antimicrob Agents Chemother. 2011 Mar 14. [Epub ahead of print].

Gantt S, Cattamanchi A, Krantz E, et al. Reduced human herpesvirus-8 oropharyngeal shedding associated with protease inhibitor-based antiretroviral therapy. J Clin Virol 2014, 60:127-32.

Haq IU, Dalla Pria A, Papanastasopoulos P, et al. The clinical application of plasma Kaposi sarcoma herpesvirus viral load as a tumour biomarker: results from 704 patients. HIV Med 2016, 17:56-61.

Hosseinipour MC, Kang M, Krown SE, et al. As-Needed versus Immediate Etoposide Chemotherapy in Combination with Antiretroviral Therapy for Mild or Moderate AIDS-associated Kaposi Sarcoma in Resource-Limited Settings: A5264/AMC-067 Randomized Clinical Trial. CID 2018, 67:251-260.

Koon HB, Krown SE, Lee JY, et al. Phase II trial of imatinib in AIDS-associated Kaposi's sarcoma: AIDS Malignancy Consortium Protocol 042. J Clin Oncol 2014, 32:402-8.

Kreuter A, Rasokat H, Klouche M, et al. Liposomal pegylated doxorubicin versus low-dose recombinant interferon Alfa-2a in the treatment of advanced classic Kaposi's sarcoma; retrospective analysis of three German centers. Cancer Invest 2005, 23:653-9.

Krown SE, Dittmer DP, Cesarman E. Pilot study of oral valganciclovir therapy in patients with classic Kaposi sarcoma. J Infect Dis 2011, 203:1082-6.

Krown SE, Lee JY, Dittmer DP; AIDS Malignancy Consortium. More on HIV-associated Kaposi's sarcoma. N Engl J Med 2008, 358:535-6.

Krown SE, Li P, Von Roenn JH, Paredes J, Huang J, Testa MA. Efficacy of low-dose interferon with antiretroviral therapy in Kaposi's sarcoma: a randomized phase II AIDS clinical trials group study. J Interferon Cytokine Res 2002, 22:295-303.

Krown SE, Moser CB, MacPhail P, et al. Treatment of advanced AIDS-associated Kaposi sarcoma in resource-limited settings: a three-arm, open-label, randomised, non-inferiority trial. Lancet 2020, 395:1195-1207.

Krown SE. AIDS-associated Kaposi's sarcoma: Is there still a role for interferon alfa? Cytokine Growth Factor Rev 2007;18:395-402.

Lajaunie R, Cuzin L, Palich R, et al. No increased risk of Kaposi sarcoma relapse in patients with controlled HIV-1 infection after switching protease inhibitor-based antiretroviral therapy. HIV Med. 2022; 23:301-306.

Laney AS, Cannon MJ, Jaffe HW, et al. Human herpesvirus 8 presence and viral load are associated with the progression of AIDS-associated Kaposi's sarcoma. AIDS 2007; 21:1541-5.

Letang E, Lewis JJ, Bower M, et al. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma: higher incidence and mortality in Africa than in the UK. AIDS. 2013 Mar 4. [Epub ahead of print].

Lichterfeld M, Qurishi N, Hoffmann C, et al. Treatment of HIV-1-associated Kaposi's sarcoma with pegylated liposomal doxorubicin and HAART simultaneously induces effective tumor remission and CD4+ T cell recovery. Infection 2005; 33: 140-7.

Lidenge SJ, Tso FY, Ngalamika O, et al. Similar Immunological Profiles Between African Endemic and Human Immunodeficiency Virus Type 1-Associated Epidemic KS Patients Reveal the Primary Role of KS-Associated Herpesvirus in KS Pathogenesis. J Infect Dis 2019, 219:1318-1328.

Lim ST, Tupule A, Espina BM, Levine AM. Weekly docetaxel is safe and effective in the treatment of advanced-stage acquired immunodeficiency syndrome-related Kaposi sarcoma. Cancer 2005; 103: 417-21.

Little RF, Aleman K, Kumar P, et al. Phase 2 study of pegylated liposomal doxorubicin in combination with interleukin-12 for AIDS-related Kaposi sarcoma. Blood 2007, 110:4165-71.

Lorusso D, Di Stefano A, Carone V, Fagotti A, Pisconti S, Scambia G. Pegylated liposomal doxorubicin-related palmar-plantar erythrodysesthesia ('hand-foot' syndrome). Ann Oncol 2007;18:1159-64.

Martin J, Laker-Oketta M, Walusana V, et al. Randomized Trial of Protease Inhibitor-Based Antiretroviral Therapy for Kaposi Sarcoma in Africa. Abstract 710, CROI 2014, Boston.

Martin-Carbonero L, Barrios A, Saballs P, et al. Pegylated liposomal doxorubicin plus highly active antiretroviral therapy versus highly active antiretroviral therapy alone in HIV patients with Kaposi's sarcoma. AIDS 2004; 18: 1737-40.

Martín-Carbonero L, Palacios R, Valencia E, et al. Long-term prognosis of HIV-infected patients with Kaposi sarcoma treated with pegylated liposomal doxorubicin. Clin Infect Dis 2008, 47:410-7.

McCormick C, Ganem D. The kaposin B protein of KSHV activates the p38/MK2 pathway and stabilizes cytokine mRNAs. Science 2005; 307: 739-41.

Meyer L, Stoehr A, Horst HA, et al. Clinical characteristics of HIV-associated Kaposi's sarcoma in the era of combination antiretroviral therapy. Oncol Res Treat 2016; 39(suppl 3):175.

Palich R, Makinson A, Veyri M, et al. Kaposi's Sarcoma in Virally Suppressed People Living with HIV: An Emerging Condition. Cancers 2021, 13:5702.

Pauk J, Huang ML, Brodie SJ, et al. Mucosal shedding of human herpesvirus 8 in men. N Engl J Med 2000, 343:1369-77.

Pica F, Volpi A. Transmission of human herpesvirus 8: an update. Curr Opin Infect Dis 2007:152-6.

Polizzotto MN, Uldrick TS, Wyvill KM, et al. Pomalidomide for Symptomatic Kaposi's Sarcoma in People With and Without HIV Infection: A Phase I/II Study. J Clin Oncol 2016, 34:4125-4131.

Pourcher V, Desnoyer A, Assoumou L, et al. Phase II Trial of Lenalidomide in HIV-Infected Patients with Previously Treated Kaposi's Sarcoma: Results of the ANRS 154 Lenakap Trial. AIDS Res Hum Retroviruses 2017;33:1-10.

Ramirez-Amador V, Esquivel-Pedraza L, Lozada-Nur F, et al. Intralesional vinblastine vs. 3% sodium tetradecyl sulfate for the treatment of oral Kaposi's sarcoma. A double blind, randomized clinical trial. Oral Oncol 2002, 38:460-7.

Rashidghamat E, Bunker CB, Bower M, Banerjee P. Kaposi Sarcoma in HIV-negative men who have sex with men. Br J Dermatol. 2014 May 10.

Reid EG, Shimabukuro K, Moore P, et al. AMC-070: Lenalidomide Is Safe and Effective in HIV-Associated Kaposi Sarcoma. Clin Cancer Res 2022; 28:2646-56.

Rokx C, van der Ende ME, Verbon A, Rijnders BJ. Peginterferon alfa-2a for AIDS-associated Kaposi sarcoma: experience with 10 patients. Clin Infect Dis 2013, 57:1497-9.

Sgadari C, Barillari G, Toschi E, et al. HIV protease inhibitors are potent anti-angiogenic molecules and promote regression of KS. Nat Med 2002, 8: 225-32.

Silverberg MJ, Neuhaus J, Bower M, et al. Risk of cancers during interrupted antiretroviral therapy in the SMART study. AIDS 2007;21:1957-63.

Simard EP, Pfeiffer RM, Engels EA. Cumulative incidence of cancer among individuals with AIDS in the United States. Cancer 2011, 117:1089-96.

Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. N Engl J Med 2005, 352:1317-23.

Stewart S, Jablonowski H, Goebel FD, et al. Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. International Pegylated Liposomal Doxorubicin Study Group. J Clin Oncol 1998, 16:683-91.

Strother RM, Gregory KM, Pastakia SD, et al. Retrospective analysis of the efficacy of gemcitabine for previously treated AIDS-associated Kaposi's sarcoma in western Kenya. Oncology 2010, 78:5-11.

Sullivan SG, Hirsch HH, Franceschi S, et al. Kaposi sarcoma herpes virus antibody response and viremia following highly active antiretroviral therapy in the Swiss HIV Cohort study. AIDS 2010, 24:2245-52.

Tulpule A, Groopman J, Saville MW, et al. Multicenter trial of low-dose paclitaxel in patients with advanced AIDS-related KS. Cancer 2002, 95:147-54.

Uldrick T, Wyvill K, Kumar P. A phase II study targeting vascular endothelial growth factor with the humanized monoclonal antibody bevacizumab in the treatment of patients with HIV-associated Kaposi sarcoma. Abstract 31, 17th CROI 2010, San Francisco.

Uldrick TS, Wyvill KM, Kumar P, et al. Phase II study of bevacizumab in patients with HIV-associated Kaposi's sarcoma receiving antiretroviral therapy. J Clin Oncol 2012, 30:1476-83.

Uldrick TS, Goncalves PH, Wyvill KM, et al. A Phase Ib Study of Sorafenib (BAY 43-9006) in Patients with KS. Oncologist 2017;22:505-e49.

9. Malignant lymphomas

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Malignant lymphomas are malignant diseases of the lymphatic system. A distinction is made between Hodgkin's lymphoma (HL) and the large group of non-Hodgkin's lymphomas (NHL). The latter are biologically and clinically divided into B and T cells or indolent (low-malignant) and aggressive (highly malignant) lymphomas. Compared with the normal population, PLWH are at significantly increased risk for malignant lymphomas, particularly aggressive B cell NHL (see Table 1). The estimated cumulative lifetime risk of NHL is 4.5% (Silverberg 2015). ART has significantly reduced the incidence of NHL, but not as impressively as Kaposi's sarcoma or most other OIs (COHERE 2009, Franceschi 2010). Thus, the relative proportion of NHL in all AIDS cases has increased. The decline is most evident in subtypes that often first appear in the setting of massive immunodeficiencies, such as primary CNS lymphoma (Polesel 2008).
In some cohorts of PLWH, malignant lymphomas have overtaken Kaposi's sarcoma as the most common malignancy (Poizot-Martin 2021), and they are now by far the most common cause of AIDS-related deaths, accounting for about 24% in France in 2010. In the Cologne-Bonn cohort, lymphomas accounted for 16% of all deaths from 2004–2010 (Ehren 2014). Lymphomas caused more deaths than PML and PCP combined, the two most dangerous OIs (Morlat 2014). NHL also ranked first among cancer-related deaths, ahead of lung cancer (Horner 2021).

Table 1: The relative risk of various non-Hodgkin's lymphomas in the US among PLWH compared with the general population 1996-2010, n=2,828 (adapted from Gibson 2014).

NHL, total	10.6
High-grade B cell lymphoma	
Diffuse large B-cell lymphoma (DLBCL)	17.6
Burkitt's lymphoma (BL)	33.7
Not classifiable	19.9
Primary CNS Lymphoma (PCNSL)	47.7
Low-grade B cell lymphoma	
Follicular NHL	1.3
T cell lymphoma	
Peripheral T-cell NHL	3.6

In PLWH malignant lymphomas are biologically very heterogeneous with differences in the frequency and extent of oncogenic mutations or cytokine dysregulation and the histogenetic origin of the malignant cells. The association with EBV and other oncogenic viruses such as HHV-8 or SV40 is also highly variable. This is also true for the extent of immunodeficiency. While Burkitt's lymphoma and HL often occur even with relatively good immune status, severe immunodeficiencies are the rule, especially in primary CNS lymphoma (PCNSL). Thus, there appear to be "opportunistic" lymphoma subtypes that arise more because of immunodeficiency, whereas in others, HIV-induced chronic B-cell stimulation seems to be more crucial. Cumulative viremia is a risk factor for the development of Burkitt's lymphoma (Zoufaly 2009, Hernández-Ramírez 2019).
However, HIV-associated lymphomas – NHL and HL – share many clinical features. They are usually diagnosed at advanced stages and often have extra-nodal manifestations. Despite a markedly improved prognosis overall, mortality risk is about twice

that of HIV-negative NHL, according to US registry data (Chao 2010, Coghill 2015). Therapy can be fraught with complications and requires close collaboration between HIV medicine and hematology-oncology.
The following will discuss systemic NHL, PCNSL, and HL separately. Castleman's disease will also be mentioned as a separate entity, although it is not a malignant lymphoma. Low-grade (indolent) or T-cell lymphomas are so rare that they will not be discussed here – their therapy should be based on the recommendations for HIV-negative patients.

Systemic non-Hodgkin's lymphoma (NHL)

The close association between NHL and AIDS has long been known – the first cases were published even before the discovery of HIV (Ziegler 1982). Since 1985, high-grade (aggressive) B-cell lymphomas have been considered AIDS-defining.
HIV-associated NHL are B cell lymphomas in more than 95% of cases. They are almost always aggressive with two histological types dominating. According to WHO classification, one is Burkitt's lymphoma, which accounts for 30–40% of cases, and the other is diffuse large B cell lymphoma (DLBCL) in 40–60%. Up to 10% of all HIV-associated lymphomas cannot be classified even by reference pathologies. Plasmablastic lymphomas (PBL) are much less common. A very small proportion (1–3%) is termed primary effusion lymphoma (PEL) and forms a largely distinct entity (see below). Evidence shows that the proportion of Burkitt's lymphoma in all NHL is increasing (Ramaswami 2016, Olszewski 2016).

Screening

There is no well-documented recommendation for screening (for example, regular sonographies, etc.). The best prevention is effective ART. It improves immune status and reduces another risk factor, namely chronic B-cell activation (Grulich 2008). The risk for NHL but not HL is favored by cumulative viremia (Shepard 2018, Kimani 2020). Parameters of immune activation and B-cell stimulation such as immunoglobulins, interleukin-6 or IL-10, and soluble CD30 (Breen 2012) or free light chains (Landgren 2010) are associated with increased lymphoma risk. Although they tell us something about the development of malignant lymphomas, they have no therapeutic or prognostic relevance and are of no importance for clinical practice (Tittle 2015).

Clinic

The leading symptom is swelling of the lymph nodes. The enlarged lymph nodes are usually gross, challenging to move, and indolent. Many affected individuals have an advanced stage of lymphoma (Ann Arbor stages III-IV) at the time of diagnosis, and B-symptoms with fever and/or night sweats and/or weight loss (at least 10% in the past six months) are present in the majority of cases (60–80%). General weakness, marked feelings of illness, and rapid physical deterioration are common. Extra-nodal involvement is also frequent, sometimes assuming large proportions. In our cohort of 203 patients, 81% had at least one extra-nodal manifestation (Hoffmann 2003). Orbits, testes, heart, breast, bladder, kidney, muscles, and bones – all imaginable organs and body regions can be affected. In particular, the gastrointestinal tract, liver, bone marrow, and the ENT area are frequently affected. CNS involvement occurs in 6% of DLBCL (Barta 2016). Depending on the location, additional symptoms may occur if extra-nodal sites are affected. These are abdominal pain due

to liver and spleen enlargement, bleeding or ileus symptoms in intestinal involvement, bone pain due to infiltration of the skeleton, or headache in brain involvement.

Diagnostics

Prompt histological diagnosis is essential. Unless a bone marrow puncture has already confirmed the diagnosis, a lymph node (for example axillary or cervical) should be removed. Merely puncturing a lymph node is often not sufficient to determine the subtype. The material must be sent to a pathology department with experience in hematopathology. The basic pathological diagnosis should include information on the subtype (Burkitt?), the proliferation rate, and the expression profile (minimum: CD20, desirable: CD10, CD138, MUM-1) since this has therapeutic consequences (see below). For practitioners, it is crucial not to accept a pathological diagnosis uncritically but to discuss it, especially if there are doubts given the clinical picture. Beware of misdiagnoses! A typical example is the diagnosis of an aggressive T-cell lymphoma. This may be confidently doubted, since T cell infiltrates may hide a variety of other (primarily infectious) diseases (lues maligna?).
All persons with NHL should be staged according to the Ann Arbor classification (Tables 2a, 2b).
Basic diagnostics and staging include chest X-ray, abdominal ultrasonography, bone marrow biopsy (aspiration is not sufficient!), and CTs of the neck, chest, and abdomen. In addition to current immune status and viral load, at a minimum, blood count, blood sedimentation rate, CRP, uric acid, LDH, liver and kidney values, electrolytes, and hepatitis A, B, and C serology should be determined. ECG and echocardiography are also necessary examinations in advance. This is the only way to objectify the possible cardiotoxicity of chemotherapy (anthracyclines!). Lung function should be examined before regimens containing bleomycin.

Table 2a: Dispersal stages according to the updated Ann Arbor classification.

I	Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or district (IE).
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single extralymphatic organ or district and its regional lymph node(s) with or without involvement of other lymph node regions on the same side of the diaphragm (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III), possibly additional localized involvement of an extralymphatic organ or district (IIIE), or simultaneous involvement of the spleen (IIIS) or simultaneous involvement of both (IIIE+S)
IV	Disseminated (multifocal) involvement of one or more extralymphatic organs with or without concomitant lymph node involvement; or isolated involvement of an extralymphatic organ with involvement of distant (nonregional) lymph nodes

Table 2b: Each stage is divided into A and B categories.

A	Absence of defined general symptoms
B	General symptoms unexplained weight loss of more than 10% in the last six months and/or unexplained persistent or recurrent fever above 38 °C and/or strong night sweats

After two cycles of chemotherapy, response to therapy should be assessed by restaging based on the initial lymphoma localization. After completion of chemotherapy, complete restaging with bone marrow biopsy (if there was initial involvement) and all CTs are required. If there is complete remission, follow-up examinations should be done at three-month intervals. After one year the intervals can be extended to six months, and twelve months after two years. Recurrences after more than two years are rare.
In Burkitt's lymphoma, a lumbar puncture should always be performed at the start of systemic chemotherapy to exclude meningeal involvement and to start intrathecal prophylaxis. In DLBCL – in analogy to HIV-negative patients – this is only reasonable if at least 4 of the following six factors are present (Schmitz 2016): Involvement of the kidneys and/or adrenal glands, age > 60 years, LDH > normal value, ECOG PS > 1, Ann Arbor stage III/IV, > 1 extra-nodal involvement.

Treatment

Any aggressive HIV-associated B-cell lymphoma should be treated quickly with chemo-immunotherapy. Even with an unfavorable initial situation (advanced stage, severe immunodeficiency), complete remission or cure remains the ultimate goal (Hoffmann 2003, Hentrich 2014, Noy 2019). For this reason alone, dose reductions should be avoided whenever possible. Surgery or radiation alone will not suffice. There is no time to waste with staging.
Internationally, the R-CHOP regimen (usually 4–6 cycles; see Table 3) is used in most cases of DLBCL. R is the abbreviation for the monoclonal antibody rituximab, which binds highly specifically to CD20-positive B cells (CD20 is expressed on most lymphoma cells). CHOP is polychemotherapy with the cytostatics cyclophosphamide, adriamycin (hydroxydaunorubicin), vincristine (Oncovin®), and prednisolone. To date, no other chemotherapy has shown a convincing advantage over CHOP. Complete remissions can be achieved at 60–80%. CHOP can be administered on an outpatient basis and is quite well tolerated. As a rule, six cycles should be given. Four cycles are sufficient only in cases of very low lymphoma risk, but no data exist on treatment reduction in PLWH (Poeschel 2019). Outpatient administration is a major advantage over similar regimens such as CDE (cyclophosphamide, doxorubicin, etoposide) or EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin), which must be given continuously intravenously over several days. The standard three-week CHOP regimen ("CHOP-21") is shown in Table 3.
As antimicrobial adjuvant therapy, we recommend – regardless of the CD4 T-cell count – cotrimoxazole until one month after chemotherapy (960 mg three times a week). The oral mucosa should be protected and treated with mouth rinses and amphotericin topicals (for example, Ampho-Moronal® lozenges). Good adherence is crucial. During chemotherapy, twice-weekly blood count checks and liver and kidney values are required.

Table 3: Standard CHOP regimen (4–6 cycles, each repeated on day 22).

Cyclophosphamide	750 mg/m² IV day 1
Doxorubicin	50 mg/m² IV day 1
Vincristine	1.4 mg/m² (maximum 2 mg) IV day 1
Prednisolone	1 x 2 tbl. at 50 mg oral, days 1–5
Mesna	20% of cyclophosphamide dose at hours 0, 4, 8 IV (short infusion) or orally

Treatment is continued according to the schedule at the full dose, provided that leukocytes return to above 3000/µl and platelets above 80.000/µl after passage of the nadir. Patients should understand, take their temperature daily, and be urged to present promptly, especially if they have a fever.

Treatment with **rituximab** is usually well tolerated but results in prolonged B-cell depletion and occasionally causes neutropenia. Cases of progressive multifocal encephalopathy (PML) have been described in HIV-negative patients (Carson 2009). However, an increased risk for PML has never been demonstrated in PLWH receiving rituximab (Hoffmann 2012).
A randomized Phase III trial (AMC 010) tested CHOP versus R-CHOP in AIDS NHL. It showed an increased rate of deaths due to bacterial infections in the rituximab arm (2% versus 14%) (Kaplan 2005). This was particularly evident at low CD4 T-cell counts (< 50/µl). These results are countered by several non-randomized studies that found no increased infection rate with rituximab (Spina 2005, Sparano 2010). Our prospective, multi-center cohort study also failed to confirm the AMC 010 data (Wyen 2012). Meta-analyses significantly improved CR rate and survival by rituximab (Castillo 2012, Barta 2013). Therefore, rituximab should be considered in principle in PLWH with CD20-positive lymphomas. Even poor immune status (< 200 CD4 T-cells/µl) is not an absolute contraindication, but we would recommend close monitoring and prophylactic administration of a quinolone (in addition to cotrimoxazole).

Modifications of CHOP

In recent years, small pilot studies have been published in which PLWH were treated with modified CHOP regimens. For example, doxorubicin was given as liposomal Caelyx® (Levine 2013) or increased cyclophosphamide doses (Costello 2004). Using CDE, potential chemotherapy resistance should be overcome with multi-day infusions (Spina 2005). This is also true for the more intensive EPOCH regimen, which is more costly to administer (Sparano 2010, Barta 2013). Complete remission rates with these therapies have ranged from 50% to 75%. There is no evidence of benefit from these modifications. On the contrary, in a randomized trial in HIV-negative patients with DLBCL, there was no advantage with R-EPOCH over R-CHOP regarding remission rates and survival (Bartlett 2019). Therefore, in our view, EPOCH or CDE should not be used outside of trials.

Which ART when?

Every (every!) person with HIV infection and NHL needs ART. ART has improved survival, response rates, and tolerability of chemotherapy (Weiss 2006, Bower 2008, Barta 2013). There are even individual cases reported of complete remission with ART alone (Birenda 2015). Given the new well-tolerated regimens, *ART-naive* patients can start ART and chemotherapy simultaneously. For example, a good regimen would be TAF+FTC plus raltegravir, as interaction risk and nephrotoxicity are low. HLA status should be available with abacavir, as abacavir HSR (feeling sick! fever!) can cause problems. TAF is preferable to TDF. *Pre-treated* patients should maintain ART during chemotherapy, but with restrictions: boosted regimens (PI/r, PI/c, elvitegravir/c) should be avoided due to the risk of increased toxicities (Spano 2016, Focà 2018) because cases of severe neurotoxicity have been described for vinblastine (Cheung 2010). Raltegravir-containing regimens would be a good option (Ezzat 2013, Welz 2017). Before starting any chemotherapy regimen, a web-based check via *www.hivdruginteractions.org* is worthwhile.

Special entities

Burkitt or Burkitt-like lymphomas (BL/BLL). BL are treated with intensive protocols including high-dose methotrexate and cytarabine due to their exceptionally high proliferation kinetics, aggressiveness, and tendency to CNS involvement. In Germany, a dose-adapted protocol of the German ALL Study Group (GMALL) is mainly used for the treatment of Burkitt's NHL/B-ALL (B-ALL protocol) (Hoffmann 2006). This consists of a pre-phase with cyclophosphamide and dexamethasone, followed by administration of block A (MTX, vincristine, ifosfamide, teniposide, Ara-C, intrathecal administration of MTX, dexamethasone and Ara-C) and block B (MTX, vincristine, cyclophosphamide, doxorubicin) three times each. Among these, 4-year survival is 72% (Xicoy 2014), but at the cost of increased toxicity (including mucositis and myelotoxicity). This very intensive chemotherapy cannot be administered on an outpatient basis. Inpatient admission for several days with close monitoring is necessary. Centers without experience with the protocol should not use it in PLWH.

Other intensive therapy regimens such as CODOX/M-IVAC are similarly effective but uncommon in Germany (Alwan 2015, Noy 2015, Vasseur 2020). Less intensive therapy with dose-adjusted EPOCH-R resulted in an impressive 87% survival rate after approximately six years in a study of 113 BL patients, 25% of whom were HIV-positive (Roschewski 2020). However, the rate of high-risk cases with bone marrow or CNS involvement was lower than in the studies with dose-intensive regimens. In addition, the intensive CODOX/M-IVAC regimen showed a significant survival advantage over EPOCH in a retrospective study of 249 HIV-BL patients (Alderuccio 2021). Overall, the prognosis of BL has improved significantly. Large cohort studies no longer show differences in survival rates between DLBCL and BL (Gopal 2013, Schommers 2015, Hentrich 2021).

Plasmablastic lymphomas are likely to be associated with DLBCL but have their own immunophenotype, usually corresponding to a post-germinal center cell: markers for the B-cell antigen CD20 are negative, whereas the plasma cell reactive antibody VS38c and CD138 are positive (Castillo 2015). The oral cavity is the predilection site, although extraoral manifestations also occur. There is a close association with EBV (Al Maki 2015, Castillo 2015). Plasmablastic lymphomas have a very high proliferation rate and grow highly aggressively. The prognosis remains poor compared to other lymphomas (Castillo 2012, Schommers 2013, Hentrich 2021). We showed on 89 NHL that a post-germinal center profile, as often found in plasmablastic lymphomas, is independently associated with a poor prognosis (Hoffmann 2005). This has since been shown by other groups as well (Dunleavy 2010). Intensive chemotherapies are not associated with any clear benefit (Castillo 2012). In contrast, administration of the proteasome inhibitor bortezomib, approved in multiple myeloma, in combination with chemotherapy appears useful (Bibas 2010, Fernandez-Alvarez 2016, Castillo 2019).

Primary effusion lymphoma (PEL), relatively rare, accounts for 1–3% of all HIV NHL (Narkhede 2018, Hentrich 2021). A distinction is made between a solid and a classic variant (Guillet 2016). The latter is often difficult to diagnose histologically due to the absence of a visible tumor mass and the malignant cells found only in body cavities (ascites, pleural or pericardial effusion). Histologically, there are similarities to immunoblastic and anaplastic cells with a non-B non-T phenotype. Any pleural or pericardial effusion from an HIV+ individual in which malignant cells are found is suspicious. Pathology should be notified of the suspicion. There is a 100% association with human herpesvirus-8 (HHV-8), which is detectable in the cells.

Response to CHOP is usually poor, and the prognosis is unfavorable (Guillet 2016, Aguilar 2020). Complete remissions with ART alone have been described (Boulanger 2001, Hocqueloux 2001), but do not serve as a basis for therapy. In the German Lymphoma Cohort, only 2 of 13 cases (15%) achieved sustained remission (Hentrich 2021). A standard therapy has not been defined. The combination of bortezomib and chemotherapy led to sometimes long-lasting remissions in a small series (Gupta 2016), but according to other case reports, bortezomib was without benefit (Boulanger 2018). Relatively good results have been reported with modifications of the EPOCH regimen (i.e., with/without rituximab, bevacizumab, or HD methotrexate) (cancer-specific survival at three years 47%), without drawing clear conclusions for practice (Lurain 2019).

Recurrence therapy, stem cell transplantation

In our cohort, the recurrence rate was recently just above 10% (Schommers 2018). Consideration should always be given to high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT). In SCT, the intensity of chemotherapy can be significantly increased by prior collection of pluripotent hematopoietic stem cells (own cells: autologous; foreign: allogeneic). Following myeloablative chemotherapy, the stem cells are reinfused. Previous studies show that immune reconstitution and long-term success do not differ from those in HIV-negative patients (Krishnan 2010, Zanet 2015, Alvarnas 2016). However, transplant-associated mortality is slightly higher (Hübel 2019).

Allogeneic SCT is reserved for rare exceptional cases (Gupta 2009, Ambinder 2019, Arslan 2019). Besides the so-called graft-vs-lymphoma effect, another effect could be used: for example, a case of an HIV-positive patient with acute myeloid leukemia who received stem cells from an HIV-negative donor homozygous for the Δ32 mutation was published – probably the first cure (see *Cure*) in HIV (Hütter 2009). However, a few more cases exist, including one woman (see *Cure*).

There are now several case reports on therapy with CAR-T-cells in PLWH who should not be principally excluded from this innovative therapy (Hattenhauer 2023). Cases with relapsed or refractory DLBCL should be presented at appropriate centers, and health insurance coverage will be considered on a case-by-case basis (Abbasi 2020, Allred 2021).

Literature

Abbasi A, Peeke S, Shah N, et al. Axicabtagene ciloleucel CD19 CAR-T cell therapy results in high rates of systemic and neurologic remissions in ten patients with refractory large B cell lymphoma including two with HIV and viral hepatitis. J Haematol Oncol 2020, 13:1-4.

Alderuccio JP, Olszewski AJ, Evans AM, et al. HIV-associated Burkitt-lymphoma: outcomes from a US-UK collaborative analysis. Blood Adv 2021, 5:2852-62.

Allred J, Bharucha K, Özütemiz C, et al. Chimeric antigen receptor T-cell therapy for HIV-associated diffuse large B-cell lymphoma: case report and management recommendations. Bone Marrow Transplant 2021, 56:569-82.

Al-Malki MM, Castillo JJ, Sloan JM, Re A. Hematopoietic cell transplantation for plasmablastic lymphoma: A review. Biol Blood Marrow Transplant 2015, 20:1877-84.

Alvarnas JC, Le Rademacher J, Wang Y, et al. Autologous hematopoietic cell transplantation for HIV-related lymphoma: results of the BMT CTN 0803/AMC 071 trial. Blood 2016, 128:1050-8.

Alwan F, He A, Montoto S, et al. Adding rituximab to CODOX-M/IVAC chemotherapy in the treatment of HIV-associated Burkitt lymphoma is safe when used with concurrent combination antiretroviral therapy. AIDS 2015, 29:903-10.

Aguilar C, Laberiano C, Beltran B, et al. Clinicopathologic characteristics and survival of patients with primary effusion lymphoma. Leuk Lymphoma 2020, 61:2093-2102.

Ambinder RF, Wu J, Logan B, et al. Allogeneic hematopoietic cell transplant for HIV patients with hematologic malignancies: The BMT CTN-0903/AMC-080 Trial. Biol Blood Marrow Transplant 2019, 25:2160-6.

Antiretroviral Therapy Cohort Collaboration (ART-CC). Variable impact on mortality of AIDS-defining events diagnosed during combination antiretroviral therapy: not all AIDS-defining conditions are created equal. Clin Infect Dis 2009, 48:1138-51.

Arslan S, Litzow MR, Cummins NW, et al. Risks and Outcomes of Allogeneic Hematopoietic Stem Cell Transplantation for Hematologic Malignancies in Patients with HIV Infection. Biol Blood Marrow Transplant 2019, 25:e260-7.

Barta SK, Xue X, Wang D, et al. Treatment factors affecting outcomes in HIV-associated non-Hodgkin lymphomas: a pooled analysis of 1546 patients. Blood 2013, 122:3251-62.

Barta SK, Joshi J, Mounier N, et al. Central nervous system involvement in AIDS-related lymphomas. Br J Haematol 2016, 173:857-66.

Bartlett NL, Wilson WH, Jung SH, et al. Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. J Clin Oncol 2019, 37:1790-9.

Bibas M, Grisetti S, Alba L, et al. Patient with HIV-associated plasmablastic lymphoma responding to bortezomib alone and in combination with dexamethasone, gemcitabine, oxaliplatin, cytarabine, and pegfilgrastim chemotherapy and lenalidomide alone. JCO 2010, 28:e704-8.

Birendra KC, Afzal MZ, Wentland KA, et al. Spontaneous regression of refractory diffuse large B-Cell lymphoma with improvement in immune status with ART in a patient with HIV: A case report and literature review. Am J Case Rep 2015, 16:347-52.

Boulanger E, Meignin V, Oksenhendler E. Bortezomib (PS-341) in patients with human herpesvirus 8-associated primary effusion lymphoma. Br J Haematol 2008, 141:559-61.

Breen EC, Hussain SK, Magpantay L, et al. B-cell stimulatory cytokines and markers of immune activation are elevated several years prior to the diagnosis of systemic AIDS-associated non-Hodgkin B-cell lymphoma. Cancer Epidemiol Biomarkers Prev 2011, 20:1303-14.

Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy following rituximab therapy in HIV negative patients: a report of 57 cases from the Research on Adverse Drug Event and Reports (RADAR) project. Blood 2009, 113:4834-40.

Castillo JJ, Furman M, Beltrán BE, et al. Human immunodeficiency virus-associated plasmablastic lymphoma: poor prognosis in the era of highly active antiretroviral therapy. Cancer 2012, 118:5270-7.

Castillo JJ, Bibas M, Miranda RN. The biology and treatment of plasmablastic lymphoma. Blood 2015, 125:2323-30.

Castillo JJ, Guerrero-Garcia T, Baldini F, et al. Bortezomib plus EPOCH is effective as frontline treatment in patients with plasmablastic lymphoma. Br J Haematol 2019, 184:679-82.

Chao C, Xu L, Abrams D, et al. Survival of non-Hodgkin lymphoma patients with and without HIV infection in the era of combined antiretroviral therapy. AIDS 2010, 24:1765-70.

Cheung MC, Hicks LK, Leitch HA. Excessive neurotoxicity with ABVD when combined with protease inhibitor-based antiretroviral therapy in the treatment of AIDS-related Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk 2010, 10:E22-5.

Coghill AE, Shiels MS, Suneja G, Engels EA. Elevated cancer-specific mortality among HIV-infected patients in the United States. J Clin Oncol 2015, 33.

COHERE Study Group. Incidence and risk factors of HIV-related non-Hodgkin's lymphoma in the era of combination antiretroviral therapy: a European multicohort study. Antivir Ther 2009, 14:1065-74.

Eberhard JM, Angin M, Passaes C, et al. Vulnerability to reservoir reseeding due to high immune activation after allogeneic hematopoietic stem cell transplantation in individuals with HIV-1. Sci Transpl Med 2020, 12(542):eaay9355.

Ehren K, Hertenstein C, Kümmerle T, et al. Causes of death in HIV-infected patients from the Cologne-Bonn cohort. Infection 2014, 42:135-40.

Ezzat HM, Cheung MC, Hicks LK, et al. Incidence, predictors and significance of severe toxicity in patients with human immunodeficiency virus-associated Hodgkin lymphoma. Leuk Lymphoma 2012, 53:2390-6.

Fernandez-Alvarez R, Gonzalez-Rodriquez AP, Rubio-Castro A, et al. Bortezomib plus CHOP for the treatment of HIV-associated plasmablastic lymphoma: clinical experience in three patients. Leuk Lymph 2016, 52:463-6.

Focà E, Cavaglià G, Rusconi S, et al. Survival in HIV-infected patients with lymphoma according to the choice of antiretroviral treatment: an observational multicentre study. HIV Med 2018, 19:523-31.

Franceschi S, Lise M, Clifford GM, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. Br J Cancer 2010, 103:416-22.

Gérard L, Meignin V, Galicier L, et al. Characteristics of non-Hodgkin lymphoma arising in HIV-infected patients with suppressed HIV replication. AIDS 2009, 23:2301-8.

Gibson TM, Morton LM, Shiels MS, Clarke CA, Engels EA. Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study. AIDS 2014, 28:2313-8.

Gopal S, Patel MR, Yanik EL, et al. Temporal trends in presentation and survival for HIV-associated lymphoma in the antiretroviral therapy era. J Natl Cancer Inst 2013, 105:1221-9.

Guillet S, Gérard L, Meignin V, et al. Classic and extracavitary primary effusion lymphoma in 51 HIV-infected patients from a single institution. Am J Hematol 2016, 91:233-7.

Gupta V, Tomblyn M, Pedersen TL, et al. Allogeneic hematopoietic cell transplantation in human immunodeficiency virus-positive patients with hematologic disorders: a report from the Center for international blood and marrow transplant research. Biol Blood Marrow Transplant 2009, 15:864-71.

Gupta A, Sen S, Marley E, et al. Management and outcomes of HIV-associated primary effusion lymphoma: A single center experience. Clin Lymphoma Myeloma Leuk 2016, 16 (Suppl): S175-180.

Gupta RK, Peppa D, Hill AL, et al. Evidence for HIV-1 cure after CCR5Δ32/Δ32 allogeneic haematopoietic stem-cell transplantation 30 months after analytic treatment interruption: a case report. Lancet HIV 2020, 7:e340-7.

Hattenhauer ST, Mispelbaum R, Hentrich M, et al. Enabling CAR T-cell therapies for HIV-positive lymphoma patients – A call for action. HIV Med 2023 Jun 15. doi: 10.1111/hiv.13514. Online ahead of print.

Hocqueloux L, Agbalika F, Oksenhendler E, Molina JM. Long-term remission of an AIDS-related primary effusion lymphoma with antiviral therapy. AIDS 2001, 15:280-2.

Hentrich M, Hoffmann C, Mosthaf F, et al. Therapy of HIV-associated lymphoma- recommendations of the oncology working group of the German Study Group of Physicians in Private Practice Treating HIV-Infected Patients (DAGNÄ), in cooperation with the German AIDS Society (DAIG). Ann Hematol 2014, 93:931-21.

Hoffmann C, Gérard L, Wyen C, Oksenhendler E. No evidence for an early excess incidence of progressive multifocal leukencephalopathy in HIV-infected patients treated with rituximab. J AIDS 2012, 60:e121-2.

Hoffmann C, Tiemann M, Schrader C, et al. AIDS-related B-cell lymphoma (ARL): correlation of prognosis with differentiation profiles assessed by immunophenotyping. Blood 2005, 106:1762-9.

Hoffmann C, Wolf E, Fatkenheuer G, et al. Response to highly active antiretroviral therapy strongly predicts outcome in patients with AIDS-related lymphoma. AIDS 2003, 17:1521-9.

Hoffmann C, Wolf E, Wyen C, et al. AIDS-associated Burkitt or Burkitt-like lymphoma: short intensive polychemotherapy is feasible and effective. Leuk Lymphoma 2006, 47:1872-80.

Horner M-J, Shiels MS, Pfeiffer RM, Engels EA. Deaths attributable to cancer in the US human immunodeficiency virus population during 2001–2015. Clin Infect Dis 2021, 72:e224-31.

Hübel K, Re A, Boumendil A, et al. Autologous stem cell transplantation for HIV-associated lymphoma in the antiretroviral and rituximab era: a retrospective study by the EBMT Lymphoma Working Party. Bone Marrow Transplant 2019, 54:1625-31.

Hütter G, Nowak D, Mossner M, et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Engl J Med 2009, 360:692-8.

Kaplan LD, Lee JY, Ambinder RF, et al. Rituximab does not improve clinical outcome in a randomized phase III trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin's lymphoma: AIDS-malignancies consortium trial 010. Blood 2005, 106:1538-43.

Kimani SM, Painschab MS, Horner MJ, et al. Epidemiology of haematological malignancies in people living with HIV. Lancet HIV 2020, 7:e641-e51.

Krishnan A, Palmer JM, Zaia JA, Tsai NC, Alvarnas J, Forman SJ. HIV status does not affect the outcome of autologous stem cell transplantation (ASCT) for non-Hodgkin lymphoma (NHL). Biol Blood Marrow Transplant 2010, 16:1302-8.

Landgren O, Goedert J, Rabkin C, et al. Circulating serum free light chains as predictive markers of AIDS-related lymphoma. JCO 2010, 28:773-9.

Levine AM, Noy A, Lee JY, Tam W, et al. Pegylated liposomal doxorubicin, rituximab, cyclophosphamide, vincristine, and prednisone in AIDS-related lymphoma: AIDS Malignancy Consortium Study 047. J Clin Oncol 2013, 31:58-64.

Lurain K, Polizzotto MN, Aleman K, et al. Viral, immunologic, and clinical features of primary effusion lymphoma. Blood 2019, 133: 1753-61.

Miles SA, McGratten M. Persistent panhypogammaglobulinemia after CHOP-Rituximab for HIV-related lymphoma. J Clin Oncol 2005;23:247-8.

Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994-1998: the Eurosida study. Lancet 2000, 356:291-296.

Morlat P, Roussillon C, Hénard S, et al. Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000. AIDS 2014, 28:1181-91.

Narkhede M, Arora S, Ujjani C. Primary effusion lymphoma: current perspectives. Onco Targets Ther 2018, 11:3747–54.

Noy A, Lee JY, Cesarman E, et al. AMC 048: modified CODOX-M/IVAC-rituximab is safe and effective for HIV-associated Burkitt lymphoma. Blood 2015, 126:160-6.

Noy A. Optimizing treatment of HIV-associated lymphoma. Blood 2019, 134:1385-94.

Olszewski AJ, Fallah J, Castillo JJ. Human immunodeficiency virus-associated lymphomas in the antiretroviral therapy era: analysis of the National Cancer Data Base. Cancer 2016, 122:2689-97.

Poizot-Martin I, Lions C, Allavena C, et al. Spectrum and incidence trends of AIDS- and non–AIDS-defining cancers between 2010 and 2015 in the French Dat'AIDS Cohort. Cancer Epidemiol Biomarkers Prev 2021, 30:554–63.

Poeschel V, Held G, Ziepert M, et al. Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial. Lancet 2019, 394:2271-81.

Polesel J, Clifford GM, Rickenbach M, et al. Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. AIDS 2008, 22:301-6.

Ramaswami R, Chia G, Dalla Pria A, et al. Evolution of HIV-associated lymphoma over 3 decades. J Acquir Immune Defic Syndr 2016, 72:177-83.

Roschewski M, Dunleavy K, Abramson JS, et al. Multicenter study of risk-adapted therapy with dose-adjusted EPOCH-R in adults with untreated Burkitt lymphoma. J Clin Oncol 2020, 38:2519-29.

Schmitz N, Zeynalova S, Nickelsen M, et al. CNS International Prognostic Index: a risk model for CNS relapse in patients with diffuse large B-cell lymphoma treated with R-CHOP. J Clin Oncol 2016, 34:3150-6.

Schommers P, Wyen C, Hentrich M, et al. Poor outcome of HIV-infected patients with plasmablastic lymphoma: results from the German AIDS-related lymphoma cohort study. AIDS 2013, 27:842-5.

Schommers P, Hentrich M, Hoffmann C, et al. Survival with AIDS-related diffuse large B-cell lymphoma, Burkitt lymphoma, and plasmablastic lymphoma in the German HIV Lymphoma Cohort. Br J Haematol 2015, 168:806-10.

Schommers P, Gillor D, Hentrich M, et al. Incidence and risk factors for relapses in HIV-associated non-Hodgkin-lymphoma as observed in the German HIV-related lymphoma cohort study. Haematologica 2018, 103:857-64.

Shepherd L, Ryom L, Law M, et al. Differences in virological and immunological risk factors for Non-Hodgkin and Hodgkin lymphoma. J Natl Cancer Inst. 2018, 110:598-607.

Silverberg MJ, Lau B, Achenbach CJ, et al. Cumulative Incidence of Cancer Among Persons With HIV in North America: A Cohort Study. Ann Intern Med 2015, 163:507-18.

Simonelli C, Tedeschi R, Gloghini A, et al. Characterization of immunologic and virological parameters in HIV-infected patients with primary effusion lymphoma during antiblastic therapy and highly active antiretroviral therapy. Clin Infect Dis 2005, 40:1022-7.

Spano JP, Poizot-Martin I, Costagliola D, et al. Non-AIDS-related malignancies: expert consensus review and practical applications from the multidisciplinary CANCERVIH Working Group. Ann Oncol 2016, 27:397-408.

Sparano JA, Lee JY, Kaplan LD, et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. Blood 2010, 115:3008-16.

Spina M, Jäger U, Sparano JA, et al. Rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide in HIV-associated non-Hodgkin lymphoma: pooled results from 3 phase 2 trials. Blood 2005, 105:1891-7.

Tittle V, Rayment M, Keeling E, et al. Serum-free light chains in HIV-associated lymphoma: no correlation with histology or prognosis. AIDS 2015, 29:1201-4.

Vasseur L, Prevot S, Mounier N et al. Favorable outcome of HIV-associated Burkitt lymphoma in the modern combined antiretroviral therapy era. Eur J Cancer 2020, 138:189-92.

Weiß R, Mitrou P, Arasteh K, et al. AIDS-related lymphoma: simultaneous treatment with combined cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy and highly active antiretroviral therapy is safe and improves survival – results of the German Multicenter Trial. Cancer 2006, 106:1560–8.

Welz T, Wyen C, Hensel M. Drug interactions in the treatment of malignancy in HIV-infected patients. Oncol Res Treat 2017, 40:120-7.

Wyen C, Jensen B, Hentrich M. Treatment of AIDS-related lymphomas: rituximab is beneficial even in severely immunosuppressed patients. AIDS 2012, 26:457-64.

Xicoy B, Ribera JM, Möller M, et al. Dose-intensive chemotherapy including rituximab is highly effective but toxic in HIV-infected patients with Burkitt's lymphoma/leukemia: Parallel study of 81 patients. Leuk Lymphoma 2014, 55:2341-8.

Zanet E, Taborelli M, Rupolo M, et al. Postautologous stem cell transplantation long-term outcomes in 26 HIV-positive patients affected by relapsed/refractory lymphoma. AIDS 2015, 29:2303-8.

Ziegler JL, Drew WL, Miner RC, et al. Outbreak of Burkitt's-like lymphoma in homosexual men. Lancet 1982, 2:631-3.

Zoufaly A, Stellbrink HJ, Heiden MA, et al. Cumulative HIV viremia during highly active antiretroviral therapy is a strong predictor of AIDS-related lymphoma. J Infect Dis 2009, 200:79-87.

Primary CNS lymphoma

Primary CNS lymphomas (PCNSL) are a late complication of HIV infection. They used to occur in up to 10% of AIDS patients, but have become rare (Polesel 2008). In nearly 100% of cases, they are EBV-associated and histologically are usually diffuse large cell non-Hodgkin lymphomas. Previously, PCNSL had the worst prognosis among AIDS-defining diseases, with a median survival of less than three months. ART has made survival times of several years and even cures possible (Hoffmann 2001, Gupta 2017, Moulignier 2017, Lurain 2020).

Clinic

Depending on the localization and size, neurological disorders occur. Epileptic seizures may be the initial manifestation. Personality changes, attention disorders, headaches, and focal deficits such as paresis are common. Fever, on the other hand, is usually absent. Because severe immunodeficiency is usually present, constitutional symptoms may obscure the problem.

Diagnostics

Cerebral CT or (better) MRI should be done expeditiously. The usually singular foci take up contrast agents, show mild to moderate edema, and often have little space-occupying activity. The most important differential diagnosis is cerebral toxoplasmosis (TE). A solitary focus with minor edema is more suggestive of PCNSL. However, 2–4 lesions are often present and are usually relatively large (over 2 cm in diameter). More than four lesions are rare.

In addition to a current toxoplasmosis serology, which, if negative, makes TE unlikely, a current CD4 T-cell count should also be available. The better the immune status, the less likely a PCNSL. In our cohort, less than 20% had more than 50 CD4 T-cells/µl at diagnosis. Above 100/µl, however, TE also becomes unlikely. In addition to physical examination, CTs of the neck, thorax, and abdomen should be used to determine whether there is secondary CNS involvement of systemic lymphoma. This should always include fundoscopy to exclude ocular involvement (up to 20%).

Besides TE, differential diagnoses include abscesses, glioblastomas, and cerebral metastases of solid tumors. In the absence of increased intracranial pressure, CSF puncture is useful to detect malignant cells. A positive EBV PCR in the CSF confirms the suspicion; however, EBV is inconclusive and often detectable even without PCNSL (Corcoran 2008). In such a case, cerebral lymphomatoid granulomatosis should also be considered, which presents a complex picture on MRI (Wyen 2006, Patsalides 2006).

Empirical toxoplasmosis therapy is usually warranted initially, preferably without steroids. If this fails, this is indicative of PCNSL. In such cases, a stereotactic brain biopsy to confirm the diagnosis cannot be omitted. However, this is only useful if steroids have not been given previously – even low doses of steroids usually make a histopathological diagnosis impossible.

Treatment

The advances in HIV-negative individuals with high-dose methotrexate-based (HD-MTX) chemotherapies and rituximab have also transformed the treatment of PLWH with PCNSL (Gupta 2017, Moulignier 2017, Lurain 2020). Cranial irradiation alone should no longer be used to avoid late neurological damage. Regardless of the specific therapy, the key is maximizing immune reconstitution with ART. Under ART

in combination with chemotherapy, durable remissions, and cures have become realistic, and there are even case reports on ART alone (McGowan 1998, Aboufila 2007, Travi 2012).

In our cohort (n=29), three out of four individuals with a CD4 T-cell increase achieved complete remission (Hoffmann 2001). Several affected persons lived relapse-free for more than ten years. This positive trend has been confirmed in numerous studies. In two recent papers, the median survival was either not yet reached (Gupta 2017) or the 5-year survival rate was 48% (Moulignier 2017). As with established approaches for HIV-negative patients, HD-MTX-based combination chemotherapies should be combined with rituximab (Ferreri 2016, Schmitt 2019, Lurain 2020). In individual cases, consolidative high-dose chemotherapy with autologous stem cell transplantation may also be considered (O'Neill 2015).

If there are clear signs of increased intracranial pressure, the rapid administration of steroids (dexamethasone 3 x 8 mg/day, then rapidly tapering off) cannot be avoided. However, it should be not been initiated before histological confirmation of the diagnosis.

Literature

Aboulafia DM, Puswella AL. Highly active antiretroviral therapy as the sole treatment for AIDS-related primary central nervous system lymphoma: a case report with implications for treatment. AIDS Patient Care STDS 2007, 21:900-7.

Corcoran C, Rebe K, van der Plas H, Myer L, Hardie DR. The predictive value of cerebrospinal fluid Epstein-Barr viral load as a primary central nervous system lymphoma marker in HIV-infected persons. J Clin Virol 2008, 42:433-6.

Ferreri AJ, Cwynarski K, Pulczynski E, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. Lancet Haematol 2016, 3:e217-27.

Gupta NK, Nolan A, Omuro A, et al. Long-term survival in AIDS-related primary central nervous system lymphoma. Neuro Oncol 2017, 19:99-108.

Hoffmann C, Tabrizian S, Wolf E et al. Survival of AIDS patients with primary central nervous system lymphoma is dramatically improved by HAART-induced immune recovery. AIDS 2001, 15:2119-2127.

Lurain K, U R, Uldrick TS, Ramaswami R, et al. Treatment of HIV-associated primary CNS lymphoma with antiretroviral therapy, rituximab, and high-dose methotrexate. Blood 2020, 136:2229-32.

McGowan JP, Shah S. Long-term remission of AIDS-related PCNSL associated with HAART. AIDS 1998, 952-954.

Moulignier A, Lamirel C, Picard H, et al. Long-term AIDS-related PCNSL outcomes with HD-MTX and combined antiretroviral therapy. Neurology 2017, 89:796-804.

O'Neill A, Mikesch K, Fritsch K, et al. Outcomes for HIV-positive patients with primary central nervous system lymphoma after high-dose chemotherapy and auto-SCT. Bone Marrow Transplant 2015, 50: 999-1000.

Patsalides AD, Atac G, Hedge U, et al. Lymphomatoid granulomatosis: abnormalities of the brain at MR imaging. Radiology 2005, 237:265-73.

Polesel J, Clifford GM, Rickenbach M, et al. Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. AIDS 2008, 22:301-6.

Schmitt AM, Herbrand AK, Fox CP, et al. Rituximab in primary central nervous system lymphoma-A systematic review and meta-analysis. Hematol Oncol 2019, 37:548-57.

Travi G, Ferreri AJ, Cinque P, et al. Long-Term Remission of HIV-Associated Primary CNS Lymphoma Achieved With Highly Active Antiretroviral Therapy Alone. J Clin Oncol 2012, 30:e119-21.

Wyen C, Stenzel W, Hoffmann C, et al. Fatal cerebral lymphomatoid granulomatosis in an HIV-1-infected patient. J Infect. 2007, 54:e175-8.

Hodgkin's lymphoma (HL)

The incidence of HL, unlike NHL, has not decreased with ART and has increased by approximately 5–15-fold in PLWH (Hernanedz-Ramires 2019, Kimani 2020, Poizot-Martin 2021). The main risk factor is a moderately decreased CD4 T-cell count (Sheperd 2018, Kimani 2020). In the D:A:D study, the hazard ratio was 6.36 with CD4 T-cells of 100–199/µl compared to >500/µl (Sheperd 2018). Viral load does not matter. There is evidence that the incidence decreases again with increasing ART duration (Kowalkowski 2014). This is also supported by recent declines in incidence in some cohort studies (Robbins 2014, Silverberg 2015, Shepard 2018). The vast majority of people with HIV-HL are on antiretroviral treatment. With viral suppression and good CD4 T-cells, HL is as common as NHL in PLWH (Hoffmann 2015). EBV can be detected in > 90%. Since HL consists mainly of reactive inflammatory cells (including many T lymphocytes – the proportion of malignant cells is only about 1%), it has been postulated that only ART-induced immune reconstitution creates a "Hodgkin-friendly" microenvironment (Gloghini 2007). Before the diagnosis of HL, there is a decrease in CD4 T-cells measured in the blood (Bohlius 2011, Hoffmann 2016).
An advanced stage at diagnosis and extra-nodal involvement is typical, whereas mediastinal involvement is much less common than in HIV-uninfected patients with HL. As in NHL, the prognosis has improved dramatically with ART. With sufficient viral suppression, there is no longer a survival difference compared with HIV-negative individuals (Montoto 2013, Besson 2015, Olszewski 2016, Sorigué 2017).

Clinic/Diagnostics

B symptoms are present in the majority of cases. Advanced stages are almost the rule. The lymphomas are usually coarse, poorly displaced, and indolent. Staging is the same as for non-Hodgkin's lymphoma (see above) but includes an ^{18}F-FDG PET-CT (PET), which may obviate the need for a bone marrow biopsy in HL. High metabolic tumor volume on initial PET is associated with an unfavorable prognosis (Louarn 2022). A lymph node should be removed whenever possible – puncture alone is less reliable. It is better to have a proper diagnosis once than to lose time unnecessarily with half-hearted examinations! Extirpation is usually possible on an outpatient basis. As with NHL, the material should be sent to reference pathologies if possible. Because of the use of bleomycin, lung function should always be examined before chemotherapy.

Treatment

As in HIV-negative HL, therapy should be based on the Ann Arbor stage and possible risk factors (extranodal involvement, more than three lymph node areas, large mediastinal tumor, or high ESR). Therapy is always curative, and the achievement of complete remission is crucial. A distinction is made between limited (I-II without risk factors), intermediate (I-II with risk factors), and advanced stages (III-IV). In limited and intermediate stages, the ABVD regimen (four double cycles) followed by radiotherapy is recommended, see Table 4. The response is excellent, with complete remission rates of 96–100% (Hentrich 2012). Administration is possible on an outpatient basis.

In HIV-negative patients with advanced-stage HL, the escalated BEACOPP regimen of the German Hodgkin Study Group is more effective than ABVD regarding response rates and long-term survival. However, it is more toxic than ABVD, and there is no experience in PLWH. In a prospective HL study, there were high response and survival

Table 4: ABVD scheme (4 double cycles, repeat on day 29).*

Adriamycin (doxorubicin)	25 mg/m² IV day 1 + 15
Bleomycin	10 mg/m² IV day 1 + 15
Vinblastine	6 mg/m² IV day 1 + 15
Dacarbazine (DTIC)	375 mg/m² IV day 1 + 15

* Because of the potent emetogenicity of dacarbazine, antiemitic combinations, including 5HT3 receptor blockers (e.g., granisetron or ondansetron), NK1 inhibitors, and dexamethasone should always be used.

rates with the lower-dose BEACOPP baseline regimen and therapy-associated deaths (Hentrich 2012+2021). Closely monitoring patients is essential, and there should be experience with BEACOPP. Unfortunately, PLWH are still excluded from most clinical therapy trials, a circumstance that is no longer justifiable (Hentrich 2012, Kaplan 2012, Montoto 2013). For the CD30 antibody-drug conjugate brentuximab vedotin in combination with AVD, there are initial results of a small Phase I trial (Rubinstein 2018); Phase 2 is still ongoing. There are no consequences for clinical practice yet. The same applies to a PET-adapted approach (Danilov 2017). Similar to NHL, the standard therapy for HL relapse is high-dose chemotherapy with autologous stem cell transplantation. Later relapses should be treated with checkpoint inhibitors such as nivolumab, which have led to impressive remissions in case reports (Sandoval-Hus 2017, Chang 2018, Serrao 2019).

In the choice of ART, the same applies as in NHL (see *NHL*) – especially the combination of booster and vinblastine should be avoided due to toxicity.

Literature

Besson C, Lancar R, Prevot S, et al. High-risk features contrast with favorable outcomes in HIV-associated Hodgkin lymphoma in the modern cART era, ANRS CO16 LYMPHOVIR Cohort. Clin Infect Dis 2015, 61:1469-75.

Bohlius J, Schmidlin K, Boué F, et al. HIV-1-related Hodgkin lymphoma in the era of combination antiretroviral therapy: incidence and evolution of CD4+ T-cell lymphocytes. Blood 2011 117:6100-8.

Chang E, Sabichi AL, Kramer JR, et al. Nivolumab Treatment for Cancers in the HIV-infected population. J Immunother 2018, 41:379-83.

Chang E, Rivero G, Patel NR, et al. HIV-related refractory Hodgkin lymphoma: a case report of complete response to nivolumab. Clin Lymphoma Myeloma Leuk 2018, 18:e143-6.

Danilov AV, Li H, Press OW, et al. Feasibility of interim positron emission tomography (PET)-adapted therapy in HIV-positive patients with advanced Hodgkin lymphoma (HL): a sub-analysis of SWOG S0816 Phase 2 trial. Leuk Lymphoma 2017, 58:461-5.

Gloghini A, Carbone A. Why would the incidence of HIV-associated Hodgkin lymphoma increase in the setting of improved immunity? Int J Cancer 2007, 120:2753-4.

Hentrich M, Berger M, Wyen C, et al. Stage-adapted treatment of HIV-associated Hodgkin lymphoma: results of a prospective multicenter study. J Clin Oncol 2012, 30:4117-23.

Hentrich M, Müller M, Wyen C, et al. Stage-adapted treatment of HIV-associated Hodgkin lymphoma: long-term results of a prospective multi-institutional study. Oncol Res Treat 2021, 44(Suppl. 2): V634.

Hoffmann C, Chow KU, Wolf E, et al. Strong impact of highly active antiretroviral therapy on survival in patients with human immunodeficiency virus-associated Hodgkin's disease. Br J Haematol 2004, 125:455-62.

Hoffmann C, Hentrich M, Gillor D, et al. Hodgkin lymphoma is as common as non-Hodgkin lymphoma in HIV-positive patients with sustained viral suppression and limited immune deficiency: a prospective cohort study. HIV Med 2015, 16:261-4.

Hoffmann C, Schommers P, Wolf E, et al. CD4+ and CD8+ T-cell kinetics in aviremic HIV-infected patients developing Hodgkin or non-Hodgkin lymphoma. AIDS 2016, 30:753-60.

Kaplan LD. Management of HIV-associated Hodgkin Lymphoma: How Far We Have Come. JCO 2012, 30:4056-8.

Kowalkowski MA, Mims MA, Day RS, et al. Longer duration of combination antiretroviral therapy reduces the risk of Hodgkin lymphoma: A cohort study of HIV-infected male veterans. Cancer Epidemiol 2014, 38:386-92.

Louarn N, Galicier L, Bertinchamp R, et al. First extensive analysis of 18F-labeled fluorodeoxyglucose positron emission tomography-computed tomography in a large cohort of patients with HIV-associated Hodgkin lymphoma: baseline total metabolic tumor volume affects prognosis. J Clin Oncol 2022, 40:1346-55.

Montoto S, Shaw K, Okosun J, Gandhi S, et al. HIV status does not influence outcome in patients with classical Hodgkin lymphoma treated with chemotherapy using doxorubicin, bleomycin, vinblastine, and dacarbazine in the highly active antiretroviral therapy era. J Clin Oncol 2012, 30:4111-6.

Olszewski AJ, Castillo JJ. Outcomes of HIV-associated Hodgkin lymphoma in the era of antiretroviral therapy. AIDS 2016, 30:787-96.

Robbins HA, Shiels MS, Pfeiffer RM, Engels EA. Epidemiologic contributions to recent cancer trends among HIV-infected people in the United States. AIDS 2014, 28:881-90.

Rubinstein PG, Moore PC, Rudek MA, et al. Brentuximab vedotin with AVD shows safety, in the absence of strong CYP3A4 inhibitors, in newly diagnosed HIV-associated Hodgkin lymphoma. AIDS 2018, 32:605-611.

Sandoval-Sus JD, Mogollon-Duffo F, Patel A, et al. Nivolumab as salvage treatment in a patient with HIV-related relapsed/refractory Hodgkin lymphoma and liver failure with encephalopathy. J Immunother Cancer 2017, 5:49.

Serrao A, Canichella M, De Luca ML, et al. Nivolumab as a safe and effective treatment in an HIV patient with refractory Hodgkin lymphoma. Ann Hematol 2019, 98:1505-6.

Shepherd L, Ryom L, Law M, et al. Differences in virological and immunological risk factors for Non-Hodgkin and Hodgkin lymphoma. J Natl Cancer Inst 2018, 110:598-607.

Silverberg MJ, Lau B, Achenbach CJ, et al. Cumulative incidence of cancer among persons with HIV in North America: a cohort study. Ann Intern Med 2015, 163:507-18.

Sorigué M, Garcia O, Tapia G, et al. HIV-infection has no prognostic impact on advanced stage Hodgkin lymphoma. AIDS 2017, 31:1445-9.

Multicentric Castleman disease (MCD)

Multicentric Castleman's disease (MCD) is a rare but highly problematic disease for those affected – not only because of the somewhat unfavorable prognosis (in HIV infection) but also because, often, neither clinicians nor pathologists really know this entity. Most of the patients suffer from severe episodes of the disease and often go through long diagnostic delays.

Compared to benign, localized hyperplasia of lymphoid tissue first described by US pathologist Benjamin Castleman in 1956, HIV-associated MCD, although neither lymphoma nor AIDS-defining, is a lymphoproliferative disorder of malignant character. It should, therefore, be distinguished from the classic, more benign, unicentric Castleman disease (UCD) seen in HIV-negative individuals (Talat 2011). In contrast to UCD, HIV-MCD is life-threatening. In the "pre-HAART era", median survival with HIV-MCD was only 14 months (Oksenhendler 1996); in the early "HAART era", mortality was still 29% (Mylona 2008). In the meantime, the prognosis has improved, especially with rituximab (Bower 2011, Hoffmann 2011, Gérard 2012, Oksenhendler 2018).

The pathogenesis of MCD is only partially understood. Crucial is an active co-infection with human herpesvirus 8 (HHV-8). Almost all are infected with HHV-8 – it is not surprising that about half of those affected also suffer from Kaposi's sarcoma, which is often present in affected lymph nodes simultaneously (Naresh 2008). In this context, the HHV-8 viral load is probably even higher in MCD than in KS (Sayer 2011, Haq 2015). HHV-8 can induce the production of a viral interleukin that is very similar or induces similar effects to human interleukin-6 ("vIL-6"). IL-6 and IL-10 are elevated in close association with HHV-8 viral load (Oksenhendler 2000). Viral IL-6 differs from human IL-6 in that it only needs to bind to one of the two IL-6 receptor subunits to exert its effect (Moore 1996, Li 2001, Suthaus 2010). Therefore, it has a much broader spectrum of target cells and thus can likely cause the clinically impressive "cytokine storms" typical of HIV MCD. However, there are very distinct cytokine profiles, sometimes with elevated viral, sometimes with elevated human IL-6 (Polizzotto 2013). Plasmablasts localized in the mantle zone of lymphoid follicles are mainly infected. HHV-8 is presented by follicular dendritic cells (FDC) (El-Daly 2010). Interestingly, however, there appear to be cases of MCD without HHV-8 (and without HIV) (Seo 2009), as well as cases of IL-6-associated inflammatory syndrome that lack the pathological features of MCD (Uldrick 2010). In these cases, it remains unclear what ultimately leads to manifestation.

It is also unclear why only very few people with HIV/HHV-8 co-infection manifest MCD. An immune defect cannot explain this. The extent of CD4 T-cell depletion seems to play a minor role; HIV MCD can occur even with normal immune status and low HIV viral load (Powles 2009). In a separate cohort of 52 cases, the majority were on antiretroviral treatment at the time of HIV-MCD diagnosis, and most had viral loads below the limit of detection (Hoffmann 2011). Poor HHV-8-specific CD8 response is also absent in MCD, in contrast to Kaposi's sarcoma (Guihot 2008). There is also evidence that the incidence of HIV MCD tends to increase (Powles 2009).
"Degenerating" into malignant lymphoma is common. Of 60 patients with HIV-MCD, 14 developed malignant lymphoma after a median observation period of 20 months (Oksenhendler 2002). The risk appears significantly lower after rituximab-containing therapies (Hoffmann 2011, Gérard 2012, Pria 2018). Typically, HHV-8-associated lymphoma subtypes that are otherwise rare can be observed, including, for example, plasmablastic lymphomas or primary effusion lymphomas.

Clinic

First are the often-impressive lymph node swellings, which can be soft on palpation (as in TB) or rock-hard (as in lymphoma). In addition, there are almost always significant B symptoms with fever, night sweats, and weight loss. Almost all affected individuals report weakness and a significant feeling of illness. The spleen is always massively enlarged. Hepatomegaly (70%), respiratory symptoms (65%), and a tendency to edema with hypoalbuminemia (55%) are also often found.
The extent of the symptoms is highly variable and sometimes fluctuates astonishingly. Typically, in relapsed cases, the disease progression and activity lasts a few days up to weeks, during which the patients often have high fevers and are severely ill. The relapses are interrupted by more extended periods, sometimes lasting several months, during which the patient is relatively well again. Lymph node regression may temporarily occur without any intervention. With the increasing duration of the disease, the frequency of relapses is increasing. Recurrences after rituximab are common, and the clinic does not differ from initial manifestations (Pria 2018).

Diagnostics

The diagnosis is made histologically from an extirpated lymph node, assuming the pathologist knows what HIV-associated multicentric Castleman's disease looks like. The germinal centers of the lymph nodes appear layered like onion skins and are interspersed with vessels. A distinction is made between a hyaline vascular and a plasma cell-rich type of Castleman's disease. Clinicians should be explicit about the suspicion of MCD. Often, KS is present in the lymph nodes at the same time (Naresh 2008). Some cases may never be correctly diagnosed.
Sonography almost always shows hepatosplenomegaly. Laboratory findings include elevated CRP, hypergammaglobulinemia, and hypalbuminemia. There is often marked anemia, often in the setting of pancytopenia or hemophagocytic syndrome (Stebbing 2009). In a relapsing course with B symptoms, splenomegaly, high CRP, and fluctuating lymph node swelling, one should never be satisfied with a pathologic diagnosis of HIV-associated lymphadenopathy. HIV alone never makes you as sick as an MCD! PET-CT can be helpful (Polizzotto 2015), but it is not routine.
In our experience, the acute phase protein CRP is particularly suitable as a diagnostic follow-up parameter to monitor success in addition to the clinic. During a relapse, CRP blood values are often far above 100 mg/l, but even normal values may be found between relapses. Sometimes, the CRP elevation slightly precedes the clinical

symptoms. The CRP should, therefore, be determined with every blood sample taken in MCD. HHV-8 viral load is also a parameter of disease progression (Marcelin 2007, Stebbing 2011, Sayer 2011) but is reliably performed by only a few laboratories.

Treatment

In HIV-MCD, something must be done quickly: the course can be fulminant. However, randomized studies, sufficient diagnostic criteria, and treatment recommendations are still lacking, as they are now available for HIV-negative idiopathic MCD (Fajgenbaum 2017, van Rhee 2018). Inclusion in an international registry such as ACCELERATE is desirable (contact via author).

Given our experience and the current data, we believe the monoclonal antibody rituximab is the drug of choice (see below). Some experts also favor the combination of rituximab and chemotherapy in aggressive courses (Bower 2010). ART should also be given if possible, although it does not always help (Aaron 2002, Sprinz 2004, Alzahrani 2014). Cases have been described in which ART exacerbated the inflammatory component of MCD (Zietz 1999).

Rituximab: This antibody against CD20-expressing cells, which is also used in B-cell lymphomas (see above), probably eliminates a large proportion of the B-cells infected by HHV-8, predominantly in the mantle zone of the lymph node. Several studies have produced very encouraging results. In a French study, 16/24 patients achieved complete remission after one year with four courses of rituximab (Gérard 2006). Overall survival at one year was 92%, and disease-free survival was 74%. In a British study, 20/21 achieved clinical remission, and 14/21 achieved radiological response (Bower 2007). Overall survival in this study was as high as 95% after two years, and disease-free survival was 79%. CRP, immunoglobulins, and HHV-8 viral load each decreased with rituximab. This was also true for cytokines such as IL-5, IL-6, and IL-10 (Bower 2009). Survival was also significantly improved with rituximab compared to conventional therapies in our retrospective cohort of 52 patients (Hoffmann 2011). Moreover, lymphomas in MCD are significantly less frequent with rituximab (Bower 2011, Gérard 2012, Pria 2017).

A dose of 375 mg per m^2 of body surface area is given once a week for four weeks. Care should be taken to ensure good hydration. Health insurance should be contacted in advance, as rituximab is not approved for MCD. Rituximab is well tolerated, and tumor lysis syndrome has not been observed. The main complication appears to be the reactivation of Kaposi's sarcoma, which probably occurs in up to one-third of cases (Bower 2007) and is challenging to treat. Combining rituximab with liposomal doxorubicin may be possible in cases with KS/MCD coincidence (Uldrick 2014). Attention should also be paid to infectious complications, especially in immunodeficiency. Even in relapses, which are not uncommon, re-administration is readily available and very effective (Powles 2007, Pria 2018).

However, in some, rituximab seems ineffective (Neuville 2005, Buchler 2008). Therefore, other approaches for which at least case reports or small case series exist will be briefly addressed in the following.

Valganciclovir: In a double-blind, randomized study, valganciclovir significantly reduced HHV-8 replication and is a potential choice for MCD treatment (Casper 2008). In a case series on HIV-MCD, 12/14 patients achieved "clinical improvement," and CRP, IL-6, and HHV-8 viral load also decreased (Uldrick 2011). However, our own experience has only partially confirmed this (Hoffmann 2011). There is a possible role for valganciclovir as maintenance therapy (Bower 2010). In contrast to valganciclovir, foscarnet or cidofovir do not appear to have any benefit (Coty 2003, Senanayake 2003, Berezne 2004).

Chemotherapy: Well-tolerated agents such as vincristine (2 mg IV as a bolus at 14-day intervals), vinblastine, or oral etoposide (50 mg daily) are effective according to some reports and also in our experience (Scott 2001, Kotb 2006). CHOP chemotherapy may also be helpful but does not significantly prolong survival.

Splenectomy: may be useful in severe cases. Speculation is that IL-6 production is curbed by removing a large HHV-8 reservoir. In 40 patients, the median survival with splenectomy was 28 versus 12 months (Oksenhendler 2002). One US study group reported that symptoms improved in 10/10 cases (Coty 2003).

IL-6 receptor blockers: There is data from Japan on several dozen HIV-negative individuals successfully treated with anti-IL-6 receptor monoclonal antibodies such as tocilizumab (Nishimoto 2005, Matsuyama 2007). Tocilizumab was approved for treating rheumatoid arthritis in 2009 under the trade name RoActemra®. Two cases of HIV-MCD showed rapid, albeit short-term, clinical improvements (Nagao 2014). For siltuximab, an anti-IL-6 monoclonal antibody, there is a randomized trial in as many as 53 negative individuals, showing durable remissions in 34% of patients (van Rhee 2014). In HHV-8 MCD, siltuximab has not yet been systematically tested because it probably does not bind to viral IL-6. However, there is evidence that it may still be effective (Polizzotto 2013).

Thalidomide: is supposed to suppress the cytokine dysregulation or the inflammatory component. There are case reports (Lee 2003, Jung 2004), some combined with rituximab (Stary 2008). We did not have a good experience with two patients; complications occurred, including pulmonary embolism.

Other immunotherapies: There are positive and negative alpha-interferon case reports (Coty 2003, Nord 2003). Steroids have no effect.

Literature

Aaron L, Lidove O, Yousry C, Roudiere L, Dupont B, Viard JP. Human herpesvirus 8-positive Castleman disease in HIV-infected patients: the impact of HAART. Clin Infect Dis 2002, 35:880-2.

Alzahrani M, Hull MC, Sherlock C, Griswold D, Leger CS, Leitch HA. Human immunodeficiency virus-associated multicentric Castleman disease refractory to antiretroviral therapy: clinical features, treatment and outcome. Leuk Lymphoma 2014 Aug 20:1-6.

Berezne A, Agbalika F, Oksenhendler E. Failure of cidofovir in HIV-associated multicentric Castleman disease. Blood 2004, 103:4368-9.

Bower M, Newsom-Davis T, Naresh K, et al. Clinical Features and Outcome in HIV-Associated Multicentric Castleman's Disease. J Clin Oncol 2011, 29:2481-6.

Bower M, Powles T, Williams S, et al. Brief communication: rituximab in HIV-associated multicentric Castleman disease. Ann Int Med 2007;147:836-9.

Bower M, Veraitch O, Szydlo R, et al. Cytokine changes during rituximab therapy in HIV-associated multicentric Castleman disease. Blood 2009, 113:4521-4.

Bower M. How I treat HIV-associated multicentric Castleman disease. Blood 2010, 116:4415-21.

Buchler T, Dubash S, Lee V, et al. Rituximab failure in fulminant multicentric HIV/human herpesvirus 8-associated Castleman's disease with multiorgan failure: report of two cases. AIDS 2008, 22:1685-7.

Casper C, Krantz EM, Corey L, et al. Valganciclovir for suppression of human herpesvirus-8 replication: a randomized, double-blind, placebo-controlled, crossover trial. J Infect Dis 2008, 198:23-30.

Castleman B, Iverson L, Menendez VP. Localized mediastinal lymph-node hyperplasia resembling lymphoma. Cancer 1956, 9: 822-830.

Coty PC, Astrow A, Gallinson D, et al. A single institution's experience treating Castleman's disease in HIV positive patients. Abstract 2485, 39th ASCO 2003, Chicago, IL/USA

El-Daly H, Bower M, Naresh KN. Follicular dendritic cells in multicentric Castleman disease present human herpes virus type 8 (HHV8)-latent nuclear antigen 1 (LANA1) in a proportion of cases and is associated with an enhanced T-cell response. Eur J Haematol 2010, 84:133-6.

Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 2017, 129:1646-1657.

Gérard L, Bérezné A, Galicier L, et al. Rituximab in Patients with HIV-associated Multicentric Castleman Disease (HIV-MCD). Castlema B-ANRS 117 Trial. Abstract 814, 13th CROI 2006, Denver.

Gérard L, Michot JM, Burcheri S, et al. Rituximab decreases the risk of lymphoma in patients with HIV-associated multicentric Castleman disease. Blood 2012, 119:2228-33.

Guihot A, Oksenhendler E, Galicier L, et al. Multicentric Castleman disease is associated with polyfunctional effector memory HHV-8–specific CD8+ T cells. Blood 2008; 111: 1387 – 1395.

Haq IU, Dalla Pria A, Papanastasopoulos P, et al. The clinical application of plasma Kaposi sarcoma herpesvirus viral load as a tumour biomarker: results from 704 patients. HIV Med 2016, 17:56-61.

Hoffmann C, Schmid H, Müller M, et al. Improved outcome with rituximab in patients with HIV-associated multicentric Castleman disease. Blood 2011, 118:3499-503.

Jung CP, Emmerich B, Goebel FD, Bogner JR. Successful treatment of a patient with HIV-associated multicentric Castleman disease (MCD) with thalidomide. Am J Hematol 2004, 75:176-7.

Kotb R, Vincent I, Dulioust A, et al. Life-threatening interaction between antiretroviral therapy and vinblastine in HIV-associated multicentric Castleman's disease. Eur J Haematol 2006, 76:269-71.

Kurzrock R, Voorhees PM, Casper C, et al. A Phase I, Open-Label Study of Siltuximab, an Anti-IL-6 Monoclonal Antibody, in Patients with B-cell Non-Hodgkin Lymphoma, Multiple Myeloma, or Castleman Disease. Clin Cancer Res 2013, 19:3659-3670.

Lee FC, Merchant SH. Alleviation of systemic manifestations of multicentric Castleman's disease by thalidomide. Am J Hematol 2003; 73: 48-53.

Li H, Wang H, Nicholas J. Detection of direct binding of human herpesvirus 8-encoded interleukin-6 (vIL-6) to both gp130 and IL-6 receptor (IL-6R) and identification of amino acid residues of vIL-6 important for IL-6R-dependent and -independent signaling. J Virol 2001, 75:3325-34.

Marcelin AG, Motol J, Guihot A, et al. Relationship between the quantity of Kaposi sarcoma-associated herpesvirus (KSHV) in peripheral blood and effusion fluid samples and KSHV-associated disease. J Infect Dis 2007, 196:1163-6.

Marrache F, Larroche C, Memain N, et al. Prolonged remission of HIV-associated multicentric Castelman's disease with an anti-CD20 monoclonal antibody as primary therapy. AIDS 2003;17:1409-10.

Matsuyama M, Suzuki T, Tsuboi H, et al. Anti-interleukin-6 receptor antibody (tocilizumab) treatment of multicentric Castleman's disease". Intern Med 2007, 46: 771–4.

Moore PS, Boshoff C, Weiss RA, Chang Y. Molecular mimicry of human cytokine and cytokine response pathway genes by KSHV. Science. 1996, 274:1739-44.

Mylona EE, Baraboutis IG, Lekakis LJ, et al. Multicentric Castleman's Disease in HIV infection: a systematic review of the literature. AIDS Rev 2008, 10:25-35.

Nagao A, Nakazawa S, Hanabusa H. Short-term efficacy of the IL6 receptor antibody tocilizumab in patients with HIV-associated multicentric Castleman disease: report of two cases. J Hematol Oncol. 2014 Jan 17;7(1):10.

Naresh KN, Rice AJ, Bower M. Lymph nodes involved by multicentric Castleman disease among HIV-positive individuals are often involved by Kaposi sarcoma. Am J Surg Pathol 2008, 32:1006-12.

Neuville S, Agbalika F, Rabian C, Brière J, Molina JM. Failure of rituximab in human immunodeficiency virus-associated multicentric Castleman disease. Am J Hematol 2005, 79:337-9.

Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood 2005, 106:2627-32.

Nord JA, Karter D. Low dose interferon-alpha therapy for HIV-associated multicentric Castleman's disease. Int J STD AIDS 2003;14:61-2.

Oksenhendler E, Boulanger E, Galicier L, et al. High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. Blood 2002, 99:2331-6.

Oksenhendler E, Boutboul D, Fajgenbaum D, Mirouse A, Fieschi C, Malphettes M, Vercellino L, Meignin V, Gérard L, Galicier L. The full spectrum of Castleman disease: 273 patients studied over 20 years. Br J Haematology 2018, 180: 206–216.

Oksenhendler E, Carcelain G, Aoki Y, et al. High levels of human herpesvirus 8 viral load, human interleukin-6, interleukin-10, and C reactive protein correlate with exacerbation of multicentric Castleman disease in HIV-infected patients. Blood 2000, 96:2069-73.

Oksenhendler E, Duarte M, Soulier J, et al. Multicentric Castleman's disease in HIV infection: a clinical and pathological study of 20 patients. AIDS 1996, 10:61-7.

Polizzotto MN, Millo C, Uldrick TS, et al. 18F-fluorodeoxyglucose Positron Emission Tomography in Kaposi Sarcoma Herpesvirus-Associated Multicentric Castleman Disease: Correlation With Activity, Severity, Inflammatory and Virologic Parameters. J Infect Dis 2015, 212:1250-60.

Polizzotto MN, Uldrick TS, Wang V, et al. Human and viral interleukin-6 and other cytokines in Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. Blood 2013, 122:4189-98.

Powles T, Stebbing J, Bazeos A, et al. The role of immune suppression and HHV-8 in the increasing incidence of HIV-associated multicentric Castleman's disease. Ann Oncol 2009, 20:775-9.

Powles T, Stebbing J, Montoto S, et al. Rituximab as retreatment for rituximab pretreated HIV-associated multicentric Castleman disease. Blood 2007;110:4132-3.

Pria AD, Pinato D, Roe J, et al. Relapse of HHV8-positive multicentric Castleman disease following rituximab-based therapy in HIV-positive patients. Blood 2017, 129:2143-2147.

Sayer R, Paul J, Tuke PW, et al. Can plasma HHV8 viral load be used to differentiate multicentric Castleman disease from Kaposi sarcoma? Int J STD AIDS 2011, 22:585-9.

Scott D, Cabral L, Harrington WJ Jr. Treatment of HIV-associated multicentric Castleman's disease with oral etoposide. Am J Hematol 2001, 66:148-50.

Senanayake S, Kelly J, Lloyd A, et al. Multicentric Castleman's disease treated with antivirals and immunosuppressants. J Med Virol 2003; 71: 399-403.

Seo HY, Kim EB, Kim JW, et al. Complete Remission in a Patient with Human Herpes Virus-8 Negative Multicentric Castleman Disease Using CHOP Chemotherapy. Cancer Res Treat 2009, 41:104-7.

Stary G, Kohrgruber N, Herneth AM, et al. Complete regression of HIV-associated multicentric Castleman disease treated with rituximab and thalidomide. AIDS 2008:22:1232-4.

Stebbing J, Adams C, Sanitt A, et al. Plasma HHV8 DNA predicts relapse in individuals with HIV-associated multicentric Castleman disease. Blood. 2011 Apr 21. [Epub ahead of print]

Stebbing J, Ngan S, Ibrahim H, et al. The successful treatment of haemophagocytic syndrome in patients with human immunodeficiency virus-associated multi-centric Castleman's disease. Clin Exp Immunol 2008, 154:399-405.

Suthaus J, Adam N, Grötzinger J, et al. Viral Interleukin-6: Structure, pathophysiology and strategies of neutralization. Eur J Cell Biol. 2010 Dec 20.

Talat N, Schulte KM. Castleman's disease: Systematic analysis of 416 patients from the literature. Oncologist 2011, 16:1316-24.

Uldrick TS, Wang V, O'Mahony D, et al. An interleukin-6-related systemic inflammatory syndrome in patients co-infected with Kaposi sarcoma-associated herpesvirus and HIV but without Multicentric Castleman disease. Clin Infect Dis 2010, 51:350-8.

Van Rhee F, Voorhees P, Dispenzieri A, et al. International, evidence-based consensus treatment guidelines for idiopathic multicentric Castleman disease. Blood 2018, 132; 2115-2124

Van Rhee F, Wong RS, Munshi N. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2014 Jul 17.

Zietz C, Bogner JR, Goebel FD, Lohrs U. An unusual cluster of cases of Castleman's disease during HAART for AIDS. N Engl J Med 1999, 340:1923-4.

10. Non-AIDS-defining malignancies

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People living with HIV have an increased risk of cancer. This applies not only to the three AIDS-defining malignancies (ADM), Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical carcinoma. There is also an overall two- to three-fold increased incidence for most non-AIDS-defining malignancies (NADM) (Franceschi 2010). For some diseases like Hodgkin's disease (see *Malignant Lymphomas*) and anal carcinoma (see below), the risk is so evident that calls have been made to classify them as AIDS-defining diseases. Breast carcinomas, on the other hand, do not appear to be more common (Latif 2011).

In recent years, some authors have suggested that instead of ADM and NADM, it is better to distinguish infection-related malignancies (IRMs) and infection-unrelated malignancies (IURMs) (Borges 2016, Shepherd 2016). However, this classification has drawbacks: infection as a cause is not always confirmed or ruled out; consider gastric carcinomas, hepatocellular carcinoma (it does not always have to be hepatitis), and some lymphomas.

NADM account for about two-thirds of all new malignancies in HIV-infected individuals (Shepherd 2016). They are thus more common than lymphoma and Kaposi's sarcoma. In developed countries, NADM result in more deaths than ADM, hepatitis C, or cardiovascular disease (Smith 2014). Among patients with virologic control, NADM are by far the most common cause of death at 19% – in contrast, hardly anyone dies of AIDS (Goehringer 2017). Figure 1 shows the percentage of malignancies among causes of death in France between 2000 and 2010 (Vandenhende 2015). In a newer French analysis restricted to the Paris area, 31% of all deaths were due to non-AIDS non-viral hepatitis-related NADM in 2020/21 (Sellier 2023).

In the D:A:D study, the major risk factors for fatal NADM were increasing age, current nicotine use, and the level of CD4 T-cells: the lower, the higher the risk for NADM. Individuals below 50 CD4 T-cells/µl had a 15-fold higher risk than those with more than 500/µl (Monforte 2008). The risk persisted once CD4 T-cells were low (Worm 2013). The correlation between NADM and immunodeficiency was also confirmed in the EuroSIDA study (Reekie 2010). However, immunodeficiency does not explain

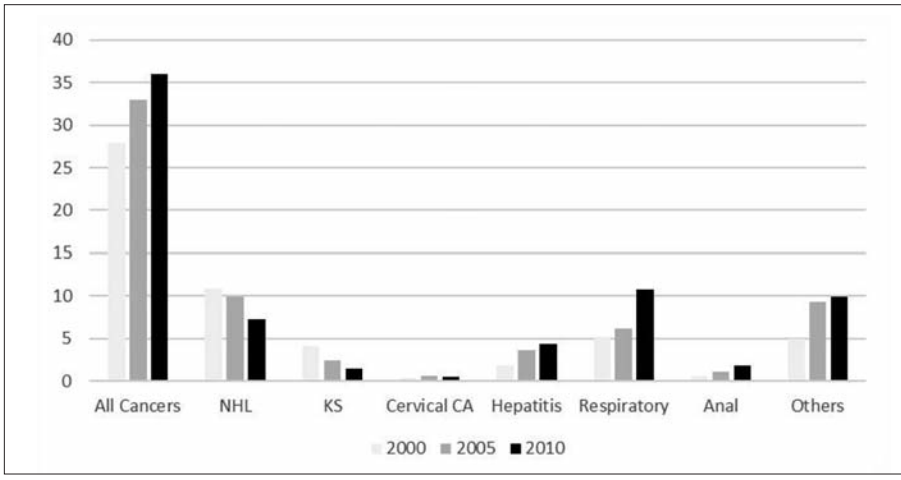

Figure 1: Malignant diseases as a proportion of causes of death. Deaths among PLWH in France in 2000 (light, n=964), 2005 (gray, n=1042), and 2010 (black, n=728). Figures according to Vandenhende 2015.

everything. Smoking contributes to the increased incidence of many tumors (Helleberg 2014), and the proportion of active smokers is still significantly higher than in the general population. Alcohol, lifestyle (UV exposure), and co-infections (HPV, HBV, HCV) also play a role. The thesis that the incidence of all malignancies will increase given the increasing age of PLWH is only partly true. The increase will mainly affect IURMs and fewer IRMs due to the aging of the HIV-infected population and high smoking prevalence (Shepherd 2016). Incidence of UIRMs appears not to be positively influenced by an earlier start of therapy (Borges 2016).

Screening and prevention

Whether PLWH need more frequent screening or earlier detection examinations is still being determined. With regard to anal carcinoma, there seems to be evidence for a benefit, but screening is controversial (see below). The situation is unclear for colon cancer, although there is evidence that neoplastic changes are found more frequently in PLWH on the occasion of screening colonoscopies (Bini 2009). There are no specific recommendations for prostate-specific antigen screening beyond discussing its utility in the general population (Tyerman 2012). For gynecologic screening, see the *Gynecology* chapter. In HCV co-infection, regular (biannual) sonography could be beneficial, as shown in a study of 70 patients: hepatocellular carcinomas were less advanced when detected, even resulting in slightly better survival (Nunez 2010).

Finally, support for smoking cessation has become an essential part of medical care – smoking is also a major contributor to mortality in HIV. While superfluous "preventive" examinations are often demanded ("Shouldn't we have another X-ray?"), it is usually forgotten: nicotine abstinence is and remains the most important preventive measure, even for malignant diseases. PLWH today lose more years of life to smoking than HIV (Helleberg 2013); non-smokers are not at increased risk for many tumors (Helleberg 2014, Shepherd 2016). US projections found cumulative lung cancer mortality risks of 29, 23, and 19% for a 40-year-old HIV-positive man with continued heavy, moderate, or light nicotine use. If this patient quits at age 40, the risk drops to 8%, 6%, and 4%, respectively. By comparison, someone who has never smoked has a cumulative lung cancer risk of 1.6% (Reddy 2017). Avoiding excessive obesity and healthy lifestyles also do more than costly screenings.

Treatment

A problem of therapy for many NADM is that little is often known about chemotherapeutic agents and ART interactions, and the new targeted agents are primarily unexplored in PLWH. Prospective studies are virtually nonexistent, and data on critical new agents are limited. Data are also still limited for checkpoint inhibitors (which interfere with the T cell response and were therefore initially used cautiously in PLWH) (Cook 2019, Luo 2022).

For many malignancies, there are only uncontrolled cohorts with HIV. In most cases, those affected are younger than those from the general population, although this could also be due to better surveillance (Shiels 2010). However, experience in entities as diverse as glioblastoma (Wang 2018), carcinoma of the colon (Chapman 2009, Alfa-Wali 2011), bladder (Gaughan 2009), prostate (Pantanowitz 2008), or esophagus (Stebbing 2010, Jensen 2017) shows that PLWH generally benefit from advances in oncology. They should generally be treated in the same way as HIV-negative individuals – although this often requires mediating discussions with oncologists, whose HIV picture is sometimes still limited today. There is considerable potential for improvement in communication (Suneja 2015).

Anal carcinoma

Anal carcinoma is one of the most common non-AIDS tumors in PLWH. It is closely associated with HPV co-infections and usually arises from pre-cancerous precursors. Regarding the frequency, sometimes dramatic reports circulate, often leading to uncertainty. It will, therefore, be discussed here in more detail than other tumors.

HPV association, epidemiology

Human papillomavirus (HPV) infections are among the most common sexually transmitted viral infections ever. HPV belongs to the *Papovaviridae* family and infects the basal cells of the epithelia of the skin and mucosa. PLWH have a 2–6-fold increased risk of anal HPV infection, independent of sex, sexual practices, and preferences. The risk of persistent HPV infections is 7-fold higher and inversely correlates with CD4 T-cell count (Piketty 2003). Nearly 100 different HPV types are now known, and about 20 are associated with anal or cervical cancer. HPV-16 and HPV-18 have a high oncogenic potential, with an increased risk of anal carcinomas.

HPV infections are present in most PLWH, often with multiple subtypes. In a meta-analysis, the pooled prevalence for anal HPV infections in HIV-positive men was 89% overall and 79% for potentially vaccine-preventable high-risk types such as HPV-16/18 (Machalek 2012). A study from Bochum (Kreuter 2005) found anal HPV infection in 86% of 103 male patients, mostly HPV-16 (53%) and -18 (27%).

Persistent HPV infection can lead to precancerous lesions, anal intraepithelial neoplasms (AIN). These are classified histologically according to the degree of dysplasia into grade I (mild), grade II (moderate), and grade III (severe). In severe AIN, the entire epidermis is affected. AINs, including those of higher grade, are widespread; AIN II/III are found in approximately 30% of HIV-positive men (Machalek 2012).

The enormous (and at first glance disturbing) prevalence of anal HPV infections and pre-cancerous precursors contrast with an overall relatively low incidence of anal carcinoma (AC). A meta-analysis of all data through the end of 2011, based on 100,000 patient-years, showed an overall incidence of 78 for the HAART era, compared with 22 in the pre-HAART era (Machalek 2012). Significant regional differences exist. For example, the incidence in the United States was most recently 147 (Chiao 2013); in the European-dominated D:A:D cohort, it was only 45 (Worm 2013), and in the Swiss cohort, it was even lower at 25 (Franceschi 2010). Thus, anal carcinoma remains a rare disease, even in HIV. However, the relative risk is significantly increased compared to the general population (where it is a rarity) – about 80-fold for MSM and 27-fold for heterosexual men, probably also in women (Silverberg 2012). The incidence may be declining in recent years (Colón-López 2018).

It follows from this discrepancy that HPV infections and higher-grade precursors do not necessarily result in tumor disease: according to currently available data, one invasive AC per year develops from 377 high-grade changes (Machalek 2012). Many AINs regress spontaneously (Tong 2013, Grulich 2014). Spontaneous clearance of HPV viruses often occurs (Goldstone 2019, Alberts 2020), but the rate is probably somewhat lower overall in HIV infection (Wei 2022).

Thus, most PLWH with HPV and AIN will not develop cancer; the estimated cumulative lifetime AC risk is about 1.5% (Silverberg 2015). Moreover, the risk is different for everyone. Many studies have shown that AC incidence is much higher for low CD4 T-cells than individuals whose CD4 T-cells never fell below 200/µl (Piketty 2012, Bertisch 2013, Chiao 2013, Duncan 2015). CD4 nadir, in particular, appears to be a significant risk factor. Cumulative viral load is also one, as is smoking (Bertisch 2013, Chiao 2013). There does not appear to be an apparent protective

effect from ART. Early ART may slow progression (Duncan 2015). However, in a separate cohort of 121 cases, most had been successfully treated with antiretroviral therapy for many years, and CD4 T-cells were at almost 400/µl (Hoffmann 2011).

Screening and treatment of precursors

In 2013, the German AIDS Society, among others, developed a guideline for preventing, diagnosing, and treating anal dysplasia and anal carcinoma in PLWH, which provides detailed instructions for action despite the limited data available (see *Dermatology*). In this guideline, routine examinations (inspection, palpation, smear, cytology) are recommended once a year for all PLWH. However, there is controversy about whether such comprehensive screening is beneficial. Given the discrepancy between enormously high AIN prevalences and the low AC incidence, there is a considerable risk of over-diagnosis, over-therapy, and the associated uncertainty for everyone involved.

Since years usually elapse between AIN and the manifestation of anal carcinoma, early treatment of AIN has a good chance of success, at least in theory. However, no treatment of pre-cancerous lesions has sufficient evidence, as shown by a Cochrane analysis (Macaya 2012). For AIN 1, topical therapy with imiquimod (or podophyllotoxin) is warranted; AIN 2+3 should be removed surgically (electrocaustic ablation using a snare) or by laser ablation. Infrared coagulation is also possible (Stier 2008). The complete clearance rate of higher-grade lesions increased to 62% in one year with repeated treatments, compared with 30% with observation alone (Goldstone 2019). In another randomized trial of 148 HIV-positive MSM with AIN, electrocautery was superior to topical treatment with imiquimod or 5-FU regarding tolerability (Richel 2012). However, recurrences were very common.

Off-label use of imiquimod (multiple manufacturers) is an option for high-grade AIN in PLWH on ART. The dosage is ½ sachet of imiquimod cream 5% topical three times per week; for severe local irritation, discontinuation for several days until irritation subsides. Duration of treatment is at least 16 weeks; if there is no response, continuation for another 16 weeks. Treatment should be discontinued after 32 weeks if no therapeutic response is observed.

Condylomas should also be eliminated (electrocoagulation, cryotherapy). Topical therapy with the immunomodulator imiquimod (i.e., Aldara® cream) is also possible here, but the effects are less impressive in PLWH. Imiquimod seems better suited as post-treatment, where it probably significantly reduces the recurrence rate. Imiquimod does not have a direct antiviral effect but probably a cytolytic-destructive effect via cytokine induction. The most important side effect is local erythema (erythema means effect!); less frequent are burning and pruritus. Severe skin reactions occur only rarely.

2022, the ANCHOR data were presented, a large randomized Phase III trial (Palefsky 2022). In this, nearly 4,500 people over 35 years of age and with HIV and biopsy-proven HSIL (high-grade squamous intraepithelial lesions, equivalent to AIN II/III) had been randomized to receive either treatment of these lesions (in 84% ablation with electrocautery, but also other methods) or only "active monitoring" (high-resolution anoscopy every six months). After an observation period of 26 months, 9 cases had occurred in the treatment arm compared with 21 cases in the treatment arm, corresponding to 173 rather than 402 cases per 100,000 person-years. Despite these results, controversy remains over the treatment of pre-cancerous lesions. Despite the immense effort, the overall clinical effect in ANCHOR was small, and overall mortality was not affected. Moreover, seven serious adverse events were observed in the treatment arm and only one in the observation arm.

Many believe that better risk stratification is needed, especially in light of these data and the limited capacity for high-resolution anoscopy. There is a need to identify those at the highest risk for developing cancer (HPV-16? DNA methylation?) and, from this, to develop viable screening and treatment strategies. Hopefully, further sub-analyses from ANCHOR will provide answers to this.

Diagnosis

The most common symptom is rectal bleeding. A person reporting blood in the stool must see a proctologist! One should not be satisfied with the "suspected diagnosis" of hemorrhoids often voiced by the patient. Other symptoms are burning, pain during defecation, or pruritus. Histologically, squamous cell carcinomas are usually present and, more rarely, transitional epithelial carcinomas. Early on, the anal canal and sphincter may be infiltrated. Regional lymph nodes are affected depending on the location of the anal carcinoma. Deep-seated anal carcinomas infiltrate inguinally, intermediate pelvic, and high-seated mesenteric. Distant metastases are rare. Nevertheless, in addition to proctoscopy and endosonography if possible, CT abdomen and pelvis should always be done.

Treatment

In manifest AC, small lesions of < 2 cm are operated on with continence preservation if possible, and adjuvant chemotherapy or radiotherapy is unnecessary. Larger lesions are treated with combined radiochemotherapy (mitomycin 10 mg/m^2 on days 1 and 29 and 5-FU 1000 mg/m^2 on days 1–5 and 29–33, followed by radiotherapy fractionated up to 50 Gy). More intensive therapies are also possible (Blazy 2005). The complications that can occur under such a regimen should be noted. What can go wrong, does go wrong: We have experienced a patient who first developed severe extravasation under mitomycin, then myocardial infarction under 5-FU, and finally perforating fecal radiation colitis. Invariably, affected patients should receive concomitant oncologic care. After completion of radiochemotherapy, proctoscopy is performed every six months. ART-naive patients should always be started on ART. Overall, the prognosis of AC does not appear to be significantly worse than in HIV-negative individuals (Chiao 2008, Hoffmann 2011, Alfa-Wali 2012). In a large study of 605 cases from 2004–2018, HIV was only a risk factor for disease-free survival in T1-2/N0 cases but not in later stages (Martin 2022).

Vaccination

An HPV vaccine that protects intraepithelial neoplasia and persistent HPV infection in cervical carcinoma (Harper 2006) also appears protective against anal carcinoma (Palefsky 2011). Approved vaccines induce an adequate immune response in PLWH (Toft 2014, Staadegard 2022). However, PLWH are usually already HPV-co-infected, so the purely protective effect of such vaccination will likely come too late. However, vaccination may also have a therapeutic effect (Anderson 2009). However, a recent large randomized trial in patients over 26 years of age yielded disappointing results. Neither persistent HPV infection nor precursors were favorably affected by the vaccine (Wilkin 2018).

Testicular tumors

Testicular tumors are the most common cancer in men between 20 and 35, and HIV infection increases the relative risk by a factor of 2–5, especially for seminomas (Goedert 2007). Two early case collections reported 34 and 35 patients, including 26 and 16 seminomas and 18 and 9 non-seminomatous germ cell tumors, respectively (Powles 2003, Fizazi 2001). Median CD4 T-cells at diagnosis ranged from 300 to 350/µl, although with a wide range. The prognosis was generally good and no worse in a matched-pair study than in HIV-negative individuals (Powles 2004). Other studies also report quite favorable courses (Fizazi 2001).

In a recent international cohort study with 92 cases, progression-free survival at 5 and 10 years was 81% and 73%, respectively, and overall survival rates were 91% and 85% (Hentrich 2022). Most were diagnosed at early stages (stage 1 at 56%). Overall, only five deaths from refractory disease were observed.

HIV-positive men with testicular cancer should be treated with the standard regimens recommended for HIV-negative patients. Depending on histology and stage, these consist of orchiectomy, lymph node extirpation or radiation, and/or platinum-based chemotherapy. High-dose therapies are also possible (Hentrich 2009). Treatment should be performed by an oncologically knowledgeable urologist (or urologist) in collaboration with an HIV center.

Lung cancer

In the general male population, lung cancer (LC) is the most frequent type of cancer leading to death; in women, it is in third place, and the trend is upward. In PLWH, the relative risk is at least doubled (Haas 2022) and increases with increasing immunodeficiency (Reekie 2011). In the United States, since about 2011, the risk of disease for lung cancer has been higher than for KS and lymphoma for people over age 60 living with HIV (Haas 2022). In France, LC is now more likely to cause death than non-Hodgkin lymphoma, accounting for about 8% of all causes of death (Vandenhende 2015). It is estimated that about 9% of all PLWH will eventually die from LC if smoking habits do not change.

Rising incidences are likely to have many reasons: first, PLWH live longer and thus have more time to develop LC, and second, PLWH smoke too much. Smoking is the most critical risk factor (Clifford 2012) for LC: time to quit – opportunities to quit are plentiful. However, there are also increasing voices calling for strategies that go beyond just smoking cessation, as many people are not ready to do so (Shuter 2021). In addition, other factors contribute to the increased risk besides age and nicotine (Review: Frega 2020). This is also supported by the fact that, with adenocarcinomas, the subtype that is most elevated is the subtype that is least associated with increased nicotine use of all LC subtypes. Because severe immunodeficiency is often not present, other factors have been postulated, including specific infections in the lung and scarring, but also increased levels of pro-inflammatory cytokines in the lung or decreased levels of glutathione, as found in HIV infection. These factors could exacerbate the damage caused by smoking. PLWH appear to be more sensitive to carcinogens (Frega 2020). In a US cohort, increased risk persisted even after adjusting for smoking, age, ethnicity, and COPD (Sigel 2012). Predisposition also plays a role. The risk is exceptionally high if the parents already have the disease (Engsing 2011).

As with HIV-negative patients, only those whose LC is detected early have a chance. Symptoms are non-specific, and diagnosis is rarely made in time. In our cohort of 72 cases from 2000–2010, only 34% were in stages I-IIIa (Hoffmann 2013). In early tumor stages, surgery should be performed with curative intention if possible;

chemotherapies only grant a delay. The median survival times in our evaluation were one year – the level of CD4 T-cells and limited stages were significant influencing factors. Long-term survival is possible in the early stages.

PLWH with LC do not have a worse overall outcome than HIV-negative LC patients (Rengan 2012). Carboplatin/gemcitabine are tolerated quite well, as are taxanes (Bridges 2008). HIV is not a contraindication for any drug. Especially with regard to potential interactions, the choice of antiretroviral options has grown significantly in recent years, and switching ART is rarely a problem. The recommendations for HIV-negative individuals should, therefore, guide treatment. Differentiation is made not only by stage but also by histologic and genetic markers. In recent years, immune checkpoint and kinase inhibitors associated with predictive biomarkers have improved prognosis. New cytostatics, angiogenesis inhibitors, and local and supportive therapies are available. Although data are limited on HIV infection, all new approaches should be considered in principle, including immune checkpoint inhibitors (ICIs), with growing experience (Cook 2019, Lavole 2022, Luo 2022). For example, in a recent analysis of 390 PWH, ICIs demonstrated differential activity across cancer types with no excess toxicity. The safety and activity of ICIs were similar between matched subgroup cohorts of PLWH and negative controls with metastatic lung cancer (El Zharif 2023).

Literature

Alberts CJ, Heard I, Canestri A, et al. Incidence and clearance of anal HPV-16 and HPV-18 infection, and their determinants, among HIV-infected men who have sex with men in France. J Infect Dis. 2020,19 221:1488-1493. Nov 22.

Alfa-Wali M, Allen-Mersh T, Antoniou A, et al. Chemoradiotherapy for anal cancer in HIV patients causes prolonged CD4 cell count suppression. Ann Oncol 2012, 23:141-7.

Alfa-Wali M, Tait D, Allen-Mersh T, et al. Colorectal cancer in HIV-positive individuals: the immunological effects of treatment. Eur J Cancer 2011, 47:2403-7.

Anderson JS, Hoy J, Hillman R, et al. A randomized, placebo-controlled, dose-escalation study to determine the safety, tolerability, and immunogenicity of an HPV-16 therapeutic vaccine in HIV-positive participants with oncogenic HPV infection of the anus. J AIDS 2009, 52:371-81.

Bertisch B, Franceschi S, Lise M, et al. Risk factors for anal cancer in persons infected with HIV: a nested case-control study in the Swiss HIV Cohort Study. Am J Epidemiol 2013, 178:877-84.

Bini EJ, Green B, Poles MA. Screening colonoscopy for the detection of neoplastic lesions in asymptomatic HIV subjects. Gut 2009, 58:1129-34.

Blazy A, Hennequin C, Gornet JM, Furco A, Gerard L, Lemann M, Maylin Cet al. Anal carcinomas in HIV-positive patients: high-dose chemoradiotherapy is feasible in the era of HAART. Dis Colon Rectum 2005, 48:1176-81.

Boesecke C, Kasapovic A, Wasmuth JC, et al. High Rates of Endoscopic Findings and Histologic Abnormalities in Routine Colonoscopy of HIV Patients: German HIV Cohort. Abstract 890, 19th CROI 2012, Seattle USA.

Borges ÁH, Neuhaus J, Babiker AG, et al. Immediate Antiretroviral Therapy Reduces Risk of Infection-Related Cancer During Early HIV Infection. Clin Infect Dis 2016, 63:1668-1676.

Bridges BB, Thomas L, Hausner PF, et al. Phase II trial of gemcitabine/carboplatin followed by paclitaxel in patients with performance status=2,3 or other significant co-morbidity (HIV infection or s/p organ transplantation) in advanced non-small cell lung cancer. Lung Cancer 2008; 61:61-6

Chapman C, Aboulafia DM, Dezube BJ, Pantanowitz L. Human immunodeficiency virus-associated adenocarcinoma of the colon: clinicopathologic findings and outcome. Clin Colorectal Cancer 2009, 8:215-9.

Chiao EY, Giordano TP, Richardson P, El-Serag HB. HIV-associated squamous cell cancer of the anus: epidemiology and outcomes in the highly active antiretroviral therapy era. J Clin Oncol 2008; 26:474-9.

Chiao EY, Hartman CM, El-Serag HB, Giordano TP, et al. The impact of HIV viral control on the incidence of HIV-associated anal cancer. J AIDS 2013, 63:631-8.

Clifford GM, Lise M, Franceschi S, et al. Lung cancer in the Swiss HIV Cohort Study: role of smoking, immunodeficiency and pulmonary infection. Br J Cancer 2012, 106:447-52.

Colón-López V, Shiels MS, Machin M, et al. Anal Cancer Risk Among People With HIV Infection in the United States. J Clin Oncol 2018, 36:68-75.

Cook MR, Kim C. Safety and Efficacy of Immune Checkpoint Inhibitor Therapy in Patients With HIV Infection and Advanced-Stage Cancer: A Systematic Review. JAMA Oncol 2019, 5:1049-1054.

Duncan KC, Chan KJ, Chiu CG, et al. HAART slows progression to anal cancer in HIV-infected MSM. AIDS 2015, 29:305-11.

El Zarif T, Nassar AH, Adib E, et al. Safety and Activity of Immune Checkpoint Inhibitors in People Living With HIV and Cancer: A Real-World Report From the Cancer Therapy Using Checkpoint Inhibitors in People Living With HIV-International (CATCH-IT) Consortium. J Clin Oncol 2023, 41:3712-23.

Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980-2002. AIDS 2006;20:1645-54.

Engsig FN, Kronborg G, Larsen CS, et al. Lung cancer in HIV patients and their parents: a Danish cohort study. BMC Cancer 2011, 11:272.

Fizazi K, Amato RJ, Beuzeboc P, et al. Germ cell tumors in patients infected by the human immunodeficiency virus. Cancer 2001, 92:1460-7.

Franceschi S, Lise M, Clifford GM, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. Br J Cancer 2010, 103:416-22.

Frega S, Ferro A, Bonanno L, et al. Lung Cancer (LC) in HIV Positive Patients: Pathogenic Features and Implications for Treatment. Int J Mol Sci. 2020 Mar; 21(5): 1601.

Gaughan EM, Dezube BJ, Bower M, et al. HIV-associated bladder cancer: a case series evaluating difficulties in diagnosis and management. BMC Urol 2009, 9:10.

Goedert JJ, Purdue MP, McNeel TS, McGlynn KA, Engels EA. Risk of germ cell tumors among men with HIV/acquired immunodeficiency syndrome. Cancer Epidemiol Biomarkers Prev 2007;16:1266-9.

Goehringer F, Bonnet F, Salmon D, et al. Causes of Death in HIV-Infected Individuals with Immunovirologic Success in a National Prospective Survey. AIDS Res Hum Retroviruses 2017, 33:187-193.

Goldstone SE, Lensing SY, Stier EA, et al. A Randomized Clinical Trial of Infrared Coagulation Ablation Versus Active Monitoring of Intra-anal High-grade Dysplasia in Adults With Human Immunodeficiency Virus Infection: An AIDS Malignancy Consortium Trial. Clin Infect Dis 2019, 68:1204-1212.

Grulich AE et al. Incidence and clearance of anal high-grade squamous intraepithelial lesions (HSIL) in HIV positive and HIV negative homosexual men. Abstract WEAB0102, 20th IAC 2014, Melbourne AUS.

Haas CB, Engels EA, Horner MJ, et al. Trends and risk of lung cancer among people living with HIV in the USA: a population-based registry linkage study. Lancet HIV 2022, 9:e700-e708.

Hakimian R, Fang H, Thomas L, Edelman MJ. Lung cancer in HIV-infected patients in the era of HAART. J Thorac Oncol 2007;2:268-72.

Harper DM, Franco EL, Wheeler C, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006, 367:1247-55.

Helleberg M, Afzal S, Kronborg G, Larsen CS, Pedersen G, Pedersen C, Gerstoft J, Nordestgaard BG, Obel Net al. Mortality Attributable to Smoking Among HIV-1-Infected Individuals: A Nationwide, Population-Based Cohort Study. Clin Infect Dis 2012 Dec 18.

Helleberg M, Gerstoft J, Afzal S, et al. Risk of cancer among HIV-infected individuals compared to the background population: impact of smoking and HIV. AIDS 2014, 28:1499-508.

Hentrich M, Schiel X, Niedermeier A, et al. Successful salvage high-dose chemotherapy and autologous stem-cell transplantation in HIV-related germ-cell tumor. Ann Oncol 2009, 20:1900-1.

Hentrich MU, Bower M, Daugaard G, et al. Outcomes of men with HIV and germ cell cancer: Results from an international collaborative study. Cancer 2022, 128:260-268.

Hoffmann C, Kohrs F, Sabranski M, et al. HIV-associated lung cancer: survival in an unselected cohort. Scand J Infect Dis 2013, 45:766-72.

Hoffmann C, Sabranski M, Wyen C, et al. Clinical characteristics and outcome of HIV+ patients with invasive anal cancer. Abstract 870, 18th CROI 2011, Boston USA.

INSIGHT START Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med 2015, 373:795-807.

Jensen BE, Oette M, Haes J, Häussinger D. HIV-Associated Gastrointestinal Cancer. Oncol Res Treat 2017, 40:115-118.

Kreuter A, Brockmeyer NH, Hochdorfer B, et al. Clinical spectrum and virologic characteristics of anal intraepithelial neoplasia in HIV infection. J Am Acad Dermatol 2005, 52:603-8.

Latif N, Rana F, Guthrie T. Breast cancer and HIV in the era of highly active antiretroviral therapy: two case reports and review of the literature. Breast J 2011, 17:87-92.

Lavole A, Mazieres J, Schneider S, et al. Assessment of nivolumab in HIV-Infected patients with advanced non-small cell lung cancer after prior chemotherapy. The IFCT-1602 CHIVA2 phase 2 clinical trial. Lung Cancer 2021, 158:146-150.

Luo L, Xu Y, Li T, et al. Immune checkpoint inhibitor therapy for cancer patients infected with HIV: A systematic review. Asia Pac J Clin Oncol 2022, 18:e17-e22.

Macaya A, Muñoz-Santos C, Balaguer A, Barberà MJ. Interventions for anal canal intraepithelial neoplasia. Cochrane Database Syst Rev. 2012 Dec 12;12:CD009244.

Machalek DA, Poynten M, Jin F, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. Lancet Oncol 2012, 13:487-500.

Martin D, Schreckenbach T, Ziegler P, et al. Evaluation of prognostic factors after primary chemoradiotherapy of anal cancer: A multicenter study of the German Cancer Consortium-Radiation Oncology Group (DKTK-ROG). Radiother Oncol 2022 Feb;167:233-238.

Monforte A, Abrams D, Pradier C, et al. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. AIDS 2008;22;2143-53.

Morlat P, Roussillon C, Henard S, et al. Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000. AIDS 2014, 28:1181-91.

Nunez M, Kikuchi L, Barreiro P, et al. Screening for hepatocellular carcinoma (HCC) in HIV/HCV-co-infected patients: impact on staging, therapy, and survival. Abstract 685, 17th CROI 2010, San Francisco USA.

Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. NEJM 2011, 365:1576-85.

Palefsky JM, Lee JY, Jay N, et al. Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer. N Engl J Med 2022, 386:2273-2282.

Palefsky JM. Anal cancer prevention in HIV-positive men and women. Curr Opin Oncol 2009, 21:433-8.

Pantanowitz L, Bohac G, Cooley TP, Aboulafia D, Dezube BJ. Human immunodeficiency virus-associated prostate cancer: clinicopathological findings and outcome in a multi-institutional study. BJU Int 2008, 101:1519-23.

Piketty C, Darragh TM, Da Costa M, et al. High prevalence of anal human papillomavirus infection and anal cancer precursors among HIV-infected persons in the absence of anal intercourse. Ann Intern Med 2003, 138:453-9.

Piketty C, Selinger-Leneman H, Bouvier AM, et al. Incidence of HIV-related anal cancer remains increased despite long-term combined antiretroviral treatment: results from the french hospital database on HIV. J Clin Oncol 2012, 30:4360-6.

Powles T, Bower M, Daugaard G, et al. Multicenter study of HIV-related germ cell tumors. J Clin Oncol 2003, 21:1922-7.

Powles T, Bower M, Shamash J, et al. Outcome of patients with HIV-related germ cell tumours: a case-control study. Br J Cancer 2004, 90:1526-30.

Reddy KP, Kong CY, Hyle EP, et al. Lung Cancer Mortality Associated With Smoking and Smoking Cessation Among People Living With HIV in the United States. JAMA Intern Med 2017, 177:1613-1621.

Reekie J, Kosa C, Engsig F, et al. Relationship between current level of immunodeficiency and non-acquired immunodeficiency syndrome-defining malignancies. Cancer 2010, 116:5306-15.

Reinhold JP, Moon M, Tenner CT, Poles MA, Bini EJ. Colorectal cancer screening in HIV-infected patients 50 years of age and older: missed opportunities for prevention. Am J Gastroenterol 2005, 100:1805-12.

Rengan R, Mitra N, Liao K, Armstrong K, Vachani A. Effect of HIV on survival in patients with non-small-cell lung cancer in the era of highly active antiretroviral therapy: a population-based study. Lancet Oncol 2012, 13:1203-9.

Richel O, De Vries H, van Noesel C, et al. Treatment of Anal Intraepithelial Neoplasia in HIV+ MSM: A Triple-arm Randomized Clinical Trial of Imiquimod, Topical 5-Fluoruracil, and Electrocautery. Abstract 135LB, 19th CROI 2012, Seattle USA.

Rudek MA, Flexner C, Ambinder RF. Use of antineoplastic agents in patients with cancer who have HIV/AIDS. Lancet Oncol 2011, 12:905-12.

Sellier P, Alexandre-Castor G, Brun A, et al. Updated mortality and causes of death in 2020-2021 in people living with HIV: a multicenter study in France. AIDS. 2023 Jul 10.

Shepherd L, Borges Á, Ledergerber B, et al. Infection-related and -unrelated malignancies, HIV and the aging population. HIV Med 2016, 17:590-600.

Shiels MS, Pfeiffer RM, Engels EA. Age at cancer diagnosis among persons with AIDS in the United States. Ann Intern Med 2010, 153:452-60.

Shuter J, Reffy KP, Hyle EP, et al. Harm reduction for smokers living with HIV. Lancet HIV 2021, 8:e652-e658.

Sigel K, Wisnivesky J, Gordon K, et al. HIV as an independent risk factor for incident lung cancer. AIDS 2012 Feb 29. [Epub ahead of print]

Silverberg MJ, Lau B, Achenbach CJ, et al. Cumulative Incidence of Cancer Among Persons With HIV in North America: A Cohort Study. Ann Intern Med 2015, 163:507-18.

Silverberg MJ, Lau B, Justice AC, et al. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. CID 2012, 54:1026-34.

Silverberg MJ, Neuhaus J, Bower M, et al. Risk of cancers during interrupted antiretroviral therapy in the SMART study. AIDS 2007; 21:1957-63.

Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. Lancet 2014, 384:241-8.

Staadegard L, Rönn MM, Soni N, et al. Immunogenicity, safety, and efficacy of the HPV vaccines among people living with HIV: A systematic review and meta-analysis. EClinicalMedicine 2022, 52:101585.

Stebbing J, Krown SE, Bower M, et al. Primary esophageal carcinoma in the era of highly active antiretroviral therapy. Arch Intern Med 2010, 170:203-7.

Stier EA, Goldstone SE, Berry JM, et al. Infrared coagulator treatment of high-grade anal dysplasia in HIV-infected individuals: an AIDS malignancy consortium pilot study. J AIDS 2008;47:56-61.

Suneja G, Boyer M, Yehia BR, et al. Cancer Treatment in Patients With HIV Infection and Non-AIDS-Defining Cancers. J Oncol Pract 2015, 11:e380-7.

Toft L, Storgaard M, Müller M, et al. Comparison of the immunogenicity and reactogenicity of Cervarix and Gardasil human papillomavirus vaccines in HIV-infected adults: a randomized, double-blind clinical trial. J Infect Dis 2014, 209:1165-73.

Tong WW, Jin F, McHugh LC, et al. Progression to and spontaneous regression of high-grade anal squamous intraepithelial lesions in HIV-infected and uninfected men. AIDS 2013, 27:2233-43.

Tyerman Z, Aboulafia DM. Review of screening guidelines for non-AIDS-defining malignancies. AIDS Rev 2012, 14:3-16.

Vandenhende MA, Roussillon C, Henard S, et al. Cancer-Related Causes of Death among HIV-Infected Patients in France in 2010: Evolution since 2000. PLoS One 2015, 10:e0129550.

Wang T, Gao T, Niu X, et al. Clinical Characteristics and Prognostic Analysis of Glioma in HIV-Infected Patients. World Neurosurg 2018 Mar 8.

Wei F, Goodman MT, Xia N, et al. Incidence and clearance of anal human papillomavirus infection in 16 164 individuals, according to HIV status, gender, and male sexuality: an international pooled analysis of 34 longitudinal studies. Clin Infect Dis 2022 Jul 23;ciac581.

Wilkin TJ, Chen H, Cespedes MS, et al. A randomized, placebo-controlled trial of the quadrivalent HPV vaccine in HIV-infected adults age 27 years or older: AIDS Clinical Trials Group protocol A5298. Clin Infect Dis 2018, 67:1339-1346.Clin Infect Dis 2018 Apr 5.

Worm SW, Bower M, Reiss P, et al. Non-AIDS defining cancers in the D:A:D Study—time trends and predictors of survival: a cohort study. BMC Infect Dis 2013, 13:471.

SECTION 4

Other Infections

11. HIV and HBV/HCV co-infections

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HIV and HCV co-infection

Epidemiology and transmission routes

Due to the same transmission routes, HIV/HCV co-infections occur frequently. In the US, 240,000 people (30% of all PLWH) are infected with both viruses. In Eastern Europe, rates are often higher (Peters 2014). For example, in Russia, because of the high number of intravenous drug users, about 70% of the 860,000 people with HIV are also HCV-positive. In Western Europe, syringe exchange programs and rehabilitation efforts significantly decreased the rate of new HCV infections due to IV drug use. In Barcelona, for example, HCV prevalence among newly diagnosed PLWH fell from 24% in 2000–02 to 10% in 2006–08 (Trevino 2009).

Since HCV is about ten times more infectious than HIV in blood-to-blood contacts, intravenous drug users and recipients of blood products are particularly affected by dual infections. Needlestick injuries have a transmission probability of less than 2% after exposure to HCV-contaminated blood, possibly even lower, i.e., by 0.3% as for HIV (Kubitschke 2007). Sexual transmission of HCV, on the other hand, is much less common compared to HBV or HIV; it is less than 1% for heterosexual intercourse. Approximately 4–8% of HIV-infected men who have sex with men (MSM) also have hepatitis C. The first cases of recently acquired HCV infection in HIV-positive MSM were observed in the early 2000s in metropolitan areas such as London, Paris, Amsterdam, and Berlin, as well as in the United States, Australia, and Taiwan. In the following decade, this developed into a global epidemic (Boesecke 2015). Risk factors for sexual transmission are co-existing infections such as syphilis or lymphogranuloma venereum, sexual practices with increased risk of injury to the mucous membranes such as fisting or group sex, but also the use of drugs such as cocaine or amphetamines (See *Chemsex*), which is sometimes also used intravenously (GMFA 2013).

The perinatal transmission rate of hepatitis C is low in immunocompetent women (< 1%) but increases up to 20% in untreated HIV-infected pregnant women with immunodeficiency. On ART, the risk is probably not increased and is less than 3% with cesarean section (Pembrey 2005). However, in HCV-mono-infected women, HCV transmission risk is unlikely to be reduced by cesarean section (Indolfi 2009).

Clinical course & interactions between HIV and HCV

The clinical course of HCV co-infection is determined by HIV-associated immunosuppression. As immunosuppression progresses, the course of hepatitis C is accelerated. Conversely, there is no particular influence of hepatitis C on the course of HIV infection (Rockstroh 2005). The latency period to liver failure or hepatocellular carcinoma is 10–20 years in co-infected individuals, compared to 30–40 years in HCV mono-infection (Benhamou 1999). ART improves immune function and thus the unfavorable course of hepatitis C. In cases of good immune reconstitution, liver failure is delayed (Pineda 2007). Therefore, early initiation of antiretroviral therapy has always been recommended in HCV co-infection, which was further emphasized in 2015 following the results of the START trial (EACS 2017). Possible hepatotoxicity of antiretroviral drugs no longer plays a relevant role today and should not be a reason to delay initiation. Hepatotoxic agents such as nevirapine and tipranavir are barely used anymore. Elevated transaminases, often temporarily elevated after ART initiation, are probably due to increased inflammatory activity of hepatitis C with

improved immune status. However, as mentioned above, long-term observations suggest that ART favors the course of hepatitis C and that the benefits clearly outweigh the possible side effects (Rockstroh 2009).

Diagnostics

Diagnosis in co-infection is the same as in HCV mono-infection (Table 1). Positive HCV antibodies (HCV Ab) prove exposure to HCV but do not distinguish between cured or chronic hepatitis C. The latter is only confirmed by detecting HCV viremia (HCV RNA). It should be noted that in the course of HIV infection, loss of HCV antibodies may occur due to immunodeficiency. Although this phenomenon has become rare with today's testing methods, it may be helpful to determine HCV RNA in cases of clinical suspicion or advanced immunodeficiency, even though the HCV Ab test is negative. This also applies to suspected recently acquired HCV infection since HCV Ab can only be detected after 1–6 months. Especially with HIV, seroconversion is often delayed: three months after HCV RNA was first detected, 37% of cases were still without HCV Ab (Thomson 2009).

In HIV/HCV co-infection, HCV viremia is, on average, one log higher than in HCV mono-infection. The level of viremia has no predictive value, and follow-up is unnecessary. We consider once-yearly determinations appropriate in the (rare) cases where HCV initially remains untreated. In rare cases, affected individuals lose their HCV RNA with increasing immunodeficiency and develop "HCV flares" with clinical symptoms when on ART (Kim 2006).

Maviret® (glecaprevir/pibrentasvir) and Epclusa® (sofosbuvir/velpatasvir), two pan-genotypically active preparations, are available. Thus, HCV genotype determination for therapy selection is only indicated when non-pan-genotypic agents are used or in the case of retreatment (EACS 2022). Six genotypes with numerous subtypes are known. Genotypes 1 and 3 dominate in Europe, 4 and 5 in Africa, and genotype 6 in Asia. Double infections with multiple genotypes are rare.

In addition, determining the degree of fibrosis is essential to estimate the extent of liver damage. The most important non-invasive procedure is the fibroscan system, which uses transelastography to assess liver stiffness, which correlates directly with the degree of fibrosis of the liver. A liver biopsy is not necessary but may provide valuable differential diagnostic information in individual cases (e.g., autoimmune hepatitis). An alternative to the fibroscan can be indices formed from serum markers correlating with the degree of fibrosis, e.g., APRI score, FIB-4, or scores such as Fibrometer or Hepascore.

In most cases, the fibrosis stage is classified on a 5-point scale analogous to the METAVIR score (0 = no fibrosis, 1 = portal fibrosis without septa, 2 = few septa, 3 = numerous septa without cirrhosis, 4 = cirrhosis). Because progression can be considerably more rapid in HIV infection, annual determinations are reasonable with a wait-and-see procedure. In a US study (Sulkowski 2007), 25% deteriorated by two or more fibrosis stages (Ishak score, stages 0–6) within only three years. In case of clinical suspicion, further investigations (skin biopsy, urine diagnostics, possibly kidney biopsy, cryoglobulins in serum) may be necessary to detect or exclude extrahepatic manifestations (vasculitis, glomerulonephritis, systemic cryoglobulinemia).

In people with liver cirrhosis, an ultrasound examination of the liver should be performed every 6–12 months to detect hepatocellular carcinoma (HCC) in time. The risk of carcinoma remains elevated in cirrhosis even after HCV eradication. Since fibrosis progression can be significantly accelerated in HIV co-infection and HCC develops in 10–30% even in the absence of cirrhosis, regular follow-up examinations should be considered for all individuals with higher-grade fibrosis (> F3) (EACS 2022).

Table 1: Diagnosis of hepatitis C coinfection in PLWH (modified after EACS 2021).

For diagnosis HCV Ab (positive 1–6 months after infection, delayed seroconversion in HIV, and loss in advanced immunodeficiency possible). HCV RNA
Clarification of other liver diseases or extrahepatic HCV manifestations Alcohol consumption, heart disease, renal insufficiency, autoimmune disease, genetic or metabolic liver disease (e.g., hemochromatosis, diabetes mellitus, obesity), and drug-induced hepatotoxicity.
To assess the liver status Degree of fibrosis (e.g., by fibroscan, liver biopsy, serum fibrosis marker). Blood count, GOT, GPT, GGT, ALP, liver synthesis parameters (e.g., coagulation, protein, albumin, cholinesterase). Semiannual liver ultrasound in cirrhosis. When cirrhosis is first diagnosed, gastroscopy (after that, every 2–3 years if no varices are present; more frequently if varices are present).
Before starting treatment HCV RNA, renal, and liver function test. HCV genotype only necessary when using non-pan-genotypic agents.
During treatment Blood count, transaminases, creatinine, bilirubin, and albumin for fibrosis ≥ F3 to week 2–4. HCV RNA at the end of therapy and 12 weeks after that (SVR).

Recently acquired hepatitis C

Recently acquired cases of HCV continue to be observed mainly among MSM. They are often preceded by sexual contact with a very high risk of infection (unprotected anal intercourse, especially with sex toys, fisting, and chemsex practices). Due to the long latency of antibody formation, the diagnosis can often only be made based on medical history, elevated transaminases (usually at least five times the upper normal limit), and HCV RNA detection. Many cases are overlooked because the infection is asymptomatic in up to two-thirds of people. Spontaneous recovery (up to 40% HCV mono-infected) is much rarer in HIV co-infection with 10–15% (Monin 2023). Favorable factors include IL28B CC genotype, female gender, sexual transmission (compared to intravenous drug use), or a clinically symptomatic course. However, there are no practical consequences. Directly Acting Agents (DAAs) have also replaced interferon-containing therapies for recently acquired hepatitis C. Guidelines recommend immediate treatment after diagnosis of HCV infection if risk behaviors persist to reduce transmission (e.g., attending sex parties, engaging in injury-prone sexual practices, active chemsex) (EACS 2022). If therapy is not immediately indicated, it should be started if there has not been a drop in HCV RNA of at least 2 logs 4 weeks after diagnosis (EACS 2022), at which time chronicity is very likely. DAA combinations with a short duration of therapy (8 weeks) should be used, analogous to treating chronically HCV-infected individuals without cirrhosis or prior treatment.

Treatment of chronic hepatitis C

The goal of treatment is a permanently negative HCV RNA, i.e., a cure. This sustained virological response (SVR) is defined as a negative HCV RNA either 12 or 24 weeks after the end of treatment (SVR12, SVR24). Since 2014/2015, various DAAs have been approved. The decisive success parameter is now SVR12; all others no longer play a relevant role.

Eradication of HCV improves prognosis in all stages of liver disease and prevents further transmission. Initiation of therapy should be considered in any HIV/HCV coinfection, even in low fibrosis stages (F0/F1), because of the increased risk of progression. Antiretroviral treatment should be given, regardless of CD4 T-cell count.

Medication

The decisive factors are the genotype and the possible presence of liver cirrhosis (Table 2). Within individual genotypes, response rates differ only minimally, consistently exceeding 95%. Ribavirin may be added to shorten the duration of therapy and/or reduce relapse rates, especially in cirrhosis. First-generation HCV protease inhibitors (PIs) such as telaprevir and boceprevir are no longer recommended. Simeprevir has since been withdrawn from the market. The tolerability of all DAAs (except ribavirin) is good. Common side effects include fatigue, headache, and nausea. Severe side effects are infrequent, as are discontinuations. However, cases of decompensation have been described in cirrhosis, so hepatically metabolized agents such as HCV PIs are contraindicated.

Table 2: Recommended DAA combinations, according to genotype (GT) in HCV-infected individuals without PI or NS5A pretreatment.

GT	DAA combination	Duration of therapy and ribavirin use (RBV)		
		Non-cirrhotic	Compensated cirrhosis	Decompensated cirrhosis CTP Class B/C
1+4	SOF/LDV ± RBV	8–12 W without RBV[1] 12 W with RBV[2]		12 W with RBV[2]
	SOF/VEL	12 W	12 W	12 W with RBV
	EBR/GZR	12 W[3]		Not recommended
	GLE/PIB	8 W	8–12[3b] W	Not recommended
2	SOF/VEL	12 W		12 W with RBV
	GLE/PIB	8 W	8–12[3b] W	Not recommended
3	SOF/VEL ± RBV	12 W[4]	12 W with RBV[5]	12 W with RBV
	GLE/PIB	8 W[6]	8–12 W[6]	Not recommended
	SOF/VEL/VOX	–	12 W	Not recommended
5+6	SOF/LDV ± RBV	12 Wo ± RBV[7]	12 W with RBV[2]	12 W with RBV
	SOF/VEL	12 W		12 W with RBV
	GLE/PIB	8 W	8–12[3b] W	Not recommended

EBR elbasvir, GLE glecaprevir, GZR grazoprevir, LDV ledipasvir, PIB pibrentasvir, RBV ribavirin, SOF sofosbuvir, VEL velpatasvir, VOX voxilaprevir.

[1] 8 weeks without RBV only in therapy-naive individuals with F< 3 and HCV RNA < 6 million IU/mL.

[2] In case of RBV intolerance, extend therapy to 24 weeks. RBV may be omitted in therapy-naïve or –experienced individuals with compensated cirrhosis and without NS5A resistance.

[3] Prolongation to 16 weeks and addition of RBV in GT1a and HCV RNA > 800,000 IU/mL and/or NS5A resistance and in GT4, prior therapy and HCV RNA > 800,000 IU/mL. 8 weeks may be considered in GT1b without prior therapy and with F0-F2 fibrosis.

[3b] 8 weeks in therapy-naive patients.

[4] RBV only in treatment-experienced individuals with NS5A resistance; if RBV intolerant, extend to 24 weeks without RBV.

[5] In the absence of a Y93H NS5A mutation, RBV can be omitted in therapy-naïve patients with compensated cirrhosis

[6] Duration of therapy to 16 weeks in GT3 patients with prior treatment failure on IFN and RBV ± SOF or SOF and RBV.

[7] In therapy-experienced (IFN/RBV/SOF) with RBV for 12 weeks or 24 weeks without RBV.

There are numerous interactions to consider when treating with DAAs and concurrent ART (Table 3), especially with boosted ART regimens. If the resistance situation allows, ART can be modified at least for the duration of HCV therapy: INSTI-based regimens with raltegravir, dolutegravir, or bictegravir may be used. It is reasonable to switch ART at least one month before DAA initiation. In addition, interaction modules are available (e.g., www.hep-druginteractions.com), which can also be used to check interactions with concomitant drugs.

Re-treatment and resistance testing

Patients treated with inadequate therapy from today's point of view (e.g., use of a too-low ribavirin dosage; standard interferon instead of PEG-interferon, interferon monotherapy) can be treated with DAAs without restrictions. Interestingly, however, even after previously unsuccessful DAA therapy, re-therapy is often successful – possibly with doubled therapy duration or with the addition of ribavirin.
Resistance testing is not recommended before initial DAA use. In case of (rare) treatment failure, resistance testing is recommended before renewed therapy to assemble the new DAA combination based on the existing resistance-associated substitutions.

Table 3: Important interactions between common HCV and HIV drugs.

	SOF	SOF/LDV	SOF/VEL	SOF/VEL/VOX	EBR/GZR	GLE/PIB
ABC	↔	↔	↔	↔	↔	↔
FTC	↔	↔	↔	↔	↔	↔
3TC	↔	↔	↔	↔	↔	↔
TAF	↔	E32%	↔	E	↔	↔
TDF	↓6%	E	E[a]	E	↓7%/14%	E29%
BIC	↔	↑7%/↓13%	↔	↑9%/↓4%	↔	E
DTG	↔	↔	↓8%	↔	↔	↔
EVG/c	↔	↑36%/78%[a]	↑[a]	↑–/–/171%	↑	↑205%/57% E47%
RAL	↓5% D27%	↓5% ↓6% D≈20%	↔	↔	↓19%/11%	E47%
DOR	↔	↑4%/↓8%	↔	↔	↓4%/↑7%	↔
EFV	↓6%	↓–/34%[a]	↓3%/53%	↓	↓54%/83%	↓
ETV	↔	↔	↓	↓	↓	↓
NVP	↔	↔	↓	↔	↓	↓
RPV	↑9%	↑10% ↑8%[a]	↑16%	↔	↑7% ↓2%	E84%
ATV/c	↔	↑[a]	↔[a]	↑	↑	↑
ATV/r	↔	↑8%/113%[a]	↑–22%/142 %[a]	↑40%/93%/331%	376%/958%	↑553%/64%
DRV/c	↑	↑ a	↔[a]	↑	↑	↑
DRV/r	↑34%	↑34%/39%	↓28%/16%[a]	↓28%/5%/143%	66%/650%	↑397%/–
LPV/r	↔	↔[a]	↓29%/12%	↑	↑271%/1,186%	↑338%/146%

Black: These substances should not be combined. Gray: Combination possible under close observation or dose adjustment. Arrows: possible change in DAA; E = increased or D = decreased level of HIV drug
a = monitoring of renal function recommended by increased TDF concentration if regimen contains TDF

Treatment in people with cirrhosis

For these patients, in particular, treatment options have improved dramatically. However, there is still a risk that liver function may deteriorate. This is particularly true in decompensated cirrhosis, where the indication must be carefully considered. An exceptionally high risk exists with a decreased serum albumin < 35 mg/dl and a platelet count < 90,000/µl. In this case, liver transplantation should be considered (see *Organ Transplantation*). Regular examinations are also necessary after successful treatment – these include, in particular, ultrasound controls regarding HCC detection and endoscopic controls regarding esophageal varices.

Literature

Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. Hepatology 1999, 30:1054-8.

Boesecke C, Grint D, Soriano V, et al. Hepatitis C seroconversions in HIV infection across Europe: Which regions and patient groups are affected? Liver Int 2015; Apr 15. Doi: 10.1111/liv.12848.

European AIDS Clinical Society -Guidelines Version 11.0, October 2022, http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html

GMFA, http://www.gmfa.org.uk/Sites/fsmagazine/pages/chem-sex-survey-results; assessed July 23rd 2015.

Indolfi G, Resti M. Perinatal transmission of hepatitis C virus infection. J Med Virol 2009, 81:836-43.

Kim AY, zur Wiesch JS, Kuntzen T, et al. Impaired hepatitis C virus-specific T cell responses and recurrent hepatitis C virus in HIV coinfection. PLoS Med 2006; 3:e492.

Kubitschke A, Bader C, Tillmann HL, et al. Injuries from needles contaminated with hepatitis C virus: how high is the seroconversion risk for medical personnel? Internist (Berl) 2007; 48:1165-72.

Monin MB, Ingiliz P, Lutz T, et al. Low Spontaneous Clearance Rates of Recently Acquired Hepatitis C Virus in Human Immunodeficiency Virus-Positive Men Who Have Sex With Men (PROBE-C Study). Clin Infect Dis. 2023 Feb 8;76(3):e607-e612.

Nattermann J, Vogel M, Nischalke HD, et al. Genetic variation in IL28B and treatment-induced clearance of hepatitis C virus in HIV-positive patients with acute and chronic hepatitis C. J Infect Dis 2011, 203:595-601.

Pembrey L, Newell ML, Tovo PA, EPHN Collaborators. The management of HCV infected pregnant women and their children European paediatric HCV network. J Hepatol 2005; 43:515-25.

Peters l, Mocroft A, Lundgren J, Grint D, Kirk O, Rockstroh J. HIV and hepatitis C co-infection in Europe, Israel, and Argentina: a EuroSIDA perspective. BMC Infect Dis 2014;14 Suppl 6:S13.

Pineda JA, García-García JA, Aguilar-Guisado M, et al. Clinical progression of hepatitis C-related chronic liver disease in human immunodeficiency virus-infected patients undergoing highly active antiretroviral therapy. Hepatology 2007, 46:622-30.

Rockstroh JK, Mocroft A, Soriano V, et al. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. J Infect Dis 2005; 192:992-1002.

Rosenthal E, Pialoux G, Bernard N, Pradier C, et al. Liver-related mortality in human-immunodeficiency-virus-infected patients between 1995 and 2003 in the French GERMIVIC Joint Study Group Network (MORTAVIC 2003 Study). J Viral Hepat 2007, 14:183-8.

Sulkowski MS, Mehta SH, Torbenson MS, et al. Rapid fibrosis progression among HIV/hepatitis C virus-co-infected adults. AIDS 2007, 21:2209-16.

Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014, 370:211-21.

Thomson EC, Nastouli E, Main J, et al. Delayed anti-HCV antibody response in HIV-positive men acutely infected with HCV. AIDS 2009; 23:89-93.

Trevino A, Rivas P, Herrero-Mendoza M, et al. Newly Diagnosed HIV-1 Individuals in Spain since Year 2000. Non-B Subtypes, and Hepatitis C and B Virus Co-infections. Abstract 300, 16th CROI 2009, Montreal.

HIV and HBV co-infection

Introduction

The hepatitis B virus is one of the most common human pathogens worldwide. Up to 95% of all people with HIV have undergone a hepatitis B infection, and about 10–15% have chronic hepatitis B. About 100,000 PLWH (6%) in the US with chronic hepatitis B. Prevalence diverges regionally and among at-risk groups (Konopnicki 2005, Alter 2006). In countries with vaccination programs, there is a decrease in HBV transmission, especially in younger populations.

HBV is mainly transmitted sexually. Transmission is also possible via blood and is even significantly more likely than HIV or HCV. In the case of a percutaneous needlestick injury, the risk is 30% (HCV < 2%, HIV approx. 0.3%). In immunocompetent adults, acute HBV infection progresses to chronic hepatitis in 2–5%; in HIV co-infection, it is five times more likely. This is probably due to immunosuppression, whereas viral factors such as the level of HBV viremia or genotype are unlikely to play a role (Bodsworth 1991).

The hepatitis B virus shares some characteristics with HIV, although it is not integrated and exists as circular DNA in hepatocytes ("closed circular supercoiled" DNA, cccDNA). Because HBV is one of the few non-retroviral viruses with reverse transcription in the replication cycle, replication can be inhibited by NRTIs. Although elimination is, in principle, possible by virus-specific cytotoxic T lymphocytes (CTL), HBV DNA can usually be assumed to persist for life (cccDNA). Reactivation is possible after many years, e.g., through immunosuppression in advanced HIV infection or chemotherapy – regardless of the antibody constellation present.

The diagnosis is made in the same way as in HIV-negative persons – possible serological test constellations are shown in Table 1. Screening includes HBs antigen, anti-HBs, and anti-HBc. If HBsAg is positive, HBeAg, anti-HBe, and HBV DNA are needed for further differentiation.

A relatively frequent finding in PLWHis the detection of isolated anti-HBc (in blood donors, less than 2%). Three situations are conceivable: 1) an early phase of acute hepatitis B (in this case, IgM antibodies are involved), 2) a so-called loss of anti-HBs many years after hepatitis B, or 3) low-replicative hepatitis B, in which HBsAg is bound by anti-HBs and is thus not detected. Most often, this is a loss of anti-HBs without clinical consequences. "Occult" infection is the detection of HBV DNA (with or without anti-HBc) and lack of detection of HBsAg. Individuals with chronic hepatitis B should constantly be tested for hepatitis D superinfection as well.

Table 1: Interpretation of HBV serological test results.

Interpretation	HBsAg	anti-HBs	anti-HBc	HBeAg	anti-HBe	HBV-DNA
No contact with HBV	–	–	–	–	–	–
Acute infection	+	–	+ (IgM)	+	–	+
Cured infection with immunity	–	+	+ (IgG)	–	+	–
Chronic hepatitis B	+	–	+ (IgG)	+	–	+
Latent/occult infection[1]	–	–	+/– (IgG)	–	–	+
Pre-core mutant	+	–	+ (IgG)	–	+	+
"Healthy" carrier	+	–	+ (IgG)	–	+	–
Immunity through vaccination	–	+	–	–	–	–

[1] Controversial. See text.

It is recommended to perform an ultrasound examination of the liver every 6 to 12 months in chronic hepatitis B patients who have already developed cirrhosis to detect hepatocellular carcinoma (HCC) in time. Since HCC develops in 10–30% even without cirrhosis, this also applies to some subgroups without cirrhosis: age > 45 years, HDV co-infection, Asian and African patients, and those with a family history of HCC (EACS 2022).
Liver biopsy is not necessary for diagnosis or treatment decisions. Detection of the degree of fibrosis by transelastography or non-invasive markers also plays a minor role. However, further useful information includes differential diagnoses (e.g., hepatotoxicity) and inflammatory activity.

The course of hepatitis B in HIV infection

HIV negatively influences the course of chronic hepatitis B. Mortality from events directly associated with liver disease is about 15 times greater than in HIV-negative individuals. In addition, the progression of hepatitis B is more rapid, and the risk of cirrhosis increases. Direct mechanisms of damage to the hepatocyte by HIV have been described, providing a pathophysiological correlate for the altered course (e.g., CCR5-mediated direct cytopathic effect and indirect upregulation of proinflammatory and apoptotic factors). Despite these unfavorable influences from HIV co-infection, hepatitis B often takes a milder course clinically despite increased viral replication. The cause of this paradox is impaired cellular immunity, which increases viral replication but simultaneously decreases hepatocyte damage. Thus, transaminases are often only slightly elevated in HBV/HIV coinfection, whereas HBV DNA is higher than in immunocompetent individuals. Accordingly, fibrosis and cirrhosis are more frequent despite lower inflammatory activity. This phenomenon is also observed in other immunocompromised individuals, such as organ transplant recipients.
There is a direct correlation between the extent of immunosuppression and the control of HBV viral replication: even in cases with apparently cured hepatitis B (anti-HBe positive, HBV DNA negative), reactivations are possible if the immune system deteriorates (Soriano 2005). Interestingly, reactivations of hepatitis B under immune reconstitution after ART initiation have also been described in isolated cases.
It is also possible that the course of HIV infection is worsened with concurrent hepatitis B. An increase in all-cause mortality and AIDS-defining events have been described (Nikolopoulos 2009, Chun 2012). In addition, the risk of hepatotoxicity of ART is about three times higher.
Whether ART and HBV therapies change the prognosis of co-infected individuals is an open question. According to some studies, such as the French GERMIVIC cohort, HBV-associated mortality decreases significantly with effective HBV treatment (Puoti 2007, Rosenthal 2009). Under TDF/TAF-containing ART for at least 12 months, the risk of HCC can be reduced by 58% (Kim 2021).

Prevention

People with HIV and with negative hepatitis B serology should be vaccinated. However, vaccination may be less effective, and about 30% have a primary non-response (only 2.5% in immunocompetent individuals). Vaccination response depends on CD4 T-cell count and level of HIV viremia. Therefore, it is recommended that patients with less than 200 CD4 T-cells/µl who are not yet receiving antiretroviral therapy first initiate ART and wait for immune reconstitution. Vaccination should follow the usual schedule (20 µg each; months 0, 1, and 6). If vaccination

response is insufficient (i.e., anti-HBs < 10 IU/mL 12 weeks after a vaccination cycle), re-vaccination may be considered. Increasing the single vaccine dose and more frequent doses may improve vaccine response (40 µg each; months 0, 1, 6, and 12) (Fonseca 2005, Launay 2011).

Since successfully vaccinated HIV patients lose about 30% of their acquired immunity per year, the anti-HBs status should be checked annually, and, if necessary, the vaccination should be refreshed (if anti-HBs titer < 100 U/l). HBV screening is recommended about once a year without successful immunization to detect re-infection in time.

If the ART contains HBV-active substances – in particular, tenofovir disoproxil fumarate (TDF) or alafenamide (TAF) – there is an excellent protective effect against *de novo* infection with hepatitis B, which is comparable to the effectiveness of successful vaccination (Heuft 2014). Especially for unsuccessful HBV vaccination, HBV-active substances should be integrated into antiviral therapy.

HIV/HBV-co-infected persons with negative HAV serology should be vaccinated against hepatitis A (months 0 and 6) since severe or fulminant courses are possible in the case of acute hepatitis A. A combination vaccination is useful for negative HBV serology (months 0, 1, and 6).

Education about prevention (safer sex, avoidance of needle re-use, etc.) or progression of liver disease should be self-evident. The latter is avoiding alcohol, nicotine (controversial), or herbal medications that may be hepatotoxic. Hepatotoxic drugs (e.g., tuberculostatic therapy) should be given with caution. Newborns of patients with chronic hepatitis B should receive hepatitis B immunoglobulin and active immunization within 12 hours post-partum.

Treatment

Due to impaired immune function in co-infected individuals, treatment of chronic hepatitis B is more problematic. Loss of HBsAg with the formation of protective anti-HBs antibodies is rarely achievable. Therefore, realistic therapeutic goals are seroconversion of HBeAg to anti-HBe and associated suppression of HBV DNA, normalization of transaminases, and improvement of liver histology. Reduction in transmission risk and possibly ART-associated hepatotoxicity are other potential benefits. As mentioned above, HBV-associated mortality is also expected to decrease if HBV replication is effectively inhibited.

Drugs with activity against HBV

Nucleoside analogs, nucleotide analogs, and interferon are available (Table 2). Compared to TDF and TAF, all other drugs play a minor role. Also effective against HIV and HBV are 3TC, FTC, and, to some extent, entecavir. Adefovir and telbivudine are effective against HBV only. Interferon, occasionally used in HBV mono-infections, plays hardly any role in HIV co-infection.

The most effective drug is tenofovir (TDF or TAF), with more than 95% of people achieving virologic control beyond five years. To date, no apparent mutations associated with phenotypic resistance have been described (this is questionable for the A194T mutation). In contrast to tenofovir, resistance mutations are relevant with other agents: For example, 3TC monotherapy selects for a mutation in the YMDD locus of the polymerase gene, which may occur in at least 20% per year (mutations at this site may fail to produce HBeAg, similar to the pre-core mutant). Potential cross-resistance exists between 3TC, FTC, entecavir, and telbivudine, which can only be partially compensated by a dose increase (e.g., entecavir is dosed higher after 3TC pre-treatment). Although adefovir has different resistance mechanisms as a

Table 2: Drugs for chronic hepatitis B in HIV co-infection (numerous generics exist for FTC, 3TC, TDF, and some combinations; see chapter on ART).

Drug	Trade name	Dosage
Adefovir	Hepsera®	10 mg daily
Emtricitabine (FTC)	Emtriva®, also in: Atripla®, Biktarvy®, Descovy®, Eviplera®, Genvoya®, Odefsey®, Stribild®, Symtuza®, Truvada®	200 mg daily
Entecavir	Baraclude®	0.5 mg (3TC-naive) 1 mg (3TC-pretreated)
Lamivudine (3TC)	Epivir®, also in: Combivir®, Delstrigo®, Dovato®, Trizivir®, Kivexa®, Triumeq®	300 mg daily. Do never use Zeffix® (dose too low for HIV!)
Telbivudine	Sebivo®	600 mg daily
Tenofovir-disoproxil (TDF)	Viread®, also in: Truvada®, Atripla®, Eviplera®, Delstrigo®, Stribild®	300 mg daily
Tenofovir-alafenamide (TAF)	Vemlidy®, also in: Biktarvy®, Descovy®, Odefsey®, Genvoya®, Symtuza®	10–25 mg daily (depending on concomitant ART or concomitant medication)
Interferon-α	Intron A®	5 MU per day
Pegylated interferon	Pegasys® PEG-Intron®	Pegasys® 180 µg 1 x / week PEG-Intron® 1.5 µg/kg 1 x / week

nucleotide analog, an A181T mutation with persistent viral replication has been described in the presence of pre-existing 3TC resistance. Combining two HBV-active drugs may delay or even prevent the development of resistance. In small cohorts, no resistance has been described when a nucleoside analog was combined with a nucleotide analog. However, there is no evidence that combination is more effective. Nevertheless, because of the potential benefits and the experience gained from HIV therapy, it is recommended. As an alternative to drug therapy, organ transplantation should also be considered in people with liver cirrhosis.

Treatment recommendations

HIV-infected individuals with hepatitis B (and also C) co-infection benefit from HIV therapy by reducing the progression of liver fibrosis. ART should include HBV-active substances – neither liver biopsy nor fibroscan is necessary for indication.

- Therapy should include TDF or TAF. Without FTC or 3TC pre-therapy, the combination of TDF/TAF with FTC or 3TC is reasonable.
- In cases of renal insufficiency, TDF can be dosed lower since the IC50 is lower for HBV than for HIV, or switch to TAF. However, tenofovir may not be considered an active component of ART.
- If tenofovir is contraindicated, entecavir is an alternative for 3TC-naive patients on fully active ART.
- Caution when switching from TDF or TAF to a compound with a low genetic barrier (i.e., FTC or 3TC; entecavir after 3TC pre-treatment): rebound due to pre-existing mutations is possible.
- In cases of persistent low HBV viremia on tenofovir, there are currently no clear options. Therapy should be continued since no resistance has been described in these cases. Adding, e.g., entecavir is not recommended in this situation.

After the start of treatment, a transient and usually moderate increase in transaminases is often observed. It is a sign of immune reconstitution and increased inflammatory activity. In case of pronounced or prolonged increase, other reasons should

be considered (increased HBV replication, resistance of HBV, lactic acidosis, hepatotoxicity of antiretroviral drugs, superinfection with other hepatitis viruses, especially HCV/HDV).

Normal transaminases (AST, ALT) and a significant reduction in HBV DNA are almost always achieved initially. However, ALT levels do not correlate well with inflammatory activity and are influenced by numerous other factors, such as hepatotoxicity of ART or other drugs, alcohol consumption, and immune reconstitution. Therefore, their importance in monitoring the success of therapy is low. Since seroconversion cannot be achieved in all cases, continuous suppression is required, similar to HIV. HBeAg seroconversion can be achieved with tenofovir at about 40% HBsAg loss in about 18% after 3.5 years of therapy (van Bremen 2020).

Caution: If HBV-active drugs are discontinued, the clinical picture of acute hepatitis, including fatal liver failure, is possible. Any interruption in therapy in HBV/HIV co-infection must, therefore, be carefully considered and avoided, especially in cirrhosis, to prevent decompensation. On the other hand, if an HBV drug loses its efficacy, it can be discontinued; then, no rapid clinical deterioration of hepatitis is to be expected. It should also be noted that the dose of all nucleos(t)ide analogs must be adjusted in renal insufficiency.

Treatment of *acute* hepatitis B is not recommended in cases with stable liver function because of the high likelihood of cure (although lower than in HIV-negative individuals) and the lack of sufficient data on this (risk of rapid development of resistance with early therapy and no further options?).

Literature

Alter M. Epidemiology of viral hepatitis and HIV co-infection. J Hepatol 2006; 44: 6-9.

Bodsworth NJ, Cooper DA, Donovan B. The influence of human immunodeficiency virus type 1 infection on the development of the hepatitis B virus carrier state. J Infect Dis 1991, 163:1138-40.

Chun H, Roediger M, Huppler Hullsiek K, et al. Hepatitis B Virus Coinfection Negatively Impacts HIV Outcomes in HIV Seroconverters. Journal of Infectious Diseases 2012:185-93.

EACS Guidelines 11.0, October 2022. http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html.

Fonseca MO, Pang LW, de Paula Cavalheiro N, et al. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. Vaccine 2005; 23:2902–2908.

Heuft MM, Houba SM, von den Berk GE, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy against primary hepatitis B virus infection. AIDS 2014, 28:999-1005.

Kim N, Newcomb C, Carbonari D, et al. Risk of HCC With Hepatitis B Viremia Among HIV/HBV-Coinfected Persons in North America. Hepatology. 2021. 74:1190-1202.

Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. AIDS 2005; 19:593-601.

Launay O, van der Vliet D, Rosenberg AR, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. JAMA 2011, 305:1432-40.

Nikolopoulos GK, Paraskevis D, Hatzitheodorou E, et al. Impact of hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: a cohort study and metaanalysis. Clin Infect Dis 2009, 48:1763-71.

Puoti M, Cozzi-Lepri A, Arici C, et al. Impact of lamivudine on the risk of liver-related death in 2,041 HBsAg- and HIV-positive individuals: results from an inter-cohort analysis. Antivir Ther 2006, 11:567-74.

Rosenthal E, Salmon-Céron D, Lewden C, et al. Liver-related deaths in HIV-infected patients between 1995 and 2005 in the French GERMIVIC Joint Study Group Network. HIV Med 2009, 10:282-9.

Soriano V, Puoti M, Bonacini M, et al. Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV international panel. AIDS 2005, 19:221-240.

Van Bremen K, Hoffmann C, Mauss S et al. Obstacles to HBV functional cure: Late presentation in HIV and its impact on HBV seroconversion in HIV/HBV coinfection. Liver Int. 2020;40:2978–2981.

12. HIV and COVID-19

CHRISTIAN HOFFMANN

At the end of October 2022, more than 35 million SARS-CoV-2 infections were reported in Germany. Suppose one considers the high number of unreported cases or cases not confirmed by PCR. In that case, considering the high number of unreported cases or cases not confirmed by PCR, it is inevitable that at least half of everyone living with HIV has now experienced a SARS-CoV-2 infection. Here, the most critical aspects relevant to daily practice in an HIV clinic will be discussed. However, given the rapidity of developments, especially with regard to variants but also with regard to therapies, this is just a snapshot.

Susceptibility to SARS-CoV-2

There are studies on PLWH with higher, as well as with comparable or even lower incidence. Where the incidence was lower, protection by antiviral therapies (see below) or immune activation has been discussed. However, other factors are probably far more critical, including primarily testing behavior and testing strategies, but also sociodemographic factors and behavioral differences. It seems almost impossible to adjust for these factors, especially in large populations. In a meta-analysis of over 30 studies, the risk of SARS-CoV-2 infection was comparable for PLWH (Wang 2022). Thus, it does not appear that HIV infection *per se* substantially increases or decreases susceptibility to SARS-CoV-2.

Morbidity and mortality

Are COVID-19 morbidity and mortality increased in HIV infection, or is HIV infection an independent risk factor? Upon closer examination, what seems straightforward at first glance becomes increasingly challenging to answer. There are several extensive studies with often several thousand patients, in which the morbidity (rate of severe illness), as well as the mortality (mainly evaluated as "in house", i.e., in-hospital), was increased compared to uninfected people (Tesoriero 2021, Bertagnolio 2022, Yang 2022). In a meta-analysis of 32 studies involving nearly 800.000 PLWH, the relative risk of serious illness was 1.25, and the relative risk of mortality was about 1.3 (Wang 2022).

However, this does not mean that HIV is an independent risk factor. PLWH differ from healthy controls concerning numerous factors that significantly affect COVID-19-related morbidity and mortality. Not all can be "matched" or adjusted for. If PLWH are hospitalized sooner than others out of concern or caution, morbidity increases (if hospitalization is considered "severe"). At the same time, overcautious hospitalizations may reduce overall in-hospital mortality. Mortality can increase if PLWH (because they have less health insurance like in the US) go to the hospital a little later. Do they smoke more, are they less overweight? This may have a significant impact on the results. Also, many studies were done in unvaccinated people and the pre-omicron era – the results could be quite different today.

In a large study out of Canada, PLWH had about two times the risk of COVID-19 hospitalization than HIV-negative individuals in crude analyses, which attenuated in propensity score-weighted models. This suggests that the risk differential can be explained by sociodemographic factors and a history of co-morbidity, underscoring the need to address these issues (Puyat 2023). In another large matched-pair study comparing COVID-19 cases of the same age and sex but at the same time of diagnosis, HIV was not an apparent risk factor (Rosenthal 2022). However, once again,

it became clear that people living with and without HIV differed markedly regarding co-morbidities and other risk factors (more smoking, more obesity in PLWH). Nevertheless, older age is by far the most critical risk factor for HIV (Tesoriero 2021, Bertagnolio 2022, Yang 2022). Fortunately, the age structure of the HIV population in most countries is relatively "favorable" – only a few PLWH are 70 years and older.

Immunosuppression as a risk factor

It is now considered certain that severe immunodeficiency is unfavorable in SARS-CoV-2 infection. It can impair both antibody and T-cell responses. Given the importance of T cell immunity in SARS-CoV-2, this finding is hardly surprising – it is one more argument in favor of early antiretroviral therapy, which should not be interrupted whenever possible.
In a combined analysis of three cohorts from Madrid, Milan, and Germany with 175 cases, PLWH with severe or fatal courses had significantly lower current CD4 T-cells and a lower CD4 nadir (Hoffmann 2020). In a multivariate analysis, a current CD4 T-cell count below 350 remained the only risk factor for a severe course. A nadir below 200 was associated with increased mortality. Many other papers have identified low CD4 T-cells and viremia as significant risk factors. One US study also found severe courses below 350 CD4 T-cells in vaccinated or breakthrough infections (Lang 2022). However, in one of the most extensive studies from Catalonia, low CD4 T-cells in 749 cases remained a risk factor only in viremic individuals (Nomah 2021). Low CD4 T-cells are a risk factor for prolonged shedding. In a larger study, this phase was a median of 27 days in individuals with less than 200 CD4 T-cells, compared with only seven days in immune healthy individuals (Meiring 2022). Thus, it may be that these individuals are infectious for extended periods. Several long courses in severe immunodeficiency have been described in which SARS-CoV-2 remained detectable, sometimes for many months (Yousaf 2021, Cele 2022, Maan 2022, Spinicci 2022). These cases fuel speculation that such cases are responsible, among other things, for the selection of new variants of SARS-CoV-2 during the months-long battle with the immune system. This has not been proven. A possible drop in CD4 T-cells during COVID-19 seems limited (Casado 2022).

Effect of ART

The initial hopes for a possible protective effect of antiretroviral therapies such as lopinavir or darunavir have been dashed. Several randomized trials, such as RECOVERY, have shown that lopinavir is ineffective – the plasma levels achieved with conventional doses are probably many times too low. The PI darunavir was already ineffective *in vitro*. Still under debate is the nucleotide analog tenofovir, which has chemical similarities to remdesivir and binds with high binding energy to the RNA-dependent polymerase of SARS-CoV-2. Several randomized trials of tenofovir as therapy or prophylaxis did not yield a congruent response, in part because of low event counts (Parienti 2021, Gaitán-Duarte 2022, Montejano 2022, Nomah 2022, Polo 2022). Overall, however, the beneficial effect of tenofovir is likely to be small (if any). In two Dutch observational cohorts of PLWH, the use of TDF, etravirine, or INSTIs was not independently associated with either the risk of incident SARS-CoV-2 infection or severe COVID-19 outcomes (Verburgh 2023). The current data do not support modifying antiretroviral therapy to include these agents to protect against SARS-CoV-2 infection and severe COVID-19 outcomes.

SARS-CoV-2 vaccination

People living with HIV should be vaccinated in any case. Like vaccinations, infections count as immunological "episodes", so they are also counted. In the German recommendations, HIV infection is considered an underlying disease "with an increased risk of severe COVID-19 courses." Furthermore, in the context of fewer than 200 CD4 T-cells and/or detectable viral load, it is considered one of the diseases "associated with a relevant limitation of vaccination response, either directly or as a result of the necessary therapy." In this case, serological checks of the vaccination success and further boosters are recommended, even beyond four vaccinations, if necessary, and mainly with mRNA vaccines. However, whether this makes sense in young PLWH and an excellent immune status is considered somewhat cautiously by many. Ultimately, a very low risk of severe disease is offset by an (albeit only slightly increased) risk of vaccine side effects (myocarditis, zoster, appendicitis).

It is noteworthy that PLWH were underrepresented in many vaccination studies. In particular, those with severe immunodeficiency were completely excluded in almost all studies. Much of the vaccination data comes from uncontrolled studies. Overall, the following can be said: vaccine response is "generally comparable" to that of uninfected individuals, especially with mRNA vaccines (Lapointe 2022). However, a recent meta-analysis analyzing 50 studies with 7,160 PLWH demonstrated that only 75.0% of PLWH achieved a seroconversion after incomplete vaccination, which improved to 89.3% after complete vaccination and 98.4% after booster vaccination. The seroconversion rates were slightly lower compared to controls at all stages, while the risk ratios for incomplete, complete, and booster vaccination were 0.87, 0.95, and 0.97, respectively, emphasizing the need for booster vaccinations in PLWH (Zhou 2023). In any case, the immune response of PLWH is better than in other immunodeficient patients, such as organ transplant recipients (Speich 2022). However, unsurprisingly, the immune response is probably also reduced in those with low CD4 T-cells (Antinori 2022, Corma-Gómez 2022) and in people over 60 years of age (Chammartin 2022).

In a study of 113,994 fully vaccinated people (33,029 PLWH), breakthrough infection rates were low, but the risk with HIV was 28% higher (Coburn 2022). Among PLWH, younger age (< 45 years), a history of COVID-19, and not receiving an additional dose of vaccine were associated with increased risk. A high CD4 T-cell count of more than 500 CD4 T-cells was protective, but suppressed viral load was not. It appears that PLWH with moderate or severe immune suppression should be included in groups prioritized for additional vaccine doses and risk-reduction strategies.

PrEP, PEP, and treatment in times of omicron

Many people believe that omicron causes "only" mild courses. However, the high case fatality rates in Hong Kong in February 2022 (higher than in Italy 2020 or in Portugal 2021!) have shown that significant mortality is to be expected when vulnerable populations are not vaccinated. Mild courses cannot be relied upon. For example, unvaccinated cancer patients have a mortality risk with omicron comparable to the alpha or delta waves (Pinato 2022).

In the meantime, there are some antibodies and drugs, such as molnupiravir (Lagevrio®) and nirmatrelvir/r (Paxlovid®), that many governments have purchased. It must be emphasized that most studies published to date have been in unvaccinated subjects and from the pre-omicron era. In addition, the effect of the antibodies, in particular, is highly dependent on the circulating variants. It seems evident that their impact may be lost entirely due to new mutations. For this reason, no clear

recommendations can currently be made as to when PLWH should receive specific therapy or prophylaxis.
We recommend specific COVID-19 therapy in cases of severe immunodeficiency with less than 200 CD4 T-cells, people older than 60, and those with co-morbidities, regardless of previous vaccinations. However, it remains a case-by-case decision. Where therapies such as nirmatrelvir/r or molnupiravir are used, interactions should be considered and are common (Lakatos 2022). If a detectable viral load is present, caution is needed with nirmatrelvir/r because the low-dose ritonavir may lead to resistance.

Avoid collateral damage

From the beginning, one concern was the collateral damage caused by the COVID-19 pandemic. In many countries, it was feared that the disruption in general health care would have significant negative consequences beyond the direct damage caused by COVID-19. Lockdown measures and fears of SARS-CoV-2 infection would significantly decline ART and TB drug supplies in several African countries (Jewell 2020). Although some initial reports also indicated that the rate of late HIV diagnoses increased significantly during lockdown (Bell 2021), it can now be assumed that, overall, the damage was not as great as feared. To mitigate the negative consequences of the pandemic, service providers and communities adapted and accelerated an array of HIV interventions to meet the needs of PLWH and those at risk of acquiring HIV in diverse geographical and epidemiological settings. As a result of these adaptations, services such as HIV treatment showed programmatic resilience and remained relatively stable (Murphy 2022).

COVID-19 and HIV – Practical consequences

- There is no evidence of increased (or reduced) susceptibility to SARS-CoV-2.
- Mortality and morbidity seem to slightly increase overall, especially in severe immunodeficiency and possibly in active viremia – another argument for ART for all!
- Overall, however, the risk is only moderately increased – even with HIV, older age is the most critical factor.
- The ART, if successful, does not need to be switched – so far, there is no (direct) evidence of efficacy against SARS-CoV-2.
- All patients should be vaccinated with mRNA vaccines (4 x, as of early 2023), more often if CD4 T-cells are less than 200 (control of antibody titer/success recommended).
- Specific therapies such as nirmatrelvir/r (beware of drug-drug interactions) should be considered in immunodeficient patients, at least in the presence of other risk factors.
- In high-incidence phases, controls and visits in the HIV center are dispensable but breaks in ARV therapy are to be avoided.

Even in Western countries, however, the care of PLWH is not always easy. Lockdowns, but also the understandable fears of those affected, influence treatment. Every effort should be made to avoid ART interruptions. Medications should not be hoarded, nor should blood tests generally be suspended. However, a sense of proportion is required, especially for older PLWH. Especially for those over 70, unnecessary risk contacts should be avoided. This applies to time-consuming journeys by public transport and long waiting times in cramped waiting rooms. What can be done by telephone or

telemedicine? While these means may not always replace the confidential direct conversation with the doctor, they still offer good options for getting through these difficult times.

Literature

Antinori A, Cicalini S, Meschi S, et al. Humoral and cellular immune response elicited by mRNA vaccination against SARS-CoV-2 in people living with HIV (PLWH) receiving antiretroviral therapy (ART) according with current CD4 T-lymphocyte count. Clin Infect Dis 2022, 75:e552-e563.

Bell N, Bracchi M, Dalla Pria A, Nelson M, Boffito M. Indirect HIV morbidity and mortality due to COVID-19. Clin Infect Dis. 2021 Feb 13:ciab128.

Bertagnolio S, Thwin SS, Silva R, et al. Clinical features of, and risk factors for, severe or fatal COVID-19 among people living with HIV admitted to hospital: analysis of data from the WHO Global Clinical Platform of COVID-19. Lancet HIV 2022, S2352-3018.

Casado JL, Vizcarra P, Vivancos MJ, et al. Low risk of bacterial co-infection, opportunistic diseases, and persistent immunosuppression in people living with HIV and COVID-19. Infection 2022 Mar 31:1-5.

Cele S, Karim F, Lustig G, et al. SARS-CoV-2 prolonged infection during advanced HIV disease evolves extensive immune escape. Cell Host Microbe 2022, 30:154-162.e5.

Chammartin F, Kusejko K, Pasin C, et al. Determinants of antibody response to severe acute respiratory syndrome coronavirus 2 mRNA vaccines in people with HIV. AIDS 2022, 36:1465-1468.

Coburn SB, Humes E, Lang R, et al. Analysis of Postvaccination Breakthrough COVID-19 Infections Among Adults With HIV in the United States. JAMA Netw Open 2022, 5:e2215934.

Corma-Gómez A, Fernández-Fuertes M, García E, et al. Severe immunosuppression is related to poorer immunogenicity to SARS-CoV-2 vaccines among people living with HIV. Clin Microbiol Infect 2022, S1198-743X(22)00276-2.

Gaitán-Duarte HG, Álvarez-Moreno C, Rincón-Rodríguez CJ, et al. Effectiveness of rosuvastatin plus colchicine, emtricitabine/tenofovir and combinations thereof in hospitalized patients with COVID-19: a pragmatic, open-label randomized trial. EClinicalMedicine 2022 Jan;43:101242.

Hoffmann C, Casado JL, Härter G, et al. Immune deficiency is a risk factor for severe COVID-19 in people living with HIV. HIV Med 2020 Dec 27.

Hoffmann C, Wolf E. Older age groups and country-specific case fatality rates of COVID-19 in Europe, USA and Canada. Infection 2021, 49:111-116.

Jewell BL, Mudimu E, Stover J, et al. Potential effects of disruption to HIV programmes in sub-Saharan Africa caused by COVID-19: results from multiple mathematical models. Lancet HIV 2020, 7:e629-e640.

Lakatos B, Kowalska J, Antoniak S, et al. Retrospective evaluation of an observational cohort by the Central and Eastern Europe Network Group shows a high frequency of potential drug-drug interactions among HIV-positive patients receiving treatment for coronavirus disease 2019 (COVID-19). HIV Med 2022, 23:693-700.

Lang R, Humes E, Coburn SB, et al. Analysis of Severe Illness After Postvaccination COVID-19 Breakthrough Among Adults With and Without HIV in the US. JAMA Netw Open 2022; 5:e2236397.

Lapointe HR, Mwimanzi F, Cheung PK, et al. People with HIV receiving suppressive antiretroviral therapy show typical antibody durability after dual COVID-19 vaccination, and strong third dose responses. J Infect Dis 2022 Jun 7:jiac229.

Maan I, Paraskevopoulou SM, Cwynarski K, et al. Prolonged SARS-CoV-2 shedding in a person living with advanced HIV and diffuse large B-cell lymphoma: a case report. Infect Dis (Lond) 2022, 54:529-533.

Meiring S, Tempia S, Bhiman JN, et al. Prolonged shedding of SARS-CoV-2 at high viral loads amongst hospitalised immunocompromised persons living with HIV, South Africa. Clin Infect Dis. 2022 Feb 2:ciac077.

Montejano R, de la Calle-Prieto F, Velasco M, et al. Tenofovir Disoproxil Fumarate/Emtricitabine and Baricitinib for Patients at High Risk of Severe COVID-19: The PANCOVID Randomized Clinical Trial. Clin Infect Dis. 2022 Jul 30:ciac628.

Murphy E, Doherty M, El Sadr W, et al. Innovations, adaptations, and accelerations in the delivery of HIV services during COVID-19. Lancet HIV. 2022 Dec;9(12):e884-e886.

Nomah DK, Reyes-Urueña J, Díaz Y, et al. Impact of tenofovir on SARS-CoV-2 infection and severe outcomes among people living with HIV: a propensity score-matched study. J Antimicrob Chemother 2022 Jun 9:dkac177.

Nomah DK, Reyes-Urueña J, Díaz Y, et al. Sociodemographic, clinical, and immunological factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes in people living with HIV: a retrospective cohort study. Lancet HIV 2021, 8:e701-e710.

Parienti JJ, Prazuck T, Peyro-Saint-Paul L, et al. Effect of Tenofovir Disoproxil Fumarate and Emtricitabine on nasopharyngeal SARS-CoV-2 viral load burden amongst outpatients with COVID-19: A pilot, randomized, open-label phase 2 trial. EClinicalMedicine 2021, 38:100993.

Pinato DJ, Aguilar-Company J, Ferrante D, et al. Outcomes of the SARS-CoV-2 omicron (B.1.1.529) variant outbreak among vaccinated and unvaccinated patients with cancer in Europe: results from the retrospective, multicentre, OnCovid registry study. Lancet Oncol 2022, S1470-2045(22)00273-X.

Polo R, García-Albéniz X, Terán C, et al. Daily tenofovir disoproxil fumarate/emtricitabine and hydroxychloroquine for pre-exposure prophylaxis of COVID-19: a double-blind placebo-controlled randomized trial in healthcare workers. Clin Microbiol Infect 2022, S1198-743X(22)00370-6.

Puyat JH, Fowokan A, Wilton J, et al. Risk of COVID-19 Hospitalization in People Living with HIV and HIV-Negative Individuals and the Role of COVID-19 Vaccination: A Retrospective Cohort Study. Int J Infect Dis. 2023 Jul 5:S1201-9712(23)00650-1.

RKI. Epidemiologisches Bulletin 2022, 40, 6. Oktober 2022 https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2022/Ausgaben/40_22.pdf?__blob=publicationFile

Rosenthal EM, Rosenberg ES, Patterson W, et al. Factors associated with SARS-CoV-2-related hospital outcomes among and between persons living with and without diagnosed HIV infection in New York State. PLoS One 2022, 17:e0268978.

Speich B, Chammartin F, Abela IA, et al. Antibody response in immunocompromised patients after the administration of SARS-CoV-2 vaccine BNT162b2 or mRNA-1273: A randomised controlled trial. Clin Infect Dis. 2022 Mar 2:ciac169.

Spinicci M, Mazzoni A, Borchi B, et al. AIDS patient with severe T cell depletion achieved control but not clearance of SARS-CoV-2 infection. Eur J Immunol 2022, 52:352-355.

Tesoriero JM, Swain CE, Pierce JL, et al. COVID-19 Outcomes Among Persons Living With or Without Diagnosed HIV Infection in New York State. JAMA Netw Open 2021, 4:e2037069

Verburgh ML, van der Valk M, Rijnders BJA, et al. No association between use of tenofovir disoproxil fumarate, etravirine, or integrase-strand transfer inhibitors and acquisition or severe outcomes of SARS-CoV-2 infection in people with HIV in the Netherlands. AIDS 2023, 37:1481-86.

Wang Y, Xie Y, Hu S, et al. Systematic Review and Meta-Analyses of The Interaction Between HIV Infection And COVID-19: Two Years' Evidence Summary. Front Immunol 2022 May 10;13:864838.

Yang X, Sun J, Patel RC, et al. Associations between HIV infection and clinical spectrum of COVID-19: a population level analysis based on US National COVID Cohort Collaborative (N3C) data. Lancet HIV 2021, 8:e690-e700.

Yousaf M, Hameed M, Alsoub H, Khatib M, Jamal W, Ahmad M. COVID-19: Prolonged viral shedding in an HIV patient with literature review of risk factors for prolonged viral shedding and its implications for isolation strategies. Clin Case Rep 2021, 9:1397-1401.

Zhou Q, Zeng F, Meng Y, Liu Y, Liu H, Deng G. Serological response following COVID-19 vaccines in patients living with HIV: a dose-response meta-analysis. Sci Rep 2023, 13:9893.

13. HIV and sexually transmitted diseases

STEFAN ESSER

Epidemiology

A sexually transmitted infection (STI) rarely comes alone. All STIs are more common in PLWH, and each favors transmission of HIV or other venereal infections. Early diagnosis and timely, consistent therapy reduce onward transmission. STI screening should also be offered to asymptomatic sexually active people who frequently have sex with many people, always including all orifices (oral, genital, anal). In the case of STIs, sexual partners should also be educated, examined and, if necessary, treated. Until healing is complete, sex should be abstained from or at least adequate protection of sex partners should be observed. An examination should be carried out after an appropriate time after treatment to ensure healing.

WHO estimates the incidence of bacterial STIs and trichomoniasis (excluding mycoplasma) to be 376 million new infections annually worldwide (WHO 2021, Rowley 2019). STIs have been increasing significantly in the last decades, particularly among men who have sex with men (MSM). New ways to prevent HIV transmission (PrEP, TasP) and the treatability of HIV infection have reduced the fear of HIV and led to a significant decrease in condom use.

Since the introduction of PrEP and concomitant STI screening (EACS 2019), the number of diagnosed STIs continues to rise. International studies observe a further decline in condom use and higher STI rates among PrEP users (Molina 2017, Serpa 2019). In Germany, both the Robert Koch Institute MSM Screening Study (chlamydia 9%, gonococcus 10%, mycoplasma 17%) and the BRAHMS Study (chlamydia 13%, gonococcus 10%, mycoplasma 19%, syphilis 4%) found high bacterial STI prevalences among MSM, regardless of HIV status. STIs were most commonly detected rectally and most STIs were asymptomatic (Jansen 2018, Streeck 2019). In the case of proven STIs, national guidelines recommend treatment of sexual partners of the last 6 months – in case of doubt, even without prior testing.

The opportunities and risks of PrEP with regard to STIs are debated. For example, PrEP reaches people at high risk of HIV and STI who have often not been medically connected; moreover, early STI detection and treatment could reduce incidence, prevalence, and resistance development in the long term (Scott 2016, Werner 2018). However, other experts doubt this and instead fear an increase in resistant pathogens due to the increased use of antibiotics (Tsoumanis 2018). How often, where and for which pathogens screening should take place remains controversial (Kenyon 2019). In IPERGAY trial, 232 MSM were randomized to take occasion-related post-exposure prophylaxis (PEP) with doxycycline 200 mg once, within 24 hours of "risky" sex (Molina 2018). After 9 months, 28 new bacterial STIs had occurred, compared with 49 in the control arm. While the time to first occurrence of new syphilis or fresh chlamydial infection was delayed by PEP, gonorrhea was unaffected. Studies of mycoplasma, resistance development, and microbiome changes are pending. Overall, the median monthly doxycycline dose in the PEP arm was 680 mg.

Many people are still not vaccinated against sexually transmitted pathogens such as human papillomaviruses (Wojcinski 2021) or hepatitis A and B viruses. Due to uncontrolled antibiotic use, the development of resistance continues to progress, especially in *Neisseria gonorrhoeae* and *Mycoplasma genitalium* (Unemo 2017). Often, STI and HIV infections are detected late. A sexual history is not part of routine medical care and is not infrequently perceived as embarrassing by all involved. Out of shame and fear of discrimination, some people with an STI present late or not at all. Many STIs

run (for a long time) without symptoms or with few symptoms (Heiligenberg 2012) and sometimes only cause symptoms after years that are not associated with a sexually transmitted disease (STD). An STI diagnosed (too) late can cause permanent damage, ranging from infertility to rheumatoid and neurological diseases, sepsis, and even death. As long as an STI has not been diagnosed and treated, it will continue to be transmitted to sexual partners.

The incidence of syphilis has also multiplied in many countries in recent years, especially among MSM, reaching a peak in Germany in 2019 (Jansen 2020) and declining slightly in 2020. Outbreaks of lymphogranuloma venereum (LGV), long an STI epidemic predominantly in the tropics and subtropics, are repeatedly observed in major European cities. Infections that have not previously been categorized as classic STIs, such as hepatitis A and C (Larson 2011) or even shigella (Aragón 2007, Daskalakis 2007, Braam 2022), are also diagnosed regionally in more significant numbers among MSM in large cities.

In both women and men, infections with human papillomaviruses (HPV) are among the most frequently sexually transmitted pathogens. While these usually heal without symptoms in the general population, they often persist in PLWH and cause condylomata acuminata or precancerous lesions, so-called intraepithelial neoplasms, from which invasive carcinomas can develop. In addition to cervical carcinomas, anal carcinomas and their precursors are increasingly diagnosed in PLWH (Esser 2015).

Even asymptomatic PLWH should be actively offered STI screening and further recommended condom use, which is most effective in protecting against all STIs (Heiligenberg 2012). Previously HIV-negative patients with STIs should be offered HIV testing and PrEP counseling. The most important STIs are discussed in more detail below. Monkeypox was also included on short notice. STIs such as hepatitis B and C, but also herpes simplex, vulvovaginal candidiasis or bacterial vaginosis, and HPV-associated neoplasms are described elsewhere.

Literature

Aragón TJ, Vugia DJ, Shallow S, et al. Case-control study of shigellosis in San Francisco: the role of sexual transmission and HIV infection. Clin Infect Dis 2007, 44:327-34.

Braam JF, Bruisten SM, Hoogeland M, et al. Shigella is common in symptomatic and asymptomatic men who have sex with men visiting a sexual health clinic in Amsterdam. Sex Transm Infect 2022 Feb 11.

Daskalakis DC, Blaser MJ. Another perfect storm: Shigella, men who have sex with men, and HIV. Comment on Clin Infect Dis 2007, 44:327-34.

EACS 2019 http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf.

Esser S, Kreuter A, Oette M, et al. German-Austrian guidelines on anal dysplasia and anal cancer in HIV-positive individuals: prevention, diagnosis, and treatment. J Dtsch Dermatol Ges 2015, 13:1302-19.

Heiligenberg M, Rijnders B, Schim van der Loeff MF, et al. High prevalence of sexually transmitted infections in HIV-infected men during routine outpatient visits in the Netherlands. Sex Transm Dis 2012, 39:8-15.

Jansen K, et al. Robert Koch Institut; 63. Deutscher STI-Kongress, 6-9.6.2018 Bochum, Deutschland, AV42.

Jansen K. Syphilis in Deutschland im Jahr 2019 – Neuer Höchststand von Infektionen. Epid Bull 2020; 49:3-13.

Kenyon C. Toward a Set of Criteria to Decide Which STIs to Screen for in PrEP Cohorts. Front Public Health 2019, 7:154.

Larsen C, Chaix ML, et al. Gaining Greater Insight into HCV Emergence in HIV-Infected Men Who Have Sex with Men: The HEPAIG Study. PLoS One 2011, 6:e29322.

Molina JM, Charreau I, et al; ANRS IPERGAY Study Group. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV 2017, 4:e402-e410.

Molina JM, Charreau I, Chidiac C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. Lancet Infect Dis 18:308-317.

Serpa JA, Huynh GN, Nickell JB, et al. HIV Pre-Exposure Prophylaxis and Increased Incidence of Sexually Transmitted Infections in the US. CID 2019, Jul 8.

Scott HM, Klausner JD. Sexually transmitted infections and pre-exposure prophylaxis: challenges and opportunities among men who have sex with men in the US. AIDS Res Ther 2016 Jan 19;13:5.

Tsoumanis A, Hens N, Kenyon CR. Is screening for chlamydia and gonorrhea in men who have sex with men associated with reduction of the prevalence of these infections? A systematic review of observational studies. Sex Transm Dis 2018, 45:615–22.

Rowley J, Vander Hoorn S, Korenromp E, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. Bull World Health Organ 2019, 97:548-562P.

Streeck H Janssen K, Crowell TA, et al. Prospective, multicenter study to assess point prevalence, incidence and recurrence of STIs in men who have sex with men in Germany (BRAHMS study). 10th IAS Mexico. TUPDC0106.

Unemo M, Jensen JS. Antimicrobial-resistant sexually transmitted infections: gonorrhoea and Mycoplasma genitalium. Nat Rev Urol 2017, 14:139-152.

Werner RN, Gaskins M, Nast A, Dressler C. Incidence of sexually transmitted infections in men who have sex with men and who are at substantial risk of HIV infection – A meta-analysis of data from trials and observational studies of HIV pre-exposure prophylaxis. PLoS One 2018, 13:e0208107.

Wojcinski M. 14 Jahre HPV-Impfung: was haben wir erreicht? [14 years of HPV vaccination: what has been achieved?] Gynakologe 2021;1-9.

Syphilis (Lues)

Syphilis is caused by *Treponema pallidum (T. p.)*, a bacterium of the Spirochaetaceae family. Treponemata are most commonly transmitted through direct sexual contact, penetrating through microlesions of the mucosa or skin. Even kissing can be contagious. With a single unprotected sexual contact, the risk of transmission is between 30% and 60%. Hematogenous or congenital transmission is rare in Western countries.

Clinic

The incubation period is usually 14–24 days. About 40–50% of infections are asymptomatic or heal spontaneously. In persistent infections, a chronic progressive systemic disease develops in stages, affecting various organ systems. However, these stages may be skipped or repeated. During the symptomatic stages of **early syphilis** (lues I and II), the risk of transmission of infection is highest. During the asymptomatic early (< 1–2 years postinfection) and late (> 1–2 years postinfection) **latent stages**, the infectiousness of syphilis is controversial or low. The symptomatic **late stages** (lues III and IV: 2–50 years post-infection) are no longer infectious (Ghanem 2020, Schöfer 2020).

Syphilis I (primary syphilis): 2 to 3 weeks after infection, the primary ulcer with ulcus durum (hard chancre, erosive chancre) appears at the inoculation site. This painless, gross ulcer with infiltrated margins, from which a clear treponema-rich irritant secretion can be obtained, is accompanied in the drainage area by a usually unilateral, gross lymphadenitis, the bubo. Untreated, the primary complex heals spontaneously after 4–6 weeks.

Syphilis II (secondary syphilis): After four weeks to 6 months, variable general symptoms appear at intervals, including lymph node swelling and symptoms in various organs. The clinical variety of common syphilides on the skin and mucous membranes ranges from exanthema typically with palmoplantar involvement, roseolae, to alopecia syphilitica, plaques muqueuses, angina specifica, condylomata lata genital and perianal, and pigmentary changes (leucoderma specificum) to lues maligna. Rising liver enzymes and ocular involvement, such as episcleritis or iritis, are uncommon. Visual field loss, dizziness, and hearing loss indicate cranial nerve involvement. Headache may be suggestive of early syphilitic meningitis cerebrospinalis. Syphilitic meningitis presents with cranial nerve palsies, intracranial pressure elevation, and other neurologic symptoms. PLWH with advanced immunodeficiency develop early neurosyphilis more often and more rapidly, which is why CSF sampling is recommended when symptoms are present.

Syphilis latens seropositiva: In the clinically asymptomatic latent stages, syphilis remains serologically detectable, and recurrence or progression is possible.

Syphilis III (tertiary syphilis): Years after the initial infection, gummatous lesions may occur that can affect any organ as tuberous or granulomatous changes with a tendency to ulceration and scarring healing. Granulomatous vascular changes can lead to mesaortitis lucia with aneurysms and, if cerebral vessels are involved, to lues cerebrospinalis. The increased incidence of cerebral insults has also been observed with syphilis.

Syphilis IV (quaternary syphilis): Without treatment, late neurosyphilis can occur after years (RKI 2022). Several forms occur. Tabes dorsalis is characterized by shooting pain, sensory ataxia, reflex pupillary rigidity (Argyll-Robertson sign), and optic atrophy. Progressive paralysis is dominated by symptoms such as headache, personality changes, speech disorders, convulsions, dementia, and apoplectic insults. Untreated progressive paralysis leads to death within 4 to 5 years.

Connatal syphilis: Diaplacental transmission usually occurs in the 4th/5th month of pregnancy. Depending on the stage of lues in the pregnant woman, either miscarriage or stillbirth occurs. In the infant, the main symptoms of lues connata praecox are rhinitis syphilitica (Coryza syphilitica), interstitial hepatitis, encephalomeningitis with hydrocephalus communicans hypersecretorius, and Parrot pseudoparalysis (ulnar epiphyseal solution due to osteochondritis syphilitica). The typical stigmata of lues connata tarda (from 3 years of age) are: Saddle nose, Parrot furrows, and Hutchinson's triad: barrel teeth, keratitis parenchymatosa, and sensorineural hearing loss.

In PLWH, syphilis more frequently shows unusual manifestations and foudroyant courses like lues maligna (Gregory 1990, Tucker 2009). Reactivations and shorter

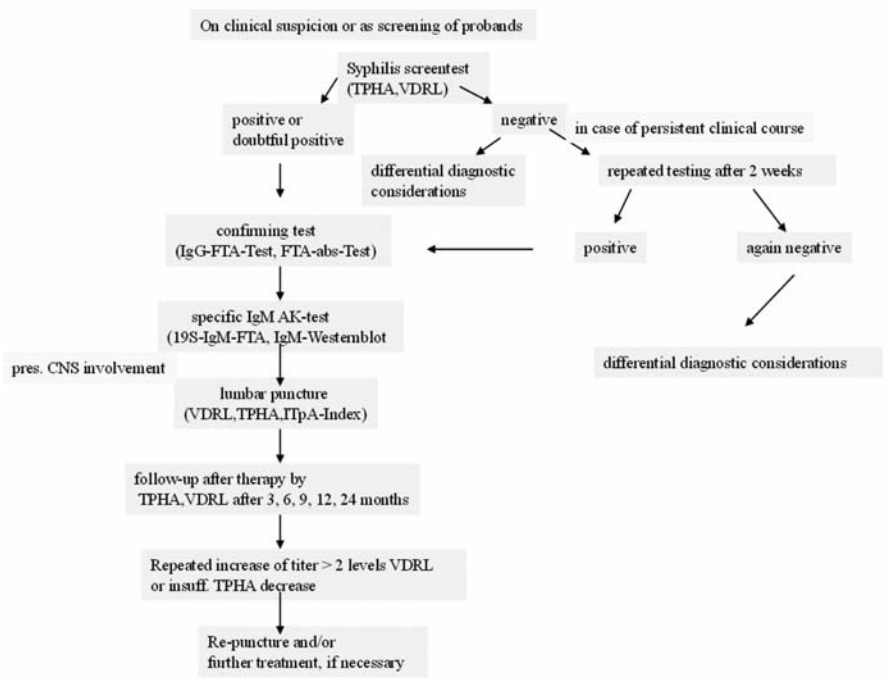


Figure 1: Diagnostic algorithm for Syphilis infection

latency periods to the late stages, including neurosyphilis, occur, as do symptoms of several stages in parallel. In 20% of co-infected persons, neurosyphilis can already be diagnosed during early syphilis using cerebrospinal fluid puncture, irrespective of the clinical symptoms (Esser 2011). The indication for CSF puncture is in co-infected individuals with suspected neurosyphilis, poor response to syphilis therapy and unexplained relapses/reactivations, low CD4 T-cells (< 350 cells/µl), detectable HIV viral load, lack of ART, and neuropsychiatric symptoms including cranial nerve involvement, late syphilis, syphilis connata, and markedly elevated serum VDRL titers (> 1:64) (Marra 2004, Ghanem 2020, Schöfer 2020,).

Diagnostics

If a primary effect is suspected, serology is usually still negative. The pathogen can be detected directly in the irritant secretion from the ulcus durum. In the elaborate dark-field microscopy of the native preparation, silver-glowing, spiral-shaped treponemes are conspicuous by their rotational and buckling movements.
IgM antibodies appear as the first serological reaction (screening test and lipoid antibody detection still negative!). Syphilis diagnosis is often difficult in PLWH. The reasons for this are not only the occasionally unspecific clinical and atypical course but also unreliable screening tests and atypical lues serologies such as a later IgM drop, fluctuating VDRL titers (Venereal Disease Research Laboratory test, detection of phospholipid antibodies). Quantitative PCR may facilitate the diagnosis and monitoring of treatment for early syphilis in the future. Because of the possible overlap of disease stages, each case with serologic evidence should be clinically evaluated neurologically. The indication for CSF puncture should be generous in cases with neurologic symptoms, as it has therapeutic consequences. Interpretation of CSF findings in co-infected individuals should include ITpA index (Intrathecal-produced Treponema pallidum antibodies: TPHA titer in CSF: TPHA titer in serum x IgG in CSF: IgG in serum), parameters of a barrier disorder, evidence of lymphomonocytic pleocytosis, and neurological symptoms should be considered and performed by experts (Schöfer 2020).

Interpretation of syphilis serology in PLWH

Luesserology is based on treponema-specific addiction tests. These are TPHA (Treponema pallidum hemagglutination test), TPPA (Treponema pallidum particle agglutination test), or EIA (enzyme-linked immunosorbent assay). If positive, treponema-specific confirmatory tests such as IgM ELISA, IgM, and IgG Western blot or 19-S IgM FTA-abs (fluorescent Treponema antibody absorption test) follow. In the case of a reactive 19-S-IgM-FTA-abs test in previously untreated patients or a renewed reactivity of the difficulty in treated patients (lues non satis curata), treatment is always needed.
False-negative test results can occur due to inadequate antibody production or suppression of IgM production at very high IgG levels. Therefore, specific tests such as FTA-ABS should be ordered in case of doubt, although false negative results can also occur. In the case of positive treponeme-specific tests, an additional (quantitative) baseline determination of the non-treponeme-specific activity parameters (lipoid antibodies, e.g., VDRL test or CFT) is required before therapy is initiated (Schöfer 2020). These correlate with the disease activity of syphilis. Extremely high VDRL antibody titers can lead to false negative test results via disrupting the antigen-antibody lattice network as a prozone phenomenon (Smith 2004). Conversely, false positive VDRL tests are possible due to the often non-specific B cell activation in HIV infection and other co-infections and co-morbidities (Paul 2021).

Diagnostic algorithm for suspected syphilis infection

The longer untreated syphilis has existed, the slower serological findings normalize after therapy. In PLWH, the IgM test can remain reactive for years, even after successful syphilis therapy. The success of treatment is then only indicated by a clear drop in the titer of the non-treponeme-specific activity parameters (reduction of the VDRL by at least two titer levels within three months). If decreased activity parameters rise again, a re-infection or reactivation is suspected: a serological differentiation is impossible! Since the activity parameters are non-specific, they often change in PLWH or run an atypical course, especially in the case of additional infections, intravenous drug use, and pregnancy (Geusau 2005, Paul 2021). Misinterpretation of increased activity parameters can lead to unnecessary therapies. In repeated reactivations, neurosyphilis should be ruled out using cerebrospinal fluid puncture.

Treatment

The generation time of *Treponema pallidum* is 30–33 hours; a therapy duration with treponemicidal levels should not fall below 10–11 days. Parenteral administration of penicillin is the therapy of choice in all stages, with the dosage and time depending on the stage. Penicillin resistance is not known to date. In the case of early syphilis, a single administration of benzathine penicillin 2.4 million IU IM is sufficient, even in PLWH (Tardocillin® or Pendysin®: 1 ampoule of 1.2 million IU IM in each buttock). Late syphilis is treated with injections at weekly intervals for at least three weeks (Schöfer 2020). Even if the time of infection is unclear, treatment should be given over three weeks.

In case of penicillin intolerance, doxycycline 2 x 100 mg per os or ceftriaxone (IM, IV) are recommended. Due to increasing resistance, macrolides should no longer be used (Lukehart 2004, Stamm 2016, Ndeikoundam Ngangro 2019). In cases where benzathine penicillin G is not available or appropriate, the following alternative therapies are recommended: for early syphilis, daily ceftriaxone 2 g IV (as a short infusion, 30 min) for ten days; for late syphilis, for 14 days. In exceptional cases, doxycycline 2 x 100 mg (not in pregnant women and children < 8 years of age) can be considered as a third choice, which should be given for 14 days in early syphilis and 28 days in late syphilis (Schöfer 2020). Good adherence is urgently required here – only briefly ineffective drug levels mean that therapy must be started again from the beginning. Simultaneous intake of dairy products and intensive light exposure should be avoided.

Neurosyphilis is treated like syphilis with cranial nerve involvement with 3 x 10 million IU or 6 x 5 million IU penicillin G IV for 21 days. In the case of penicillin intolerance, neurosyphilis can also be treated with ceftriaxone 2 g once daily intravenously for about 10–21 days after a single initial dose of 4 g ceftriaxone (Schöfer 2020).

Cross-allergies (< 10%) between penicillins and cephalosporins are possible. The alternative is then doxycycline 2 x 100 mg/daily. Controlled penicillin hardening (habituation) in specialized centers can be performed under inpatient conditions (readiness for resuscitation) up to the full therapeutic dose despite suspected penicillin allergy.

At the beginning of syphilis treatment, the Jarisch-Herxheimer reaction should be distinguished from a penicillin allergy, regardless of the stage. Depending on the stage of syphilis, the Jarisch-Herxheimer reaction is observed in almost 20% within the first 48 hours after the first antibiotic administration. Due to the release of pyrogenic, vasoactive endotoxins due to the rapid decay of bacteria, exanthema and flu-like symptoms such as chills, fever, and joint or muscle pain may occur. The Jarisch-

Herxheimer reaction can be prevented or significantly reduced in its clinical manifestation by a single administration of 0.5–1 mg/kg prednisolone per os or intravenously before the first antibiotic administration (Schöfer 2020).

The success of therapy is monitored clinically and serologically 3, 6, 12, 18, and 24 months after the end of treatment. It is indicated by the healing of clinical symptoms and a significant drop in the titer of the non-treponemal activity parameters (reduction of the VDRL at least two titer levels within three months). A rebound may signify re-infection or reactivation requiring treatment. This is assumed if serological titers increase by more than two titer levels from baseline after the end of therapy. Even in PLWH, the IgM test should no longer be reactive after two years at the latest following sufficient treatment. If the IgM test was no longer reactive, a renewed reactivity means a re-infection or reactivation requiring treatment – see above (Schöfer 2020).

Despite the detection of treponemal antibodies, there is no immunity either after healing or after successful treatment. A new infection is possible immediately after the antibiotic levels have dropped.

Literature

Czelusta A, Yen-Moore A, Van der Staten M et al. An overview of sexually transmitted diseases. Part III. Sexually transmitted diseases in HIV-infected patients. J Am Acad Dermatol 2000, 43: 409-32.

Esser S, Riehemann A, Jablonka R, et al. Diagnosis of Early Neurosyphilis (NSI) by Cerebrospinal Fluid (CSF) in HIV-infected Patients with Primary (LI) or Secondary (LII) Syphilis-Infection (SI). Abstract H1-1396, 51st ICAAC 2011, Chicago.

Geusau A, Kittler H, Hein U, Dangl-Erlach E, Stingl G, Tschachler E. Biological false-positive tests comprise a high proportion of Venereal Disease Research Laboratory reactions in an analysis of 300,000 sera. Int J STD AIDS 2005, 16:722-6.

Ghanem KG, Ram S, Rice PA. N Engl J Med 2020, 382:845-854.

Gregory N, Sanchez M, Buchness MR. The spectrum of syphilis in patients with HIV infection. J Am Acad Derm 1990, 6:1061-67.

Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in Treponema pallidum in the United States and Ireland. N Engl J Med 2004, 351:154-8.

Marra CM, Boutin P, McArthur JC, et al. A pilot study evaluating ceftriaxone and penicillin G as treatment agents for neurosyphilis in human immunodeficiency virus-infected individuals. Clin Infect Dis 2000; 30:540-4.

Marra CM, Maxwell CL, Tantalo L, et al. Normalization of cerebrospinal fluid abnormalities after neurosyphilis therapy: does HIV status matter? CID 2004 38:1001-6.

Medical Society for the Study of Venereal Diseases (MSSVD). Clinical standards for the screening and management of acquired syphilis in HIV-positive adults. London, 2008. http://www.bashh.org/documents/1316/1316.pdf.

Medical Society for the Study of Venereal Diseases (MSSVD). UK National guidelines on the management of syphilis 2008. www.guideline.gov/content.aspx?id=14277.

Ndeikoundam NN, Viriot D, Fournet N, et al. Bacterial sexually transmitted infections in France: recent trends and patients' characteristics in 2016. Euro Surveill 2019 Jan;24.

Paul G, Wesselmann J, Adzic D, et al. Predictors of serofast state after treatment for early syphilis in HIV-infected patients. HIV Med 2021, 22:165-171.

Peterman TA, Heffelfinger JD, Swint EB, Groseclose SL. The changing epidemiology of syphilis. Sex Transm Dis 2005, 32: S4-S10.

Schöfer H, Endres M, Esser S, et al. Diagnosis and treatment of syphilis: Update of the S2k guidelines 2020 of the German STI Society (DSTIG) in cooperation with the following specialist societies: DAIG, dagnä, DDG, DGA, DGGG, DGHM, DGI, DGN, DGPI, DGU, RKI. Hautarzt 2020, 71:969-999.

Sellati TJ, Wilkinson DA, Sheffield JS, et al. Virulent Treponema pallidum, lipoprotein, and synthetic lipopeptides induce CCR5 on human monocytes and enhance their susceptibility to infection by HIV type1. J Inf Dis 2000, 181: 283-93.

Smith G, Holman RP. The prozone phenomenon with syphilis and HIV-1 co-infection. South Med J 2004, 97:379-382.

Stamm LV. Syphilis: Re-emergence of an old foe. Microb Cell 2016, 27:363-370.

Taiwan HIV and Syphilis Study Group, Comparison of effectiveness of 1 dose versus 3 doses of Benzathine Penicillin in treatment of early syphilis in HIV-infected Patients: Multicenter, prospective observational study in Taiwan. Abstract 872, 20th CROI 2013, Atlanta.

Tucker JD, Shah S, Jarell AD, et al. Lues maligna in early HIV infection case report and review of the literature. Sex Transm Dis 2009, 36:512-4.

Gonorrhea (gonorrhea)

Gonorrhea is caused by gram-negative diplococci *Neisseria gonorrhoeae*. These bacteria, which are widespread worldwide, develop regionally varying resistances. They typically affect the mucous membranes of the genitourinary tract, rectum, pharynx, and eyes and are almost exclusively sexually transmitted (with the exception of neonatal conjunctivitis). The incubation period is 2–10 days.

Clinic

In men, the primary symptoms of urethritis are frequent urination, burning during urination, and pain in the urethra. Characteristic is the "bonjour drop", purulent fluorine from the urethra after several hours of micturition abstinence, which can be easily stroked out. Concomitant balanitis often exists. If left untreated, gonorrhea can lead to prostatitis. Symptoms may include burning at the end of micturition, pain in the perineal area, and prostate enlargement. Epididymitis is another complication. In women, gonorrhea is usually asymptomatic. Vaginal colonization is possible only in girls before puberty. Involvement of the cervix and adnexa can lead to peritonitis and "pelvic inflammatory disease".
Extragenitally, gonorrhea manifests as pharyngitis or proctitis. Conjunctivitis is rarely transmitted perinatally, so the previously standard credé prophylaxis for newborns is no longer used in most Western countries. Systemic infections with fever, arthritides, and endocarditides up to gonococcal sepsis are rare (Rompalo 1987). Often, other STIs exist, especially co-infections with chlamydia (Abraham 2013).

Diagnostics

PCR or nucleic acid amplification tests show high sensitivity and specificity but say nothing about possible resistance. In the case of urogenital manifestation, detection is usually successful from the initial urine stream. Swabs are taken urethral, anally, pharyngeal, and endocervical in women. If pus is not spontaneously discharged, affected individuals should not have urinated for four hours before the urethral swab. Diagnosis from the smear can already be established by microscopic detection of intracellular gram-negative diplococci in the methylene blue or Gram preparation. Cultural cultivation of smear material is mainly used for the detection of resistance. Molecular biological methods for monitoring and identifying resistance are currently being developed and are expected to complement or even replace culture in the future.
Worldwide, *Neisseria gonorrhoeae* is increasingly developing regionally varying resistance: since the 1970s to penicillin, since the 1980s to spectinomycin and tetracycline, and since 2000 to ciprofloxacin (50–70% of all isolates worldwide). Meanwhile, resistance to azithromycin has been increasingly described (Crisholm 2009, Buder 2018+2019), as well as to 3rd generation cephalosporins (Bala 2010, Ison 2010, Chisholm 2011, Unemo 2011, Buder 2019). Rarely resistance to ceftriaxone has been published (Chisholm 2009, Ison 2010, Unemo 2017). Isolated cases of clinical resistance occurred primarily with treatments below 1 g (IM or IV) (Fifer 2016). Globally, the incidence of multidrug-resistant pathogens is increasing (Buder 2019). *Neisseria gonorrhoeae* has been classified as a "superbug" by the CDC since 2012 (CDC 2012) and as "priority 2" by the WHO in the global priority list for antibiotic-resistant bacteria (WHO 2017).
Surveillance data from 2016–2020 from the German gonococcal resistance network GORENET observed persistently high rates of resistance to ciprofloxacin (around 60%) and penicillin (15%) in Germany. The rate of azithromycin-resistant isolates fluctuated during the observation period and most recently rose to 12%. Against

cefixime, it was 0.9%. The resistance rate to ceftriaxone remains low (0.2%). No resistant isolates to ceftriaxone or spectinomycin were recorded in GORONET in 2019 and 2020. Older studies from the network found resistance to tetracyclines in about 40% (Buder 2019).

Treatment

The regional resistance situation should be taken into account when selecting therapy. In many countries, there is a lack of systematic studies, and many practitioners treat suspected cases without cultural evidence of the pathogen. So far, resistance to fluoroquinolones, tetracyclines, and penicillin G has been detected. National guidelines recommend a single IM or IV administration of 1,000–2,000 mg ceftriaxone with or without additional concurrent administration of 1,500 mg azithromycin for uncomplicated gonococcal infection of the cervix, urethra, and rectum. Because of the resistance situation and frequent chlamydial co-infections, combinations of cephalosporins and azithromycin or doxycycline are given. Single-stage antibiotic therapy is preferred in high-risk groups. Even in asymptomatic individuals, success should be monitored no earlier than two weeks after completion of treatment.
In cases of treatment failure, intolerance to cephalosporins, and in persons infected with *Neisseria gonorrhoeae* in regions with high resistance rates (e.g., Southeast Asia) (travel returnees), treatment should always be based on resistance tests.

Literature

Abraham S, Poehlmann C, Spornraft-Ragaller P. Gonorrhea: Data on antibiotic resistance and accompanying infections at the University Hospital Dresden over 10 years. J Dtsch Dermatol Ges 2013, 11:241-9.

Bala M, Sood S. Cephalosporin Resistance in Neisseria gonorrhoeae.J Glob Infect Dis 2010, 2:284-90.

Buder S, Dudareva S, Jansen K et al. GORENET study group. Antimicrobial resistance of Neisseria gonorrhoeae in Germany: low levels of cephalosporin resistance, but high azithromycin resistance. BMC Infect Dis 2018; 18: 44.

Buder S, Schöfer H, Meyer T, et al. Bacterial sexually transmitted infections. J Dtsch Dermatol Ges. 2019, 17:287-315.

CDC: Increases in Fluoroquinolone-Resistant Neisseria gonorrhoeae Among Men Who Have Sex with Men -United States, 2003, and Revised Recommendations for Gonorrhea Treatment, 2004. MMWR 2004 ; 53: 335-8.

Chisholm SA, Alexander S, et al. Collaborative Group Emergence of a Neisseria gonorrhoeae clone showing decreased susceptibility to cefixime in England and Wales. J Antimicrob Chemother. 2011 Aug 16.

Chisholm SA, Neal TJ, Alawattegama AB, et al. Emergence of high-level azithromycin resistance in Neisseria gonorrhoeae in England and Wales. J Antimicrob Chemother 2009, 64:353-8.

CDC. Cephalosporin-Resistant Neisseria gonorrhoeae Public Health Response Plan; CDC: Atlanta, GA, USA, 2012; pp. 1–43.

Cole MJ, Chisholm SA, Hoffmann S, Stary A, Lowndes CM, Ison CA. European Surveillance of Sexually Transmitted Infections Network. European surveillance of antimicrobial resistance in Neisseria gonorrhoeae. Sex Transm Infect 2010, 86:427-32.

Enders M, Turnwald-Maschler A, Regnath T. Antimicrobial resistance of Neisseria gonorrhoeae isolates from the Stuttgart and Heidelberg areas of southern Germany. Eur J Clin Microbiol Infect Dis 2006, 25:318-22.

Fifer H, Natarajan U, Jones L, et al. Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhea. N Engl J Med 2016, 374:2504-6.

Handsfield HH, Dalu ZA, Martin DH, et al. Multicenter trial of single-dose azithromycin vs. ceftriaxone in the treatment of uncomplicated gonorrhea. Azithromycin Gonorrhea Study Group. Sex Transm Dis 1994, 21:107-11.

Ison CA, Hussey J, Sankar KN, et al. Gonorrhoea treatment failures to cefixime and azithromycin in England, 2010. Euro Surveill 2011, 16(:p11.

Moodley P, Sturm AW. Ciprofloxacin-resistant gonorrhoea in South Africa. Lancet 2005, 366: 1159.

Rompalo AM, Hook EW 3rd, Roberts PL, et al. The acute arthritis-dermatitis syndrome. The changing importance of Neisseria gonorrhoeae and Neisseria meningitidis. Arch Intern Med 1987, 147: 281-3.

Roy K, Wang SA, Meltzer MI. Optimizing treatment of antimicrobial-resistant Neisseria gonorrhoeae. Emerg Infect Dis 2005, 11: 1265-73.

Selb R, Bremer V, Jansen K, et al. Einführung einer Meldepflicht für N. gonorrhoeae mit verminderter Empfindlichkeit gegenüber Azithromycin, Cefixim oder Ceftriaxon Epid Bull 2020;10:6 –12.

Unemo M, Golparian D, Stary A, Eigentler A. First Neisseria gonorrhoeae strain with resistance to cefixime causing gonorrhoea treatment failure in Austria, 2011. Euro Surveill 2011, 16. pii: 19998.

Unemo M, Bradshaw CS, Hocking JS, et al. Sexually transmitted infections: challenges ahead. Lancet Infect Dis 2017, 17:e235-79.

WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics; 2017. http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf.

Chlamydia, lymphogranuloma venereum (LGV)

Chlamydiae undergo a complex replication cycle, live obligately intracellularly, and can persistently infect host cells over time. Genitoanal infections caused by *Chlamydia trachomatis* are the most common bacterial STI worldwide. Women are particularly affected (Rowley 2019). Chlamydia strains are classified into different serotypes by membrane proteins: serotypes D-K are widely distributed in Europe and cause sexually transmitted urogenital and anal infections and conjunctivitis and pneumonia following perinatal transmission. Serotypes L1-3 are the cause of lymphogranuloma venereum (LGV). Whereas LGV used to be considered a disease of the tropics, local outbreaks have been occurring in Europe and the US for several years, especially in large cities (Gotz 2004, Krosigk 2004).

Clinic

In men, genital chlamydiosis caused by serotypes D-K – if symptomatic- usually presents as urethritides with mostly glassy-turbid fluorine. However, similar to gonorrhea, MAGI (Male Accessory Gland Infection), epididymitis, prostatitis, or proctitis also occur. Reactive arthritis in the context of Reiter's syndrome (see below) is also possible.
In women, the infection causes symptoms in about 20% and may then manifest as urethritis, cervicitis, bartholinitis, salpingitis, endometritis, pelvic inflammatory disease (PID), perihepatitis (Fitz-Hugh-Curtis syndrome), proctitis, and arthritis. In cervicitis, there is usually purulent fluorine. Possible consequences of salpingitis include sterility due to tubal occlusion or extrauterine pregnancy. Chlamydia screening is covered by payers for pregnant women and women up to the age of 25.
In LGV, a primary lesion initially develops at the site of infection. After a few weeks, very painful swellings of the regional lymph nodes (bubo) form, which may exude. After healing, scars develop that can cause drainage problems and fistulas by blocking the lymphatic vessels. Highly painful and often therapy-refractory proctitis and peri- and intra-anal ulcerations are also typical (Peerenboom 2006). More than 90% of L1-3 infections detected in Germany occurred in HIV-infected MSM and mainly cause painful proctitis (Martin-Iguacel 2010). Urethritides without proctitis, on the other hand, are relatively rare.
Reiter's disease refers to the symptom triad of urethritis (sterile yellowish discharge), conjunctivitis (serous or purulent), and arthritis (especially knee, foot, and sacroiliac joints; pain until immobility). There is usually a genetic predisposition (HLA-B27) and chlamydial infection. The incidence in male PLWH is tenfold higher than in the general population. The course is chronic-recurrent. Skin symptoms: erythema with sterile pustules on the palms and soles, later psoriasiform skin changes, hyperkeratotic, scaly, weeping foci (= keratoderma blenorrhagicum), balanitis circinata (disc-shaped, polycyclic, erosive foci).

Diagnostics

Because of their high sensitivity and specificity, nucleic acid amplification tests (men: initial stream urine; women: swabs) are the method of choice (Morre 2005). Resistance has been rare in *Chlamydia trachomatis* (Buder 2019). Procedure: When swabbing with a dry cotton swab, obtain epithelial cells with some pressure for a few seconds and then send the cotton swab in the dry tube to the laboratory (now mostly routine test). Regular testing is usually only for *Chlamydia trachomatis*. PCR detection of serovars L1-3 (therapeutic consequence, see below!) has usually only been performed on specific requests in specialized laboratories. Regardless of the

serovar, detection is always an indication for treatment. The serological determination of antibodies against Chlamydia is used to diagnose chronic invasive infections and plays no role in venereology.

Treatment

Treatment is with doxycycline 2 x 100 mg over 7–14 days. The single dose of 1,000–1,500 mg azithromycin or 1 x 500 mg over three days, still considered an alternative until 2016, is no longer recommended everywhere without restriction. However, it can be regarded as when nonadherence to the doxycycline regimen is a substantial concern. It might require posttreatment evaluation and testing because it has demonstrated lower treatment efficacy among persons with rectal infection (CDC 2021). Alternatives are moxifloxacin 1 x 400 mg or erythromycin 4 x 500 mg over seven days. For anorectal chlamydial infection, doxycycline is more effective than azithromycin (Lau 2021).

LGV requires a significantly longer duration of therapy: doxycycline 2 x 100 mg should be given for at least three weeks. Some experts recommend this if the serotype remains unclear in PLWH with proctitis and chlamydia detection (Mohrmann 2011). So far, resistance has not been a problem with *Chlamydia trachomatis* (Buder 2019). At the earliest, success should be monitored eight weeks after the end of treatment. In Reiter's disease, additional treatment with anti-rheumatic drugs can be given, if necessary, short-term high doses of steroids. Alternatively, sulfasalazine, methotrexate, and anti-TNF-alpha antibodies (etanercept, adalimumab, infliximab) and other biologics have been used (Adizie 2016).

Literature

Adizie T, Moots RJ, Hodkinson B, et al. Inflammatory arthritis in HIV-positive patients: A practical guide. BMC Infect Dis 2016 Mar 1;16:100.

Buder S, Schöfer H, Meyer T, et al. Bacterial sexually transmitted infections. J Dtsch Dermatol Ges 2019, 17:287-315.

CDC: Sexually Transmitted Infections Treatment Guidelines, 2021. https://www.cdc.gov/std/treatment-guidelines/chlamydia.htm

European Guideline for the management of chlamydial infection. Int J STD AIDS 2001; 12: S30-3. http://www.iusti.org/Guidelines.pdf.

Gotz HM, Ossewaarde JM, Nieuwenhuis RF, et al. A cluster of lymphogranuloma venereum among homosexual men in Rotterdam with implications for other countries in Western Europe. Ned Tijdschr Geneeskd 2004, 148: 441-2.

Jebbari H, Alexander S, Ward H, et al. Update on lymphogranuloma venereum in the United Kingdom. Sex Transm Infect 2007, 83:324-6.

Krosigk A, Meyer T, Jordan S, et al. Auffällige Zunahme des Lymphogranuloma venereum unter homosexuellen Männern in HH. JDDG 2004, 8: 676-80.

Lau A, Kong FYS, Fairley CK, et al. Azithromycin or Doxycycline for Asymptomatic Rectal Chlamydia trachomatis. N Engl J Med 2021, 384:2418-2427.

Martin DH, Mroczkowski TF, Dalu ZA, et al. A controlled trial of a single dose of azithromycin for the treatment of chlamydial urethritis and cervicitis. N Engl J Med 1992, 327: 921-5.

Martin-Iguacel R, Llibre JM, Nielsen H, et al. Lymphogranuloma venereum proctocolitis: a silent endemic disease in men who have sex with men in industrialised countries. Eur J Clin Microbiol Infect Dis 2010, 29:917-25.

Morre SA, Spaargaren J, Fennema JS, et al. Real-time polymerase chain reaction to diagnose lymphogranuloma venereum. Em Inf Dis 2005, 11:1311-2.

Nieuwenhuis RF, Ossewaarde JM, van der Meijden WI, Neumann HA. Unusual presentation of early lymphogranuloma venereum in an HIV-1 infected patient: effective treatment with 1 g azithromycin. Sex Transm Infect 2003, 79: 453-5.

Paavonen J. Pelvic inflammatory disease. From diagnosis to prevention. Dermatol Clin 1998, 16: 747-56.

Perenboom RM. Lymphogranuloma venereum proctitis: An emerging sexually transmitted disease in HIV-positive men in the Netherlands. Drugs Today (Barc) 2006; 42: Suppl: 43-5.

Rowley J, Vander Hoorn S, Korenromp E, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. Bull World Health Organ. 2019;97(8):548-562P.

Schachter J, Grossman M, Sweet RL, et al. Prospective study of perinatal transmission of Chlamydia trachomatis. JAMA 1986, 255: 3374-7.

Genitoanal mycoplasma infections

The pathogens *Mycoplasma hominis*, *Ureaplasma urealyticum* and other Mycoplasma species frequently colonize the genital tract of healthy women and men. However, the pathogenic significance of these pathogens is controversially discussed. *Mycoplasma (M.) genitalium* remains asymptomatic in 40–75% (Jansen 2020) but is responsible for 10–35% of non-chlamydial or non-gonococcal urethritides in men. In women, it is reported to be associated with cervicitis, acute endometritis, and pelvic inflammatory disease (PID) (Buder 2019). Proctitis can also be caused by *M. genitalium (*Chow 2021). Often, *M. genitalium* is not screened for when an STI is suspected, although detection influences the choice of antibiotic therapy, and resistance has increased significantly in recent years (Dumke 2019, Spornraft-Ragaller 2020). During STI screening of MSM in various specialized centers independent of clinical symptoms, *Mycoplasma genitalium* was most frequently detected rectally (Jansen 2020).

Clinic, diagnostics

In addition to genitoanal dysfunction, urethritis, proctitis, and SARA (sexually acquired reactive arthritis), additional menstrual cramps, cervicitis, PID, and tubular infertility occur in women and balanoposthitis and epididymitis in men. NAAT or multiplex PCR studies from swabs and/or urine are used to detect this small cell wall-less microorganism. In addition, the use of appropriate assays to detect antibiotic resistance is recommended.

Treatment

Due to the increasing development of resistance in *M. genitalium,* resistance testing is recommended even for uncomplicated infections (Jensen 2022). The calculated use of azithromycin should be avoided (de Salazar 2020). European guidelines recommend azithromycin per os over five days to treat macrolide-susceptible *M. genitalium (*Jensen 2022): once each 500 mg on the first treatment day and 250 mg on the following treatment days 2–5. Macrolide-resistant or persistent infections should be treated with moxifloxacin 400 mg per os over 7–10 days and in case of complications (PID, epididymitis) over 14 days. The resistance rate to moxifloxacin is also increasing alarmingly in Germany (Dumke 2019, Spornraft-Ragaller 2020). Despite low eradication rates (just under 30%), the alternative is oral doxycycline 2 x 100 mg for 14 days. Pristinamycin can be obtained from international pharmacies and taken per os at 4 x 1 g over ten days as a reserve antibiotic. Increasingly complex therapeutic algorithms are being used to treat resistant *M. genitalium* infections, as cases have now been described that failed to respond even to pristinamycin (Durukan 2020). To avoid false positive test results, a success control should not be performed until six weeks after the start of therapy.

Multiplex PCR for sexually transmitted pathogens usually includes testing for mycoplasma. While this is useful in symptomatic STI patients, screening of asymptomatic individuals is controversial. A proven infection with *M. genitalium* should be treated regardless of symptoms to avoid potential long-term complications (e.g., infertility).

Literature

Buder S, Schöfer H, Meyer T, et al. Bacterial sexually transmitted infections. J Dtsch Dermatol Ges. 2019 Mar;17(3):287-315.

Chow EPF, Lee D, Bond S, et al. Nonclassical pathogens are causative agents of proctitis in men who have sex with men. Open Forum Infect Dis 2021, 8:ofab137.

Dumke R, Ziegler T, Abbasi-Boroudjeni N, Rust M, Glaunsinger T. Prevalence of macrolide- and fluoroquinolone-resistant Mycoplasma genitalium strains in clinical specimens from men who have sex with men of two sexually transmitted infection practices in Berlin, Germany. J Glob Antimicrob Resist. 2019 Sep;18:118-121.

Durukan D, Doyle M, Murray G, et al. Doxycycline and Sitafloxacin Combination Therapy for Treating Highly Resistant Mycoplasma genitalium. Emerg Infect Dis 2020, 26:1870-1874.

Jansen K, Steffen G, Potthoff A, et al.; MSM Screening Study group. STI in times of PrEP: high prevalence of chlamydia, gonorrhea, and mycoplasma at different anatomic sites in men who have sex with men in Germany. BMC Infect Dis 2020, 20:110.

Jensen JS, Cusini M, Gomberg M, et al. 2021 European guideline on managing Mycoplasma genitalium infections. J Eur Acad Dermatol Venereol. 2022 Feb 19. doi: 10.1111/jdv.17972. Epub ahead of print.

de Salazar A, Barrientos-Durán A, Espadafor B, et al. Macrolide and fluoroquinolone resistance of Mycoplasma genitalium in southern Spain, 2018-2019. Sex Transm Infect 2021, 97:8-10.

Spornraft-Ragaller P, Dumke R. Prevalence and antibiotic resistance of rectal Mollicutes in HIV-infected men who have sex with men at the University Hospital of Dresden, Germany. Infection 2020, 48:259-265.

Unemo M, Salado-Rasmussen K, Hansen M, et al. Clinical and analytical evaluation of the new Aptima Mycoplasma genitalium assay, with data on M. genitalium prevalence and antimicrobial resistance in M. genitalium in Denmark, Norway and Sweden in 2016. Clin Microbiol Infect. 2017 Sep 18.

Chancroid

The genital ulcer disease chancroid is caused by *Haemophilus ducreyi*. It is endemic in tropical and subtropical areas. In the last two decades, the incidence of chancroid has declined sharply in many countries.

Clinic, diagnostics

Usually, after 2–7 days, one or more ulcers that look like frayed ulcers develop at the site of entry, which is generally genital or perianal. These are not indurated ("soft" chancre) but typically cause severe pain. In about half of cases, regional lymph nodes are swollen, as in LGV, usually unilaterally and very painful. Balanitis or phimosis, or paraphimosis are less common. Clinical diagnosis is difficult because of the wide variety of symptoms, which can mimic ulcerative genital infections such as syphilis or even herpes simplex. Smears sometimes show "fish-train-like" gram-negative rods. A more reliable clue is provided by purulent punctate from inguinal lymph nodes (Lewis 2003, King 1996). Biopsies are taken from the ulcer margin to exclude malignancy.

Treatment

Azithromycin, as a single dose of 1 g to 1.5 g, is considered the treatment of choice (Martin 1995, Romero 2017). Alternatively, ceftriaxone 250 mg (IM or IV) or erythromycin 4 x 500 mg for 4–7 days are used. Ciprofloxacin 2 x 500 mg, given for three days, is also effective. Lymph nodes severely swollen and at risk of rupture should not be cleft but punctured to relieve them (Lewis 2003, Romero 2017). If abscesses ("bubones") occur, antibiotic treatment should be given for at least two weeks. There are few publications on *Haemophilus ducreyi* in PLWH (King 1998, Romero 2017).

Literature

King R, Choudhri SH, Nasio J, et al. Clinical and in situ cellular responses to Haemophilus ducreyi in the presence or absence of HIV infection. Int J STD AIDS 1998, 9: 531-6.

King R, Gough J, Ronald A, et al. An immunohistochemical analysis of naturally occurring chancroid. JID 1996, 174: 427-30.

Lewis DA. Chancroid: Clinical manifestations, diagnosis, and management. Sex Transm Infect 2003, 79: 68-71.

Martin DH, Sargent SJ, Wendel GD Jr, et al. Comparison of azithromycin and ceftriaxone for the treatment of chancroid. Clin Inf Dis 1995, 21: 409-14.

Romero L, Huerfano C, Grillo-Ardila CF. Macrolides for treatment of Haemophilus ducreyi infection in sexually active adults. Cochrane Database Syst Rev. 2017 Dec 11;12(12): CD012492.

Granuloma inguinale (donovanosis, granuloma venereum)

Low-contagious granuloma inguinale is caused by *Klebsiella granulomatis* and was endemic in tropical and subtropical areas. It is now considered nearly extinct (O'Farrell 2018, Muller 2020). Sporadic infections are introduced in Europe (RKI 2022).

Clinic, diagnostics

After an incubation period of 1–2 weeks (days – 3 months), the primary effect appears at the entry site as a painless, rapidly disintegrating papule. In the further course, subcutaneous nodules, multiple easily bleeding ulcerations, and sometimes monstrous granulations develop in the surrounding area and slowly spread peripherally. Extensive tissue destruction is accompanied by lymphedema. Diagnosis is made by PCR, culturing, or microscopic detection of the pathogen from a tissue curettage stained according to Giemsa (intracellular bipolarly stained, coccoid rods, so-called Donovan's corpuscles.

Treatment

Macrolides, doxycycline, fluoroquinolones, or trimethoprim-sulfamethoxazole should be used for at least 21 days or until lesions completely heal. Azithromycin 1 g weekly is recommended as the treatment of choice (O'Farrell 2018). Additionally, wound debridement or excision of lesions may be necessary.

Literature

Muller EE, Kularatne R. The changing epidemiology of genital ulcer disease in South Africa: has donovanosis been eliminated? Sex Transm Infect 2020, 96:596-600.

O'Farrell N, Hoosen A, Kingston M. 2018 UK national guideline for managing donovanosis. Int J STD AIDS 2018, 29:946-948.

Condylomata acuminata (genital warts)

Human papillomaviruses (HPV) exclusively infect epithelial cells and are among the most common sexually transmitted viral infections. The incubation period is at least three weeks. Transmission through smear infection or contaminated objects is also possible. In addition to promiscuity and smoking, immunodeficiency and other genital diseases are important risk factors. Most HPV infections can be eradicated. The onset of clinical symptoms of HPV infection may take months to years. Among PLWH, persistent HPV infection is high (up to 90%). Of the HPV subtypes, more than 20 can lead to genitoanal infections. "Low-risk" (LR) are distinguished from "high-risk" (HR) HPV types. LR-HPV infections cause condylomata acuminata, while persistent HR-HPV-infected epithelial cells may transform malignantly, from which carcinomas and their precursors may develop. Co-infection with multiple HPV subtypes, including oncogenic ones, is common in PLWH. The risk of persistent and symptomatic HPV infection is 7-fold higher and correlates inversely with CD4 T-cell count (Piketty 2003). PLWH more often show clinical symptoms, a chronic course, recurrences, and malignant degeneration. In recent years, an increase in HPV-associated intraepithelial neoplasia (IN) and carcinoma has been observed despite ART. In the US, 6 of the 10 most common malignancies in PLWH are caused by persistent HR-HPV infections: anal carcinoma, cervical carcinoma, oropharyngeal carcinoma,

and vulvar and penile carcinoma. The risk of anal carcinoma is over 80 times higher for male PLWH than in the general population, with a frequency of 35–70/100,000 (Chiao 2006, Silverberg 2012, Yarchoan 2018). PLWH with anal carcinoma often have a history of condylomata acuminata (Hoffmann 2011). Adequate follow-up and regular screening following treatment of HPV-associated lesions may prevent the development of cervical, anal, and other HPV-associated carcinomas (Revollo 2019, Palefsky 2022).

Clinic

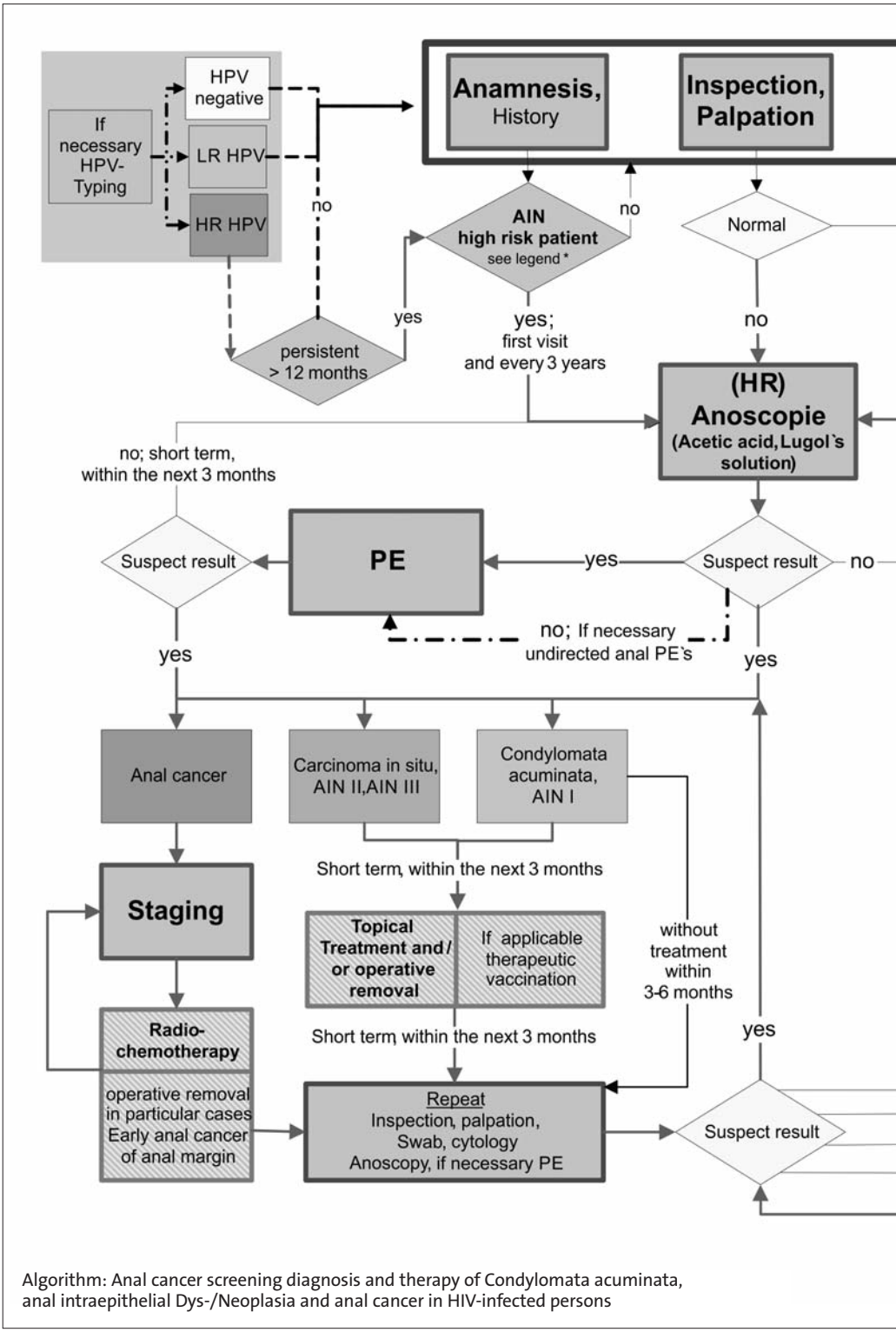
Most HPV infections are asymptomatic, are eradicated during the course, and therefore not diagnosed. The most common clinical manifestation of sexually transmitted HPV infections is genital warts. Spontaneous remissions are also possible with symptomatic infections. However, giant condylomas and carcinomas may also develop with persistent HPV infection.

Condylomata acuminata are usually caused by the "LR" HPV subtypes HPV 6 or HPV 11. Genital warts are not an obligate precursor of genitoanal intraepithelial neoplasia and carcinoma but are often difficult to differentiate clinically and are associated with an increased frequency of additional, persistent associated HR-HPV infections. In addition to the predilection sites, genital, peri- and intra-anal condylomas may occur enorally and in the urethra. Condylomas affect the sexual life of affected individuals and can lead to hygienic and psychological problems. Rare symptoms include itching, burning, or bleeding, usually due to mechanical forces. Condylomata acuminata are clustered with other HPV-associated intraepithelial lesions and carcinomas. Early detection of HPV-associated lesions is helpful because some time may elapse between the development of anal carcinoma and the appearance of condylomata and anal intraepithelial neoplasia.

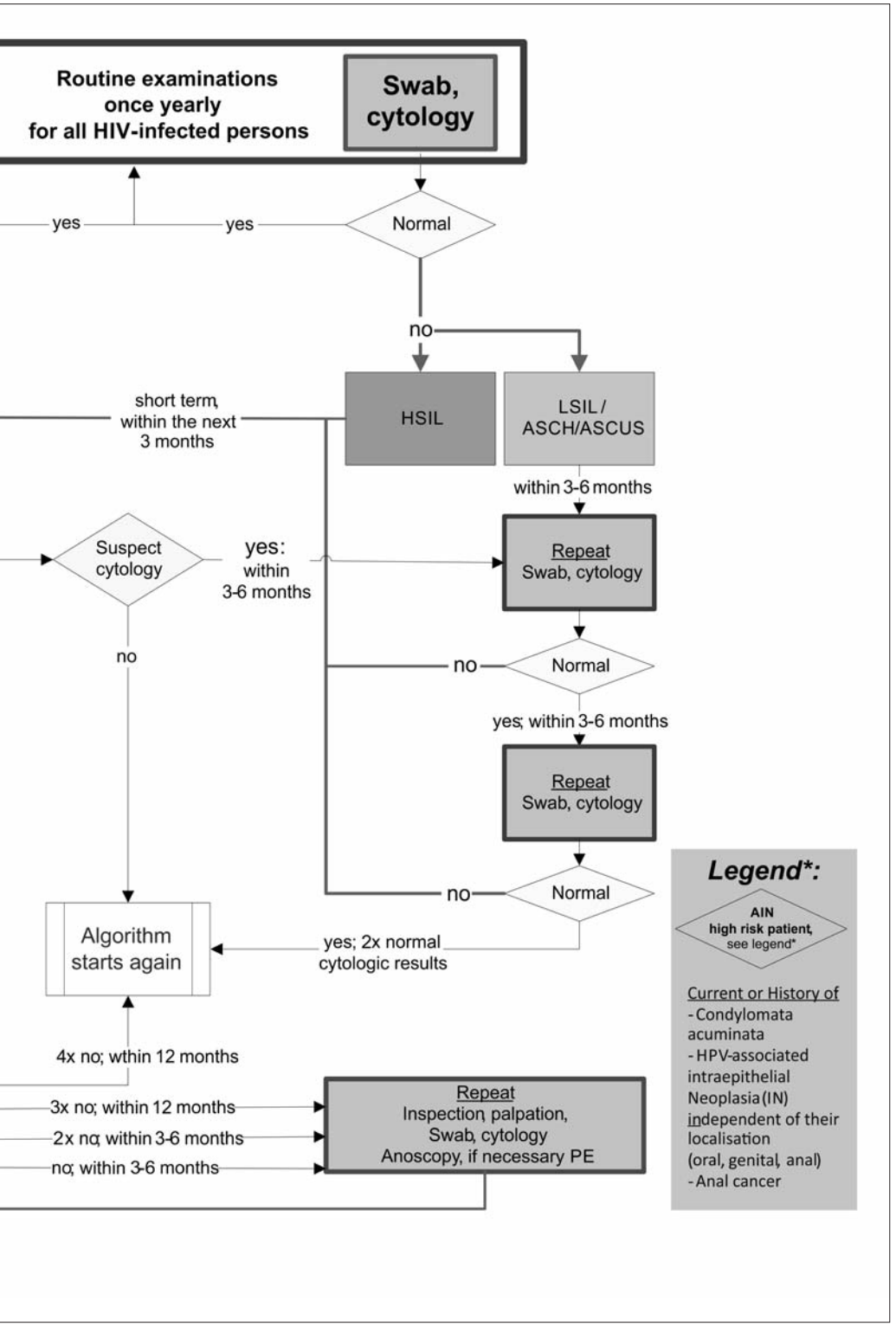
Diagnostics

The diagnosis of genital warts is usually made clinically. Trial biopsies to exclude malignancy are recommended before starting therapy. They are strongly indicated in cases of therapeutic resistance, early recurrence, and rapid or suspected infiltrative growth. Cytologic smears are another screening method for cervical and anal carcinomas and their precursors. Anal cytologic smear findings are usually classified according to the Bethesda system. This distinguishes between normal, inflammation and various atypia: atypical squamous cells (ASC: -US (undetermined significance), -H (cannot exclude HSIL), atypical glandular cells (ACG), low-grade or high-grade squamous intraepithelial lesion (LSIL or HSIL). The sensitivity and specificity of cytological anal smears are unsatisfactory so far, so an additional HPV typing for screening, as in cervical carcinoma, is discussed (Panther 2004, Esser 2020). Any repeatedly abnormal (ASC-H, LSIL, HSIL) cytological findings should prompt a colposcopy or proctoscopy (Duerr 2006).

High-resolution anoscopy/colposcopy (HRA) as the gold standard for early detection of HPV-associated lesions is offered in specialized centers. It improves the accuracy of genital, peri- and intra-anal inspection for necessary sample biopsies, especially after application of acetic acid (3 percent mucosa, 5 percent skin) and additional staining with Lugol's solution (caution: containing iodine). Histologically, condylomata acuminata, intraepithelial neoplasia according to severity grade I-III (IN), and invasively growing carcinomas are differentiated. The anatomic localization is indicated in advance. Thus, an AIN III corresponds to an anal carcinoma *in situ*. In addition, the HPV subtype can also be determined to distinguish between high-



Algorithm: Anal cancer screening diagnosis and therapy of Condylomata acuminata, anal intraepithelial Dys-/Neoplasia and anal cancer in HIV-infected persons


Routine examinations
once yearly
for all HIV-infected persons
Swab,
cytology
yes
yes
Normal
no
short term,
within the next
3 months
HSIL
LSIL /
ASCH/ASCUS
within 3-6 months
Suspect
cytology
yes:
within
3-6 months
Repeat
Swab, cytology
no
no
Normal
yes; within 3-6 months
Repeat
Swab, cytology
no
Normal
Algorithm
starts again
yes; 2x normal
cytologic results
4x no; wthin 12 months
3x no; within 12 months
2x no; within 3-6 months
no; within 3-6 months
Repeat
Inspection, palpation,
Swab, cytology
Anoscopy, if necessary PE
Legend*:
AIN
high risk patient,
see legend*
Current or History of
- Condylomata
acuminata
- HPV-associated
intraepithelial
Neoplasia (IN)
independent of their
localisation
(oral, genital, anal)
- Anal cancer

risk/low-risk types. If persistent HR-HPV subtypes are detected for over one year, HRA is indicated (Ledger 2000).
Men living with HIV, especially MSM, should be screened proctologically just as with HIV-infected women (Jamieson 2006, Scott 2008, Wexler 2008, Esser 2015, Revollo 2019, Palefsky 2022). All PLWH with a history of genitoanal or oral-genital warts, IN, or carcinoma are at increased risk for developing anal carcinoma. HRA with smears and timely targeted sampling, as well as timely treatment of HPV-associated lesions, can prevent fatal tumor growth and avoid mutilating surgeries such as rectal amputation, anus praeter, etc. (Kreuter 2003, Pindea 2008, Esser 2015, Revollo 2019, Palefsky 2022). Rectal palpation and external inspections of the anogenital region are insufficient for PLWH screening. By the time anal carcinoma becomes palpable, it is usually well advanced. Why PLWH cytological, virological, colposcopic, and proctoscopic examinations are necessary in addition to the routinely performed genitoanal palpations and inspections, and how is clarified in a German-Austrian guideline developed by various professional societies (Esser 2015).
Patients at high risk for developing anal carcinoma should undergo anoscopy with appropriate tissue staining (acetic acid, Lugol's solution) and targeted specimen biopsy if necessary.
All conspicuous HPV-associated, clinically relevant findings should be treated immediately. Therapy does not differ from that in HIV-negative patients. Since the transition from persistent HPV infection to intraepithelial neoplasia and anal carcinoma can occur more rapidly, the necessary measures should be initiated promptly.

Treatment

To date, there is no satisfactory treatment for condylomas. Recurrences are common, even after adequate treatment and even in immunocompetent individuals (40–60% after tissue-destructive therapy procedures). Nevertheless, all clinically conspicuous findings should be removed early, even at the risk of repeated interventions. Treatment requires surgical removal as completely as possible with histologic control of dignity and depth of invasion. In addition to surgical excision, scissor cutting, and electrocaustic ablation, condylomas can be removed by laser surgery, infrared coagulation, caustics such as trichloroacetic acid (Bilbilis 2021) or podophyllotoxin, local chemotherapy or cryotherapy with liquid nitrogen. Many practitioners subsequently attempt to reduce the high recurrence rate by adjuvant local immunotherapy with imiquimod (Aldara® cream). Imiquimod is approved for topical treatment of HPV-related lesions and can also be used successfully as a sole therapy primarily for flat, low hyperkeratotic condylomas (Kreuter 2008). For intra-anal treatments, formulations for tampositories containing imiquimod exist (off-label, extemporaneous formulation). Local therapy with imiquimod is usually prolonged (at least three months). Without surgical intervention, the treatment duration is several months. Adherence-reducing side effects such as inflammation, itching, and burning are common. An herbal 10% ointment containing purified dry extract of green tea leaves (*Camellia sinensis*) is also approved as a drug for dermal topical therapy of external genital and perianal condylomata (Abramovits 2010). Condylomas can also be treated locally or systemically with interferons (often not covered by health insurance, the low initial cure rate of 31% – but reports of a much lower recurrence rate than destructive therapies). In a prospective study, electrocaustic ablation of HPV-associated genitoanal lesions was superior to local immunotherapy with imiquimod and topical chemotherapy (Richel 2013).
Effective preventive vaccination is available against the most common genitoanal low-risk types HPV-6/11 and the high-risk types HPV-16/18/31/33/45/45/52/58.

Studies in children and adolescents living with HIV have shown good tolerability and good efficacy with sufficient CD4 T-cell counts (Wilkin 2010, Weinberg 2012). The current EACS guidelines recommend vaccination with the nanovalent HPV vaccine in a 3-dose schedule (months 0, 2, 6–12) until 26 years of age for all PLWH and until 40 years of age for HIV-positive MSM (EACS 2021).

Unlike protective vaccines, progress with therapeutic vaccines is still pending. Isolated cases of lower recurrence rates after ablation of HPV-associated lesions and therapeutic off-label use of preventive vaccines have been reported (Swedish 2012). However, a randomized ACTG trial of the therapeutic use of quadrivalent HPV vaccine, which enrolled more than 500 PLWH with conspicuous HPV-associated anal findings excluding diagnosed carcinomas, was discontinued because it failed to demonstrate efficacy on HPV infection or cytologic results (Wilkin 2016).

Literature

Abramovits W, Gupta AK. Veregen (sinecatechins ointment) 15%. Skinmed 2010, 8:46-9.

Bilbilis K, Lax H, Kreuter A, et al. Efficacy and safety of topical trichloroacetic acid vs. electrocautery for treating anal intraepithelial neoplasia in HIV-positive patients. TECAIN – a prospective randomized controlled trial. 10th IAS 2021 Berlin, Germany (A-IAS2021-00988).

Cusini M, Salmaso F, Zerboni R, et al. 5% Imiquimod cream for external anogenital warts in HIV-infected patients under HAART therapy. Int J STD AIDS 2004; 15:17-20.

Duerr A, Paramsothy P, Jamieson DJ, et al. Effect of HIV infection on atypical squamous cells of undetermined significance. CID 2006, 42:855-61.

EACS. http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html.

Esser S, Kreuter A, Oette M, et al. German-Austrian guidelines on anal dysplasia and anal cancer in HIV-positive individuals: prevention, diagnosis, and treatment. J Dtsch Dermatol Ges 2015, 13:1302-19.

Esser S, Kreuter A, Potthoff A, et al. Need for optimization of screening methods for anal intraepithelial neoplasia in PLWH. P623, 27th CROI 2020.

Gross G, Von Krogh G. Human Papillomavirus Infections in Dermatovenereology. CRC Press, Boca Raton, New York, London, Tokyo (1997).

Hagensee ME, Cameron JE, Leigh JE, et al. Human papillomavirus infection and disease in HIV-infected individuals. Am J Med Sci 2004; 328: 57-63.

Hoffmann C, Sabranski M, Wyen C, et al. Invasive anal cancer in HIV-infected patients – clinical characteristics and outcome. Abstract 870, 18th CROI 2011, Boston.

https://www.eacsociety.org/media/final2021eacsguidelinesv11.0_oct2021.pdf.

Jamieson DJ, Paramsothy P, Cu-Uvin S, et al. HIV Epidemiology Research Study Group. Vulvar, vaginal, and perianal intraepithelial neoplasia in women with or at risk for human immunodeficiency virus. Obstet Gynecol 2006; 107: 1023-8.

Karlsson R, Jonsson M, Edlund K, et al. Lifetime number of partners as the only independent risk factor for human papillomavirus-infection: a population based study. Sex Transm Dis 1995, 22: 119-26.

Koutsky L. Epidemiology of genital human papillomavirus infection Am J Med 1997; 102: 3-8.

Kovach BT, Stasko T. Use of topical immunomodulators in organ transplant recipients. Dermatol Ther 2005; 18:19-27.

Kreuter A, Potthoff A, Brockmeyer NH, et al. Imiquimod leads to a decrease of human papillomavirus DNA and to a sustained clearance of anal intraepithelial neoplasia in HIV-infected men. J Invest Dermatol 2008, 128:2078-83.

Kreuter A, Reimann G, Esser S, et al. Screening and therapy of anal intraepithelial neoplasia (AIN) and anal carcinoma in patients with HIV-infection. DMW 2003, 128:1957-62.

Ledger WJ, Jeremias J, Witkin SS. Testing for high-risk human papillomavirus types will become a standard of clinical care. Am J Obstet Gynecol 2000; 182: 860-65.

Manzione CR, Nadal SR, Calore EE. Postoperative follow-up of anal condylomata acuminata in HIV-positive patients. Dis Col Rect 2003; 46:1358-65.

Maw R. Comparing Guidelines for the management of anogenital warts. Sex Transm Infect 2000; 76: 153.

Palefsky J, Lee J, Darragh T, et al. Treatment of anal high-grade.squamous intraepithelial lesions to prevent anal cancer. CROI 2022 #106.

Palefsky JM, Holly EA, Efirdc JT, et al. Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. AIDS 2005, 19:1407-14.

Panther LA, Wagner K, Proper J, et al. High resolution anoscopy findings for men who have sex with men: inaccuracy of anal cytology as a predictor of histologic high-grade anal intraepithelial neoplasia and the impact of HIV serostatus. Clin Infect Dis 2004, 38:1490-2.

Pineda CE, Berry JM, Jay N, Palefsky JM, Welton ML. High-resolution anoscopy targeted surgical destruction of anal high-grade squamous intraepithelial lesions: a ten-year experience. Dis Colon Rectum 2008, 51:829-35; discussion 835-7.

Revollo B, Videla S, Llibre JM, et al. Routine screening of anal cytology in HIV-infected subjects and the impact on invasive anal cancer. A prospective cohort study. Clin Infect Dis 2019 Sep 4.

Richel O, de Vries HJ, van Noesel CJ, Dijkgraaf MG, Prins JM. Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial. Lancet Oncol 2013; 14:346-53.

Scott H, Khoury J, Moore BA, Weissman S. Routine anal cytology screening for anal squamous intraepithelial lesions in an urban HIV Clinic. Sex Transm Dis 2008, 35:197-202.

Silverberg MJ, Lau B, Justice AC, et al. Risk of Anal Cancer in HIV-Infected and HIV-Uninfected Individuals in North America. Clin Infect Dis 2012, 54:1026-34.

Swedish KA, Factor SH, Goldstone SE. Prevention of recurrent high-grade anal neoplasia with quadrivalent human papillomavirus vaccination of men who have sex with men: a nonconcurrent cohort study. Clin Infect Dis 2012; 54:891-8.

Von Krogh G, Lacey CJN, Gross G, Barrasso R, Schneider A. European Course on HPV-Associated Pathology: Guidelines for the diagnosis and management of anogenital warts. Sex Transm Inf 2000, 76:162-8.

Weinberg A, Song LY, Saah A, et al. Humoral, mucosal, and cell-mediated immunity against vaccine and nonvaccine genotypes after administration of quadrivalent human papillomavirus vaccine to HIV-infected children. J Infect Dis 2012, 206:1309-18.

Wexler A, Berson AM, Goldstone SE, et al. Invasive anal squamous-cell carcinoma in the HIV-positive patient: outcome in the era of highly active antiretroviral therapy. Dis Colon Rectum 2008;51:73-81.

Wilkin T, Huichao C, Cespede M et al. ACTG A5298: a Phase 3 Trial of the Quadrivalent HPV Vaccine in older HIV-infected Adults. Abstract 161, 23th CROI 2016, Boston, USA.

Wilkin T, Lee JY, Lensing SY, Stier EA, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. J Infect Dis 2010, 202:1246-53.

Yarchoan R, Uldrick TS. HIV-Associated Cancers and Related Diseases. N Engl J Med. 2018 Mar 15;378:1029-1041.

Shigellosis

Shigellae (S) are Gram-negative enterobacteria with a worldwide distribution, into different pathogenic serogroups according to biochemical characteristics and antigens (group A: *S. dysenteriae,* B: S. *flexneri,* C: S. *boydii,* D: S. *sonnei*). The pathogens of shigellosis (shigella dysentery) possess an endotoxin involved in the inflammation of the intestinal mucosa. In addition, *S. dysenteriae* type 1 forms an exotoxin that can lead to severe clinical pictures with circulatory insufficiency and central nervous symptoms.

Humans are the only relevant reservoir for *Shigella*. Transmission is through the fecal-oral route, predominantly through direct contact, such as smear infections in the case of inadequate hand hygiene. Sexual transmission among MSM is common (Aragón 2007, Daskalakis 2007, Zayet 2021, Braam 2022). S*higella* is rather vulnerable outside the human body. However, in warmer countries, infections can be found through contaminated drinking water or food and contaminated bathing water.

Even less than 100 microorganisms ingested perorally are sufficient to cause shigellosis. *Shigellae* multiply in the intestine and are excreted in the stool. The incubation period is rarely longer than 12–96 hours. Following the acute phase of illness, contagiousness persists as long as shigella is excreted in the stool – usually no longer than four weeks. Asymptomatic shedders hinder the containment of shigellosis.

As with hepatitis A, regional clusters of sexual transmissions among MSM have been observed in many countries during recent years (Keay 2014, Mohan 2018). Among 389 MSM attending the Amsterdam Centre for sexual health in 2020, *shigella* prevalence was 2.8% in asymptomatic men, 3.7% in men who recently had diarrhea, and 4.4% in men with current diarrhea (Braam 2022).

Antimicrobial resistance is increasing (Niyogi 2007, Gaudreau 2010, Hoffmann 2013, Nüsch-Inderbinen 2016, Zayet 2021).

Clinic

The clinical course varies considerably, ranging from asymptomatic excretory diarrhea to profound watery diarrhea, with mucous-bloody-purulent diarrhea and life-threatening septic-toxic events. Shigellosis usually begins as watery diarrhea and may progress to inflammatory colitis. Abdominal cramps (colic and tenesmus) are typical. Up to 50 defecations per day can occur, often accompanied by dehydration and protein loss. The disease is usually self-limiting within seven days. Severe courses are associated with fever, mucous-bloody, and purulent diarrhea. Focal ulceration and necrosis may occur, predominantly in the distal colon, and in extreme cases, progress to colonic dilatation and perforation with peritonitis and sepsis.
In rare cases (1–3%), shigellosis manifests outside the intestine: the cytotoxin (Shiga toxin) produced by *S. dysenteriae* serotype 1 (SD1) is almost identical to Shiga toxin 1 (verotoxin 1) of enterohemorrhagic *E. coli (*EHEC) and also causes hemolytic uremic syndrome (HUS). Other possible consequences are infectious arthritis (dysentery rheumatoid) and Reiter's syndrome.
Other infectious diseases such as typhoid, schistosomiasis, or amoebiasis may have been transmitted at the same time as the *shigella* or an HIV infection may be present, which additionally impairs the course of the disease.

Diagnostics

The suspected diagnosis should be confirmed bacteriologically. Fresh stool samples or freshly taken rectal swabs in a buffered transport medium (30% glycerol in 0.6% NaCl solution), transferred to appropriate culture media as quickly as possible, are suitable for this purpose. The samples should be obtained before antibiotic therapy, and an antibiogram should be prepared to adjust the initiated antibiotic therapy if necessary.
To identify the sources and routes of infection, pathogens can be typed at specialized reference centers (molecular biological subdifferentiation using pulsed-field gel electrophoresis – PFGE). Some physicians recommend stool testing for *shigella* for PLWH with diarrhea and STI screening for all patients with shigellosis who have not traveled to an endemic area (Keay 2014).

Treatment

Due to its high infectivity, antibiotic treatment is recommended. According to a Cochrane review, bacterial excretion is reduced, the duration of excretion and illness is shortened, and symptoms are alleviated. However, regularly updated local or regional antibiotic sensitivity patterns to different species and strains are required to guide empiric therapy (Christopher 2010). Due to the increasing development of resistance, treatment should follow resistance testing. In principle, antibiotics from the quinolone group, azithromycin, trimethoprim-sulfamethoxazole, tetracycline, doxycycline, and ampicillin are suitable for long-term treatment of *shigella* carriers. Gyrase inhibitors such as ciprofloxacin (2 x 500 mg/day) for five to seven days are the agents of choice. The choice of therapy depends on the antibiogram (Niyogi 2007, Gaudreau 2010, Hoffmann 2013, Zayet 2021, RKI 2022). In patients in good general health, symptomatic therapy with oral fluid replacement may be sufficient. In both very young and elderly patients, as well as in the presence of severe comorbidities, fluid and electrolyte losses must be compensated parenterally. Motility inhibitors should be avoided.

Preventive and control measures

The basis of prevention is hygiene (personal, drinking water and food hygiene, hygiene in communal facilities). Effective hand hygiene is crucial. An alcohol-based disinfectant can supplement thorough hand washing with soap and water. In countries with poor sanitation, consider "peel it, boil it, cook it or forget it". Condoms do not provide adequate protection against sexual transmission. During and in the days following diarrheal illness (until *shigella* excretion is ruled out), sexual contact should be avoided.

During the entire period of illness, but also in the case of excretions, all objects and surfaces that may have come into contact with infectious excretions must be disinfected. Laundry should be washed at least 60°C or soaked in suitable disinfectant solutions for 12 hours and washed as everyday household laundry. Toilet seats, toilet lids, bed frames, sinks, and bathtubs must be disinfected daily in healthcare facilities. Darkroom operators and sex party organizers should ensure soap dispensers are installed for hand washing. Sharing of inadequately disinfected dildos or lubricant cans should be avoided. Hot tubs should be adequately chlorinated.

Persons who have contracted shigellosis or are suspected of having contracted shigellosis are not allowed to work in food establishments. This also applies to the rare cases without symptoms who shed shigella in their feces for many months after acute infection. Return to work is possible after recovery and with three negative stool samples 1–2 days apart. The first stool sample should be taken no earlier than 24 hours after the appearance of the formed stool or 24 hours after the end of antibiotic therapy. In the case of prolonged excretion of pathogens, an individual solution should be found with the health department. Contact persons must provide evidence of a negative stool sample at the end of the incubation period.

Literature

Aragón TJ, Vugia DJ, Shallow S, et al. Case-control study of shigellosis in San Francisco: the role of sexual transmission and HIV infection. Clin Infect Dis 2007, 44:327-34.

Baer JT, Vugia DJ, Reingold AL, et al. HIV infection as a risk factor for shigellosis. Emerg Infect Dis 1999; 5:820-3.

Braam JF, Bruisten SM, Hoogeland M, et al. Shigella is common in symptomatic and asymptomatic men who have sex with men visiting a sexual health clinic in Amsterdam. Sex Transm Infect. 2022 Feb 11:sextrans-2021-055274.

Christopher PR, David KV, John SM, Sankarapandian V. Antibiotic therapy for Shigella dysentery. Cochrane Database Syst Rev 2010; 8:CD006784.

Daskalakis DC, Blaser MJ. Another perfect storm: Shigella, men who have sex with men, and HIV. Comment on CID 2007, 44:327-34.

Gaudreau C, Ratnayake R, Pilon PA, Gagnon S, Roger M, Lévesque S. Ciprofloxacin-Resistant Shigella sonnei among Men Who Have Sex with Men, Canada, 2010. Emerg Infect Dis 2011; 17:1747-50.

Hoffmann C, Sahly H, Jessen A, et al. High rates of quinolone-resistant strains of Shigella sonnei in HIV-infected MSM. Infection 2013, 41:999-1003.

Keay R, Singh G, Abdul-Latif M, Rayment M, Nelson M. Shigella flexneri enteritis in risk-taking HIV-infected MSM. J Infect 2014, 68:103-4.

Marcus U, Zucs P, Bremer V, et al. Shigellosis – a re-emerging sexually transmitted infection: an outbreak in men having sex with men in Berlin. Int J STD AIDS 2004; 15:533-7.

Mohan K, Hibbert M, Rooney G, et al. What is the overlap between HIV and shigellosis epidemics in England: further evidence of MSM transmission? Sex Transm Infect 2018, 94:67-71.

Niyogi SK. Increasing antimicrobial resistance—an emerging problem in the treatment of shigellosis. Clin Microbiol Infect 2007; 13:1141-3.

Nüesch-Inderbinen M, Heini N, Zurfluh K, et al. Shigella Antimicrobial Drug Resistance Mechanisms, 2004–14. Emerg Infect Dis 2016, 22:1083-5.

Zayet S, Klopfenstein T, Pierron A, et al. Shigella sonnei, an emerging multidrug-resistant sexually transmitted pathogen in Franche-Comté, France. Emerg Microbes Infect 2021, 10:1702-1705.

Mpox

STEFAN ESSER, CHRISTIAN HOFFMANN

The natural hosts of Mpox virus (MPXV) are various rodents. Monkeys and humans are not required for the viral life cycle and thus are only incidental hosts. When transmitted to humans, this zoonosis can cause pox-like symptoms. In mid-May 2022, increased cases were first described in Europe through human-to-human transmission, initially in the United Kingdom, Portugal, and Spain, and shortly thereafter in numerous other countries, with more than 85,000 cases worldwide as of January 2023 (WHO). After a sharp increase in global numbers of MPXV infections since May 2022, case numbers declined significantly from August 2022 due to intensive public health efforts (Srivastava 2023). Only isolated cases have been reported in Europe since mid-October 2022, with some local outbreaks in early 2023.

Affected groups

Among the 546 cases in a German MSM cohort, 256 (46.9%) were PLWH (Hoffmann 2022). Of these, most had a normal immune status with a median CD4 T-cell count of 691/µl. Only 17% and 3% had CD4 T-cell counts of less than 500 and 350/µl, respectively. A total of 4% were viremic at the last measurement with HIV RNA above 50 copies/mL, although only 4/10 had HIV RNA above 200 copies/mL. The second largest affected group, with 232 (42.5%) cases, were PrEP users, and the remaining 58 cases (10.6%) were MSM without known HIV infection or PrEP. Over half of all patients had been diagnosed with another STI recently, and one-third had been diagnosed concurrently with MPXV infection (Hoffmann 2022). MSM, with frequently changing sex partners and visitors to sex parties, are particularly affected by MPXV infections. Similar observations have been made in other cohorts worldwide (Iñigo Martínez 2022, Tarín-Vicente 2022, Thornhill 2022). Thus, in most cases, sexual transmission is likely involved in the current outbreak.

Clinic

Almost all those infected with MPXV suffer from skin/mucosal lesions at diagnosis (99%), more than half have a fever, and just under half have swelling of the lymph nodes, some painful. A few days after infection, skin lesions typically develop synchronously, first macules and papules, then the characteristic indented vesicles and pustules with central scabs or crusts. In the further course, erosions and ulcerations, some covered with crusts or eschar, develop and may persist for more than three weeks before the coverings fall off and spontaneous healing finally occurs (see also picture plates). Scarring is possible, especially with ulcerations. Some lesions are very painful; others are entirely indolent. However, besides typical smallpox, there are lesions in which one does not expect to find MPXV. MPXV can be confused with many other infectious diseases, especially syphilis, herpes simplex, varicella, or dell warts, but also with non-infectious skin diseases such as erythema exsudativum multiforme (also known as Stevens-Johnson syndrome). Thus, in suspected cases of MPXV, appropriate differential diagnoses should be considered and diagnostically confirmed.

By far, the majority of smallpox lesions have manifested anally or genitally. Only 12% of our own cohort had neither genital nor anal involvement (Hoffmann 2022). Among these, cases were quite frequently found in the region of the lips or even with isolated pharyngeal ulcers, which can be accompanied by massive lymph node swelling and sometimes cause considerable dysphagia and pain. Only 4% were the

lesions confined to the trunk and extremities. High rates of anogenital disease patterns have also been reported in Spain, the UK, and other countries (Thornhill 2022, Tarín-Vicente 2022, Girometti 2022). Overall, the localization of MPXV in the 2022 outbreak differs markedly from those of previous outbreaks. Previously, in Africa, lesions were primarily localized at the face and extremities, much less genitally and virtually none anally (Jezek 1987, Yinka-Ogunleye 2019).

In 83% of the patients in our cohort, the disease was localized with a maximum of 10 lesions. Only a few patients had 50 or more lesions. The most common general symptoms were fever, headache, limb pain, and often painful swelling of the lymph nodes. The duration of symptoms rarely exceeded seven days. Night sweats occurred relatively infrequently. Extremely painful proctitis happened in some patients (15%), and bacterial superinfections were also reported. The complications that are quite common in Africa, such as pneumonia and involvement of the eyes or CNS, were seen very rarely in the 2022 outbreak.

However, the spectrum of courses is broad, ranging from asymptomatic cases that come to attention during STI screening (rare) to severe complications requiring hospitalization. However, most illnesses to date have turned out to be relatively mild. Unlike in previous outbreaks, where mortality ranged from 1% to 11% (Beer 2019), less than 100 deaths have been observed worldwide. Our cohort's hospitalization rate was 4%, with no difference between MSM with and without HIV. However, most patients were predominantly young, immunocompetent, and otherwise healthy. Hospitalizations were primarily due to complications, largely massive swelling of the lymph nodes and genitalia, extensive involvement of the entire integument, bleeding, or due to refractory pain that could not be managed as an outpatient, especially in the case of anal involvement.

Contrary to earlier reports, HIV infection *per se* does not appear to be a risk factor, at least if HIV infection is treated adequately and there is no severe immunodeficiency. In these situations, severe courses are undoubtedly possible (Boesecke 2022). In a global cohort of 382 cases among PLWH with advanced immune deficiency, a severe necrotizing form of Mpox appears to behave like an AIDS-defining condition, with a high prevalence of fulminant dermatological and systemic manifestations and death (Mitjà 2023). Overall, 107 (28%) of 382 cases were hospitalized, of whom 27 (25%) died. Of note, an immune reconstitution inflammatory syndrome to Mpox was suspected in 21 (25%) of 85 people initiated or re-initiated on ART, of whom 12 (57%) the 21 died (Mitjà 2023).

Diagnostics

Diagnosing an MPXV infection is based on clinical findings and a positive PCR. In our experience, PCR in smears of anal and genital lesions is almost always reliably positive. However, diagnosis is also often successful from lesions located at the extremities and trunk. In most cases, it is not necessary to open the lesions. Sometimes, it is surprising how long the PCR remains positive. PCR from a throat swab is also positive in about half of the cases, especially in cases of sore throat (often reported only when asked) and especially in pharyngeal ulcers. However, Ct values in the throat are usually significantly higher, which explains the probably very low rate of droplet infections.

Treatment

The focus is on preventing bacterial superinfections and symptomatic treatment, especially local treatment (Tannosynt, zinc shake mixture) and adequate analgesia. Drugs such as tecovirimat, cidofovir, or brincidofovir are currently unavailable in most countries or are very limited (Hermanussen 2022, Mitjà 2023). However, they are not needed in the vast majority of cases. More extensive studies have not demonstrated efficacy in humans for any of these treatments.

Prevention and vaccination

In most guidelines, isolation of patients is recommended for the entire disease duration, at least three weeks. Health departments apply the RKI recommendations very differently in our experience. The rate of household infections is low, well below the 8% described in a 2018 review (Beer 2018). Nevertheless, WHO reports more than 550 MPXV cases among healthcare workers worldwide in the current outbreak, suggesting the need for adequate protection in this population.

As there is no specific vaccine for Mpox, smallpox vaccines are used given cross-reactivity in the laboratory and some encouraging results from animal studies. Laboratory studies (Gilchuk 2016) and clinical observations (Jezek 1987, Karem 2007) suggest that smallpox vaccination provides some, but not complete, protection against Mpox. In the German cohort, a total of 13% were shown to have been vaccinated against smallpox in childhood (Hoffmann 2022). The timing of smallpox vaccination was likely at least 40 years previous; compulsory vaccination ended in most countries many years ago, mainly in the 70's and 80's. Preliminary data provide some limited evidence for a milder course of disease with a history of a smallpox vaccination (Hoffmann 2022).

It remains to be seen whether the smallpox vaccination campaign in sexually active MSM (with a modified vaccinia virus Ankara) will actually provide substantial protection against severe infections and effectively prevent contagions. Breakthrough infections are not uncommon, especially among those vaccinated only once. At least one study suggests vaccine protection in PLWH is no worse than in HIV-negative persons (Greenberg 2013).

In addition to the indicated vaccinations, vaccinations were recommended for known close contacts of confirmed MPXV-infected persons and vaccinations as post-exposure prophylaxis for asymptomatic persons up to 14 days after confirmed contact.

However, the currently observed worldwide decline in the number of infections is probably due less to vaccination than to the fact that MPXV is not well adapted to humans. Transmission requires close contact (usually sex), but unlike HIV, the infectivity of affected individuals is short (a few weeks, not years). In addition, MPXV infection usually makes visible changes, and asymptomatic transmissions are rare. Nevertheless, it seems possible that Mpox may establish itself as a new STI among MSM.

Literature

Beer EM, Rao VB. A systematic review of the epidemiology of human monkeypox outbreaks and implications for outbreak strategy. PLoS Negl Trop Dis 2019, 13(10):e0007791.

Boesecke C, Monin M, van Bremen K, et al. Severe monkeypox-virus infection in undiagnosed advanced HIV infection. Infection 2022 (in press).

Gilchuk I, Gilchuk P, Sapparapu G, et al. Cross-Neutralizing and Protective Human Antibody Specificities to Poxvirus Infections. Cell 2016, 167:684-694.e9.

Girometti N, Byrne R, Bracchi M, et al. Demographic and clinical characteristics of confirmed human monkeypox virus cases in individuals attending a sexual health center in London, UK: an observational analysis. Lancet Infect Dis 2022 Jul 1:S1473-3099(22)00411-X.

Greenberg RN, Overton ET, Haas DW, et al. Safety, immunogenicity, and surrogate markers of clinical efficacy for modified vaccinia Ankara as a smallpox vaccine in HIV-infected subjects. J Infect Dis 2013, 207:749-58.

Hermanussen L, Grewe I, Tang HT, et al. Tecovirimat therapy for severe monkeypox infection: Longitudinal assessment of viral titers and clinical response pattern-A first case-series experience. J Med Virol. 2022 Sep 30.

Hoffmann C, Jessen H, Wyen C, et al. Clinical Characteristics of Monkeypox Virus Infections Among Men with and without HIV: A Large Outbreak Cohort in Germany. HIV Medicine 2022, Sep 4.

Hoffmann C, Wolf E, Jessen H, Bickel M, Boesecke C; DAIG and DAGNAE. Is there any evidence for milder courses of monkeypox virus infections with childhood smallpox vaccination? Infection. 2022 Sep 20.

Iñigo Martínez J, Gil Montalbán E, Jiménez Bueno S, et al. Monkeypox outbreak predominantly affecting men who have sex with men, Madrid, Spain, 26 April to 16 June 2022. Euro Surveill 2022, 27:2200471.

Jezek Z, Szczeniowski M, Paluku KM, et al. Human monkeypox: clinical features of 282 patients. J Infect Dis 1987, 156:293-8.

Karem KL, Reynolds M, Hughes C, Braden Z, Nigam P, Crotty S, et al. Monkeypox-induced immunity and failure of childhood smallpox vaccination to provide complete protection. Clin Vaccine Immunol 2007; 14:1318-27.

Mitjà O, Alemany A, Marks M, et al. Mpox in people with advanced HIV infection: a global case series. Lancet 2023, 401:939-949.

Srivastava S, Kumar S, Jain S, et al. The Global Monkeypox (Mpox) Outbreak: A Comprehensive Review. Vaccines (Basel). 2023;11:1093.

Tarín-Vicente EJ, Alemany A, Agud-Dios M, et al. Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational cohort study. Lancet 2022 Aug 8:S0140-6736(22)01436-2.

Thornhill JP, Barkati S, Walmsley S, et al. Monkeypox Virus Infection in Humans across 16 Countries – April-June 2022. N Engl J Med. 2022 Jul 21.

14. Vaccinations

GEORG HÄRTER

Morbidity and mortality of some vaccine-preventable diseases can be higher in people living with HIV (PLWH). In principle, vaccination status should be reviewed (see chapter *Checklist: The New Patient*), and the standard and indicated vaccinations should be carried out according to current recommendations (Härter 2013, Ehl 2018, EACS 2022).
Immunologically, HIV infection leads to a loss of CD4 T-cells and a significant restriction of B cell function, especially during prolonged viremia (Hu 2015). This is also accompanied by reduced immunity to vaccinations already given. Especially in cases of advanced immunodeficiency, it may be helpful to determine antibody titers (Ehl 2018).

Principles of vaccination in PLWH*

- Vaccinations should be administered according to national guidelines for the general population.
- Non-replicating vaccines (e.g., whole inactivated, polysaccharide, conjugated and subunit vaccines, or virus-like particles) are safe in PLWH.
- Live (replicating) vaccines (e.g., MMR, VZV, yellow fever) are contraindicated in severe immunodeficiency (CD4 T-cell count < 200/µl or < 14%).
- Vaccinations should preferably be given after HIV suppression and immune reconstitution, otherwise, immunogenicity is lower.
- If HIV replication is high (e.g., in acute retroviral syndrome), it is more favorable to wait before vaccinating.
- Repeat vaccinations after immune reconstitution, if necessary, determine antibody levels.
- Polysaccharide vaccines should be avoided due to reduced immunogenicity.
- Rapid vaccination regimens (e.g., hepatitis B, TBE, rabies, Japanese encephalitis) should be avoided due to possible lower vaccine response.
- In advanced immunodeficiency, the vaccination status of close contacts (partner, family, friends) should also be checked and supplemented if necessary.

* According to EACS 2022, BHIVA 2015 Vaccination Guidelines

Practical procedures

Education: Patients must be informed about the dangers posed by the respective disease, the extent of the protective effect, and the risks and side effects of vaccinations within the setting of HIV infection.

Timing: Vaccination should preferably take place after initiation of antiretroviral therapy, i.e., after immune reconstitution and when HIV RNA is suppressed. Vaccination should not be given during a severe acute infection; a mild infection without fever is not an obstacle. Live parenteral vaccines such as MMR, varicella, or yellow fever vaccines must be applied either on the same day or at least four weeks apart. No live vaccines, except yellow fever vaccine, should be given for three months after immunoglobulins.

Booster versus renewed basic immunization: The latter is only necessary if no vaccinations are documented or remembered. A basic immunization that has been started will also be completed at a later date ("every vaccination counts"). However, vaccinations given in cases of clear immunodeficiency should be repeated (see above).

Vaccination risk assessment: In principle, inactivated (non-replicating) vaccines are safe and unproblematic and can be given at any stage of HIV infection (Ehl 2018). Live vaccines pose a risk of manifest vaccine illness, including yellow fever and measles/mumps/rubella and varicella vaccines. Nevertheless, live vaccines are generally not contraindicated and are feasible when CD4 T-cell counts are > 200/µl or > 14% (EACS 2022). Transient increases in HIV RNA following vaccination have been described after influenza vaccination but are usually not clinically relevant (Zanetti 2002).

Environmental vaccination

If immune status is poor, care should be taken to ensure that persons in the immediate environment are vaccinated (including annual influenza vaccination). However, there is a risk of infection with some live vaccinations, therefore:

- No oral polio vaccination or smallpox vaccination to persons who are in close contact with PLWH with severe immune deficiency
- As the rotavirus vaccine virus is shed during the first weeks after administration of the rotavirus vaccine, PLWH with severe immune deficiency should avoid diaper changes in children for four weeks after rotavirus vaccination (Rubin 2014).
- They should also avoid contact with skin lesions after varicella/live-replicating zoster vaccination; vaccine varicella can be treated prophylactically with acyclovir.

Vaccinations of HIV-positive children

Only a few variations from the recommendations apply to all children (Ehl 2018, BHIVA 2015). The classification of immunosuppression differs in children younger than six years from adults (Ehl 2018). In the previous CDC classification, severe immunodeficiency was defined as a CD4 T-cell count < 15% in all children. However, according to the newer classification, it is mainly the absolute counts that should be considered (CDC 2014). However, the percentage threshold < 15% still applies in many recommendations (Menson 2012).

The following procedure appears practical: live vaccinations (MMR, VZV, yellow fever, rotavirus) are contraindicated in severe immunodeficiency. This is defined according to CDC as follows: < 1 year: CD4 T-cell count < 750/µl (relative < 26%); 1 to < 6 years: CD4 T-cell count < 500/µl (< 22%); > 6 years: CD4 T-cell count < 200/µl (< 14%). Above these values, live vaccination should be performed according to the general recommendations (Ehl 2018). This explicitly includes rotavirus vaccination. Family members of children with severe immunodeficiency should be vaccinated if they have not already undergone the infections. Because vaccine response is reduced and possibly shortened in children living with HIV, determining antibody levels is recommended (Ehl 2018).

Vaccinations in detail (selected vaccinations)

Tetanus/diphtheria/pertussis/polio: After primary immunization in childhood, booster vaccination against diphtheria and tetanus is also helpful for PLWH every 10 years. A combination vaccine with polio and/or pertussis is available. Since 2009, a single pertussis booster has been recommended for all adults using the combination mentioned above. In addition, a vaccination against pertussis with a Tdap combination vaccine should be given for every (!) pregnancy at the beginning of the 3rd trimester, regardless of previous vaccinations. For polio, a single booster vaccination is recommended after primary immunization. In some countries, however, an additional vaccination may be necessary (see *HIV and travel*).

Pneumococcus: As there is an increased risk of invasive pneumococcal infections, all PLWH should be vaccinated (Yin 2012, Lee 2014). Compared to pneumococcal polysaccharide vaccines (PPSV), conjugate vaccines (PCV) provide higher and longer-lasting protection (Nunes 2012). Most guidelines recommend a sequential use: with no prior pneumococcal vaccination, vaccinate first with 13-valent PCV13 or PCV15 and then after 6–12 months (8 weeks at the earliest) with 23-valent PPSV23 (EACS 2022); PLWH < 200 CD4 T-cells/µl should delay the vaccination until their immunity had been reconstituted with ART (Lee 2014). If available and recommended by the national authorities, a single PCV10 can be given. If the PPSV23 vaccination was less than six years ago, PCV13 or PCV15 is vaccinated at least 12 months apart with a booster after six years (CDC 2012). For PPSV23 vaccination of more than six years ago, regular sequential vaccination with PCV13 or PCV15 and PPSV23 is given.

Influenza: Given a higher risk of severe courses and increased influenza-associated mortality for PLWH (Lin 2001), vaccination should be given annually before the start of influenza season (Anema 2008, EACS 2022). Children under ten receive two doses four weeks apart at the time of initial vaccination. Because influenza remains a relevant cause of febrile respiratory illness even after vaccination (Klein 2007), contacts in the private and medical sectors should also be vaccinated annually. As higher immunogenicity seems achievable with adjuvanted vaccines (Durier 2013), we believe these should be preferred, especially in PLWH with poor immune status. Tetravalent vaccines, according to the antigen combination currently recommended by WHO, which contain influenza A strains and the B strains of the Victoria and Yamagata lineages, are recommended (STIKO 2022a, EACS 2022). Due to a slight superiority of vaccine efficacy in older people, a tetravalent high-dose vaccine with the current antigen combination recommended by WHO is now recommended for persons over 60 in some countries (STIKO 2022a).

Hepatitis B: All PLWH with negative HBV serology should be vaccinated (Bailey 2008). However, the overall effectiveness of hepatitis B vaccination is reduced (van den Berg 2009). Hepatitis A vaccination indications should be assessed beforehand, as the combination vaccine may be more immunogenic (van der Wielen 2006). Depending on current CD4 T-cells, CD4 nadir, and other factors such as viral load, sex, and age, sufficient anti-HBs titers are achieved in only 20–70%, most likely in those PLWH with > 350 CD4 T-cells/µl and undetectable viral load (Okwen 2014). Multiple and/or higher doses and more effective adjuvants have been successful (Whitaker 2012). Although an optimal vaccination strategy has not yet been clearly defined, there is consensus regarding the following (BHIVA 2015, EACS 2022):

- If seronegative, vaccination is recommended as early as possible after HIV diagnosis
- Check vaccination success (anti-HBs level) 4–8 weeks after the last dose or after vaccinations in childhood or the past.
- re-vaccination in case of missing or suboptimal vaccination success (in some countries, anti-HBs < 100, in others < 10 IU/l).

Most guidelines initially recommend the regular vaccination schedule with three doses of 10–20 µg antigen. In the UK, a 4-dose vaccination schedule (0, 1, 2, and 6 months) is recommended (Geretti 2016). Anti-HBs should be monitored annually if CD4 T-cell count < 350/µl and/or HIV viral load control is inadequate (Geretti 2016). In case of non-response to standard vaccination, the following options are possible or recommended:

- If anti-HBs titer is > 10 but < 100 IU/L, one booster vaccination (EACS 2022) with a follow-up antibody level check.
- If the anti-HBs titer is < 10 IU/l, repeat the vaccination cycle with 3–4 applications

at months 0, 1, (2), and 6 (EACS 2022). Double-dose or the high dose vaccine (HBVaxPro 40 µg) shows response rates of 80–90% (Launay 2011+2016) and could be considered.
- The first vaccination cycle with 4 doses of an ASO4C-adjuvanted vaccine (Fendrix®) could also be considered. PLWH with prior non-response showed an excellent vaccine response at 95% and 82%, a highly protective response with anti-HBs > 100 IU/L (de Silva 2014).
- Another possibility is a vaccination cycle with three applications (0, 1, and 6 months) with the combination vaccine (Twinrix®) in a double-dose; vaccination response is 95% (Cardell 2008).

Individuals who still do not show an adequate vaccine response should be serologically tested for HBV annually and receive TDF- or TAF-based ART, as it is protective regarding HBV (EACS 2022).

There are now two other vaccines that show improved response in the elderly and those with underlying chronic diseases compared to the standard vaccine (Engerix B®):

1. The adjuvanted recombinant vaccine Heplisav-B® (EU approval in 2021) is given only twice for primary immunization at months 0 and 1 (Jackson 2018).
2. PreHevbri® is a recombinant vaccine with the three antigens S, pre-S1, and pre-S2 HBsAg (Vesikari 2021), now licensed in Europe. Although published data in PLWH are still lacking for both vaccines, they are attractive candidates, especially for non-responders.

The management of "isolated" anti-HBc detection (negative HBs antigen, anti-HBs < 10 IU/l), a frequent serological constellation in HIV infection (14–44%), is controversial. The reasons could be either false positive results or loss of anti-HBs after infection or occult hepatitis B (positive HBV DNA with negative HBs antigen). Success rates in PLWH with three vaccinations were 40% (Chakvetadze 2010) and 52% (Piroth 2016), respectively, vs. 24% after one vaccination (Morsica 2017). Three vaccinations can increase the response. However, vaccination is not generally recommended for the constellation of isolated anti-HBc (EACS 2022).

Hepatitis A has an increased incidence among PLWH (Fonquernie 2001). In recent years, outbreaks have occurred among MSM in major European cities (Werber 2017). Vaccination status or serostatus should be checked in MSM; vaccination is recommended in specific populations at risk (travelers, MSM, IVDU, hepatitis B or C coinfection, chronic liver disease, and close contact with children) (EACS 2022). A monovalent vaccine is usually recommended. Due to the frequent lack of response, especially in those with poor immune status, the following dose intervals are recommended: three doses at months 0, 1, and 6 for CD4 T-cell counts < 350/µl; or two doses at months 0 and 6–12 for CD4 T-cell counts > 350/µl (Tseng 2013, Ehl 2018). Combination vaccination with hepatitis B is less effective than mono-vaccine when CD4 T-cells are low and viremia is present (Jimenez 2013). Success should be monitored: antibody levels > 20 mIU/mL are considered protective (Ehl 2018); below that, a booster with the monovalent vaccine is recommended.

Measles: Because measles is often severe (Kaplan 1992), all PLWH without a history of vaccination or infection should be vaccinated twice, at least one month apart, if possible. Vaccination protection should also be considered when traveling abroad (see *HIV and Travel*). Vaccination is possible from CD4 T-cells > 200/µl (> 14%) (different cut-offs in children) with absent or only mild clinical HIV symptoms. Primarily, the MMR combination vaccine is used (live vaccine!). Depending on the risk, post-exposure immunoglobulins are indicated in some situations (STIKO 2022a).

Human papillomavirus (HPV): Vaccination is now one of the standard vaccinations for female and male adolescents aged 9–17 years. However, this recommenda-

tion does not consider sexually active people aged >17 or high-risk groups (especially MSM). In the United States, vaccination is recommended for all adolescents/adults up to age 26 (Kim 2017). EACS recommends vaccination for all PLWH up to age 45 (EACS 2022). A study in MSM showed a significant decrease in intraepithelial neoplasia (AIN) for the quadrivalent vaccine, potentially reducing the incidence of anal carcinoma (Palefsky 2011+2017). Due to the lack of recommendations in some countries, in PLWH or persons at increased risk (e.g., MSM), vaccination can only be performed after application to the health insurance company or as a pay-as-you-go service. The 9-valent vaccine is preferred.

Varicella/herpes zoster: Similar to measles, varicella may be life-threatening in PLWH (Perronne 1990). Individuals without a history of varicella or zoster should be serologically screened and vaccinated if CD4 T-cells are above 200/µl (Geretti 2016, Rubin 2014). Vaccine complications can be treated with acyclovir. Vaccine viruses can reactivate as zoster, but this occurs less frequently than with wild virus. Herpes zoster, a complication after chickenpox infection, occurs much more frequently in PLWH than in uninfected persons (Jansen 2013). The adjuvanted inactivated vaccine (Shingrix®) is recommended for all persons >60 years of age and persons with immunosuppression, including PLWH, >50 years of age. Immunogenicity and tolerability have been shown in PLWH (Berkowitz 2015).

Meningococci: The risk of invasive meningococcal infections increases in PLWH (Miller 2014, Cohen 2011). In some countries, the 4-valent conjugate vaccine (ACWY) (usually one vaccination, two at two-month intervals if CD4 T-cell count < 200/µl) and meningococcal B vaccine (2–3 doses according to vaccine manufacturer) are recommended for persons with immunodeficiency (Ehl 2018). Because clusters of severe infections have occurred among MSM in several major cities, vaccination may also be considered for high-risk HIV-negative individuals, e.g., gay events like parades (Simon 2013). Meanwhile, there is also evidence that meningococcal B vaccination provides some protection against *Neisseria gonorrhoeae* (Wang 2022), which may become interesting in PrEP counseling. Notably, only the 4CMenB vaccine (Bexsero®) leads to potential cross-protection against gonorrhea (Ruiz Garcia 2021). Meningococcal vaccination is essential in travel medicine (see *HIV and travel*).

COVID-19: Vaccines against SARS-CoV-2 have a good protective effect against severe COVID-19 or death. There are currently eight vaccines licensed in the EU (as of July 2023):

- two mRNA vaccines (BioNTech/Pfizer's Comirnaty® and Moderna's Spikevax®),
- two vector-based vaccines (AstraZeneca's Vaxzevria® and Janssen-Cilag's Jcovden® (previously COVID-19 Vaccine Janssen)),
- an inactivated, adjuvanted protein vaccine from Novavax (Nuvaxovid®),
- a recombinant, adjuvanted protein vaccine (VidPrevtyn Beta®),
- a recombinant, adjuvanted protein vaccine (Bimervax®) and
- an inactivated, adjuvanted whole-virus-containing vaccine (Valneva®).

Please refer to updated national recommendations and manufacturer information for individual approvals and dosing intervals. In PLWH with suppressed viral load and CD4 T-cell counts > 500/µl, vaccination response, humoral immune response, and tolerability are comparable to the general population (Levy 2021, Brumme 2022, Hensley 2022). In case of significant immunosuppression (CD4 T-cell count < 200/µl), (multiple) booster vaccinations may be necessary (EACS 2022).

Respiratory Syncytial Virus (RSV): RSV infections substantially cause severe respiratory illness, especially in older adults. In May 2023, the FDA approved the first vaccines to prevent RSV-associated lower respiratory tract disease in adults aged

≥ 60 years. RSV vaccines have demonstrated moderate to high efficacy in preventing RSV-associated respiratory illness and potentially lower morbidity and mortality among older adults. RSV vaccines should be administered once, preferentially given before the seasonal peak of RSV infections (Melger 2023). Data concerning PLWH are lacking. For older PLWH, it seems advisable to follow national guidelines.

Mpox: PLWH represented about 38–50% of the 2022 global Mpox outbreak cases. Severe complications and deaths were more common, especially in individuals with a CD4 T-cell count of < 100/µl. The mortality was around 14% in persons with CD4 counts < 200/µL and nearly 30% in those with CD4 counts < 100/µl (Orkin 2023). Smallpox vaccines are considered to be effective in providing protection against Mpox. The modified vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine (Imvamune®, Imvanex® or Jynneos®) is a live, non-replicating, modified vaccinia vaccine that is approved for use in Europe. Its use in PLWH is safe, although vaccine response in those with uncontrolled viremia or CD4 < 100 has not been established. Two vaccinations at least four weeks apart are recommended. Usually, one vaccination is sufficient for those vaccinated against smallpox in the past. PLWH should receive two booster vaccinations according to the EMA product information for Imvanex. According to the author, this applies especially to those with CD4 T-cell counts < 200/µL. Although there is some evidence that the MVA-BN vaccination induces only low levels of MPXV-neutralizing antibodies in healthy adults, the correlation of these for the protection of disease remains unclear (Zaeck 2023). Case-control studies revealed an adjusted vaccine efficacy (VE) against Mpox of 75.2% for partial and 85.9% for complete vaccination (Dalton 2023). Additionally, another large case-control study showed an estimated adjusted vaccine effectiveness of 66% for two doses and 35% for one amount, respectively (Deputy 2023). As these results suggest better protection of the two-dose vaccination route, some experts recommend the two-vaccine route, irrespective of former vaccinations against smallpox, in all PLWH at risk for Mpox. The following tables provide an overview of the current recommendations.

Table 1: Special features and rationale for selected infections (adapted from EACS 2022). For explanations, see the text.

Infection	Vaccination rationale/recommendation
Influenza	More frequent occurrence of pneumonia. It is explicitly recommended for all PLWH.
Hepatitis A	Indication vaccination (travel, MSM, IVD, active hepatitis B or C infection)
Hepatitis B	Infection risk and pathways as for HIV. HIV accelerates the progression of liver disease–generally, all HBV-seronegative PLWH.
Pneumococcus	More common invasive disease with severe course. It is recommended for all PLWH.
Meningococci	Increased incidence. All PLWH (MenACWY and B).
Herpes zoster/ VZV	Incidence and severe courses are more common with both chickenpox and herpes zoster. HZV vaccination is recommended from age 50.
HPV	Transmission routes similar to HIV. The incidence of cervical and anal carcinoma are increased.
Hemophilus influenzae type b	No longer generally recommended. Increased incidence only within the pre-HAART era

Table 2: Standard, indicated, and travel vaccinations (adapted from Härter 2016, EACS 2022). See also texts and specialized information.

Vaccination against	Vaccination schedule	Booster vaccination
Standard vaccinations		
Tetanus/ diphtheria	Adults: Next Td vaccination once as Tdap combination vaccination	Every ten years
Pertussis	Next Td vaccination, once as a Tdap combination vaccination	None, only for, e.g., women of childbearing age, health care workers every 10 years. Pregnant women at every pregnancy (beginning of the 3rd trimester)!
Polio	Primary immunization according to national guidelines	Once after basic immunization
Measles/Mumps/ Rubella*	2 vaccinations for those born after 1970, minimum interval 4 weeks	None
Varicella*	2 doses at intervals of 6–8 weeks	None
Rotavirus	Recommended for infants	None
Indication vaccinations are recommended for all PLWH		
Hepatitis A	0 and 6–12 months, 0, 1 and 6 months, respectively	After > 25 years
Hepatitis B	0, 1, and 6 months, or rapid immunization days 0/7/21 and 12 months)	Every 10 years or none
Herpes zoster (age > 50 years)	2 vaccinations at an interval of 2–6 months	Unclear
Influenza	Annually	Annually
Meningococcal (ACW135Y), tetra-valent conjugate vaccine	Once or twice in PLWH (interval > 2 months)	After 5 years?
Meningococcal group B	2–3 vaccinations (according to age and manufacturer, see technical information)	Unclear
Pneumococcus	Sequentially with PCV13, PCV15, or PCV20, followed by PPSV23 after 6–12 months (only after PCV132 and PCV15)	Every 5 years
SARS-CoV-2/ COVID-19	At least 3 vaccinations, preferably mRNA vaccine	Annually?
Indication or travel vaccinations, which may be indicated according to risk		
Cholera	2 vaccinations at intervals of > 1 week to < 6 weeks	Every 2 years
TBE	2 vaccinations at 1–3 month intervals and 1 vaccination after 5–12 months or rapid immunization	Every 3–5 years

Table 2: Continuation

Vaccination against	Vaccination schedule	Booster vaccination
Human papillomaviruses	2 or 3 vaccinations at 6 month intervals (0, 1, and 6 months).	None
Japanese encephalitis	2 vaccinations before departure (days 0/28) or rapid immunization (0 and 7), preferably combined with rabies vaccination	In case of renewed stay in an endemic area 12 months after primary immunization
Rabies	1 vaccination each on days 0/7/28 or 0/7/21 or rapid immunization (0/3/7), preferably in combination with Japanese encephalitis. Alternatively, the WHO schedule with 2 vaccinations (0 and min. 7 days) Post-exposure: active and passive according to exposure level and national recommendations.	After 1 year (rabies vaccine HDC) or 2–5 years (Rabipur®). After risk contact and successful primary immunization: 2 further active vaccinations (days 0/3)
Typhoid (i.m.)	Once	After 3 years
Typhoid (oral)*	1 capsule on days 1/3/5	3 years
Yellow fever*	Once	For PLWH, every 10 years
Mpox	2 vaccinations at intervals of > 4 weeks	Unclear
Dengue Fever	2 vaccinations at intervals of 3 months	Unclear
Respiratory syncytial virus	Once	Unclear

*NOTE: Live vaccines are contraindicated in people with CD4 T-cells < 200/µl (14%).

Links

- Advisory Committee on Immunization Practices (ACIP): list of available recommendations at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- Departmerntt of Health (UK). Immunisation Against Infectious Disease – "The Green Book": www.gov.uk/government/publications/green-book-the-complete-current-edition
- British HIV Association (for HIV patients and others): www.bhiva.org
- WHO: www.who.int/immunization/en

Literature

Anema A, Mills E, Montaner J, Brownstein JS, Cooper C. Efficacy of influenza vaccination in HIV-positive patients: a systematic review and meta-analysis. HIV Med 2008;9:57-61.

Bailey CL, Smith V, Sands M. Hepatitis B vaccine: a seven-year study of adherence to the immunization guidelines and efficacy in HIV-1-positive adults. Int J Infect Dis 2008;12:e77-83.

BHIVA-2015-Vaccination Guidelines: British HIV Association guidelines on the use of vaccines in HIV-positive adults 2015. https://www.bhiva.org/file/NriBJHDVKGwzZ/2015-Vaccination-Guidelines.pdf

Berkowitz EM, Moyle G, Stellbrink HJ, et al. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized, placebo-controlled study.

Brumme ZL, Mwimanzi F, Lapointe HR, et al. Humoral immune responses to COVID-19 vaccination in people living with HIV receiving suppressive antiretroviral therapy. NPJ Vaccines 2022, 7:28.

Cardell K, Akerlind B, Sallberg M, Fryden A. Excellent response rate to a double dose of the combined hepatitis A and B vaccine in previous nonresponders to hepatitis B vaccine. J Infect Dis 2008, 198:299-304.

CDC. General Recommendations on Immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2011;60:1-64.

CDC. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2012;61:816-9

CDC. Revised surveillance case definition for HIV infection—United States, 2014. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports. 2014;63(Rr-03):1–10

Chakvetadze C, Bani-Sadr F, Le Pendeven C, et al. Serologic response to hepatitis B vaccination in HIV-Infected patients with isolated positivity for antibodies to hepatitis B core antigen. Clin Infect Dis 2010; 50:1184–6.

Cohen C, Singh E, Wu HM, et al. Increased incidence of meningococcal disease in HIV-infected individuals associated with higher case-fatality ratios in South Africa. AIDS 2010, 24:1351-60.

Dalton AF, Diallo AO, Chard AN, et al., Estimated Effectiveness of JYNNEOS Vaccine in Preventing Mpox: A Multijurisdictional Case-Control Study — United States, August 19, 2022–March 31, 2023. MMWR 2023, 72:553–558.

Deputy NP, Deckert J, Chard AN, et al. Vaccine Effectiveness of JYNNEOS against Mpox Disease in the United States. N Engl J Med 2023; 388:2434-2443.

de Silva TI, Green ST, Cole J, et al. Successful use of Fendrix in HIV-infected non-responders to standard hepatitis B vaccines. J Inf 2014, 68:397-9.

Durier C, Desaint C, Lucht F, et al. Long-term immunogenicity of two doses of 2009 A/H1N1v vaccine with and without AS03(A) adjuvant in HIV-1-infected adults. AIDS 2013, 27:87-93.

EACS Treatment Guidelines Version 11.1 – October 2022. https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf

Ehl S, Bogdan C, Niehues T et al. Impfen bei Immundefizienz. Anwendungshinweise zu den von der Ständigen Impfkommission empfohlenen Impfungen. Bundesgesundheitsbl 2018; 61:1034–1051

Fonquernie L, Meynard JL, Charrois A, et al. Occurrence of acute hepatitis A in patients infected with HIV. Clin Infect Dis 2001;32: 97-9.

European Medical Agency (EMA) product information Imvanex. https://www.ema.europa.eu/en/documents/product-information/imvanex-epar-product-information_en.pdf

Geretti AM, Brook G, Cameron C, et al. British HIV Association Guidelines on the Use of Vaccines in HIV-Positive Adults 2015. HIV Med 2016; 17(Suppl 3: S2–S81

Härter G, Grüner B. Better prognosis: when and which screening methods and immunizations in HIV-infected people. MMW Fortschr Med 2013, 155 Suppl 1:32-5.

Härter G, Manfras BJ. Impfungen und Prophylaxe Reisemedizinische Beratung für HIV-Patienten. MMW Fortschr Med 2016, 158 Suppl 1:38-42.

Hensley KS, Jongkees M, Geurts van Kessel CH et al. SARS-CoV-2 vaccine immunogenicity in PLWH in the Netherlands. Abstract 292, CROI 2022.

Hu Z, Luo Z, Wan Z et al. HIV-associated memory B cell perturbations. Vaccine 2015; 33: 2524–2529

Jackson S, Lentino J, Kopp J, et al. Immunogenicity of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant compared with a licensed hepatitis B vaccine in adults. Vaccine. 2018 Jan 29;36(5):668-674.

Jansen K, Haastert B, Michalik C, et al. Incidence and risk factors of herpes zoster among hiv-positive patients in the german competence network for HIV/AIDS (KompNet): a cohort study analysis. BMC Infect Dis 2013 Aug 10;13:372.

Jimenez HR, Hallit RR, Debari VA, Slim J. Hepatitis A vaccine response in HIV-infected patients: are TWINRIX and HAVRIX interchangeable? Vaccine 2013; 31:1328-33.

Kaplan LJ, Daum RS, Smaron M, McCarthy CA. Severe measles in immunocompromised patients. JAMA 1992;267:1237-41.

Kim DK, Riley LE, Harriman KH, et al. Recommended immunization schedule for adults aged 19 years or older, United States, 2017. Ann Intern Med 2017; 166:209–18.

Klein MB, Lu Y, DelBalso L, Coté S, Boivin G. Influenzavirus infection is a primary cause of febrile respiratory illness in HIV-infected adults, despite vaccination. Clin Infect Dis 2007, 45:234-40.

Launay O, van der Vliet D, Rosenberg AR, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. JAMA 2011, 305:1432-40.

Launay O, Rosenberg AR, Rey D, et al. Long-term Immune Response to Hepatitis B Virus Vaccination Regimens in Adults With Human Immunodeficiency Virus 1: Secondary Analysis of a Randomized Clinical Trial. JAMA Intern Med 2016, 176:603-10.

Lee KY, Tsai MS, Kuo KC, et al. Pneumococcal vaccination among HIV-infected adult patients in the era of combination antiretroviral therapy. Hum Vaccin Immunother 2014; 10:3700-10.

Levy I, Wieder-Finesod A, Litchevsky V, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in people living with HIV-1. Clin Microbiol Infect .2021, 1851-1855.

Lin JC, Nichol KL. Excess mortality due to pneumonia or influenza during influenza seasons among persons with AIDS. Arch Int Med 2001;161:441-6.

Malin JJ, Wörmann B, Kluge S, et al. S1-Leitlinie SARS-CoV-2 Prä-Expositionsprophylaxe. Available at: https://www.awmf.org/uploads/tx_szleitlinien/092-002l_S1_SARS-CoV-2_Prae-Expositionsprophylaxe_2022-05_01.pdf

Melgar M, Britton A, Roper LE, et al. Use of Respiratory Syncytial Virus Vaccines in Older Adults: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023 of the Advisory Committee on Immunization Practices — United States, 2023. MMWR, July 21, 2023, Vol. 72, No. 29: 793-801.

Menson EN, Mellado MJ, Bamford A, et al. Paediatric European Network for Treatment of AIDS (PENTA) Vaccines Group; PENTA Steering Committee; Children's HIV Association (CHIVA). Guidance on vaccination of HIV-infected children in Europe. HIV Med 2012;13:333-6;e1-14.

Miller L, Arakaki L, Ramautar A, et al. Elevated risk for invasive meningococcal disease among persons with HIV. Ann Intern Med 2014;160:30-7.

Mitjà O, Alemany A, Marks M, et al. Mpox in people with advanced HIV infection: a global case series. Lancet 2023, 401(10380):939-949.

Morsica G, Bagaglio S, Spagnuolo V, et al. Immune response to hepatitis B vaccination in HIV-positive individuals with isolated antibodies against hepatitis B core antigen: Results of a prospective Italian study. PLoS One. 2017 Sep 1.

Nunes MC, Madhi SA. Safety, immunogenicity and efficacy of pneumococcal conjugate vaccine in HIV-infected individuals. Hum Vaccin Immunother 2012;8:161-73.

Okwen MP, Reid S, Njei B, Mbuagbaw L. Hepatitis B vaccination for reducing morbidity and mortality in persons with HIV infection. Cochrane Database Syst Rev 2014;10:CD009886.

Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. NEJM 2011, 365:1576-85.

Palefsky JM. HPV-associated anal and cervical cancers in HIV-infected individuals: Incidence and prevention in the antiretroviral therapy. Curr Opin HIV AIDS 2017, 12: 26–30.

Perronne C, Lazanas M, Leport C, et al. Varicella in patients infected with the HIV. Arch Dermatol 1990;126:1033-6.

Piroth L, Launay O, Michel ML, et al. Vaccination Against Hepatitis B Virus (HBV) in HIV-1-Infected Patients With Isolated Anti-HBV Core Antibody: The ANRS HB EP03 CISOVAC Prospective Study. J Infect Dis 2016, 213:1735-42.

Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host. CID 2014;58:e44-e100.

Ruiz García Y, Sohn, WY, Seib KL, et al. Looking beyond meningococcal B with the 4CMenB vaccine: the Neisseria effect. npj Vaccines 2021, 6, 130. https://doi.org/10.1038/s41541-021-00388-3

Simon MS, Weiss D, Gulick RM. Invasive meningococcal disease in men who have sex with men. Ann Intern Med 2013;159:300-1.

STIKO 2022a. Ständige Impfkommission: Empfehlungen der Ständigen Impfkommission (STIKO) beim Robert-Koch-Institut 2022. Epid Bull 2022;4:3-66 | DOI 10.25646/9285.2

Tseng TY, Chang SY, Liu WC, et al. Comparative effectiveness of two doses versus three doses of hepatitis A vaccine in human immunodeficiency virus-infected and -uninfected men who have sex with men. Hepatology. 2013 May;57(5):1734-41.

van den Berg R, van Hoogstraten I, van Agtmael M. Non-responsiveness to hepatitis B vaccination in HIV seropositive patients; possible causes and solutions. AIDS Rev 2009;11:157-64.

van der Wielen M, Van Damme P, Chlibek R, Smetana J, von Sonnenburg F. Hepatitis A/B vaccination of adults over 40 years old: comparison of three vaccine regimens and effect of influencing factors. Vaccine 2006;24:5509-15.

Vesikari T, Langley JM, Segall N, et al. Immunogenicity and safety of a tri-antigenic versus a mono-antigenic hepatitis B vaccine in adults (PROTECT): a randomised, double-blind, phase 3 trial. Lancet Infect Dis 2021, 21:1271-81.

Vesikari T, Finn A, van Damme P, et al. Immunogenicity and Safety of a 3-Antigen Hepatitis B Vaccine vs a Single-Antigen Hepatitis B Vaccine: A Phase 3 Randomized Clinical Trial. JAMA Netw Open 2021, 4(10):e2128652.

Wang B, Giles L, Andraweera P, et al. Effectiveness and impact of the 4CMenB vaccine against invasive serogroup B meningococcal disease and gonorrhoea in an infant, child, and adolescent programme: an observational cohort and case-control study. The Lancet Infectious Diseases 2022, S1473-3099(21)00754-4

Werber D, Michaelis K, Hausner M, et al. Ongoing outbreaks of hepatitis A among men who have sex with men (MSM), Berlin, November 2016 to January 2017 – linked to other German cities and European countries Euro Surveill 2017, 22: 30457.

Whitaker JA, Rouphael NG, Edupuganti S, Lai L, Mulligan MJ. Strategies to increase responsiveness to hepatitis B vaccination in adults with HIV-1. Lancet Infect Dis 2012;12:966-76.

Yin Z, Rice BD, Waight P, et al. Invasive pneumococcal disease among HIV-positive individuals, 2000–2009. AIDS 2012;26:87–94.

Zaeck LM, Lamers MM, Verstrepen BE, et al. Low levels of monkeypox virus-neutralizing antibodies after MVA-BN vaccination in healthy individuals. Nat Med 2023, 29:270-278.

Zanetti AR, Amendola A, Besana S, et al. Safety and immunogenicity of influenza vaccination in individuals infected with HIV. Vaccine 2002;20 suppl 5:B29–B32.

15. HIV and travel medicine

GEORG HÄRTER

People living with HIV (PLWH) are keen to travel. According to one Danish study, about half of them took trips outside Europe; of these, only 38% received travel medicine advice before the trip (Nielsen 2014). About 20% experienced health problems during or after the trip. Other studies also found an increased risk of travel-associated infections, especially gastrointestinal infections (Salit 2005, Aung 2015). People with migrant backgrounds who visit their countries of origin, so-called "visiting friends and relatives" (VFR), are particularly at risk. They are often over-represented among PLWH (Sherrarf 2009, Schwartz 2015). Therefore, comprehensive travel medicine advice on vaccinations and prophylaxis (especially malaria) is essential. With a CD4 T-cell count < 200/µl and/or AIDS, the risk of severe infections is significantly increased and reduces the response to vaccination. It is recommended to postpone the trip until immune reconstitution (stable CD4 T-cell count > 200/µl). Planning should begin at least 6 to 8 weeks before departure. For tropical travel, travel medicine experts should be consulted. Current recommendations are provided by various websites (see links at end of chapter). Long-term travelers should familiarize themselves with the medical care available in the destination country.
ART should also be taken continuously during travel. It is essential to have sufficient antiretroviral medication to allow for a possible delayed return. Time differences should also be considered. Sometimes, there may be difficulties in carrying drugs to a destination. Medical certificates in English may help.

First-aid kit, other preventive measures

In addition to ART, further medication should also be considered. Sunscreen, plasters and bandages, wound disinfection, fever thermometer, and, if necessary, tick forceps are essential items in a first-aid kit. Medication that contains aspirin as an analgesic should be avoided, as it can increase the risk of bleeding in infections that cause thrombocytopenia, especially malaria and dengue fever. Preferred analgesics include acetaminophen, novaminsulfone, ibuprofen, or diclofenac. Anti-diarrheal agents (see section on travel diarrhea), antiemetics, antihistamines, and ointments against insect bites should also be included. Condoms are also recommended; according to one study, PLWH have only about 50% "safer sex" when traveling (Salit 2005) (see *Sexually Transmitted Infections*).
Thrombosis prophylaxis should also be discussed. This includes sufficient fluid intake (no alcohol!), exercise, and, if necessary, wearing compression stockings. Travelers with one or more risk factors for venous thromboembolism should consider graduated compression stockings and/or LMWH for flights longer than 6 hours.

Vaccinations

As part of a travel medical consultation, the vaccination status with regard to the recommended standard and indicated vaccinations should be checked and, if necessary, refreshed. It should be noted that influenza infections occur in the southern hemisphere mainly from April to September and in the tropics throughout the year. The indication for additional vaccinations depends on the destination, duration, and type of travel, but should be more generous than for healthy individuals (Chadwick 2007). Often, consultation with a tropical medical institution is advisable.

Yellow fever: The vaccination must be documented in an international (yellow) vaccination certificate ("International certificates of vaccinations and vaccination book") or a corresponding certificate in authorized vaccination centers. A potent vaccine (Stamaril®), based on the attenuated 17D vaccine virus strain, is a live chicken egg protein-based vaccine. WHO assumes lifelong vaccine protection after a single vaccination (WHO 2013). The following WHO wording is recommended in the vaccination card: "valid for life if the person is vaccinated". However, this has not yet been implemented in the entry regulations of all countries. In case of doubt, the current recommendations should be checked on the WHO homepage (WHO 2021). It is unclear whether lifelong immunity applies to PLWH (Gotuzzo 2013). German authorities recommend a booster for PLWH with appropriate indications, usually after ten years (STIKO 2022). Immunosuppression is formally a contraindication to live vaccination. People with < 200 CD4 T-cells/µl (< 14%) should not be vaccinated; above that, an increased adverse event rate is not expected (Barte 2014). In addition to good immune status, viremia is critical. With undetectable or low replication, the response is usually good (Pacanowski 2012), and vaccination is recommended only after ART initiation with stable HIV suppression. Another limitation of yellow fever vaccination is an age > 60 years, as an increased rate of side effects, including neurotropic and viscerotropic side effects, has been observed. If vaccination is not possible for medical reasons, an exemption certificate should be issued ("cannot be vaccinated against yellow fever for medical reasons").

Hepatitis A: Vaccination is not only very relevant when traveling to tropical countries but also when traveling to the Mediterranean or Eastern Europe (Nothdurft 2007). It has a rapid uptake, and the protective effect occurs after about 10–14 days, while the incubation period of hepatitis A is relatively long (15–50 days). Passive immunization with immunoglobulins is only indicated in exceptional cases. The duration of protection after a single vaccination is 6–12 months, then the booster > 25 years. Combination vaccines with hepatitis B and typhoid fever are available (see Table 2).

Rabies: There are several vaccines licensed in Europe, but the regimens differ slightly (see Table 2, chapter *Vaccinations*). Neutralizing antibodies persist for longer than ten years after primary immunization. Therefore, WHO no longer recommends routine boosters for travelers. Studies have also shown that a shortened vaccination schedule (0, 3, and 7 days) provides good vaccine protection, at least in the short term; however, it should be boostered before traveling again with potential rabies exposure after one year (Cramer 2016). However, data on the shortened vaccination schedule in PLWH are lacking. Another option is the so-called "WHO schedule" with only two doses (days 0 and 7), but explicitly only in people without immunosuppression. The author believes that the shortened "WHO regimen" and "rapid vaccination regimen" should not be preferred in PLWH because of the lack of data. As an alternative to pre-exposure immunization, post-exposure immunization can be performed, but it is not always available everywhere, especially in rural areas. Post-exposure prophylaxis must also be given after previous prophylactic vaccination, but only two active immunizations and no passive immunizations are necessary.

Typhoid fever: is endemic, especially in countries with poor hygiene and sanitary conditions. Especially on the Indian subcontinent and in Southeast Asia, the risk of infection with *Salmonella typhi is* increased. Various vaccines are available in Europe: the parenteral polysaccharide vaccine Typhim® or Typherix® and the oral live attenuated vaccine Typhoral®. For the latter, mucosal immunity is also elicited so that a limited protective effect for *Salmonella paratyphi* A+B is also postulated. Live vaccines are contraindicated with a CD4 T-cell count < 200/µl (< 14%), and a 4-week inter-

val should be maintained between them and other live vaccines (e.g., yellow fever). The overall protective efficacy for both vaccines is limited (a 3-year protection rate of approximately 55% for Typhim® 2-year protection rate for Typhoral® about 58%) (Anwar 2014).

Japanese encephalitis: This arthropod-borne flavivirus infection is endemic in large parts of Asia, especially Southeast and East Asia. It is usually asymptomatic or with flu-like courses but rarely with severe neurological symptoms. The risk of infection is increased, especially in rural areas and during the rainy season, but is generally low in the usual tourist destinations. Vaccination (Ixiaro®) is recommended, especially for long-term stays in rural endemic areas (> 1 month). Risk factors are age > 50 years, diabetes mellitus, arterial hypertension, immunodeficiency (!), chronic kidney disease, and homozygosity for CCR5 Δ32. Rapid immunization (0 and 7 days) has been shown to have a protective effect, as it has for rabies (Cramer 2016), but data are lacking in PLWH. The conventional vaccination schedule should be preferred.

TBE: Tick-borne encephalitis (TBE) is caused by flaviviruses. Transmission usually occurs via tick bites. There are three subtypes: a European (FSME), a Siberian (RSSE), and a Far Eastern subtype. Therefore, vaccination is recommended for risk areas in Europe and for stays with tick exposure (e.g., outdoor activities) in Eastern Europe and Central Asia. Two vaccines with slightly different vaccination schedules are available in Europe (following manufacturer's instructions). The primary immunization (3 vaccinations) should always be carried out with the same vaccine; booster vaccinations can also be carried out with an alternative preparation.

Cholera: Two vaccines (Dukoral® and Vaxchora®) are available in Europe. They are well-tolerated, oral inactivated vaccines. Vaccination is generally recommended for travel to areas with current outbreaks. A certificate is required in some cases for entry into certain countries. The induced antitoxic mucosal antibodies in the gut also partially protect against enterotoxic *E. coli* (ETEC), a common pathogen of traveler's diarrhea. However, a meta-analysis failed to demonstrate a sufficient protective effect against ETEC-related traveler's diarrhea (Ahmed 2013). Vaccination must be weighed on an individual basis.

Meningococci: Outbreaks occur mainly in the dry season (January to May) in the so-called "meningitis belt" in Africa. Knowledge of the worldwide distribution of different serotypes is vital for vaccination recommendations: in Africa, predominantly serotypes are A, less frequently C, X, W-135. In Europe, North America, Australia, and New Zealand, B and C predominate (Harrison 2009). In travel medicine, the tetravalent conjugate vaccine against A, C, W-135, and Y (Nimenrix® or Menveo®) should always be used; the polysaccharide vaccines should be avoided. Vaccination is recommended for travel to the "meningitis belt", to countries with recent outbreaks, and for close contact with the local population, e.g., medical personnel and development workers. Vaccination against A, C, W-135, and Y is mandatory for pilgrims to Mecca. Vaccination against meningococcal B (Bexsero® or Trumenba®) may be helpful for travel to European countries, North America, and New Zealand.

Polio: The national authorities usually recommend primary immunization and a single booster. However, when traveling to different countries, a booster vaccination may be necessary for individual protection and to prevent the export of circulating virus strains. Poliovirus transmission is predominantly fecal-oral. Of the original circulating wild polioviruses (WPV), only WPV-1 still exists. WPV-1 is endemic in Afghanistan and Pakistan, as well as in Malawi. In addition to WPV-1, mutant vaccine-derived polioviruses (cVDPV) circulate in many countries, for example, an

outbreak of cVDPV-2 in Nigeria with a spread in neighboring countries. WHO updates the list of countries with special requirements every quarter (WHO 2022). The following table summarizes the recommendations (WHO 2022).

Table 1: Country-specific recommendations for polio.

Indication	Countries	Vaccination recommendation
WPV1-endemic cVDPV1-3	Afghanistan, Malawi, Pakistan cVDPV-1: Yemen, Madagascar cVDPV-3: Israel, Palestine cVDPV-2: Afghanistan, Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Djibouti, D.R. Congo, Egypt, Ethiopia, Gambia, Guinea, Guinea-Bissau, Iran, Liberia, Madagascar, Mauritania, Mozambique, Niger, Nigeria, Pakistan, Rep. Congo, Senegal, Sierra Leone, Somalia, South Sudan, Tajikistan, Uganda, Ukraine, Yemen	A detection requirement exists for WP1 cVDPV-1 and cVDPV-3 in endemic countries. •Stay ≤ 4 weeks: booster vaccination if the last vaccination was over ten years ago •Stay > 4 weeks: Vaccination should be only four weeks to 12 months ago when leaving the affected country
Vulnerable, politically unstable, or surveillance not secured	Algeria, Bosnia-Herzegovina, Burundi, China, Côte d'Ivoire, Gabon, Ghana, Haiti, Indonesia, Iraq, Kenya, Kiribati, Comoros, Laos, Libya, Malaysia, Mali, Myanmar, East Timor, Papua New Guinea, Philippines, Romania, Sudan, Syria, Togo, Vanuatu, Venezuela	Booster vaccination if the last vaccination was more than 10 years ago
Other	Saudi Arabia	Vaccination is compulsory for entry from risk regions. The vaccination must be 4 weeks to 12 months ago

The vaccination should be documented in the vaccination certificate as an international certificate (analogous to yellow fever). Polio booster shots – also in the context of travel medicine – are considered indicated vaccinations and can, therefore, be carried out at the expense of statutory health insurance.

Influenza: is often forgotten in travel medicine. Possibly, influenza vaccination is the most essential travel vaccination. The seasonal activity in the southern hemisphere in the northern summer months should be considered! Therefore, an updated vaccine should also be ordered and vaccinated for travelers to the southern hemisphere via the international pharmacy.

COVID-19: Since the beginning of the COVID-19 pandemic, international travel has played an essential role in the spread and infection of SARS-CoV-2. Completing vaccination protection according to the current national recommendations is strongly recommended (see *Vaccinations*). The entry restrictions, approved vaccines, and vaccination schedules valid in the destination country should be checked on the website of the National Foreign Offices. Vaccines approved in the EU are recognized in all countries with few exceptions.

Ebola: There are now two vector virus vaccines against the Zaire ebola variant. These are relevant for medical personnel in an outbreak area mission; vaccination does not affect tourist travel.

Mpox: Smallpox vaccines are considered effective in protecting against Mpox. Two vaccinations with the modified vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine (Imvamune®, Imvanex® or Jynneos®) should be recommended to PLWH, especially if traveling abroad to Gay Pride events (see *Vaccinations* for more details).

Dengue Fever: Dengue is a mosquito-borne viral infection that is common in (sub-)tropical countries. Dengue outbreaks tend to have seasonal patterns, with transmission often peaking during and after rainy seasons. Since the beginning of 2023, dengue outbreaks have been recorded in the WHO Region of the Americas, with the highest number of dengue cases in Brazil, Peru, and Bolivia. In the past, about 70% of cases occurred in Asia, especially in Southeast Asia. Due to global warming, dengue spreads to new areas, including Europe (WHO 2023).

Available vaccines: The first approved vaccine was a live-attenuated, quadrivalent vaccine (Dengvaxia®). Due to several severe dengue cases after wild-type virus infection following the vaccination (Halstead B 2017), it is now licensed only in individuals 6 to 45 years of age with test-confirmed previous dengue infection. The vaccine is not licensed and not recommended for regular travelers to endemic countries. Since the end of 2022, another live-attenuated, tetravalent vaccine has been approved in the EU (Qdenga®). Studies showed a summarized vaccine efficacy against dengue fever of 61.2% and against hospitalization due to severe dengue of 84.1% (Biswal 2019, Bsiwal 2020, Lopez-Medina 2022, Rivera 2022). Subgroup analysis revealed an insufficient efficacy against specific subtypes such as DENV-3 and -4 (Rivera 2022). In contrast to Dengvaxia®, there are no signals for severe infections after the vaccination in seronegative individuals. Therefore, a pre-vaccination test is not necessary. In approximately 50% of the vaccinated seronegative individuals, a transient viremia can be seen, followed by mild symptoms with headache, chills, and exanthema in some individuals (Tricou 2020). The vaccination schedule is two vaccinations with a time interval of 3 months. Early counseling and vaccination should be considered. There is evidence of (short-term?) vaccine efficacy of 81% after the first vaccination (Biswal 2020). It should be regarded as a live vaccine; therefore, PLWH with CD4 T-cell counts < 200/µl (< 14%) should not be vaccinated. A general recommendation of Qdenga® at this juncture is difficult. The following persons seem to profit from vaccination before traveling to dengue-endemic areas:

- Long-term or frequent travelers, e.g. professional ex-patriates
- Visiting friends and relatives from dengue-endemic areas for longer stays
- People who have already had a dengue virus infection
- People with a high risk for severe infections, e.g. older people, obese people, people with coagulation disorders, or severe chronic illness.
- Women of child-bearing potential planning a pregnancy in an endemic area.

Noteworthy, due to the live-attenuated vaccine formulation, Qdenga® is contraindicated in pregnancy. Additionally, pregnancy should be avoided for at least four weeks after the last vaccination.

Entry requirements and health insurance

In some countries, there are, unfortunately, still entry restrictions for PLWH, especially for longer stays for work or study. To avoid problems, those affected should know the entry regulations of the destination country. An overview is provided by a database (www.hivtravel.org). Travel insurance policies almost always exclude pre-existing conditions and often explicitly reject PLWH. However, travel insurance policies abroad include pre-existing HIV infection (e.g., World First).

Specific risks

Travel diarrhea

Enteric infections are the most common imported infections after long-distance travel (Steffen 2015, Schlagenhauf 2015). About 10–40% of travelers have diarrhea during a two-week stay. PLWH are at increased risk for diarrhea and pathogens such as Cryptosporidia, *Isospora belli*, and *Giardia lamblia* (Steffen 2015). The risk varies regionally: it is highest in Africa, the Indian subcontinent, Southeast Asia, and South America. The most common pathogens are bacteria; however, lambliasis (*Giardia lamblia*) is increasing in incidence and is often a relevant problem. The most common bacterial pathogens worldwide are *Campylobacter, Salmonella (non-typhi), and Shigella* (Schlagenhauf 2015). It should be noted that *Campylobacter* species are becoming increasingly resistant to quinolones (up to 90%!), especially on the Indian subcontinent and in Southeast Asia (Ricotta 2014). In addition, the selection of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae with the use of antibiotics for traveler's diarrhea is an increasing problem. In particular, the combination of loperamide and antibiotics showed evidence of ESBL in 71% of travelers' diarrhea patients in one study (Kantele 2016). In Europe, there have also been several outbreaks of enteritis in MSM with the detection of highly resistant strains of *Shigella* (ECDC 2022).

The standard recommendation, "Boil it, cook it, peel it, or forget it" makes sense, but studies have not proven the effectiveness. Additionally, in tropical countries, avoid ice cubes in bars or restaurants, as they can be contaminated. The benefit of prophylactic intake of probiotics is not proven. The prophylactic use of antibiotics, especially quinolones, is not recommended due to resistance. However, the non-absorbable antibiotic rifaximin can undoubtedly reduce the incidence of traveler's diarrhea, although there is no protection against invasive bacterial pathogens (Steffen 2015).

In addition to oral rehydration, preparations containing tannin albuminate and ethacridine lactate (Tannacomp®) are suitable for self-therapy in short, mild courses. Motility inhibitors (loperamide) may also be used temporarily, but prolonged use should be discouraged. Antibiotic self-therapy should be used in moderate or more severe courses with systemic symptoms (fever and/or bloody diarrhea). Due to the increasing quinolone resistance, especially in *Campylobacter* species, azithromycin is a good choice; relevant resistance is rare (Steffen 2015, Tribble 2007).

Malaria prophylaxis

Malaria occurs in tropical and subtropical regions of Africa, South America, Central America, and Asia. The vector mosquitoes are females of the *Anopheles* species. The most common forms are malaria tropica and malaria tertiana. The latter is essential to consider because late relapses can also occur in malaria tertiana due to forms of the pathogen that can persist in the liver (hypnozoites) for up to 1 year. PLWH are at increased risk for malaria and complicated cases. On the other hand, malaria can adversely affect the course of HIV infection (Flateau 2011, van Geertruden 2014). Therefore, counseling on malaria prophylaxis is essential. The basis for this is exposure prophylaxis with consistent mosquito protection. This can reduce the risk by up to 90%. In addition, other arthropod-borne infections are also prevented, e.g., dengue fever, chikungunya, Zika virus, or tick-borne diseases. Exposure prophylaxis includes consistently using repellents on uncovered skin areas during the day and at night. Preferred repellents are those with DEET or icaridin as the active ingredient. In addition, skin-covering, light-colored clothing should be worn during the

twilight hours. Other essential measures are sleeping under mosquito nets (preferably impregnated) and/or sleeping in rooms with air conditioning. Due to widespread resistance to chloroquine and sulfadoxine/pyrimethamine, prophylaxis with atovaquone/proguanil or doxycycline is additionally recommended in high-risk areas. Mefloquine can only be recommended to a limited extent and for specific indications (e.g., long-term stays, pregnant women, children) due to neuropsychiatric side effects. However, chemoprophylaxis does not fully protect against malaria. Therefore, malaria should always be ruled out in cases of fever after a tropical stay. In some areas with low or moderate malaria risk, emergency self-treatment ("standby") is recommended as an alternative. Consider relevant interactions with antiretroviral agents (see www.hiv-druginteractions.org). Doxycycline has the lowest potential (Abgrall 2013), but phototoxicity may be problematic.
Visiting friends and relatives (VFRs) are an essential group in malaria consultation. These have frequently experienced malaria episodes in their country of origin in decreasing disease intensity and are often negligent with chemoprophylaxis. However, acquired partial immunity to malaria is lost with stays of more than six months outside the endemic areas.

Respiratory infections, TB

Respiratory infections are among the most common health problems after travel (Schlagenhauf 2015). Therefore, sufficient vaccination protection against pneumococcus and influenza (seasonal activity in the southern hemisphere in the northern summer months!) should always be ensured.
The risk of tuberculosis is significantly higher in almost all (sub-) tropical countries. An interferon assay (IGRA) is helpful before and after longer trips (Rieder 2001, Bhadelia 2007). People with reactive tests (or after known high-risk exposure) should be treated like latent tuberculosis if necessary (see *TB*). High-risk areas such as hospitals, prisons, or homeless shelters should be avoided, or appropriate masks should be worn.

Measles

According to WHO, more than 20 million cases and about 600,000 deaths worldwide in 2002. Measles occurs more frequently and is more severe in PLWH, and the virus is shed for longer, a particular problem in Africa (Moss 2006). Studies from the US showed a high mortality rate, mainly due to giant cell pneumonitis (Kaplan 1996). For non-immune PLWH, active or passive immunization is recommended before traveling to areas with an increased risk of measles (see *Vaccinations*).

Leishmaniasis

Visceral leishmaniasis (kala azar) is a feared opportunistic disease because of its life-threatening course, often delayed diagnosis, and limited treatment options (see *OI*). In northern Europe, most cases are imported from Mediterranean countries, especially during long journeys. PLWH have a higher risk of infection (Weitzel 2005), especially with CD4 T-cells below 200/µl (Kaplan 1996). Infection may be latent and not manifest until many years after exposure. Particularly in cases of poor immune status, the risk in Mediterranean countries should be underlined. To avoid it, mosquito protection measures should be followed (see above); because of the small size of the vectors, a fine-mesh mosquito net with impregnation is advisable.

Endemic mycoses

These are rare but can be life-threatening and manifest themselves even years after residence in an endemic area. Infections with *Penicillium marneffei*, *Histoplasma capsulatum,* or *Cryptococcus neoformans* are among the most common opportunistic infections in the corresponding endemic areas and are thus frequent indicator diseases (Lortholary 2013) (see *OI*). Particular exposure risks, including with dust or soil (construction sites, agriculture, gardening, or excavations), should be avoided by immunodeficient individuals. In individual cases (especially with advanced immunodeficiency), primary prophylaxis may be considered with fluconazole or itraconazole, depending on the pathogen.

Sexually transmitted infections (STDs)

Travel is associated with more frequent sexual contact and less frequent condom use (Matteelli 2001). STD risk is significantly increased (Richens 2006). Twenty-three percent of HIV-positive travelers reported sexual contact with new partners, with only 58% using a condom (Salit 2005). Travelers should be aware of STDs, and condoms should be recommended.

Other parasites

The following parasitic pathogens are relevant:

Strongyloides stercoralis, a nematode found in the tropics/subtropics, is transmitted by cutaneous invasion of larvae on contact with contaminated soil. Immunocompromised individuals may develop an often lethal "hyperinfection syndrome." It is relatively rare in PLWH; risk factors are therapy with corticosteroids or HTLV-1 infections (Toledo 2015).

Trypanosoma cruzi, the causative agent of Chagas disease, is endemic in Latin America and is transmitted by predatory bugs. Oral infections through contaminated fruit or sugarcane juice are also possible. In cases of severe immunodeficiency, chronic infection can lead to severe encephalitides, with lesions resembling cerebral toxoplasmosis in terms of image morphology (Rocha 1994).

Babesia sp. are globally occurring protozoa transmitted by ticks. Life-threatening diseases clinically resembling malaria occur frequently in immunodeficient individuals (Falagas 1996).

Free-living amoebae are inhabitants of wetlands worldwide. *Acanthamoeba sp*. and *Balamuthia mandrillaris,* as opportunistic pathogens, can cause granulomatous encephalitis and severe local infections of the skin and cornea in PLWH (Barratt 2010).

Schistosoma sp., the causative agent of schistosomiasis, is less effective in treating PLWH (Kallestrup 2006) and, like other worm infections, has a negative impact on HIV infection via chronic immune stimulation (Secor 2006). Freshwater bathing in regions with endemic schistosomiasis (especially Africa, Southeast Asia, and South America) should be discouraged.

Medical problems after the trip

Any illness that is temporally related to a trip should be clarified immediately. The rarity of many tropical diseases often leads to delayed diagnosis (Weitzel 2005). In addition, tropical diseases often manifest themselves atypically in HIV (Karp 1999).

The already broad differential diagnosis is even more complex after travel abroad and requires close cooperation between HIV specialists and tropical medicine institutions.

Links

World Health Organization, WHO: current news, country information, information on vaccinations, etc.: www.who.int

ProMedMail: International Society for Infectious Diseases page with current outbreaks: http://www.promedmail.org/

Global database in cooperation with the European Aids Treatment Group on restrictions for HIV-infected persons: http://www.hivtravel.org/

Example of travel insurance with HIV: www.world-first.co.uk

Literature

Abdolrasouli A, McMillan A, Ackers JP. Sexual transmission of intestinal parasites in men who have sex with men. Sex Health 2009;6:185-94.

Abgrall S, Le Bel J, Lele N, et al. Lack of effect of doxycycline on trough concentrations of protease inhibitors or non-nucleoside reverse transcriptase inhibitors in HIV-infected patients. HIV Clin Trials 2013, 14:313-8.

Ahmed T, Bhuiyan TR, Zaman K, et al. Vaccines for preventing enterotoxigenic Escherichia coli diarrhoea. Cochrane Data Syst Rev 2013 7:CD009029.

Anwar E, Goldberg E, Fraser A, et al. Vaccines for preventing typhoid fever. Cochrane Database Syst Rev. 2014 Jan 2;1:CD001261.

Aung AK, Trubiano JA, Spelman DW. Travel risk assessment, advice and vaccinations in immunocompromised travellers (HIV, solid organ transplant and haematopoeitic stem cell transplant recipients): A review. Travel Med Infect Dis 2015, 13:31-47.

Barratt JL, Harkness J, Marriott D, et al. Importance of nonenteric protozoan infections in immunocompromised people. Clin Micr Rev 2010;23:795-836.

Barte H, Horvath TH, Rutherford GW. Yellow fever vaccine for patients with HIV infection. Cochrane Database Syst Rev. 2014 Jan 23;1:CD010929.

Bhadelia N, Klotman M, Caplivski D. The HIV-positive traveler. Am J Med 2007, 120:574-80.

Biswal S, Reynales H, Saez-Llorens X, et al. Efficacy of a Tetravalent Dengue Vaccine in Healthy Children and Adolescents. N Engl J Med 2019, 381:2009-19.

Biswal S, Borja-Tabora C, Martinez Vargas L, et al. Efficacy of a tetravalent dengue vaccine in healthy children aged 4-16 years: a randomised, placebo-controlled, phase 3 trial. Lancet 2020, 395:1423-33.

Chadwick DR, Geretti AM. Immunization of the HIV infected traveller. AIDS 2007; 21:787-94.

Cramer JP, Jelinek T, Paulke-Korinek M, et al. One-year immunogenicity kinetics and safety of a purified chick embryo cell rabies vaccine and an inactivated Vero cell-derived Japanese encephalitis vaccine administered concomitantly. J Travel Med 2016, 23.

European Centre for Disease Prevention and Control. Increase in extensively-drug resistant Shigella sonnei infections in men who have sex with men in the EU/EEA and the UK – 23 February 2022. ECDC: Stockholm; 2022

Falagas ME, Klempner MS. Babesiosis in patients with AIDS: a chronic infection presenting as fever of unknown origin. Clin Infect Dis 1996;22:809-12.

Flateau C, Le Loup G, Pialoux G. Consequences of HIV infection on malaria and therapeutic implications: a systematic review. Lancet Inf Dis 2011;11:541-56.

Gotuzzo E, Yactayo S, Córdova E. Efficacy and duration of immunity after yellow fever vaccination: systematic review on the need for a booster every 10 years. Am J Trop Med Hyg 2013, 89:434-44.

Halstead SB. Dengvaxia sensitizes seronegatives to vaccine enhanced disease regardless of age. Vaccine 2017, 35:6355-6358. doi: 10.1016/j.vaccine.2017.09.089.

Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. Vaccine. 2009 Jun 24;27 Suppl 2:B51-63.

Hayes C, Elliot E, Krales E, Downer G. Food and water safety for persons infected with human immunodeficiency virus. CID 2003;36(Suppl 2):S106-9.

Igreja R. Travel medicine and HIV infection. Review. Int J STD AIDS 2008;19:577-80.

Kallestrup P, Zinyama R, Gomo E, et al. Schistosomiasis and HIV in rural Zimbabwe: efficacy of treatment of schistosomiasis in individuals with HIV coinfection. Clin Infect Dis 2006;42:1781–9.

Kantele A, Mero S, Kirveskari J, Lääveri T. Increased Risk for ESBL-Producing Bacteria from Co-administration of Loperamide and Antimicrobial Drugs for Travelers' Diarrhea. Emerg Infect Dis 2016, 22:117-20.

Kaplan JE, Hu DJ, Holmes KK, et al. Preventing opportunistic infections in human immunodeficiency virus-infected persons: implications for the developing world. Am J Trop Med Hyg 1996;55:1-11.

Karp CL, Neva FA. Tropical infectious diseases in HIV-infected patients. CID 1999;28:947-63.

Kendall ME, Crim S, Fullerton K, et al. Travel-associated enteric infections diagnosed after return to the United States, Foodborne Diseases Active Surveillance Network (Food- Net), 2004-2009. CID 2012 Jun;54 Suppl 5:S480-7.

Lopez-Medina E, Biswal S, Saez-Llorens X, et al. Efficacy of a Dengue Vaccine Candidate (TAK-003) in Healthy Children and Adolescents 2 Years after Vaccination. J Infect Dis 2022, 225:1521-32.

Lortholary O, Charlier C, Lebeaux D, Lecuit M, Consigny PH. Fungal infections in immunocompromised travelers. Clin Infect Dis 2013;56:861-9.

Matteelli A, Carosi G. Sexually transmitted diseases in travelers. Clin Infect Dis 2001;32:1063-7.

Moss WJ, Griffin DE. Global measles elimination. Nat Rev Microbiol 2006;4:900-908.

Nielsen US, Jensen-Fangel S, Pedersen G, et al. Travelling with HIV: a cross sectional analysis of Danish HIV-infected patients. Travel Med Inf Dis 2014, 12:72-8.

Nothdurft HD, Dahlgren AL, Gallagher EA, et al. The risk of acquiring hepatitis A and B among travelers in selected Eastern and Southern Europe and non-European Mediterranean countries: review and consensus statement on hepatitis A and B vaccination. J Travel Med 2007, 14:181-7.

Pacanowski J, Lacombe K, Campa P, et al. Plasma HIV-RNA is the key determinant of long-term antibody persistence after Yellow fever immunization in a cohort of 364 HIV-infected patients. J Acquir Immune Defic Syndr 2012, 59:360-7.

Richens J. Sexually transmitted infections and HIV among travellers: a review. Travel Med Infect Dis 2006;4:184-95.

Ricotta EE, Palmer A, Wymore K, et al. Epidemio- logy and antimicrobial resistance of international travel-associated Campylobacter infections in the United States, 2005-2011. Am J Public Health 2014, 104:e108-14.

Rieder HL. Risk of travel-associated tuberculosis. Clin Infect Dis 2001;33:393-6.

Rivera L, Biswal S, Saez-Llorens X, , et al. Three-year Efficacy and Safety of Takeda's Dengue Vaccine Candidate (TAK-003). Clin Infect Dis 2022, 75:107-17.

RKI. Infektionsepidemiologische Jahrbuch meldepflichtiger Erkrankungen für 2014. Verfügbar unter: http://www.rki.de/DE/ Content/Infekt/Jahrbuch/Jahrbuch_2014. pdf?__blob=publicationFile

Rocha A, de Meneses AC, da Silva AM, et al. Pathology of patients with Chagas' disease and AIDS. Am J Trop Med Hyg 1994;50:261-8.

Salit IE, Sano M, Boggild AK, Kain KC. Travel patterns and risk behaviour of HIV-positive people travelling internationally. CMAJ 2005;172:884-8.

Schlagenhauf P, Weld L, Goorhuis A, et al. Travel-associated infection presenting in Europe (2008-12): an analysis of EuroTravNet longitudinal, surveillance data, and evaluation of the effect of the pre-travel consultation. Lancet Infect Dis 2015, 15:55-64.

Schwartz BS, Rosen J, Han PV, et al. Immunocompromised Travelers: Demographic Characteristics, Travel Destinations, and Pretravel Health Care from the U.S. Global TravEpiNet Consortium. Am J Trop Med Hyg 2015, 93: 1110–1116.

Secor WE. Interactions between schistosomiasis and infection with HIV-1. Parasite Immunol 2006;28:597–603.

Sherrard AW, McCarthy AE. Travel patterns and health risks for patients infected with HIV. Travel Med Infect Dis 2009;7:291-5.

Steffen R, Hill DR, DuPont HL. Traveler's diarrhea: a clinical review. JAMA 2015, 313:71-80.

Toledo R, Muñoz-Antoli C, Esteban JG. Strongyloidiasis with emphasis on human infections and its different clinical forms. Adv Paras 2015;88:165-241.

Tribble DR, Sanders JW, Pang LW, et al. Traveler's diarrhea in Thailand: randomized, double-blind trial comparing single-dose and 3-day azithromycin-based regimens with a 3-day levofloxacin regimen. Clin Infect Dis 2007, 44:338-46.

Tricou V, Low JG, Oh HM, et al. Safety and immunogenicity of a single dose of a tetravalent dengue vaccine with two different serotype-2 potencies in adults in Singapore: A phase 2, double-blind, randomised, controlled trial. Vaccine 2020;38:1513-1519.

van Geertruyden JP. Interactions between malaria and human immunodeficiency virus anno 2014. Clin Microbiol Infect 2014;20:278-85.

Weitzel T, Muhlberger N, Jelinek T, et al. Imported leishmaniasis in Germany 2001-2004: data of the SIMPID surveillance network. Eur J Clin Microbiol Infect Dis 2005;24:471-6

WHO. World Health Organization. WHO Position paper on vaccines and vaccination against yellow fever. Weekly epidemiological record. 5 July 2013, 88th year. No. 27, 2013, 88, 269– 284.

WHO. World Health Organization. Countries with risk of yellow fever transmission and countries requiring yellow fever vaccination (May 2021). https://www.who.int/publications/m/item/countries-with-risk-of-yellow-fever-transmission-and-countries-requiring-yellow-fever-vaccination-(may-2021).

WHO. World Health Organization. Statement of the Thirty-first Polio IHR Emergency Committee. https://www.who.int/news/item/11-03-2022-statement-of-the-thirty-first-polio-ihr-emergency-committee.

WHO. World Health Organization. Dengue and sever dengue. Fact sheet. March 17, 2023. https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue.

16. HIV-2 infection

DIRK BERZOW AND CHRISTIAN HOFFMANN

HIV-2 is less prevalent than HIV-1, with approximately 1–2 million people infected with HIV-2 living predominantly in West Africa (Gottlieb 2018). The following summarizes the significantly limited data compared to HIV-1.

Discovery and origin

In 1986, Luc Montagnier and colleagues isolated a new human retrovirus from patients of West African origin (Guinea-Bissau and Cape Verde Islands). These patients presented clinically with the full symptoms of AIDS, but the sera did not react at all or weakly with the *env* or *gag* epitopes of HIV-1 (Clavel 1986). The virus was named HIV-2, another primate lentivirus in addition to HIV-1. At the amino acid level, there is a 60% match in the chains coding the gag and pol proteins and a 30–40% match in the chains coding for the env proteins (Guyader 1987). HIV-2 originated from a cross-species transmission of SIV from sooty mangabeys to humans in West Africa. Nine subtypes are known to date. The most common, subtype A, occurs primarily in Senegal, Gambia, Guinea-Bissau, Côte d'Ivoire, Ghana, and the Cape Verde Islands; subtype B occurs in Côte d'Ivoire, Ghana, Burkina Faso, and Mali. Subtypes C-I are extremely rare ("dead-end infections"). To date, there is no evidence of differences between subtypes with regard to clinical course or treatment (Visseaux 2016).

Epidemiology

In the country with the highest HIV-2 prevalence worldwide, Guinea-Bissau, there is a decreasing trend. In 1987, adult prevalence was estimated at 8.9%; in 2017, it was 3.4%. During the same time, the prevalence of HIV-1 increased from 0 to 4% (Jespersen 2020). Senegal, Gambia, Sierra Leone, and Côte d'Ivoire are reported to have a 1–5% prevalence. Other West African countries have a prevalence of below 1% (Visseaux 2016). In Europe, the countries with the highest HIV-2 case numbers are Portugal (with an n of approximately 2000), France (around 1200), and Spain (about 400). HIV-2 cases also occur in European countries such as Great Britain, Belgium, the Netherlands, Italy, and Germany, and countries such as Mozambique, Angola, Brazil, India (Goa region), and the United States (Berzow 2020). In the Portuguese CHLO cohort (Centro Hospitalar de Lisboa Ocidental, n=180), 64% of the individuals are female, with a mean age of 43 years at diagnosis (Perpetua Gomez, personal communication).

Diagnostics

Today's 4th generation screening tests (antibody and antigen immunoassays) contain HIV-1 and HIV-2 antigens, and HIV-2 antibodies are reliably detected. However, the time between infection and seroconversion may be several weeks longer. In addition, a lower sensitivity can be assumed for antigen detection (p26 instead of p24!). In case of a positive HIV screening test without detection of HIV-1 RNA or in case of very low HIV-1 RNA, explicit testing for HIV-2 antibodies should be performed – especially in West African patients and their potential partners. Standardized HIV-1/HIV-2 immunoblots or other antibody differentiation tests should be used as confirmation. Nucleic acid assays such as HIV-2 RNA PCR are unsuitable as confirmatory tests since there is often no measurable viral load, even without therapy.

Occasionally, it can be problematic to distinguish HIV-2 mono-infection from dual (HIV-1/HIV-2) infection. However, dual infection is rare in Europe. With modern antibody differentiation tests, their proportion was only 0.1% of new HIV-2 infections in one French study (CNdS 2017). Dual infection could be missed if HIV-1 and HIV-2 are not differentiated in the confirmatory test. In this case, ART inappropriate for HIV-2 may fail to achieve immunologic success despite a drop in HIV-1 viral load. In this case, it is advisable to reconsider dual infection and to contact specialized laboratories.

Transmission

HIV-2, like HIV-1, is transmitted sexually, perinatally, and hematogenously. However, the sexual transmission rate is 3–9 times lower (Gilbert 2003). As in peripheral blood, less virus is detectable in seminal fluid and genital secretions in HIV-2 (Gottlieb 2006). Transmission at birth or through breastfeeding is also several times less frequent (O'Donovan 2000). In the French ANRS cohort, only two vertical transmissions occurred among 223 pregnant women living with HIV-2 between 1986 and 2007, although only 57% of the women were receiving ART and 68% delivered vaginally (Burgard 2010).

Features of pathogenesis and course

Disease progression in HIV-2 infection is different from that in HIV-1. Both the proportion of "progressors" and the speed are lower. In African cohorts, many infected individuals remained clinically asymptomatic for the first few years (Berry 2002). However, this asymptomatic phase is also not indefinite. Over a more extended period, disease progression eventually occurs in most cases. In the French cohort, 6% remained asymptomatic over eight years, and 9% remained without detectable viral load over ten years (Thiebaut 2011). About 55% were already in need of treatment for disease progression at the time of diagnosis (Drylewicz 2008). In a long-term cohort study from Guinea-Bissau, 40% of 464 HIV-2-positive persons had developed AIDS after ten years, compared with 80% of 404 HIV-1-positive persons. Rates after 15 years were 50% and 90%, respectively. With HIV-2, AIDS, and death occurred after an average of 14.3 and 15.6 years, compared with 6.3 and 8.2 years with HIV-1 (Esbjörnsson 2018). In the case of progression, HIV-2 also shows the typical spectrum of opportunistic infections and AIDS disease (Jaffar 2004).

Another distinctive feature of HIV-2 is the approximately 30–100-fold lower viremia than HIV-1 (MacNeil 2007). In contrast, the amount of proviral DNA is about the same, with about 200 copies per 10,000 PBMC (Popper 2000, Matheron 2003). Replication of HIV-2 is thought to be blocked during late transcription to mRNA (Soares 2012).

In the French HIV-2 cohort, plasma RNA averaged only 1,000 copies/mL, and 52% had no detectable viral load (Matheron 2003). A plasma viral load above 1,000 copies/mL is considered high. It is a positive predictor of disease progression. PLWH with low viral load (< 100 copies/mL) are usually "non-progressors," with minimal immune activation and T cell impairment. Highly viremic individuals with HIV-2 (> 1,000 copies/mL) show no differences, immunologically or clinically, compared to people with HIV-1 (Hegedus 2014, Hansmann 2005). Because disease progression can occur in approximately 20% even without viremia (Hoenge 2019), CD4 T-cell count remains an essential parameter for monitoring (before and during therapy).

In untreated individuals, the average annual drop in CD4 T-cells is 9/µl yearly (Drylewicz 2008), about one-fifth of the usual decline in HIV-1 (Matheron 2003). This drop correlates with the viral load level and the immune activation degree

(Soares 2011). A continuous drop of more than 10% per year (Hansmann 2005) or a drop to less than 200/µl (Matheron 2003) is associated with disease progression and mortality (Schim van der Loeff 2010, Hegedus 2014). In a study from Guinea-Bissau, the CD4 T-cell count at first diagnosis of AIDS with HIV-2 was 237/µl, compared with 137/µl for HIV-1 (Esbjörnsson 2018).
Some immunological correlates have been found for the clinical differences with HIV-1 infection. For example, T cells' functionality and regenerative capacity (especially CD8 T-cells) are better preserved in HIV-2 infection. HIV-2 induces lower immune activation, lower ß2-microglobulin levels, and lower expression of apoptosis markers than HIV-1, although immune activation is similar at higher levels of viremia (Nyamweya 2013, Angin 2016, Buggert 2017). Neutralizing antibodies are often better in HIV-2 regarding breadth and binding strength (Marcelino 2012). *In vitro* tests showed a low cross-neutralization activity between HIV-2 and HIV-1 antibodies (Rodriguez 2007).

Dual infection with HIV-1 and HIV-2

Dual infections occur especially in high-incidence areas. According to one meta-analysis, mortality is similar to HIV-1 mono-infection (Prince 2014). Without treatment, HIV-1 appears to "outcompete" HIV-2 during progression: in a Senegalese cohort, both viruses were often detectable in blood and genital secretions initially. The more advanced the infection, the more likely it was that only HIV-1 was found (Raugi 2013). Superinfections are also possible. A patient from Portugal has been described, with immune recovery and virological suppression for over a decade, who presented with a severe decline in the CD4 T-cell count secondary to HIV-2 superinfection (Ceia 2019). This case suggests that HIV-2 superinfection should be considered in the presence of an unexplained and sustained decline in CD4 T-cell count in HIV-1 infection with viral load suppression.

Antiretroviral therapy for HIV-2 infection

All antiretroviral drugs were developed against HIV-1 only. Given the numerous polymorphisms in HIV-2, it is essential to note that not all agents used with HIV-1 are sufficiently adequate for HIV-2 (Ekouevi 2014, Menendez-Arias 2014, Berzow 2020).

Not effective against HIV-2 are:
- All approved NNRTIs
- The fusion inhibitor T-20 (enfuvirtide)
- The entry inhibitor fostemsavir, probably due to polymorphisms (Mendoza 2020)
- Some PIs (no efficacy of nelfinavir, ritonavir, fosamprenavir, tipranavir, insufficient efficacy of indinavir and atazanavir)

Effective against HIV-2 are:
- All NRTIs
- The PIs darunavir, lopinavir, and boosted saquinavir
- All integrase inhibitors (INSTIs)
- The co-receptor antagonist maraviroc (for R5 tropism)

For new agents, data is still scarc (only *in vitro* data):
- The INSTI cabotegravir appears to have the same activity as dolutegravir and bictegravir (Le Hingrat 2020) but is not an option for HIV-2 because of the fixed combination with the NNRTI rilpivirine.
- Ibalizumab is effective but expensive and difficult to obtain in many countries (Le Hingrat 2020).

- The capsid inhibitor lenacapavir shows activity *in vitro* (Yant 2019). However, in cell cultures, the EC50 is higher than for HIV-1. According to the SmPC (Summary of Product Characteristics), lenacapavir is "15- to 25-fold less active against HIV-2 isolates."
- The NRTTI islatravir showed good activity against HIV-2 *in vitro* (Wu 2017).
- There are no published data on maturation inhibitors.

Treatment recommendations and guidelines

Despite the modest data situation, there are now recommendations and guidelines (based on comparatively small studies, case reports, and *in vitro* data), such as:

- French guidelines from 2016 (CNdS 2016)
- British BHIVA guidelines 2021 (Reeves 2021)
- Spanish "Guidelines for Non-Endemic Regions" 2020 (Mendoza 2020)
- Recommendations for Europe of an "EU Expert Group" 2020 (Berzow 2020)
- US Guidelines (National Institute of Health 2019, New York State Department of Health AIDS Institute 2022) and
- Global guidelines (Gottlieb 2018)

A summary of these recommendations is presented below.

Monitoring before starting therapy

Plasma RNA and CD4 T-cells should be measured every 3–6 months, depending on individual clinical and immune status, and if disease progression is suspected. Any HIV-2 RNA above the limit of detection should be confirmed promptly.

Resistance testing

The prevalence of transferred primary resistance was 5% in the French cohort. (Charpentier 2013) and 2% in Portugal. If possible, initial resistance testing (or subsequent testing if not available) should always be performed. If plasma RNA is too low, resistance testing from proviral DNA can be attempted.

Start of therapy

Unlike HIV-1, there is no consensus for an optimal starting point. Since 2019, US and British guidelines recommend treatment for all HIV-2-infected persons (DHSS 2019). This strategy (treatment upon diagnosis) is also recommended by renowned experts as the basis for achieving the UN 90-90-90 targets (Gottlieb 2018). Other European guidelines consider that there are limited treatment options for HIV-2. Moreover, regarding potential "elite controllers", therapy should primarily be initiated when it is "really" necessary for clinical, virological, and immunological reasons. On the other hand, there is a caveat regarding starting too late, especially since immune reconstitution (increase in CD4 T-cells) is often much lower under ART according to older studies (Benard 2011, Matheron 2006). According to these considerations, initiation of ART is

- ***mandatory*** for patients with symptoms (CDC category B and C) or with dual infection
- ***recommended*** for patients with less than 500 CD4 T-cells/µl and/or a drop of more than 30/µl per year for at least three years (only recommended by the "EU expert group"), repeated detection of HIV-2 RNA in plasma, co-morbidities such as chronic hepatitis B, primary HIV infection, and during pregnancy
- ART can be deferred in patients with the following criteria: absent symptoms and criteria for non-progression, i.e., stable CD4 T-cells above 500/µl and an HIV-2 RNA permanently below the detection limit.

Treatment

First-line treatment of HIV-2 should consist of a combination of two NRTIs and either an INSTI or one of the effective boosted PIs.

Table 1: Recommended first-line therapy for HIV-2 (for women, follow warnings and dosing instructions regarding pregnancy).

Backbone (NRTI)		Third agent
TAF/FTC or TDF/FTC Alternatives: TAF/3TC or TDF/3TC or ABC/3TC	**plus**	INSTI: Dolutegravir or Bictegravir Alternative: Raltegravir, Elvitegravir/c or PI: Darunavir/r/c Alternative: Lopinavir/r *Booster drugs: c: Cobicistat, r: Ritonavir*

Available data:

PI-based regimens in HIV-2

In one study, 126 patients showed an excellent immunological response and an average CD4 T-cell increase of 88/µl after one year on boosted PIs, mostly in lopinavir/r (Benard 2011). The increase in the West African IeDEA cohort of 287 patients was as high as 191/µl (Balestre 2016). Both studies showed that boosted PI regimens were superior to a combination of three NRTI or unboosted PI. Data for good *in vitro* efficacy are available for darunavir/r, ranked first among PIs in the guidelines. In most cases, darunavir can be given once daily at 800 mg (with 100 mg ritonavir); for resistance-associated mutations such as I84V and/or L90M, darunavir/r should be given twice daily (2 x 600/100 mg). Although data on cobicistat and HIV-2 are not yet available, comparable boosting can be assumed.

INSTI-based regimens in HIV-2

Raltegravir: 30 patients treated with TDF/FTC experienced a CD4 T-cell increase of 87/µl after one year. Only one patient developed virological failure (Matheron 2018).

Elvitegravir/c: 30 patients treated with TDF/FTC experienced a CD4 T-cell increase of 161/µl after one year. Only one patient had > 50 copies of HIV-2 RNA/mL after week 36 (Ba 2017).

Dolutegravir: was used in 62 Indian patients. The mean CD4 T-cell increase was 72 cells/µl after 18 months; 7 patients showed virological failure, and three clinical events occurred (Pujari 2020). In 24 French ANRS HIV-2 cohort patients, the mean CD4 gain was 54 cells/µl over 28 months. Overall, 23 patients had an HIV-2 RNA < 40 copies/mL, and one discontinued dolutegravir due to weight increase (Joly 2023).

Bictegravir/TAF/FTC: was used successfully in 62 patients in a Portuguese open-label phase II trial. The median CD4 increase after one year was 96 cells/µl, with no virological failure (Pacheco 2023).

In vitro studies suggest that second-generation INSTIs are more effective against HIV-2 (Le Hingrat 2018, Reeves 2021).

Monitoring before therapy

Under ART, treatment success should be monitored by HIV-2 plasma RNA and CD4 T-cells as follows:

- After starting or switching therapy, at months 1, 3, and 6.

- With CD4 T-cell count below 200/µl every three months, with CD4 between 201 and 499/µl every 3 to 6 months (depending on adherence and clinical situation), and with CD4 T-cells above 500/µl every six months.
- If disease progression is suspected, immediately.
- In case of pregnancy, every three months and monthly in the last trimester.

Treatment failure

Viral load alone is not a sufficient parameter for therapeutic success, and it may not be detectable even before ART initiation. CD4 T-cell progression and clinical condition are much more critical. Treatment failure is likely if (Berzow 2020):
- HIV-associated symptoms occur or do not improve while on ART,
- CD4 T-cells continue to decline in number, and/or

HIV-2 plasma RNA is detectable while on ART.
In these cases, testing for resistance to NRTI, PI, and INSTI should be initiated immediately. If plasma RNA is low and undetectable, a resistance test from proviral DNA can be attempted.

Recommended agents – second-line treatment

Second-line treatment should consider genotypic resistance testing, tolerability, and adherence. If a PI was used in first-line treatment, a switch to an INSTI is recommended (and *vice versa*). Maraviroc, AZT, saquinavir/r, and effective new substances may also be considered. With maraviroc, a genotypic tropism test should be done. A biomathematical tool for interpretation (sequence analysis of the V3 loop) is available online via genotopheno.org.

Resistance

The differences between HIV-2 and HIV-1 in the amino acid sequence in the *pol* gene explain the variable efficacy of antiretroviral agents (Camacho 2012). Resistance pathways for HIV-2 have been described for NRTIs, PIs, and INSTIs (Moranguinho 2023). Polymorphisms in the RT region at positions 181(I), 188(L), and 190(A) explain the ineffectiveness of NNRTIs (Colson 2005).

NRTIs: Typical polymorphisms of the HIV-2 RT are T69N, V75I, V118I, L210N, T215S and K219E (Menendez-Arias 2014). The mechanism of "pyrophosphorolysis-mediated primer unblocking" while on AZT, leading to the emergence of TAMs in HIV-1, does not appear to play a role in HIV-2 (Menendez-Arias 2014). The following resistance mutations occur most frequently (most of which arose from the use of older regimens with AZT, d4T, and ddI): Q151M (50%), K65R (13%), M184V (25%), L74V, and V115Y (Trevino 2011). In the Portuguese ADR resistance cohort (153 cases with resistance mutations, 2007–2019), RT mutations involved M184V/I in 58%, Q151M in 18%, and K65R in 15% (Perpetua Gomez, personal communication).
The multi-resistance mutation Q151M is seen more frequently and earlier than in HIV-1. In contrast, S215ACFLYV (this position is highly polymorphic in HIV-2) is observed less often or only after prolonged administration of AZT and d4T (Menendez-Arias 2014, Tzou 2020).
The viral fitness of HIV-2 is reduced by M184V, as in HIV-1 (Deuzing 2015), but the efficacy of AZT is not reinforced (Smith 2009). V111I is a mutation typical of HIV-2. It increases the imprecision of RT and leads to a higher mutation rate but simultaneously "restores" the limited viral fitness at K65R and Q151M (Deuzing 2015).

PIs: Polymorphisms were seen at 47 of 95 amino acid positions in another French study (Damond 2005). The major polymorphisms affecting the substrate binding site are V32I, I47V, L76M, and V82I (Menendez-Arias 2014). Common resistance mutations include V47A, G48V, I54M, I82F, L90M, and L99F (Charpentier 2014).

Resistance can occur more rapidly (Camacho 2012, Menendez-Arias 2014). At some positions, even one mutation seems to be enough (Trevino 2011, Raugi 2013, Charpentier 2014). This concerns V47A (lopinavir), I50V (darunavir), I54M (lopinavir and darunavir), and L90M (saquinavir). The combination I54M+I84V+L90M can lead to high-level resistance to all PIs. In the Portuguese ADR cohort, PI resistance occurred with the following frequency: L90M 26%, I54M 14%, I50V 8%, V47A 6%, I82F and I84V 2% (Perpetua Gomez, oral communication).

Integrase inhibitors (INSTIs): Polymorphisms were found at 33% of amino acid positions in therapy-naive patients (Perez-Bercoff 2010). Under raltegravir, the known resistance mutations T92Q, T97A, Y143C/G, Q148H/K/R, and N155H were found (Charpentier 2011, Smith 2012); under elvitegravir, E92G/Q, T97A, Q148K/R, Y143C, and N155H (Smith 2012). For dolutegravir, resistance-associated mutations have been described at positions E92Q, T97A, G104S+Q148R, Q148K, and N155H, among others (Descamps 2015, Smith 2015). Bictegravir is thought to have a very similar resistance profile (Smith 2019, Obermeier 2022). Insertion 231ins causes high-level resistance to raltegravir, elvitegravir, dolutegravir, and partial resistance to bictegravir (Le Hingrat 2019).

CCR5 antagonists: HIV-2 can use diverse co-receptors. CCR5 and CXCR4 are the most important, as in HIV-1. X4-tropic isolates are found only in advanced-stage and low CD4 T-cells (Visseaux 2014). *In vivo,* there are case reports for maraviroc in salvage therapy (Descampes 2015).

Interpretation rules and algorithms for HIV-2 resistance mutations

Table 2 shows an assessment of the most important resistance mutations based on study data and case reports by the European *HIV-2EU Group* (Charpentier 2015, updated 2022). These algorithms are available as a continuously updated internet tool for entering the entire nucleotide sequence after sequencing and for entering the known resistance mutations (HIV2EU tool, http://www.hiv-grade.de).
The listed therapy-induced resistance mutations have been confirmed by a more considerable recent work (analysis of gene sequences from 739 PI-, 611 NRTI-, and 321 INSTI-treated individuals before and after initiation of therapy) (Tzou 2020).

Treatment of dual infection

The start of therapy should be based on the same criteria as for HIV-1 infection. The choice of drugs should consider that there is good activity against HIV-2. A Spanish study of 20 patients with dual infection showed a virologic response (for both viruses) at 80%. There was an average CD4 T-cell increase of 212/µl over 13–48 months (Requena 2019).

Table 2: HIV-2 RAMs (according to "HIV-2EU group resistance interpretation rule set").

NRTI	Resistance	Partial resistance
AZT	Q151M S215ACFLYV + another mutation from (N69ST, K70R, V115F, K223R)	S215ACFLYV
3TC/FTC	M184V	K65R
ABC	K65R Q151M M184V + one mutation from (L74V, Y115Y)	two mutations (D67N, K70RN, M184V, S215ACFLYV)
TDF/TAF	K65R Q151 + V111I	

Table 2: Continuation

PI	High level of resistance	Medium resistance
SQV	G48V L90M	I84V
LPV	V47A I54M Two RAMs out of (I82F, I84V, L90M)	V62A+L99F I82F I84V L90M
DRV	I50V I54M I84V + L90M	I84V L90M
INSTIs	**High level of resistance**	**Medium resistance**
RAL	E92Q + T97A Q148HKR N155HR One of (E92Q, T97A) + Y143CGR 231ins	E92Q Y143CGR
EVG	E92QG T97A + Y143C Q148HKR N155H 231ins	Y143C
DTG	Q148K E92Q + N155H T97A + N155H G140S + Q148HR 231ins	E92Q T97A + Y143C Q148R N155H
BIC	Q148K E92Q + N155H T97A + N155H G140S + Q148HR	E92Q T97A + Y143C Q148R N155H 231ins

Literature

Angin M, Wong G, Papagno L, et al. Preservation of Lymphopoietic Potential and Virus Suppressive Capacity by CD8 + T Cells in HIV-2-Infected Controllers. J Immunol 2016; 197:2787-2795.

Ba S, Raugi D, Smith R, et al. A trial of fixed dose combination of elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate for the initial treatment of HIV- 2 infections: 48 week results from Senegal, West Africa. Abstract #MOPEB0294, 9th IAS 2017, Paris.

Balestre E, Ekouevi D, Tchounga B, et al. Immunologic response in treatment-naive HIV-2-infected patients: the IeDEA West Africa cohort. Journal of the International AIDS Society 2016, 19:20044.

Benard A, van Sighem A, Taieb A, et al. Immunovirological response to triple nucleotide reverse-transcriptase inhibitors and ritonavir-boosted protease inhibitors in treatment-naive HIV-2-infected patients. CID 2011, 52: 1257-1266.

Berry N, Jaffar S, Schim van der Loeff M, et al. Low level viremia and high CD4 % predict normal survival in a cohort of HIV type-2-infected villagers. AIDS Res Hum Retroviruses 2002, 18: 1167-73.

Berzow D, Descamps D, Obermeier M, Charpentier C, et al. Human Immunodeficiency Virus-2 (HIV-2): A Summary of the Present Standard of Care and Treatment Options for Individuals Living with HIV-2 in Western Europe. Clin Infect Dis 2021, 72:503-509.

Buggert M, Frederiksen J, Lund O, Betts MR, et al. CD4+ T cells with an activated and exhausted phenotype distinguish immunodeficiency during aviremic HIV-2 infection. AIDS 2016, 30:2415-2426.

Burgard M, Jasseron C, Matheron S, et al. Mother-to-Child Transmission of HIV-2 Infection from 1986 to 2007 in the ANRS French Perinatal Cohort EPF-CO1. CID 2010, 51:833–843.

Camacho R. Special aspects of the treatment of HIV-2-infected patients. Intervirology 2012; 55: 179-183.

Ceia F, Silva-Pinto A, Carvalho AC, et al. Human Immunodeficiency Virus (HIV) 2 Superinfection in a Patient Receiving Antiretroviral Therapy With Longstanding HIV-1 Viral Load Suppression. Open Forum Infect Dis 2019, 6:ofz063.

Charpentier C, Camacho R, Ruelle J, et al. HIV-2EU-Supporting Standardized HIV-2 Drug-Resistance Interpretation in Europe: An Update. Clin Infect Dis 2015;61:1346-7.

Charpentier C, Eholié S, Anglaret X, et al. Genotypic resistance profiles of HIV-2-treated patients in West Africa. AIDS 2014, 8: 1161-1169.

Charpentier C, Roquebert B, Delelis O, et al. Hot spots of integrase genotypic changes leading to HIV-2 resistance to raltegravir. AAC 2011, 55,1293-95.

Charpentier C, Visseaux B, Bénard A, et al. Transmitted drug resistance in French HIV-2-infected patients. AIDS 2013, 27:1671-4.

Clavel F, Guetard D, Brun-Vezinet F, et al. Isolation of a new human retrovirus from West African patients with AIDS. Science 1986, 233: 343.

CNdS. Groupe d'experts pour la prise en charge du VIH CNdS. Prise en charge médicale des personnes vivant avec le VIH. Infection VIH-2; Diversité des VIH-1, 2016. https://cns.sante.fr/wp-content/uploads/2017/01/experts-vih_diversite.pdf.

Colson P, Henry M, Tivoli N, et al. Polymorphism and drug-selected mutations in the reverse transcriptase gene of HIV-2 from patients living in southeastern France. J Med Virol 2005, 75:381-90.

Damond F, Brun-Vezinet F, Matheron S et al. Polymorphism of the HIV-2 protease gene and selection of drug resistance mutations in HIV-2-infected patients treated with protease inhibitors. J Clin Microbiol 2005, 43:484-7.

Descamps D, Peytavin G, Visseaux B, et al. Dolutegravir in HIV-2-Infected Patients With Resistant Virus to First-line Integrase Inhibitors From the French Named Patient Program. CID 2015, 60:1521-7

Deuzing IP, Charpentier C, Wright DW, et al. Mutation V111I in HIV-2 reverse transcriptase increases the fitness of the nucleoside analogue-resistant K65R and Q151M viruses. J Virol 2015, 89:833-43.

Drylewicz J, Matheron S, Lazaro E, et al. Comparision of viro-immunological marker changes between HIV-1 and HIV-2 infected patients in France AIDS 2008, 22: 457-68.

Ekouevi DK, Tchounga BK, Coffie PA, et al. Antiretroviral therapy response among HIV-2 infected patients: a systematic review. BMC Infect Dis 2014, 14:461.

Esbjörnsson J, Månsson F, Kvist A, et al. Long-term follow-up of HIV-2-related AIDS and mortality in Guinea-Bissau: a prospective open cohort study. Lancet HIV 2018, S2352-3018.

Gilbert PB, McKeague IW, Eisen G, et al. Comparison of HIV-1 and HIV-2 infectivity from a prospective cohort study in Senegal. Stat Med 2003, 22:573-93

Gottlieb GS, Hawes SE, Agne HD, et al. Lower levels of HIV RNA in semen in HIV-2 compared with HIV-1 infection: implications for differences in transmission. AIDS 2006; 20: 895–900.

Gottlieb GS, Raugi DN, Smith RA. 90-90-90 for HIV-2? Ending the HIV-2 epidemic by enhancing care and clinical management of patients infected with HIV-2. Lancet HIV 2018, 5: e390-e9.

Guyader M, Emerman M, Sonigo P, et al. Genome organization and transactivation of the human immunodeficiency virus type 2. Nature 1987, 326, 662–669

Hansmann A, Schim van der Loeff MF, et al. Baseline plasma viral load and CD4 cell percentage predict survival in HIV-1- and HIV-2-infected women in a community-based cohort in The Gambia. JAIDS 2005; 38: 335–341

Hegedus A, Nyamweya S, Zhang Y, et al. Protection versus pathology in aviremic and high viral load HIV-2 infection-the pivotal role of immune activation and T-cell kinetics. J Infect Dis 2014, 210:752-61.

Hoenge B L, Petersen MS, Jespersen S, et al. T-cell and B-cell perturbations identify distinct differences in HIV-2 compared with HIV-1-induced immunodeficiency., AIDS 2019, 33:1131–1141

Jaffar, S, Grat A, Whitworth J, et al. The natural history of HIV-1 and HIV-2 infections in adults in Africa: a literature review. Bull WHO 2004; 82, 462–469.

Jespersen S, Månsson F, Lindman J, et al. HIV treatment in Guinea-Bissau: room for improvement and time for new treatment options. AIDS Res Ther 2020,17:3.

Joly V, Ferré V M, Cresta M, et al., Immunovirological and Clinical Follow up of HIV 2 Patients Receiving BIC/FTC/TAF, CROI, Poster # 539

Le Hingrat Q, Collin G, Lê M, et al. A new mechanism of resistance of HIV-2 to integrase inhibitors: a 5 amino-acids insertion in the integrase C-terminal domain. Clin Infect Dis 2018 Nov 1

Le Hingrat Q, Collin G, Bachelard A, et al. Ibalizumab shows in vitro activity against group A and group B HIV-2 clinical isolates. AIDS. 2022 Mar 8.

MacNeil A, Sarr A, Sakale J, et al. Direct evidence of lower viral replication rates in vivo in human immunodeficiency virus type 2 (HIV-2) infection than in HIV-1 infection. J Virol 2007a, 81: 5325-30.

Marcelino J, Borrego P, Nilsson C, et al. Resistance to antibody neutralization in HIV-2 infection occurs in late stage disease and is associated with X4 tropism. AIDS 2012, 26: 2275-2284.

Matheron S, Damond F, Benard A, et al. CD4 cell recovery in treated HIV-2-infected adults is lower than expected: results from the French ANRS CO5 HIV-2 cohort. AIDS 2006, 20:459-462.

Matheron S, Descamps D, Gallien S, et al. First-line Raltegravir/Emtricitabine/Tenofovir Combination in Human Immunodeficiency Virus Type 2 (HIV-2) Infection: A Phase 2, Noncomparative Trial (ANRS 159 HIV-2). Clin Infect Dis 2018, 67:1161-1167.

Matheron S, Pueyo S, Damond F, et al. Factors associated with clinical progression in HIV-2 patients: The French ARNS cohort. AIDS 2003, 17; 2593-2601.

Mendoza C, Lozano AB, Caballero E, Cabezas T, Ramos JM, Soriano V. Antiretroviral Therapy for HIV-2 Infection in Non-Endemic Regions. AIDS Rev 2020, 22:44-56.

Menendez-Ariaz M, Alvarez M. Antiviral therapy and drug resistance in human immunodeficiency virus type 2 infection, Antivir Res 2014; 102:70-86.

Moranguinho I, Taveira N, Bártolo I. Antiretroviral Treatment of HIV-2 Infection: Available Drugs, Resistance Pathways, and Promising New Compounds. Int J Mol Sci. 2023 Mar 21;24(6):5905

National Institute of Health, Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents, Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV, 2019, available at https://aidsinfo.nih.gov/guidelines

New York State Department of Health AIDS Institute, Shah S, Diagnosis and Management of HIV-2 in Adults, 2022, https://www.ncbi.nlm.nih.gov/books/NBK558318/

Nyamweya S, Hegedus A, Jaye A, et al. Comparing HIV-1 and HIV-2 infection: Lessons for viral immunopathogenesis. Rev Med Virol 2013; 23: 221-240

O'Donovan D, Ariyoshi K, Milligan P, et al. Maternal plasma viral RNA levels determine marked differences in mother-to-child transmission rates of HIV-1 and HIV-2 in The Gambia. AIDS 2000, 14: 441-8.

Pacheco P, Marques N, Rodrigues P, et al., Safety and Efficacy of Triple Therapy with Dolutegravir plus Two NRTIs, in Treatment-Naïve HIV-2 Patients – Results from a 48-week Phase II Study. Clin Infect Dis. 2023 Jun 8:ciad339.

Perez-Bercoff D, Triqueneaux P, Lambert C. et al. Polymorphisms of HIV-2 integrase and selection of resistance to raltegravir. Retrovirology 2010, 7: 98.

Popper S, Sarr A, Travers K, et al. Lower Human Immunodeficiency Virus (HIV) Type 2 viral load reflects the difference in pathogenicity of HIV-1 and HIV-2. J Infect Dis 1999, 180:1116-21.

Prince P, Matser A, van Tienen C, et al. Mortality rates in people dually infected with HIV-1/2 and those infected with either HIV-1 or HIV-2: a systematic review and meta-analysis. AIDS 2014, 28:549-58

Pujari S, Patel A, Gaikwad S, et al. Effectiveness of dolutegravir-based antiretroviral treatment for HIV-2 infection: retrospective observational study from Western India. J Antimicrob Chemother 2020, 75:1950-1954.

Raugi D, Gottlieb G, Sow P, et al. HIV-1 outcompetes HIV-2 in dually infected Senegalese individuals with low CD4+ counts. AIDS 2013; 27: 2441-2450.

Raugi D, Smith RA, Ba S, et al. Complex patterns of protease inhibitor resistance among antiretroviral treatment-experienced HIV-2 patients from Senegal: implications for second-line therapy. Antimicrob Agents Chemother 2013, 57:2751-60.

Reeves I, Cromarty B, Deayton J, et al. British HIV Association guidelines for the management of HIV-2 2021. HIV Med 2021 Dec;22 Suppl 4:1-29

Requena S, Caballero E, Lozano AB, et al. Treatment outcome in dually HIV-1 and HIV-2 coinfected patients living in Spain. AIDS 2019, 33:2167-2172.

Rodriguez S, Sarr A, MacNeil A, et al. Comparison of heterologous neutralizing antibody responses of human immunodeficiency virus type 1 (HIV-1)- and HIV-2-infected Senegalese patients: distinct patterns of breadth and magnitude distinguish HIV-1 and HIV-2 infections. J Virol 2007, 81:5331-8.

Shah S, Diagnosis and Management of HIV-2 in Adults, New York State Department of Health AIDS Institute, 2022, https://www.ncbi.nlm.nih.gov/books/NBK558318/

Schim van der Loeff MF, Larke N, Kaye S, et al. Undetectable plasma viral load predicts normal survival in HIV-2-infected people in a West African village. Retrovirology 2010, 7:46.

Smith R, Anderson D, Pyrak CL, et al. Antiretroviral drug resistance in HIV-2: three amino acid changes are sufficient for classwide nucleoside analogue resistance. J Infect Dis 2009, 199:1323-6.

Smith RA, Raugi DN, Pan C, et al. In vitro activity of dolutegravir against wild-type and integrase inhibitor-resistant HIV-2. Retrovirology 2015, 12:10.

Smith RA, Raugi DN, Wu VH, et al. Comparison of the Antiviral Activity of Bictegravir against HIV-1 and HIV-2 Isolates and Integrase Inhibitor-Resistant HIV-2 Mutants. Clin Exp Immunol 2019 Feb 17.

Smith, R, Raugi D, Pan C, et al. Three main mutational pathways in HIV-2 lead to high-level raltegravir and elvitegravir resistance: implications for emerging HIV-2 treatment regimens. PLoS One 2012, 7:e45372.

Soares R, Tendeiro R, Foxall R, et al. Cell-associated viral burden provides evidence of ongoing viral replication in aviremic HIV-2-infected patients. J Virol 2011, 85:2429-38.

Thiebaut R Matheron S, Taieb A, et al. Long-term nonprogressors and elite controllers in the ARNS CO5 HIV-2 cohort. AIDS 2011, 25:865-867.

Treviño A, de Mendoza C, Caballero E, et al. Drug resistance mutations in patients infected with HIV-2 living in Spain. JAC 2011; 66:1484-8.

Tzou PL, Descamps D, Rhee SY, et al. Expanded Spectrum of Antiretroviral-Selected Mutations in Human Immunodeficiency VirusIV Type 2. J Infect Dis. 2020, 221:1962-1972.

Visseaux B, Charpentier C, Rouard C, et al. HIV-2 X4 tropism is associated with lower CD4+ cell count in treatment-experienced patients. AIDS 2014; 28: 2160-2

Visseaux B, Damond F, Matheron S, Descamps D, et al. HIV-2 molecular epidemiology. Infect Genet Evol 2016; 46: 233-40

Wu VH, Smith RA, Masoum S, Raugi et al. MK-8591 (4'-Ethynyl-2-Fluoro-2'-Deoxyadenosine) Exhibits Potent Activity against HIV-2 Isolates and Drug-Resistant HIV-2 Mutants in Culture. Antimicrob Agents Chemother 2017, 61(8):e00744-17.

Yant SR, Mulato A, Hansen D, et al. A highly potent long-acting small-molecule HIV-1 capsid inhibitor with efficacy in a humanized mouse model. Nat Med 2019, 25:1377-1384.

SECTION 5

Women and Children

17. HIV and women

ANNETTE HABERL

Sex and gender-specific factors significantly impact the prevention and treatment of HIV. Of note, a distinction must be made between the genetically determined biological sex and gender and the "social sex" which is determined by socially and culturally ascribed characteristics.

More than half, about 20,7 of the 39,0 million PLWH globally, are female. Women and girls accounted for 46% of all new infections in 2022 (UNAIDS 2023). In the high-prevalence countries of sub-Saharan Africa, young women aged 15–24 account for 25% of new HIV infections. Among men of the same age, the infection rate is 8%. One reason for the increased transmission risk among young women is the sexual violence they still face in many countries (UNAIDS 2018). In addition, women are anatomically at higher risk of infection than men during unprotected sexual contact. The mucosal surface of the female genital tract is larger and more sensitive than that of men. Microtrauma of the vaginal and cervical mucosa occurs quickly and increases the risk of infection.

In Western Europe, the proportion of women among PLWH is 30% on average. In Germany and Spain, it is comparatively low at 20%, while in France, it is highest at 39% (WAVE 2017). Women account for about one-third of new HIV diagnoses in Europe. Older women, in particular, are at risk of being diagnosed late (*www.ecdc.europe.eu*). The main transmission route among women is unprotected heterosexual contact.

The course of an untreated HIV infection can be different in women and men. During acute infection, HIV is taken up by dendritic cells (plasmacytoid dendritic cells pDC). These cells belong to the antigen-presenting cells that can recognize HIV with a Toll-like receptor (TLR7). The DC respond with the release of interferon-alpha, a signaling substance for activation of CD8-positive T cells. The female sex hormone progesterone can increase interferon-alpha production in the DC, which explains the greater immune activation in women during the early phase of HIV infection. As a result, viral load is initially lower in women than men. However, the more robust immune activation leads to more rapid disease progression during untreated infection (Meier 2009). Sex-specific differences in immune activation were also seen in treated HIV infection. Inflammatory markers decreased to a lesser extent in women with ART than in men (Mathad 2014).

Menopause and HIV

While the focus in the care of women living with HIV has been on child-bearing and pregnancy issues for a long time, the transition from pre- to post-menopause is now becoming increasingly important. Numerous studies have described differences in the course of menopause compared to HIV-negative women. In the Women Interagency HIV Study (WIHS), the age at onset of menopause was 47.7 versus 48.0 years (Cejtin 2012). Other studies saw an even earlier onset of menopause. In one study, the risk was increased by 73% (Schoembaum 2005), but in another, premature menopause was found in only 12% (Pommerol 2011). Women with HIV are more likely to experience menopausal symptoms (Ferreira 2007, Looby 2014). In the PRIME (Positive Transitions Through the Menopause) study, conducted in the UK from June 2015 to April 2018, 89% of approximately 1000 study participants experienced menopausal symptoms. Strikingly, only 10% received hormone therapy. Physicians feared potential interactions between ART and hormone replacement

therapy as the primary reason for their reluctance (Tariq 2019). This concern is unwarranted because the potential interactions are well-known from experience with oral contraceptives, and in addition, interaction tables for menopausal therapy are available online (*www.hiv-druginteractions.org*). In clinical practice, interdisciplinary care of peri- and post-menopausal women living with HIV should be aimed at in order to classifying symptoms and treating them early.

Antiretroviral therapy

To date, there are no specific recommendations for HIV treatment in women. No gender-specific differences were found in a meta-analysis by the FDA, which analyzed treatment responses in 43 randomized trials from 2000–2008. However, women accounted for only 20% of the more than 20,000 study participants (Soon 2012). Due to the low proportion of women in clinical trials investigating new HIV drugs, there is an ongoing lack of sex-specific data. In addition, the desire to have children and the onset of pregnancy have been exclusion criteria for participation in registration trials. Sex- and gender-specific differences often only become apparent in everyday clinical practice and usually years after a drug has been approved. In the meantime, however, the regulatory authorities explicitly demand study data. At the same time, regulations are being revised to make it easier for women of childbearing age to participate in studies and thus generate data more quickly.

There are also sex- and gender differences in the occurrence of adverse events. Gastrointestinal side effects were more likely to manifest as nausea and vomiting in women, whereas men more frequently complained of tolerable diarrhea due to previously prescribed ART (Floridia 2008, Squires 2011). Differences are also still evident with newer HIV drugs. In a German study, for example, the discontinuation rate of dolutegravir due to neuropsychiatric side effects was threefold higher in women (Hoffmann 2017). Concerning weight gain, possibly due to integrase inhibitors, female sex is an independent risk factor (Kerchberger 2020, Venter 2020). Sex differences in pharmacokinetics may influence efficacy and tolerability and are multifactorial. Body weight, proportion of fat, and the influence of hormones on plasma protein binding are essential. Differences in diet and exposition time in the gastrointestinal tract are significant for bioavailability. The female hormone progesterone may increase the activity of the CYP3A4 system in the liver. Finally, organ size plays a role in the elimination of a drug. Relevant differences between women and men are possible in all of the above. Unfortunately, it takes an average of six years after the approval of an HIV drug for data on pharmacokinetics in pregnancy to become available – for data on breastfeeding, i.e., the lactability of the drugs, even eight years (Orkin 2019).

ART for women of childbearing potential – or, given the high rate of unplanned pregnancies – ART for young women as a whole remains a particular challenge. Ideally, young women living with HIV should receive a treatment that can be continued at the onset of pregnancy. However, forming an intersection of adult and pregnancy guideline recommendations still results in limited treatment options for young women. New drugs and administrations may be eliminated due to limited or no knowledge about their use in pregnancy. In clinical practice, it is a balancing act taking into account both the woman's needs and the potential risks to the unborn child. Data from the German HIV Pregnancy Registry show that women who became pregnant while on ongoing ART were 44% treated with a PI-based regimen. If ART was not initiated until pregnancy, the proportion of PI regimens increased to 62%. Integrase inhibitors were used pre-conceptually in 25% of women. That proportion increased to 37% when ART was started upon pregnancy (Haberl 2023).

HIV pre-exposure prophylaxis (PrEP) has so far hardly been used by women in Germany and also in other European countries (Fitzgerald 2023), although data on its effectiveness and tolerability are available, and guidelines recommend PrEP for women with a high transmission risk (www.daignet.de; www.eacsociety.org). The main barrier is the lack of information for potential female PrEP users. Women are not reached through the network of HIV focus centers but need counseling in gynecological and primary care practices or even in travel medicine. When prescribing PrEP, it should be noted that the protective effect starts later in women than in men. This delayed effectiveness can be explained by the poorer accumulation of tenofovir (TDF) in the vaginal tissue compared to the rectal mucosa (Patterson 2011). Therefore, on-demand PrEP is not considered for women. An alternative to oral PrEP for women in the near future may be intramuscular cabotegravir (CAB). The HPTN 084 study showed the superiority of CAB IM in women compared to oral PrEP with TDF/FTC (Delany-Moretlwe 2022).

The higher rate of treatment discontinuation in women with HIV compared to men has been investigated in numerous studies. Side effects, but also socioeconomic and psychosocial factors, had an impact on continuous adherence. In particular, depression, which is more common in women anyway, and lack of support in the social environment have a negative impact on treatment success. The GRACE study identified childcare responsibilities, unemployment, and transportation problems as major causes of adherence problems among women (Squires 2013). A prospective study of health-related quality of life in the Frankfurt HIV cohort showed significant differences between women and men. In the Mental Health Score (MCS) men and women with HIV scored significantly lower overall than the general population. However, there was also a significant difference between HIV+ women and men, with a lower score for women (Kuhlen 2018).

Fear of HIV-related discrimination continues to burden especially women with HIV. Most of them lead a strenuous double life for fear of HIV disclosure. In addition to effective HIV treatment, reducing stigmatization and discrimination is a decisive factor for a good quality of life in women living with HIV.

Literature

Abdool Karim SS, Passmore JS, Baxter C. The microbiome and HIV prevention strategies in women. Curr Opin HIV AIDS 2018, 13:81-87.

Barber TJ, Geretti AM, Anderson J, et al. Outcomes in the first year after initiation of first-line HAART among heterosexual men and women in the UK CHIC Study. Antivir Ther 2011, 16:805-14.

Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women. NEJM 2016 Feb 22.

Bonfanti P, Valsecchi L, Parazzini F et al. Incidence of adverse reactions in HIV patients treated with protease inhibitors. J AIDS 2000, 23:236-45.

Cejtin A. Care of the human immunodeficiency virus-infected menopausal woman. Am J Obstet Gynecol 2012, 207:87-93.

Currier JS, Spino C, Grimes J, et al. Differences between women and men in adverse events and CD4+ responses to nucleoside analogue therapy for HIV infection. The Aids Clinical Trials Group 175 Team. J AIDS 2000, 24:316-24.

Delany-Moretlwe S, Hughes JP, Bock P, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. Lancet 2022, 399:1779-1789.

FDA advisory on nevirapine. AIDS Treat News 2005, 409:7

Ferreira CE, Pinto-Neto AM, Conde DM, et al. Menopause symptoms in women infected with HIV: prevalence and associated factors. Gynecol Endocrinol 2007, 23:198-205.

Fitzgerald N, Coltart H, Dominguez, et al. PrEP for women in Europe: a systematic literature review. HIV Med. 2023 Jul;24(7):765-776. doi: 10.1111/hiv.13458. Epub 2023 Apr 23. PMID: 37088558.

Fletcher CV, Anderson PL, Kakuda TN, et al. Concentration-controlled compared with conventional antiretroviral therapy for HIV infection AIDS 2002, 16:551-60.

Floridia M, Giuliano M, Palmisano L, et al. Gender differences in the treatment of HIV infection. Pharmacological Research 2008; 58:173-182.

Gandhi M, Bacchetti P, Miotti P, et al. Does patient sex affect human immunodeficiency virus levels? Clin Infect Dis 2002, 35:313-22.

Haberl A. 22. Interdisziplinäre Fachtagung HIV und Schwangerschaft, Oberursel, June 2-3, 2023

Hilier, LA Meyn, K Bunge, et al. Impact of vaginal microbiota on genital tissue and plasma concentrations of tenofovir. Abstract 86LB, CROI 2017, Seattle.

Jackson KA, Rosenbaum SE, Kerr BM, et al. A population pharmacokinetic analysis of nelfinavir mesylate in human immunodeficiency virus-infected patients enrolled in a phase III clinical trial. Antimicrob Agents Chemother 2000, 44:1832-7.

Jarrin I, Moreno S, Ingle S, et al. The Antiretroviral Therapy Cohort Collaboration (ART-CC). Sex differences in mortality rates among HIV-positive patients: the Antiretroviral Therapy Cohort Collaboration (ART-CC). Antivir Ther 2015,20:21-8.

Kerchberger AM, Sheth AN, Angert CD, et al. Weight Gain Associated With Integrase Stand Transfer Inhibitor Use in Women. Clin Infect Dis 2020, 71:593-600.

Kuhlen C, et al. Quality of Life Assessment Among HIV-Positive Patients: Significant Gender Differences in the Mental Component Score (MCS), 8th International Workshop on HIV & Women, Boston, 2-3 March 2018

Looby SE, Shifren J, Corless I, et al. Increased hot flash severity and related interference in perimenopausal human immunodeficiency virus-infected women. Menopause 2014, 21:403-9.

Mathad J, Gupte N, Balagopal A, et al. Sex-related inflammatory marker changes pre- and post-ART initiation. Abstract 853, 21st CROI 2014, Boston.

Meier A, Chang JJ, Chan ES, et al. Sex differences in the toll-like receptor-mediated response of plasmacytoid dendritic cells to HIV-1. Nat Med 2009, 15:955-959.

Moore RD, Fortgang I, Keruly J, Chaisson RE. Adverse events from drug therapy for HIV disease. Am J Med 1996, 101:34-40.

Nel A, Bekker LG, Bukusi E, et al. Safety, Acceptability and Adherence of Dapivirine Vaginal Ring in a Microbicide Clinical Trial Conducted in Multiple Countries in Sub-Saharan Africa. PLoS One 2016, 11:e0147743.

Nicastri E, Leone S, Angleletti C, et al. Sex issues in HIV-1-infected persons during highly active antiretroviral therapy: a systematic review. J Antimicrob Chemother 2007, 60:724-32.

Orkin C. Plenary Session, EACS 2019, Basel, 7. Nov 2019

Patterson KB, Prince HA, Kraft E, et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. Sci Transl Med 2011, 3:112re4.

Pfister M, Labbé L, Hammer SM, et al. Population pharmacokinetics and pharmacodynamics of efavirenz, nelfinavir, and indinavir: ACTG Study 398. Antimicrob Agents Chemother 2003, 47:130-7.

Pommerol M, Hessamfar M, Lawson-Ayanyi S, et al. Menopause and HIV infection: age at onset and associated factors, ANRS CO3 Aquitaine cohort. Int J STD AIDS. 2011, 22:67-72.

www.rki.de.

Schoenbaum EE, Hartel D, Lo Y, et al. HIV infection, drug use, and onset of natural menopause. Clin Infect Dis 2005, 41:1517-24.

Soon GG, Min M, Struble KA, et al. Meta-analysis of gender differences in efficacy outcomes for HIV-positive subjects in randomized controlled clinical trials of antiretroviral therapy (2000-2008). AIDS Patient Care STDS 2012, 26:444-53.

Squires KE, Johnson M, Yang R, et al. Comparative gender analysis of the efficacy and safety of atazanavir/ritonavir and lopinavir/ritonavir at 96 weeks in the CASTLE study. J Antimicrob Chemother 2011, 66:363-70.

Squires K, Feinberg J, Bridge DA, et al. Insights on GRACE (Gender, Race, And Clinical Experience) from the patient's Perspective: GRACE Participant Survey. AIDS Patient Care and STDs 2013, 27:352-62.

Tariq S, Burns F, Gilson R, et al. PRIME (Positive Transitions Through the Menopause) Study: A Protocol for a Mixed Methods Study Investigating the Impact of the Menopause on the Health and Well-Being of Women Living With HIV in England. BMJ Open 2019, 9(6).

Touloumi G, Pantazis N, Antoniou A, et al. CASCADE Collaboration. Highly active antiretroviral therapy interruption: predictors and virological and immunologic consequences. J AIDS 2006; 42:554-61.

UNAIDS, www.unaids.org.

Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. Lancet HIV 2020: e666-e676.

18. HIV and gynecology

ANKE REITTER AND ANNETTE HABERL

Gynecologists are particularly important for preventing, diagnosing, and treating HIV infection. Women see them regularly from their youth, and sexual health is on the agenda anyway. It makes sense to address sexually transmitted infections such as HIV in gynecological practice. This works well in the context of prenatal care, and HIV testing rates of over 85% are now achieved in Germany (Beermann 2020). Beyond childbearing and pregnancy, however, HIV testing could be offered more frequently in gynecological practices than it has been to date. Especially in women over 50, HIV diagnosis is too often made only at an advanced stage of infection (*www.ecdc.europa.eu*).

Gynecologists also play a crucial role in HIV pre-exposure prophylaxis (PrEP). The success of PrEP depends mainly on how well potential users can be reached. While men with a high risk are informed about PrEP via HIV care centers, organizations, or internet forums, there is a lack of comparable forums for women. This prevention tool will be available for women only if information on PrEP is also located in gynecological practices. As the protective effect of PrEP starts later in women than in men, PrEP on demand is not an option for women. Intramuscular cabotegravir (CAB) could make PrEP more attractive to women. PrEP approval of this INSTI has already been granted in the US and has been applied for in Europe.

Cooperation between gynecological centers and HIV centers should always be sought. Contact persons should be known at the local level. If, for example, an initial HIV diagnosis is made in the gynecological practice, this requires the fastest possible presentation at an HIV focus center. This way, possible interactions between antiretroviral therapy and hormone preparations can be clarified quickly.

Gynecological screening

Women living with HIV are at increased risk for cervical dysplasia and carcinoma, genital ulcers, vaginal infections, and genital condylomas if untreated. ART reduces AIDS-defining diseases, including cervical carcinoma, via sustained viral load suppression and immune reconstitution.

Gynecological examination with a Pap smear is obligatory for all women. Cells are taken from the cervix and microscopically classified using a special stain (Table 1). When HIV infection is first diagnosed, the importance of gynecologic screening should be explained, and regular participation in screening examinations should be recommended. Particular attention should be given to contraception in younger women and in older women, to postmenopausal issues.

Guidelines for cancer screening may differ markedly between countries. There is considerable variation in screening methods, starting age, stopping age, and screening interval between countries. In Germany, the following gynecological check-ups are offered by health insurance, depending on age:

- From age 20–34, annual cervical cancer screening (Pap smear).
- From age 35, an additional test ("co-test") for HPV is optional in addition to the existing annual Pap smear. If the results are normal, the screening interval is then extended to three years.
- Annual examination for chlamydia (in urine) until age 25.
- After age 30, a palpation examination and a lymph node scan of the breast once a year.
- From age 50 to 70, a mammography every two years.
- At or after age 35, baseline mammography/sonography can be performed.

Given the risk of cervical and anal dysplasia, screening, especially Pap smears of the cervix and anus, is of great importance for all women, including those living with HIV. Recommended intervals vary depending on findings and risk status. The risk of breast cancer is not increased by HIV infection. The usual further preventive examinations are colon cancer screening from age 50 (examination for occult blood; colonoscopy from age 55) and skin cancer screening every two years.

Human papillomaviruses (HPV)

Over 50% of sexually active people have had contact with one or more of the more than 100 HPV subtypes. The infection usually resolves within a few months in immunocompetent individuals. Chronic HPV infection can lead to genital warts, condylomata acuminata (mostly "low-risk" LR-HPV, subtypes 6 or 11), and intraepithelial and invasive neoplasms in the lower female genital tract (the "high-risk" HR-HPV subtypes 16 and 18).

The diagnosis of condylomata acuminata is usually visual. A biopsy is necessary if the diagnosis is unclear, the condylomas do not respond to therapy or are progressive, or if the warts are pigmented, indurated, fixed, or ulcerated. Simple genital warts of the vulva or vagina (LR-HPV types 6, 11, less commonly types 42, 43, and 44) can be treated initially with podophyllin or imiquimod. In case of extensive infestation or recurrence, laser vaporization should be considered.

HPV vaccination

Around 125 countries have introduced HPV vaccines, many offering access to girls (and boys) aged 9–14 worldwide (2–3 vaccinations at months 0, 2, and 6). The CDC recommends vaccination for all PLWH until the end of the 26th year of life (CDC 2015, Meites 2019). In Germany and some other countries, however, general health insurances currently do not cover vaccination of adults. HIV-positive children and adolescents should be vaccinated before their first sexual contact.

HPV and cervical cancer

Cervical carcinoma is a squamous cell carcinoma in more than 80%, and in more than 98%, the carcinogenic HR-HPV types 16, 18, but also 31, 33, 35, 58, etc. are involved. If the HPV test is positive, clarification with cytology is the international standard. If cytology is abnormal, up to 40% of cervical intraepithelial neoplasia (CIN) III can be detected by colposcopy and biopsy, depending on the severity of the Pap result. CIN III risk with a cytology-negative but HPV-positive result is present in 4–9%, necessitating further smear checks (Ronco 2014, Cruickshank 2019).

HPV self-test

In principle, HPV self-testing is also possible today, but it does not replace screening with regular inspection of the cervix (Arbyn 2014, Zhang 2019). Alternatively, many guidelines on cervical cancer screening recommend immunocytochemical testing for the biomarker p16/Ki-67, which appears more accurate than the Pap test. Still, there is not yet as much data on this.

With increasing ART duration and improvement in CD4 T-cell count, HR-HPV prevalence appears to decrease. This also reduces the prevalence of CIN II and CIN III (Menon 2017). A high CD4 T-cell count potentially has a protective effect against cervical neoplasia, but the direct impact of ART is not established (Kelly 2017, Zhang 2020). However, a recent meta-analysis shows that early ART initiation with good adherence reduces the incidence and progression of cervical dysplasia to cervical carcinoma (Kelly 2018).

Rapid virological control with functional, complete local strengthening of the mucous membranes seems to be essential. In the case of poor adherence and HIV disease progression, gynecologic screening must be more closely performed, as in these cases, infections with HR-HPV types and progression of dysplasias are more likely (Kelly 2018).

Treatment of cervical dysplasia

The treatment of cervical dysplasia (cervical intraepithelial neoplasia/CIN) and cervical carcinoma is the same in HIV-positive and -negative women. However, PLWH have an increased risk of recurrence and should be monitored closely (Heard 2005). The goal of surgical therapy for cervical dysplasia is the complete removal of the transformation zone with all neoplastic lesions.

Table 1: Management according to cervical cytology (Pap findings), histological classification, and HPV status (modified according to German guidelines on prevention of cervical carcinoma, 2017).

Pap smear Histology	Management	OP procedure	Conservative/Controls
I	Annual/triennial checks		HPV as co-test
II	Often, inflammatory cell changes Control after three months		Local treatment of the infection/remediation of the flora
IIID CIN I (mild dysplasia) *	Colposcopic cytological control every 6 months (only in case of HPV-HR positivity)	Loop conization, laser conization/vaporization (in case of persistence of findings, HPV-HR positivity, and wish of the patient)	Up to 24 months (only relevant in case of HPV-HR positivity)
IIID CIN II (moderate dysplasia)	Colposcopic cytological control every 6 months (only in case of HPV-HR positivity).	Loop conization, laser, laser conisation/ vaporization (in case of persistence of findings, HPV-HR positivity, and wish of the patient)	Up to 12 months (only relevant in case of HPV-HR positivity)
IVa/IVb (CIN III severe dysplasia)	Therapy	Conization (loop, laser, needle, knife)	In pregnancy, close monitoring with biopsy or extended treatment postpartum

* In the case of CIN I and histologically expressed suspicion of endocervical involvement, close cytological/colposcopic controls and, if necessary, conization should be performed (especially in the case of HR-HPV positivity).

Anal dysplasias

In PLWH, HPV infection is often multifocally localized. The risk of concurrent cervical and anal dysplasias is increased (Holly 2001). Unlike cervical dysplasia, there is no regular screening program for anal dysplasia. Anal HPV infection also initially results in local dysplasia, which may progress to anal carcinoma after years. Anal carcinomas develop in 90% from dysplastic precursors called anal intraepithelial neoplasia (AIN) due to HR-HPV (Forman 2012). The risk of anal carcinoma is increased 7- to

28-fold compared to HIV-negative women. This has not yet led to increased attention to screening everywhere (Wells 2020, Rodriquez 2021). CD4 T-cell counts normalized by ART appear to reduce the risk of disease; a direct effect of ART is controversial (Gonzalez-Ruiz 2004). A thorough inspection of the anal region and, if necessary, smear/HPV diagnostics are recommended.

Cycle and menopause

Whether HIV affects the female cycle is still a matter of controversy. It is equally unclear whether HIV accelerates the onset of menopause. Studies show contradictory results (Imai 2013, Van Ommen 2021). The average age of onset of menopause in the general population in many Western countries is between 50 and 52. Diagnostic workup is the same as for HIV-negative women. ART interactions with menopausal hormone therapy are possible when boosted substances are used. Hot flashes, sleep disturbances, and mood swings are reported as the most common symptoms of menopause (Ferreira 2007). The expression of symptoms may be increased in women living with HIV (Tariq 2019). The duration of vasomotor symptoms is approximately 7–8 years and begins on average 4.5 years before the last menstrual period (Avis 2015).

Post-menopausal bone and lipid metabolism changes may be exacerbated by HIV infection or its treatment, possibly increasing the risk of osteoporosis and cardiovascular disease.

Menopausal hormone therapy is always an individual decision after weighing the advantages and disadvantages. HIV infection is not a contraindication to hormone therapy (Haberl 2018). Interactions with ART should be considered (www.hiv-druginteractions.org).

Contraception

Women with a completely suppressed viral load who do not use a condom should be advised individually on contraception. The condom, which can protect partners of untreated women from HIV transmission, has a comparatively low contraceptive effect: the Pearl index (number of pregnancies in 100 patient-years) is 2–12 compared to 0,1–0,9 for ovulation inhibitors. Spermicides are also not recommended. Nanoxynol-9 damages the vaginal mucosa.

The following methods are available: combined oral contraception (COC), patch, ring, *progesterone-only pill* (POP), copper IUD, hormonal IUD, hormonal injection, and implant. These contraceptive methods do not affect the course of HIV infection (Phillips 2013). When choosing a method or preparation, general contraindications should be considered (e.g., age, obesity, smoking, thrombophilia, post-thrombosis/embolism, diabetes mellitus, hypertension, migraine, liver tumors).

Possible interactions of hormonal contraceptives with ART should be considered (https://www.hiv-druginteractions.org). No interactions with hormonal contraceptives are seen with NRTIs; the newer NNRTIs etravirine, rilpivirine, and doravirine, the integrase strand transfer inhibitors (INSTIs) raltegravir, bictegravir, dolutegravir, and cabotegravir IM, and the CCR5 antagonist maraviroc. Boosted protease inhibitors, the boosted INSTI elvitegravir, and the old NNRTIs efavirenz and nevirapine interact with ethinylestradiol and progestin via cytochrome P450. Enzyme inducers for CYP3A4 (including rifampicin, rifabutin, and some antiepileptic drugs) are also problematic, and the effects of the interactions are hardly predictable due to lack of data (Robinson 2012).

When prescribing hormonal contraceptives, the risk of inadequate contraceptive

protection due to interactions with ART should be considered, and, if necessary, a preparation with a high estrogen or progestin dose should be selected. Metabolic effects must also be considered: progestogen-only preparations have a particularly unfavorable effect on lipid and insulin metabolism in women living with HIV (Womack 2009).
Many studies have investigated whether contraception increases the risk of HIV transmission. Hormonal contraception, copper intrauterine devices (IUDs), and levonorgestrel-containing IUDs do not increase the risk (Patel 2017, Stringer 2007, Heikinheimo 2006). Conflicting data are available on the "three-month injection," which contains 150 mg of medroxyprogesterone acetate (Polis 2014, WHO 2015, Ralph 2015).

Other infections

Before the introduction of antiretroviral therapies, recurrent genital tract infections, bacterial vaginosis, genital herpes, and vulvovaginal candidiasis were very common. Frequency and severity correlated with immune status and viral load. Other sexually transmitted infections besides HIV are also diagnosed more frequently. The therapy of women living with HIV does not differ from that of HIV-negative patients. Common to all genital infections is the damage or weakening of the mucosa caused by the infection and thus an increased permeability with the risk of further infections and an increased risk of transmission of HIV.

Table 2: Common genital infections: Diagnosis, therapy and unique features.

	Bacterial vaginosis	**Genital herpes**	**Vulvovaginal candidiasis**
Diagnosis	Thin fluorine Amine odor of fluorine White grayish Smear Microscopic ("Clue cells") Native preparation Amine test (drops 10% KOH typical odor)	Painful blisters/ulcerations Serological/virological (smear)	Thin fluorine Amine odor of fluorine Whitish fluorine Itching Burning Colposcopic Smear/culture Urine
Most common pathogens	Gardnerella vaginalis	Human herpes virus type 2 (HSV-2)	Candida albicans
Therapy	Metronidazole systemic Tablet (2 x 500 mg/day for 7 days or 2 g once or 2x2 g within 48 hours) Local: Clindamycin vaginal cream	Acyclovir local/systemic	Local azole for 1–3 days (e.g., clotrimazole 2% cream 5 g intravaginally 1 x daily for 3 days or miconazole vaginal suppositories 200 mg 1 x daily for 3 days)
Differential diagnosis	Trichomonads	Lues, "Chancroid" (haemophilus ducreyi)	Trichomonads
Prevention	Local strengthening, e.g., lactobacilli	Prophylaxis with Acyclovir 200–400 mg x 1 daily orally	Use prophylaxis fluconazole 1 x 200 mg/week
Partner treatment	Not mandatory	Barrier method during intercourse until healing, treatment for symptoms	Only in case of complaints co-treatment

Practically, therapy should always disinfect and strengthen the local milieu, e.g., by supplying lactic acid bacteria suppositories, and vitamin C locally (Vagiflor®, Vagi-Hex®, Fluomizin®). For example, vaccination with Lactobacillus strains to reconstitute the physiological Döderlein flora may be considered in recurrent non-specific colpitis. Study data from large study collectives are available on this, but not for women living with HIV. In HIV-negative women, these preparations can reduce the recurrence rate by up to 80% (e.g., Gynatren®, Lyseen®).

Summary

Gynecologists play a crucial role in the prevention and treatment of HIV infection. Collaboration with HIV centers ensures optimal care. PLWH should be aware of the early detection and treatment options for genital HPV-associated dysplasia and neoplasia. Effective HIV therapy can now reduce the risk of cervical dysplasia/neoplasia to the level of HIV-negative women. At least annual screening, including screening for anal dysplasia, is recommended for all women.

Interactions of HIV drugs with hormone preparations are now well studied. They may be clinically relevant in individual cases. Individual therapy modifications ensure the success of contraceptive or hormonal therapies. A new topic for gynecological practice is PrEP. Gynecologists have a central role in reaching those women who could benefit from this prevention method.

Literature

Arbyn M, Verdoodt F, Snijders PJ, et al. Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: a meta-analysis. Lancet Oncol 2014; 15: 172–83.

Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Int Med 2015; 175: 531

Beermann S, Jacob J, Dudareva S, et al. Gelingt das Screening von Schwangeren auf HIV, Syphilis und Hepatitis B in Deutschland? Eine Analyse auf Basis von Routinedaten. Bundesgesundheitsbl 2020, 63:1143–1150.

Cruickshank M, Murray G, Parkin D, et al. Cytological surveillance compared with an immediate referral for colposcopy in management of women with low-grade cervical abnormalities: multicentre randomised controlled trial. BMJ 2009; 339: b2546.

Ferreira CE, Pinto-Neto AM, Conde DM, et al. Menopause symptoms in women infected with HIV: Prevalence and associated factors. Gynecol Endocrinol 2007; 23: 198–205.

Forman D, de Martel C, Lacey C, et al. Global burden of human papillomavirus and related diseases. Vaccine; 30(Suppl. 5) 2012, F12–F23.

Gonzalez-Ruiz C, Heartfield W, Briggs B, et al. Anorectal pathology in HIV/AIDS-infected patients has not been impacted by highly active antiretroviral therapy. Dis Colon Rectum 2004; 47: 1483-652.

Haberl A. Infektion und Menopause: Symptome werden häufig der HIV-Infektion zugeordnet. Dtsch Arztebl 2018, 115: [9].

Harris TG, Burk RD, Palefsky JM, et al. Incidence of cervical squamous intraepithelial lesions associated with HIV serostatus, CD4 cell counts, and human papillomavirus test results. JAMA 2005, 293:1471-6.

Heard I, Potard V, Foulot H, et al. High rate of recurrence of cervical intraepithelial neoplasia after surgery in HIV-positive women. J AIDS 2005, 39:412-8.

Heffron R, Donnell D, Rees H, et al for the Partners in Prevention HSV/HIV Transmission Study Team. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. Lancet Infect Dis 2012, 12:19-26.

Heikinheimo O, Lähteenmäki P. Contraception and HIV infection in women. Hum Reprod Update. 2008, 1-11.

Heikinheimo O, Lehtovirta P, Suni J, Paavonen J. The levonorgestrel-releasing intrauterine system (LNG-IUS) in HIV-infected women – effects on bleeding patterns, ovarian function and genital shedding of HIV. Hum Reprod 2006;21:2857–2861.

Holly EA, Ralston ML, Darragh TM, Greenblatt RM, Jay N, Palefsky JM. Prevalence and risk factors for anal squamous intraepithelial lesions in women. J Natl Cancer Inst 2001;93:843–849.

Imai K, Sutton MY, Mdodo R, Del Rio C. HIV and Menopause: A Systematic Review of the Effects of HIV Infection on Age at Menopause and the Effects of Menopause on Response to Antiretroviral Therapy. Obstet Gynecol Int 2013:340309.

Kelly HA, Sawadogo B, Chikandiwa A, et al. Epidemiology of high-risk human papillomavirus and cervical lesions in African women living with HIV/AIDS: effect of antiretroviral therapy. AIDS 2017, 31:273-285.

Kelly H, Weiss HA, Benavente Y, et al. Association of antiretroviral therapy with high-risk human papillomavirus,cervical intraepithelial neoplasia, and invasive cervical cancer in women living with HIV: a systematic review and meta-analysis. Lancet HIV 2018, 5:e45-e58.

Kurzbericht des BMG-geförderten Forschungsvorhabens "Evaluation der Einführung der HIV-Präexpositionsprophylaxe als Leistung der Gesetzlichen Krankenversicherung (EvE-PrEP), 23.02.2022, www.daignet.de.

Leitlinien der Deutschen Dermatologischen Gesellschaft, der Deutschsprachigen Mykologischen Gesellschaft und der Arbeitsgemeinschaft für Infektionen und Infektionsimmunologie (AGII) der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe 2006. Link: www.dggg.de.

Leitlinien der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG), Arbeitsgemeinschaft Infektiologie und Infektimmunologie (AGII), Berufsverband der Frauenärzte e.V. (BVF), etc. Stand 6/20088/2010. Link: www.dggg.de.

Marcus U. HIV infections and HIV testing during pregnancy, Germany, 1993 to 2016. Eurosurveillance 2019, 24(48):1900078.

Menon S, Rossi R, Zdraveska N, et al. Associations between highly active antiretroviral therapy and the presence of HPV, premalignant and malignant cervical lesions in sub-Saharan Africa, a systematic review: current evidence and directions for future research. BMJ Open 2017, 7:e015123.

Meites E, Szilagyi PG, Chesson HW, et al. Human Papillomavirus Vaccination for Adults: Updated Recommendations of the Advisory Committee on Immunization Practices MMWR 2019, 68, 698-702.

Patel RC, Baeten JM, Heffron R, et al. Brief Report: Hormonal Contraception Is Not Associated With Reduced ART Effectiveness Among Women Initiating ART: Evidence From Longitudinal Data. J AIDS 2017, 75:91-96.

Phillips SJ, Curtis KM, Polis CB. Effect of hormonal contraceptive methods on HIV disease progression: a systematic review. AIDS 2013; 27: 787–794.

Polis CB, Phillips SJ, Curtis KM, et al. Hormonal contraceptive methods and risk of HIV acquisition in women: a systematic review of epidemiological evidence. Contraception 2014; 90: 360–390.

Pommerol M, Hessamfar M, Lawson-Ayayi S, et al. Menopause and HIV infection: age at onset and associated factors, ANRS CO3 Aquitaine cohort. Int J STD AIDS 2011, 22: 67–72.

Ralph LJ, McCoy SI, Shiu K, Padian NS. Hormonal contraceptive use and women's risk of HIV acquisition: a meta-analysis of observational studies. Lancet Infect Dis 2015, 15:181-9.

Robinson JA, Jamshidi R, Burke AE. Contraception for the HIV-positive woman: a review of interactions between hormonal contraception and antiretroviral therapy. Infect Dis Obstet Gynecol 2012: 890160.

Rodriguez SA, Higashi RT, Betts AC, et al. Anal Cancer and Anal Cancer Screening Knowledge, Attitudes, and Perceived Risk Among Women Living With HIV. J Low Genit Tract Dis 2021, 25:43-47.

Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet 2014; 383: 524–32.

Stringer EM, Giganti M, Carter RJ, et al. Hormonal contraception and HIV disease progression: a multicountry cohort analysis of the MTCT-Plus Initiative. AIDS 2009; 23 Suppl 1:S69-77.

Stringer EM, Kaseba C, Levy J, et al. A randomized trial of the intrauterine contraceptive device vs. hormonal contraception in women who are infected with the human immunodeficiency virus. Am J Obstet Gynecol 2007, 197: 144.e1–144.e8.

Stringer EM, Levy J, Sinkala M, et al. HIV disease progression by hormonal contraceptive method: secondary analysis of a randomized trial. AIDS 2009, 23:1377-82.

Tariq S, Burns F, Gilson R, et al. PRIME (Positive Transitions Through the Menopause) Study: A Protocol for a Mixed Methods Study Investigating the Impact of the Menopause on the Heath and Well-Being of Women Living With HIV in England. BMJ Open 2019, 9:e025497.

Wells JS, Flowers L, Paul S, Nguyen ML, Sharma A, Holstad M. Knowledge of Anal Cancer, Anal Cancer Screening, and HPV in HIV-Positive and High-Risk HIV-Negative Women. J Cancer Educ 2020, 35:606-615.

WHO. Hormonal contraceptive methods for women at high risk of HIV and living with HIV. 2014 Guidance statement. https://www.who.int/reproductivehealth/publications/family_planning/en/.

CDC. https://www.cdc.gov/vaccines/vpd/hpv/hcp/recommendations.html.

Van Ommen CE, King EM, Murray MCM. Age at menopause in women living with HIV: a systematic review. Menopause 2021, 28:1428-1436.

Womack JA, Scherzer R, Cole SR, et al. Hormonal contraception and metabolic outcomes in women with or at risk for HIV infection. JAIDS 2009: 581-7.

Zhang L et al. Zervixkarzinomscreening. Wie effektiv ist der HPV-Selbsttest? Geburtshilfe Frauenheilkd 2019; 79(02): 115.

Zhang DY, Chen W, Zhang HY, et al. Cervical neoplastic lesions in relation to CD4 T-lymphocyte counts and antiretroviral therapy among women with clinical stage 1 HIV in Yunnan, China. Kaohsiung J Med Sci 2020 Jan 8.

19. Pregnancy and HIV

Therapy for the mother and prophylaxis for the newborn baby

MECHTHILD VOCKS-HAUCK

HIV infection of the newborn has become rare in Western Europe and the United States since the introduction of antiretroviral transmission prophylaxis and elective sectio. While the perinatal HIV transmission rate in Europe was approximately 15% in the early 1990s, it is now less than 1% (Connor 1994, Townsend 2014, DHHS 2023). HIV infections postpartum are preventable unless mothers with HIV infection breastfeed without prophylaxis.

Current ART guidelines primarily recommend integrase inhibitors (INSTIs) in initial therapy. There have been restrictions on this substance class due to potential embryotoxicity. Since approximately 75% of HIV-positive women in Western industrialized nations become pregnant. At the same time, already on ART and a large part of embryogenesis has already been completed by the time pregnancy is established, this restriction has implications primarily for the preconceptional choice of therapy. As a rule, the existing therapy is continued during pregnancy.

In the following, the American and European guidelines (EACS 2021, DHHS 2023) for HIV therapy in pregnancy summarized, the German-Austrian recommendations are also taken into account (DAIG 2020). Constantly updated recommendations can be found at www.AIDSinfo.nih.gov or at www.europeanaidsclinicalsociety.org/guidelines.asp.

ART before and during pregnancy

Pre- and periconceptional ART

INSTIs are preferred in many adult primary therapy guidelines, in part because of the high resistance barrier of dolutegravir and bictegravir (EACS 2022, DHHS 2023). Dolutegravir and raltegravir are also preferred in pregnant women, and dolutegravir is unreservedly preferred in DHSS guidelines. However, the current EACS guidelines recommend "discussing" the use of dolutegravir because of a low (non-significant) risk of neural tube defects (NTDs) in the first 6 weeks (EACS 2022). Women without safe anticonception should be fully informed of the inconclusive, rare NTD risks of neural tube defects with dolutegravir at the time of conception: In the Tsepamo trial, the initial prevalence of NTD dropped from 0.94% (4/426) by 2018 to 0.15% (9/5860) by 2021, compared with 0.07% (22/22475) under other regimens not containing dolutegravir and also 0.07% among those not exposed to HIV (APR 2023). Bictegravir cannot yet be recommended due to insufficient data (approximately 140 pregnancies). Data on raltegravir are known from more than 400 pregnancies with periconceptional exposure. Elvitegravir/c is not well suited due to insufficient levels during pregnancy. Data from pregnancies under cabotegravir are not available. The recommended PIs are darunavir/r (BID) and atazanavir/r (QD). The NNRTIs rilpivirine and efavirenz are recommended as alternatives. Doravirine is not (yet) established, and the resistance barrier is higher than for rilpivirine. Nevirapine is no longer recommended; dual and cobicistat-boosted therapies are not recommended for pregnancy.

Continuation of ART during pregnancy

Existing ART with INSTIs – including dolutegravir – can be left in the first trimester according to DHHS guidelines (DHHS 2023), as pregnancy is usually confirmed after the first four to six weeks of development. Neural tube defects may develop during this period. According to the EACS guidelines, it should be discussed whether

dolutegravir therapy should be modified in the first six weeks (EACS 2022). If a change in therapy is decided in the first trimester, it is likely to be safe regarding viral suppression and neonatal outcomes (Peyronnet 2019) (see below). Raltegravir (400 mg BD) can be left in place. Substances containing cobicistat as an enhancer can be exchanged or continued under close plasma level and viral load monitoring in the second and third trimesters. This should also be considered for single-dose darunavir/r and, if appropriate, for sufficient dual therapies. Efavirenz may be continued based on recent embryotoxicity results. Rilpivirine (RPV) has been without apparent embryotoxicity in over 500 documented exposures. No pregnancy outcomes have yet been documented for rilpivirine long-acting. For doravirine, there is data from a placental perfusion model with evidence of high placental transfer and accumulation (Pencolé 2020).

If the initial diagnosis of HIV infection is made late, e.g., in the third trimester, it requires immediate therapy, preferably with INSTIs such as dolutegravir and raltegravir, to rapidly reduce viral load and achieve complete suppression by the time of delivery. With complete suppression to below 50 HIV RNA copies/mL by 34–36 weeks of gestation at the latest, perinatal transmission becomes unlikely. In these cases, intrapartum intravenous transmission prophylaxis with AZT is not necessary (DAIG 2020). Vaginal delivery is then performed. If the viral load was undetectable throughout the pregnancy, neonatal postexposure prophylaxis (neo-PEP) may also be omitted. If viral load was detectable just before delivery, pre/intrapartum ART is boosted with i.v. AZT for transmission prophylaxis during delivery. Sectio is performed, and postnatal mono-exposure prophylaxis with AZT is extended to combination prophylaxis in the child (see below).

Start of ART during pregnancy

Approximately one-quarter of pregnant women with HIV infection are first diagnosed during prenatal care. European and American guidelines recommend treatment irrespective of immune status and viral load. Before starting therapy, a resistance test and, if necessary, subtyping should be performed. It should be noted that despite the lack of approval, NRTIs other than AZT are preferred as part of the therapy, provided that the resistance test and expected toxicity do not contradict this. If HIV is diagnosed in the first trimester, ART should be started as soon as possible. However, the urgency of the indication depends on the viral load level and CD4 T-cell count. If the values are good, it should be considered to wait for the first 6–8 weeks. In principle, the choice of agents should be the same as for non-pregnant women. AZT is usually discontinued. Dual therapies are not recommended in pregnancy due to lack of data but may be continued with monthly viral load monitoring.

Dolutegravir is the drug of choice in the DHSS recommendations. Because of the minimal increase neural tube defects (NTDs) in an early study in Botswana, EACS guidelines recommend waiting until (approximately eight weeks gestation). As shown above, bictegravir is not (yet) recommended due to lack of data. No increased malformation rates have been reported with raltegravir (BID) in over 400 documented pregnancies. Elvitegravir boosted with cobicistat is not recommended in pregnancy due to low active levels. As an NNRTI, rilpivirine is preferred for viral loads less than 100,000 copies/mL and CD4 T-cell counts greater than 200/µL (DAIG 2020). Viral loads should also be carefully controlled because of approximately 20–50% low total and trough levels. Efavirenz is recommended as an alternative. Periconceptional teratogenicity in primates has not been confirmed in humans in over 1,300 pregnancies. Nevirapine is now mentioned only by DAIG (2020) as an alternative NNRTI. Data on doravirine are lacking. The PIs darunavir (twice daily) and atazanavir boosted with ritonavir are considered alternatives.

Table 1: Special features of ART in pregnancy.

Resistance testing, if necessary, HIV subtyping before starting therapy
Dolutegravir in the first trimester, if necessary, only from 8 weeks of gestation (initial 2018 Tsepamo study with increased incidence of neural tube defects)
Bictegravir has no data; therefore, it is not recommended.
In the 2nd and 3rd trimesters, Raltegravir 400 mg BID
Cobicistat in 2nd and 3rd trimesters has insufficient plasma levels, especially with Elvitegravi/c, so avoid or monitor viral load closely
Replace darunavir/c with darunavir/r BID or close viral load monitoring
If taken preconception, continue raltegravir (400 mg BID), rilpivirine, or darunavir/r
Efavirenz (Sustiva®) has no embryotoxicity (no neural tube defects)
Nevirapine is not recommended due to increased toxicity (v.a. >250 CD4 T-cells/µl) but may be continued if pre-conceptional therapy is in place
Rilpivirine has decreased plasma levels, close viral load monitoring during 2nd/3rd trimester
Checking hemoglobin and liver values about monthly
Viral load every two months: prepartum in 34–36 weeks of gestation
Risk disclosure Teratogenicity: Only AZT is approved for perinatal transmission prophylaxis, but it is rarely used anymore
If viral load <50 reached at the latest 34–36 weeks of gestation: no i.v. AZT intrapartum

Prophylaxis in antiretrovirally pre-treated pregnant women

In the case of efficient ART (<50 copies/mL) with fixed combination preparations, this is left in place, and AZT is dispensed with as a component of combination prophylaxis ("non-AZT prophylaxis"). The NRTI backbone usually consists of TAF/FTC, TDF/FTC, or ABC/3TC.

Interruption of therapy in the first trimester

Women who have to interrupt their ART, e.g., because of hyperemesis, should not resume it until the medication is expected to be tolerated again. Especially if the pregnancy is diagnosed very early, fear of possible embryotoxic effects may lead to interruption until after the first trimester. However, there are indications that after interruption of therapy during pregnancy, complete viral suppression may be more difficult in the further course.

If ART is interrupted, NRTIs, PIs, or INSTIs should be discontinued and restarted simultaneously to avoid resistance. Because the gestational age can usually not be determined precisely, the restart is usually scheduled after 13+0 weeks of gestation. Due to their long half-life, NNRTIs should be discontinued up to three weeks before NRTIs to avoid resistance; alternatively, the NNRTI can be replaced by an INSTI, or a PI boosted with ritonavir beforehand.

ART for initial HIV diagnosis in the 2nd and 3rd trimesters

For later initial diagnosis, mainly if this occurs at the end of the second and in the third trimester, dolutegravir or raltegravir are preferably recommended for rapid viral load reduction, in each case in combination with two NRTIs.

Potential fetotoxicity due to accumulation, especially with pre/intrapartum administration, and perinatal transmission risk must be carefully weighed. For women whose viral load is detectable on existing ART due to compliance or resistance issues, resistance testing is performed and, if possible, switched to a combination with

dolutegravir or raltegravir or added to existing therapy. The rapid viral load reduction typical of INSTIs is essential to minimize the risk of transmission.

Therapy monitoring

Especially in case of reduced immune status, ART is continued with careful laboratory and ultrasound controls. If necessary, the viral load and CD4 T-cell count should be checked bi-monthly (at the beginning monthly), and the remaining pregnancy support should be carried out according to general pregnancy guidelines and obstetric criteria.
Always viral load should be measured in 34 to 36 weeks of gestation to plan the mode of delivery. Hemoglobin and transaminases are checked monthly. If treated with PIs, glucose levels should be monitored closely. Resistance and plasma levels, if applicable, are determined at therapy initiation and failure.

Hepatitis B and/or C co-infection

An NRTI combination of TAF or TDF and FTC or 3TC should preferably be used as a backbone in HBV coinfection (Funk 2020). The newborn is actively and passively immunized against hepatitis B within 12 hours. There is little data on treating HCV coinfection with oral DAAs in pregnancy. A phase I study of sofosbuvir/ledipasvir in 28 pregnant women with HCV genotype 1 mono-infection showed an SVR 12 of 100% (Chappell 2019). However, there is usually no urgency, and HCV therapy can be deferred until after pregnancy. Interferon is contraindicated, and ribavirin is considered embryo- and fetotoxic. Hepatitis coinfection may be associated with increased liver toxicity from ART. Therefore, it is recommended that liver values be checked approximately every four weeks (DAIG 2020, DHHS 2023). The mode of delivery for both coinfections depends on the HIV situation (see below).

HIV drugs during pregnancy

NRTIs (nucleoside analogs)

Nucleoside analogs are placentally acceptable. For NRTIs such as AZT, 3TC/FTC, abacavir, and TDF, the teratogenicity risk should certainly not exceed 1.5-fold (Antiretroviral Pregnancy Registry 2023). Most experience is with AZT, but it is now considered only an alternative. Follow-up of more than 20,000 infants revealed no serious adverse effects from AZT prophylaxis despite the potential mitochondrial toxicity described (The Perinatal Safety Review Working Group 2000), even with exposure in the embryonic period. The combinations of ABC/3TC and TDF/FTC have not resulted in increased congenital malformation rates. With abacavir, hypersensitivity reaction (HSR) should be considered (see chapter *ART*), and HLA-B*5701 testing before initiation of therapy is mandatory. No HSR-related complications have been reported in abacavir-exposed fetuses. Since most women with HIV become pregnant while on existing ART, toxicities of individual agents can now only be detected in large prospective studies. Further studies are needed on long-term effects in HIV- and ART-exposed, uninfected children (see below).
TDF and FTC also have good placental clearance. A meta-analysis of 17 studies found TDF to be safe for pregnant women and infants (Nachega 2017, Lockman 2021). A previously reported lower neonatal bone density and low birth weight of up to 19% with TDF in combination with various PIs (Rough 2018, Sebkiari 2019, PROMISE 077BF/FF) have not been conclusively resolved. With tenofovir-based PrEP in pregnancy, no growth disturbances were observed in newborns or in the first year of life in a small study (Heffron 2018).

Human placental transfer of TAF is low (Brooks 2021). No increased teratogenicity could be demonstrated in animal experiments. TAF is preferred over TDF in current DHHS recommendations. Despite greater weight gain with dolutegravir and TAF, gestational diabetes did not develop, and pregnancy outcome was superior to efavirenz and TDF (Chinula 2022, Lockman 2021). However, due to insufficient data, the BHIVA 2020 recommends TAF only from the 2nd trimester.

NNRTIs

Nevirapine is no longer used as first-line therapy (DHHS 2023). If pregnancy occurs while on nevirapine, it can be continued regardless of CD4 T-cell count and potential hepatotoxicity monitored. If there is an increased perinatal risk of transmission, the newborn receives one dose of nevirapine immediately after birth, another after 48–72 hours, and a third after another 96 hours. In addition to prophylactic, empiric therapeutic doses are used in neonates (see below). Efavirenz has not been confirmed to have potential human embryotoxicity (Martinez de Tejada 2018). The Tsepamo study from Botswana also found a low NTD rate of 0.04 in children born to women who had taken efavirenz periconceptually. However, a twofold increased risk of microcephaly was reported in a study of 141 children (Williams 2020). As a recommended alternative, oral rilpivirine is moderately placental (cord blood/maternal ratio 0.35–0.81), and plasma concentrations were 20–50% lower in the last trimester than postpartum. There is insufficient data on long-acting injectable (LA) rilpivirine (see below: LA cabotegravir). Etravirine showed 34% increased plasma concentrations in the third trimester, and the placental transfer rate was 0.52 (variable from 0.19 to 4.25) (Mulligan 2016); fetotoxicity was estimated to be low. Doravirine showed no reproductive toxicity in animal experiments. Insufficient human *in vivo* data are available. People with suppressed viral load may continue doravirine with frequent viral load monitoring or switch to an ARV regimen recommended for use in pregnancy.

Protease inhibitors (PIs)

PIs are also considered alternative ART in pregnancy. Possible diabetogenic effects and hepatotoxicity should be monitored every one to two months, especially in advanced pregnancy. Unlike darunavir and atazanavir, lopinavir/r is no longer recommended due to side effects.

Mild hyperbilirubinemia of approximately 1.5 mg/dl in neonates has been described with atazanavir/r at a placental transfer rate of approximately 20%. Intracellular levels were not significantly decreased during pregnancy. Increased risks for congenital skin anomalies and musculoskeletal malformations were not observed in approximately 1,500 first-trimester exposures, for an overall malformation rate of 2.11%.

Darunavir/r is the preferred protease inhibitor when a PI-based regimen is indicated (DHHS 2023). DRV has low placental clearance; despite decreasing plasma levels during pregnancy, dose adjustment is usually unnecessary (Schalkwijk 2019). However, a dose of 800/100 mg darunavir/r is considered suboptimal, with a 33–44% decrease in plasma concentrations during pregnancy and a 17–27% decrease with a single dose. Therefore, darunavir/r is recommended at 600/100 BD if therapy is continued in pregnancy. NRTI-sparing monotherapies resulted in 92.8% HIV suppression in a pilot study (Mandelbrot 2021). Darunavir/c is not recommended in the second and third trimesters because plasma levels of darunavir were 56 and 50% lower under cobicistat and 63% and 59% lower for cobicistat than postpartum (Crauwels 2019). ATV/r is an alternative PI regimen with once-daily dosing.

An increase in preterm births with PI-containing ART (Townsend 2010, Powis 2011, Sibiude 2012, Watts 2013, Schneidman 2023) has been confirmed in several studies.

Alfa-fetoprotein levels and progesterone are reported to be decreased under PI regimens, but unconjugated estriol and human chorionic gonadotropin levels are not.

Entry and fusion inhibitors

The placental toxicity of maraviroc is moderate, with a ratio of 0.25. Like T-20, the substance is now hardly needed. Fostemsavir (FTR) is placentally acceptable in animal experiments.

Integrase inhibitors

The good placental clearance of INSTI is an advantage for late-onset transmission prophylaxis. With dolutegravir, trough plasma levels were not significantly decreased in the third trimester. The unbound component appeared elevated in the third trimester compared with postpartum concentrations (Colbers 2019). The fetomaternal ratio is 1.38 (0.63–1.81) (Colbers 2019). Accumulation was reported in a preterm infant because of a fourfold longer half-life and twofold longer in mature neonates. Dolutegravir is preferred over raltegravir for acute infections because of its lower resistance rates (DHHS 2023). In a prospective study in Botswana of dolutegravir in early pregnancy, an initially significant risk of neural tube defects was not seen later in larger numbers of cases – incidence was 0.3 versus 0.1% with ART regimens without dolutegravir.

Table 2: HIV medications in pregnancy (GW = week of gestation).

NRTIs (placenta-permeable)	TAF/TDF + FTC	Bone density ↓ in newborns at TDF
	ABC + 3TC o. FTC	Because of HSR: HLAB5701 test is obligatory
	AZT + 3TC	Only alternative, AZT is metabolized in the placenta Risk for mitochondriopathy: DDI>D4T>AZT>3TC>>ABC>TDF/TAF
NNRTIs (placenta-permeable)	Efavirenz	No neural tube defects, usable in the 1st trimester
	Etravirine	Variable transfer ratio 0.52 (0.19–4.25), PK in pregnancy unchanged
	Nevirapine	No longer recommended, hepatotoxicity ↑, especially with > 250 CD4 T-cells; rapid resistance
	Rilpivirine	AUC 30% ↓ ; placental transfer 0.5 (0.35–0.81)
	Doravirine	Placental transfer 0.5, insufficient data
PIs (low placenta-permeable)	Darunavir/r	Low placental toxicity, 2 x daily dosage
	Darunavir/c	Low levels, therefore avoid or close VL monitoring
	Atazanavir/r	Alternative recommended PI, alternative ARV, hyperbilirubinemia,
	Lopinavir/r	2 x daily dosing, dose increase if necessary, lipids ↑
Integrase inhibitors (high placental transfer)	Dolutegravir	Rather not before 8 weeks of gestation due to neural tube defects; placental transfer 1.38 (0.63–1.81), HWZ ↑ at NG, higher resistance barrier than RAL
	Raltegravir	Rapid reduction of viral load, half life ↑ in NG, BID
	Elvitegravir/c	Low levels; not recommended as initial therapy
	Bictegravir	High placental transfer in individual cases PM transfer, insufficient data
	Cabotegravir IM	Long half-life, insufficient data on pregnancy

Raltegravir is now recommended as an alternative rather than preferred ARVs for use in pregnancy (DHHS 2023). It also shows good placental transfer and rapid viral load reduction. *In vitro,* it does not affect neonatal hyperbilirubinemia. Compared with efavirenz, it showed no differences in neonatal size and weight. If raltegravir is taken during pregnancy, before and during delivery, there is a risk of accumulation in the neonate. Therefore, potentially subsequent neonatal PEP with raltegravir is not recommended until 1–2 days. Elvitegravir/c is not used for initial therapy due to lowered plasma levels in the 2nd and 3rd trimesters. No toxicities have been reported with bictegravir from 235 pregnancies. No embryofetotoxicity has been reported in animal experiments. Placental transfer was low in *ex vivo* models, as it was for cabotegravir. In contrast, high placental transfer was present for bictegravir, with a fetomaternal ratio of 1.42 (Bukkems 2021). According to pharmacokinetics models, dose adjustment in pregnancy is unnecessary (Atoyebi 2022). However, due to insufficient data about the use of bictegravir in pregnancy, people who present on this regimen with a suppressed viral load may continue their current treatment with frequent viral load monitoring or switch to an ARV regimen that is recommended for use in pregnancy (DHHS 2023). Some pregnancy data exist for long-acting injectable cabotegravir and rilpivirine (Patel 2023). Counseling is recommended to support informed decisions about whether to continue with frequent viral load monitoring or consider switching to a three-drug regimen recommended for use in pregnancy.

Teratogenicity and long-term effects in children after intrauterine ART exposure

Overall, embryonic and fetal toxicity appears low (APR 2023). However, long-term data are incomplete. In a prospective study of 2,644 ART-exposed, uninfected children, neurologic symptoms were seen in 0.26%, and language development delays were seen in other follow-up (Wedderburn 2019). Delays in auditory evoked potentials and nonspecific changes in cerebral MRIs of children perinatally exposed to AZT and 3TC were described. In another study, no developmental delays could be demonstrated in children exposed to HIV and in 64% exposed to AZT at 24 months of age compared with children not exposed to HIV and/or ART (Chaudhury 2017). Cardiac changes were transient (Garcia-Otero 2016) or undetectable. Elevated lactate levels, impaired hematopoiesis, and metabolic changes regarding hyperlactatemia syndrome can be detected in children long after antiretroviral prophylaxis. A meta-analysis of 22 studies found increased mortality in HIV- and ART-exposed children. Mitochondrial toxicities associated with prenatal ART exposure have been described (Poirier 2015) as having immunologic defects and a higher incidence of severe infections and hospitalizations (Slogrove 2017). Furthermore, growth disturbances have been noted in children with prenatal ART exposure (Sudfeld 2016) and persistent lower weight curves in the first year of life (Le Roux 2019). Alterations in lipid metabolism were reported by Williams 2016. Overweighed HIV-exposed adolescents were at greater risk for elevated blood pressure compared with overweighed children and adolescents in the general population (Jao 2019). Furthermore, neurocognitive impairment has been reported in prenatally ART-exposed children. However, many studies are inconsistent and methodologically inadequate, and high-quality long-term studies are needed.

Risk of perinatal HIV infection

About 75% of HIV is transmitted during or in the last weeks before birth. About 10% of vertical HIV infections occur before the third trimester, and 10–15% occur through breastfeeding. The likelihood of HIV transmission correlates with viral load and treat-

ment duration. This is also true for women on ART (Table 3). The probability is extremely low if the viral load is below the detection limit. Vaginal births have thus become possible, as has the omission of post-exposure prophylaxis in the newborn (neo-PEP). In contrast, lack of or inadequate HIV suppression increases the risk of transmission. The combination of plasma viremia and prematurity and/or premature rupture of membranes poses an additional transmission risk. It is, therefore, essential to reduce plasma viremia and improve the mother's immune status. ART should also be taken at the prescribed times during delivery, if possible. Resistance is still thought to be involved in about 20% of the current HIV transmission rate of less than 2%. The risk is increased in women infected with HIV perinatally, but it remains below 1% even here.

Table 3: Risk factors of perinatal HIV transmission.

High maternal viral load, low CD4 T-cell count
Mother's disease
Vaginal delivery if ≥ 50 HIV RNA copies/mL without ART (DHHS: if >1000 copies/mL)
Premature rupture of membranes of more than four hours in HI viremia
Premature birth with viremia (< 37th week of pregnancy)
Breastfeeding in the setting of viremia

Medical prevention, in addition to maternal ART, includes:
- Antiretroviral prophylaxis before and during birth (with HI viral load >50 copies/mL in 36 weeks of gestation) by INSTIs (dolutegravir, raltegravir) and AZT intravenously
- The primary cesarean section on the laborless uterus, as vaginal delivery increases the risk of transmission at a viral load of ≥50 copies/mL
- The postnatal antiretroviral postexposure prophylaxis of children (escalated).
- The avoidance of breastfeeding

Transmission prophylaxis pre/intrapartum at <50 copies/mL: low transmission risk

Combination therapy of pregnant women with two NRTIs and either INSTI, boosted PI, or NNRTI is sufficient as preexposure prophylaxis of perinatal HIV transmission, provided the viral load is below 50 copies/mL (<1,000 copies/mL according to US guidelines). Intravenous AZT administration during delivery is not recommended. Neonatal PEP can also be omitted if the viral load is consistently below 50 copies/mL before and during pregnancy (DAIG 2020).

Prophylaxis for ≥ 50 copies/mL: increased risk of transmission

If there is a standard risk and the viral load is above 50 copies/mL prepartum, resistance testing is performed, adherence is evaluated, and ART is escalated with an INSTI if necessary. At parturition, intravenous AZT is administered. While the transmission rate was 0.05 and 0.3% for less than 50 copies/mL, it is 1.1 and 1.5% between 50 and 399 copies/mL, and 2.8 and 4.1% for a prepartum viral load of >400 copies/mL (Townsend 2014). Delivery is by sectio. Neonatal combination prophylaxis is probably reasonable. Depending on the assessment of risk, mono-PEP with AZT for four weeks is given to the infant or dual- or triple-combination prophylaxis is given.

Intrapartum prophylaxis/therapy without prior treatment

If HIV infection is not known until the time of birth, mother and newborn receive dual or triple prophylaxis with AZT (plus FTC/3TC as well as an INSTI and/or

nevirapine (in the newborn) (increased risk with low viral load or significantly increased risk with high viral load and/or obstetric complications). The 2022 US guidelines recommend dolutegravir as an alternative for acute HIV infection in pregnancy because of lower HIV resistance rates than raltegravir.

Table 4: Transmission prophylaxis for prepartum viral load ≥ 50 HIV RNA copies/mL.

Resistance testing, if necessary, therapy escalation, e.g., with an INSTI Two NRTI + plus INSTI or PI/r
During delivery (elective sectio at the earliest from 37 + 0 weeks of gestation), AZT is infused intravenously into the mother for standard prophylaxis if VL > 50 (DHHS: > 1,000) copies/mL*: 2 mg/kg i.v. as "loading dose" over 1 hour approx. 3 hours preoperatively/prepartum). 1 mg/kg i.v. intraoperatively/intrapartum) until the child develops
In the newborn, AZT monoprophylaxis within 6 hours postpartum: 2 (4) mg/kg orally every 6 (12) hours for 4** weeks or if orally intolerant: 1.5 mg/kg i.v. every 6 hours for 10 days In case of additional risk factors, extended postnatal prophylaxis (combination Neo-PEP).

* The benefit of intravenous AZT at viral load <50 (<1,000) copies/mL is not specific (DAIG 2020, DHHS 2023, EACS 2022). Therefore, AZT can then be omitted
** 4 weeks e.g. at >50 to <1,000 copies/mL. In case of additional risk factors, extended PEP (see below).

Treatment during birth

Prerequisites for a vaginal delivery mode

If the viral load is less than 50 copies/mL before delivery (viral load negative at 34 to 36 weeks of gestation), the advantage of elective (primary) sectio over vaginal delivery is no longer demonstrable (Townsend 2014). Therefore, in most countries, unless obstetric complications are anticipated, these women are scheduled for a vaginal delivery, which is lower risk compared with a sectio. The rate of vaginal deliveries in Western Europe is approximately 50%. In the American guidelines, vaginal delivery is recommended if the viral load is less than 1,000 copies/mL, if necessary with intravenous AZT administration.

No increased risk has been demonstrated with surgical vaginal delivery (e.g., vacuum extraction). Similarly, premature rupture of the membranes, amniotic infection syndrome, and prematurity are not thought to pose an increased risk of transmission if the viral load is negative. Even extreme prematurity of <30 weeks of gestation is unlikely to pose an increased risk if viral load is consistently negative. Previous studies on transmission risk have sometimes reached divergent results (Townsend 2010). Therefore, even in preterm infants, monoexposure prophylaxis with AZT for 2 (to 4) weeks is sufficient. Neonatal PEP can be dispensed if the viral load is constantly undetectable during pregnancy.

Elective caesarian section for elevated viral load prepartum

If there is a risk of transmission due to incomplete reduction of the viral load (noncompliance, later prepartum HIV diagnosis), ART is started or escalated if time permits (see above), and AZT is infused intravenously as transmission prophylaxis during delivery. Sectio is performed electively before the onset of labor and at the earliest from 37+0 weeks of gestation using a low-bleeding surgical technique, according to Misgav-Ladach, swiftly and by experienced gynecologists. Blunt dissection and development of the child in the standing amniotic sac are considered ideal.

Table 5: Prophylaxis for low transmission risk in preterm and mature infants and prepartum viral load (VL) <50 HIV RNA copies/mL.

Low risk	Mother	Child
≥ 35 weeks of gestation of mothers with HI-VL prepartum <50 without adherence problems	Combination, e.g., TDF + FTC (3TC) or ABC/(AZT) + FTC (3TC) plus INSTI, alternatively PI/r, NNRTIs possible if indicated, vaginal	Within 6 hrs postpartum AZT 2 x 4 mg/kg orally 2(–4) weeks, alternative: i.v. 2 x 3mg/kg* Sustained VL below 50 copies/mL during pregnancy: Neo-PEP dispensable
Premature birth 30+0–34+6 weeks of gestation and VL <50 Premature birth ** < 30+0 weeks of gestation and VL < 50	Combination, e.g. AZT + FTC (3TC) or TDF + FTC (3TC) plus INSTI, alternatively PI/r, if necessary NNRTI Mode of birth according to obstetric criteria; see above	2 x 2 mg/kg orally or 2 x 1.5 mg/kg i.v., from day 15: 2 x 3 mg/kg orally AZT 2–4 weeks for preterm birth <30+0 weeks of gestation from day 29

* For oral feeding problems; p.p. = postpartum. VL = viral load, HIV RNA copies/mL.

Table 6: Prophylaxis for increased risk: viral load ≥ 50 copies/mL.

Increased risk	Mother	Child
Mother without sufficient HIV therapy before and during delivery (viral load ≥ 50 copies/mL): Especially after vaginal delivery No ART pre- and/or intrapartum	If necessary, escalation of ART with, e.g., Dolutegravir or Raltegravir	≥35 weeks of gestation: AZT 2 x 4 mg/kg orally: AZT dosage for preterm birth <35+0 weeks of gestation: 2 x 2 mg/kg orally or 2 x 1.5 mg/kg i.v., from day 15: 2 x 3 mg/kg orally (for preterm birth <30+0 weeks of gestation from day 29) for 4–6 weeks plus if necessary 3TC** 2 x 2 mg/kg over 2 weeks plus Nevirapine* 2 mg/kg within 2 h to 48 h + 2nd dose 48 h after 1st *** Or if appropriate, raltegravir**** 1.5 mg/kg up to 7 days, 2 x 3 mg/kg 8-28 days, > 4 wks u. >3kg 2 x 6 mg/kg

*See chapter NNRTIs. **Caution: neutropenia in combination with AZT, in preterm infants: rather not use 3TC; *** according to DHHS 2023: 1st dose: after birth until 48 h, 2nd dose: 48 h after 1st, 3rd dose: 96 h after 2nd **** Approval for newborns ≥37 weeks of gestation ≥2 kg.

In the case of premature birth, the caesarian (C-) section is also essential for obstetric reasons to avoid hypoxia of the premature baby; the specifics for prophylaxis are listed above. In case of premature rupture of membranes of less than four hours, a C-section is reasonable if the situation still allows it. If it takes more than four hours, there is no advantage over vaginal delivery. However, this should be done quickly, as the risk of HIV transmission increases by about 2% per hour, depending on viral load. It is then essential to extend precautions to the child (Table 6).

Unknown HIV status

If the HIV status is unknown at the time of birth and a suspicion exists, a rapid HIV test is recommended. Because of the high but insufficient specificity, using two rapid tests from different manufacturers is advisable. If one test is negative, there is probably no infection.

Treatment of the newborn

Standard postnatal prophylaxis for VL < 50 copies/mL: low risk

Postnatal transmission prophylaxis in the case of negative viral load and low risk of transmission begins, if possible, within the first 4–6 hours after birth with oral or intravenous AZT prophylaxis in the case of gastrointestinal symptoms. The duration of standard oral prophylaxis is two (to four) weeks (Vocks-Hauck 2001, Neubert 2013). For negative viral load, DAIG (2020) and the British HIV Association (BHIVA 2020) suggest two weeks in newborns whose mothers have been on antiretroviral treatment for at least 10 weeks and in whom a negative viral load has been documented at least twice, most recently four weeks or later before delivery (at or after 36 weeks of gestation), and four weeks in the United States. If HIV was already undetectable preconceptually up to delivery, neonatal PEP may be omitted entirely (DAIG 2020).

Prophylaxis for increased transmission risk with VL ≥ 50 copies/mL

An increased risk exists at a viral load above 50 copies/mL. In the US guidelines, a viral load of 1,000 copies/mL is considered the limit for increased risk of transmission. Still, escalation of Neo-PEP is considered reasonable at a prepartum viral load of 50 to 1,000 copies/mL. Additional risks such as prematurity, premature rupture of the membranes, amniotic infection syndrome, viral load far above 1,000 copies/mL before birth, lack of transmission prophylaxis, cut injury to the child during sectio, and aspiration of bloody amniotic fluid from the gastrointestinal or respiratory tract if the mother's viral load is detectable before delivery are criteria for escalation.

In children with these additional transmission risks, combination prophylaxis of AZT+3TC and three administrations of nevirapine are recommended. In the first week, this is administered immediately after birth, 48 hours after the first dose, and 96 hours after the second dose. Newborns receive prolonged AZT prophylaxis (see below) for four to six weeks. Because of the increased toxicity with the combination, 3TC is recommended for only two weeks. In very small preterm infants, dose recommendations exist for AZT and NVP, so only dual prophylaxis may be possible here. Raltegravir has approval in neonates >37 weeks of gestation and weighing more than 2 kg. If INSTIs were given long-term during pregnancy or before birth, there is a risk of accumulation in the newborn. Therefore, it is recommended that INSTI-PEP not be started in the newborn until the second or third day of life. If late initiation of prenatal therapy has failed to prevent an intrauterine infection that has already occurred, empiric combination therapy started neonatally will transition to ART in the infant. Dolutegravir is approved in infants weighing 3 kg or more and four weeks of age.

The UK guidelines recommend nevirapine, raltegravir, and TDF in double doses intrapartum to achieve an initial dose in the preterm infant if the woman is at risk of preterm birth and presents late in pregnancy.

Data on PIs are limited to neonates. Lopinavir/r was associated with increased cardiac toxicity in preterm infants. Adrenal insufficiency was also observed in neonates who were prenatally exposed to lopinavir/r and received postnatal PEP for 30 days. Therefore, it is used in the first two weeks of life only in exceptional cases. In premature infants, administration is not recommended until two weeks after the expected date of birth.

Procedure in the absence of pre- and intranatal prophylaxis

Combination prophylaxis with AZT(+3TC) begins as early as possible within the first 6 to 12 hours after birth. In addition, postnatal nevirapine prophylaxis is given in three doses or raltegravir. Because of the toxicity of lopinavir/r, its use in mature

Table 7: Studies of antiretroviral prophylaxis in neonates.

Short name	Medium Daily dose	Most common Side effects	Studies/Approval in newborns
AZT Retrovir®	2 x 4 mg/kg, 2 x 2 mg/kg for premature infants <35 weeks of gestation, from day 15: 2 x 3 mg/kg, for < 30 weeks of gestation from day 29	Anemia, neutropenia in combination with 3TC, mitochondriopathy	(P)ACTG 076, 316, 321, 331 (FG) 353, 354, 358,HIVNET 012 III Approval
3TC Epivir®	2 x 2(3) mg/kg in newborns (< 30 days), 2 x 4 mg/kg in ≥ 4 wks	Gastrointestinal symptoms, mitochondriopathy in combination intolerance in premature infants	PACTG 358 NICHD/HPTN 040/ PACTG1043 Limited data
FTC Emtriva®	1 mg/kg immediately post-natal or 2 mg/kg after 12 h; 3 mg/kg for neonates < 3 mo	Gastrointestinal symptoms, mitochondriopathy	ANRS 12109 Gilead PK Study
ABC Ziagen®	1 x 2–4 mg/kg; > 1 mo. 2 x 8 mg/kg (study).	Hypersensitivity reaction, mitochondriopathy, lactic acidosis	PACTG 321
TDF Viread®	Mother 600 mg intrapartum; newborn 6 mg p.n. daily (1st week); 1 x 8 mg in children ≥ 2 years	Osteopenia, nephrotoxicity	NCT00120471 HPTN 057; ANRS12109 (step 2)
NVP Viramune®	14 days 1 x 2–4 mg/kg or 1 x 120 mg/m², then 2 x 3.5–4 mg/kg or 2 x 120 mg/m² (maximum 2 x 200 mg), 6 mg/kg	Hepatotoxicity, exanthema, hyperbilirubinemia	PACTG 316,356, HIVNET 012
Lopinavir/r Kaletra®	2 x 300/75 mg/m² in children >2 < 6 weeks; in premature infants >2 wks after calculated date	Gastrointestinal, cardiotoxic and adrenal insufficiency in newborns, not in newborns <2 wk; in premature infants not until 2 wk after the calculated date	PACTG P 1030 IMPAACTG P1060 Admission: Children >2 Wo
Dolutegravir Tivicay®	Approx.1 mg/kg children ≥ 3–6 kg u. 4 wks = 5 mg	Gastrointestinal and CNS adverse events	IMPAACT P 1093
Raltegravir Isentress®	1x1.5 mg/kg up to 7 days (>2 kg), 2x3 mg/kg day 8-28, then 2 x 6 mg/kg children ≥ 4 wk ≥3 kg	for newborns: half-life ↑	IMPAACT P 1066 IMPAACT P 1110 Admission 2019

(P)ACTG = (Pediatric) AIDS Clinical Trials Group; IMPAACTG = International Maternal Pediatric Adolescent ACTG; HIV-NAT = HIV-Netherlands Australia Thailand Research Collaboration; ANRS = Agence Nationale de Recherche sur le Sida; HPTN = HIV Prevention Trials Network; NCT = NIAID (National Institute of Allergy and Infectious Diseases) Clinical Trials.

Note: Except for AZT in mature infants, dosages were taken from studies. Unapproved substances should be used in neonates only in studies.

infants has not been recommended until two weeks of age and in preterm infants until two weeks after the calculated date of birth. If HIV infection is unknown until after birth, early initiation of combination prophylaxis/therapy appears significantly more effective. Because of potential accumulation, combination PEP/start with raltegravir is not initiated until 1–2 days after birth.

Counseling and care for women breastfeeding under ART

In countries without limited access to safe drinking water and where substitute foods are readily available, breastfeeding continues to be discouraged. Even with a negative viral load, there is a residual risk of HIV transmission, and ART toxicity may be prolonged (Yuhin 2016).

In several European countries such as Germany, 83% of all children without HIV exposure were initially breastfed in 2007–2011, on average for eight months. Women with HIV infection expressed the wish to breastfeed their child in 38% of cases (Kahlert 2018). This was implemented and documented under the professional supervision of interdisciplinary teams of midwives, psychologists, and physicians. Infections did not occur in this group of more than 50 mother-infant pairs (Haberl 2021). In 72 people who breastfed in the US and Canada, there was no HIV transmission to the child (Levison 2023). The transfer of well-breastfed antiretroviral agents (Waitt 2019) into the infant's plasma is low. It is 3–8% of the maternal concentration. Breast milk transfer studies of efavirenz (BM/P ratio 0.82, Olagunju 2019), etravirine (3.21, Spencer 2019), FTC (3.01), and TDF (0.015, Waitt 2018) and TAF each resulted in low or undetectable levels in the infant. In women taking PrEP while breastfeeding, estimated plasma levels of TDF/FTC were <0.01 and 0.5%, respectively, compared to the pediatric doses (Mugwanya 2016).

Further studies on HIV prevention in newborns

A review of neonatal pharmacokinetics studies is provided in Table 7. Careful documentation of clinical data is needed to improve ART during pregnancy and prophylaxis of perinatal HIV infection (www.APRegistry.com).

Literature

Antiretroviral pregnancy registry. Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 January 2023. http://www.apregistry.com

Atoyebi SA, Bunglawala FS, Cottura N, et al. PBPK Modeling of long-acting injectable cabotegravir in pregnancy. Abstract 686, CROI 2022.

Barlow-Mosha L, Serunjogi R, Kalibbala D, et al. Prevalence of neural tube defects, maternal HIV status, and antiretroviral therapy from a hospital-based birth defect surveillance in Kampala, Uganda. Birth Defects Res 2022; 114: 95-104

Benki-Nugent SF, Yunusa R, Mueni A, et al. Lower neurocognitive functioning in HIV-exposed uninfected children compared with that in HIV-unexposed children. J Acquir Immune Defic Syndr 2022, 89:441-7.

British HIV Association. BHIVA guidelines on the management of HIV in pregnancy and postpartum 2018 (2020 third interim update). 2020. Available at: http://www.bhiva.org/pregnancy-guidelines

Bollen P, Freriksen J, Konopnicki D, et al. Pharmacokinetics of antiretroviral agents in HIV-infected pregnant women network. The effect of pregnancy on the pharmacokinetics of total and unbound Dolutegravir and its main metabolite in women living with HIV. Clin Infect Dis 2021, 72:121-127.

Brooks KM, Momper JD, Pinilla M, et al. IMPAACT P1026s Protocol Team. Pharmacokinetics of tenofovir alafenamide with and without cobicistat in pregnant and postpartum women living with HIV. AIDS 2021; 35:407-417

Byrne L, Sconza R, Foster C, et al. Pregnancy incidence and outcomes in women with perinatal infection. AIDS 2017; 31: 1745-54

Brooks KM, Pinilla M, Stek AM, et al. Pharmacokinetics of tenofovir alafenamide with boosted protease inhibitors in pregnant and postpartum women living with HIV: Results from IMPAACT P1026s. J Acquir Immune Defic Syndr 2022 Feb 21.

Bundesamt für Gesundheit (BAG). Empfehlungen der eidgenössischen Kommission für sexuelle Gesundheit (EKSG) zur Prävention der HIV-Übertragung von der Mutter auf das Kind. 2016; Bulletin 4: 80-81 bag.admin.ch

Bukkems VE, Necsoi C, Tenario CH, et al. Tenofovir alafenamide plasma concentrations are reduced in pregnant women living with HIV: data from the PANNA Network. Clin Infect Dis 2021, Dec 5

Chappell CA, Krans E, Bunge K, et al. A phase 1 study of Ledipasvir/Sofosbuvir in pregnant women with hepatitis C virus. CROI 2019 Abstract # LB87

Chaudhury S, Williams PL, Mayondi GK, et al. Neurodevelopmental delay of HIV-exposed and HIV-unexposed uninfected children at 24 months. Pediatrics 2017. 140: pii: 20170998.

Chinula L, Goldberg E, Ziemba L, et al. Pregnancy hemoglobin A1c and glucose with DTG vs EFV, TDF vs TAF: IMPAACT 2010. Abstract 967, CROI 2022

Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of HIV type 1 with zidovudine treatment. NEJM 1994; 331:1173-80.

Crauwels HM, Osiyemi O, Zorilla C, et al. Reduced exposure to darunavir and cobicistat in HIV-1-infected pregnant women receiving a darunavir and cobicistat-based regimen. HIV Med 2019; 20: 227-343

Cressey TR, Punyawudho B, Le Coeur, et al. Assessment of Nevirapine prophylactic and therapeutic dosing regimens for neonates. J AIDS 2017; 75: 554-60

Delaugerre C, Chaix ML, Blanche S, et al. Perinatal acquisition of drug-resistent HIV-1 infection: mechanism and long term outcome. Retrovirology 2009; 19: 85

Deutsche AIDS-Gesellschaft (DAIG), Österreichische AIDS-Gesellschaft (ÖAG), Robert Koch Institut et al. Deutsch-Österreichische Leitlinien zur Therapie in der Schwangerschaft und zur Prophylaxe beim Neugeborenen. Stand September 2020. http://www.daignet.de ; und awmf.org.

Deutsche AIDS-Gesellschaft (DAIG), Österreichische AIDS-Gesellschaft (OÄG), Robert Koch Institut, et al. Deutsch-Österreichische Leitlinien zur antiretroviralen Therapie der HIV-Infektion. Stand September 2020

Department of Health and Human Services USA (DHHS). Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Recommendations of the panel on clinical practices for treatment of HIV. May 26, 2023. http://www.AIDSinfo.nih.gov

Department of Health and Human Services USA (DHHS). Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. January 31, 2023. http://www.AIDSinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf

Department of Health and Human Services USA (DHHS), Guidelines for the use of antiretroviral agents in pediatric HIV infection. April 11, 2013 http://www.AIDSinfo.nih.gov

Dickinson L, Walimbwa S, Singh Y, et al. Infant exposure to Dolutegravir through placental and breast milk transfer: a population pharmacokinetic analysis of DolPHIN-1. Clin Infect Dis 2021; 73: 1200-7.

Dunk CE, Serghides L. Protease inhibitor-based antiretroviral therapy in pregnancy: effects on hormones, placenta, and decidua. Lancet HIV 2022:120-9

Eke AC, Brooks KM, Gebreyohannes RD, et al. Tenofovir alafenamide use in pregnant and lactating women living with HIV. Expert Opin Drug Metab Toxicol 2020, 16:333-342. 29.

Eke AC, Stek AM, Wang J, Kreitchmann R, et al. Darunavir Pharmacokinetics With an Increased Dose During Pregnancy. J AIDS 2020;83:373-380.

European AIDS Clinical Society (EACS). Clinical Management and Treatment of HIV Infected Adults in Europe. English Version 11.1. Oktober 2022. http://www.europeanaidsclinicalsociety.org/guidelines.asp

European Collaborative Study. Mother-to-child transmission of HIV infection in the era of HAART. Clin Infect Dis 2005; 40: 458-65.

Funk AL, Lu Y, Yoshida K, et al. Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of hepatitis B virus: a systematic review and meta-analysis. Lancet Infect Dis 2021; 21:70-84

Garcia-Otero L, Lopez M, Gomez O, et al. Zidovudine treatment in HIV-infected pregnant women is associated with fetal cardiac remodelling. AIDS 2016; 30: 1392-401

García-Otero L, López M, Goncé A, et al. Cardiac remodeling and hypertension in HIV-uninfected infants exposed in utero to antiretroviral therapy. Clin Infect Dis 2021; 73:586-593.

Gotham D, Hill A, Pozniak AL. Candidates for inclusion in a universal antiretroviral regimen: tenofovir alafenamide. Curr Opin HIVAIDS 2017; 4: 324-33

Haberl L, Audebert F, Feiterna-Sperling C, et al. Not Recommended, But Done: Breastfeeding with HIV in Germany. AIDS Patient Care STDs 2021; 35: 33-38

Heffron R, Mugo N, Hong T, et al. Pregnancy outcomes and infant growth among babies with in-utero exposure to tenofovir-based preexposure prophylaxis for HIV prevention. AIDS. 2018; 32: 1707-13

Jacobs TG, van Aerde KJ, Colbers A, Burger DM. Raltegravir-based postnatal HIV prophylaxis therapy in a neonate after in-utero Dolutegravir exposure. Pediatr Infect Dis J 2022; 41: 131-2

Jao J, Jacobson DL, Yu W, et al. A comparison of metabolic outcomes between obese HIV-exposed uninfected youth from the PHACS Smartt study and HIV-unexposed youth from the NHANES study in the United States. J Acquir Immune Defic Syndr 2019; 81: 319-27

Joseph NT, Satten GA, Williams RE, et al. The effect of antiretroviral therapy for the treatment of HIV-1 in pregnancy on gestational weight gain. Clin Infect Dis. 2021: Epub ahead of print. PMID: 34864949.

Kahlert CR, Aebi-Popp K, Bernasconi E, et al. Is breastfeeding an equipoise option in effectly treated HIV-infected mothers in a high-income setting. Swiss Med Wkly 2018; https://doi.org/10.4414/smw.2018.14648

Kapetanovic S, Giganti MJ, Abzug MJ, et al. International maternal pediatric adolescent AIDS clinical trials (IMPAACT) network. Plasma biomarker factors associated with neurodevelopmental outcomes in children with perinatal HIV infection and controlled viremia. AIDS 2021; 35: 1375-84

Le Roux SM, Abrams EJ, Donald KA, et al. Growth trajectories of breastfed HIV-exposed uninfected and HIV-unexposed children under conditions of universal maternal antiretroviral therapy: a prospective study. Lancet Child Adolesc Health 2019; 3: 243-44.

Lé MP, Pencolé L, Peytavin G, et al. Placental transfer of doravirine, a recent HIV-1 NNRTI in the ex vivo human cotyledon perfusion model. J Antimicrob Chemother 2021;76: 2364-7.

Levison J, McKinney J, Duque A, et al. Breastfeeding among people with HIV in North America: a multisite study. Clin Infect Dis. 2023 Apr 20; ciad235.doi 10.1093

Lyerly AD, Beigi R, Bekker LG, et al. Ending the evidence gap for pregnancy, HIV and co-infections: ethics guidance from the PHASES project. J Int AIDS Soc 2021, 24:e25846.

Lockman S, Brummel SS, Ziemba L, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. Lancet 2021, 397:1276-1292.

Lommerse J, Clarke D, Kerbusch T, et al. Maternal-neonatal raltegravir population pharmacokinetics modeling: implications for initial neonatal dosing. CPT Phamacokinetics Syst Pharmacol 2019: doi: 10.1002/psp4.12443

Mandelbrot L, Ceccaldi PF, Duro D, et al. Placental transfer and tissue accumulation of dolutegravir in the ex vivo human cotyledon perfusion model. PLoS One 2019, 14(8):e0220323.

Mandelbrot L, Tubiana R, Frange PH, et al. NRTI-sparing strategy to prevent perinatal HIV transmission, ANRS 168 monogest trial. Abstract 570, CROI 2021

Martinez de Tejada B, European Pregnancy and Paediatric HIV Cohort Collaboration Study Group. Birth defects after exposure to Efavirenz-based antiretroviral therapy at conception/first trimester of pregnancy: a multicohort analysis. J Aquir Immune Defic Syndr 2019; 80: 316-24

Momper JD, WanewbornJ, Stek A, et al. IMPAACT P1026s Protocol Team. Pharmacokinetics of darunavir and cobicistat in pregnant and postpartum women with HIV. AIDS 2021, 35:1191-1199

Mugwanya KK, Hendrix CW, Mugo NR, et al. Pre-exposure prophylaxis use by breastfeeding HIV-uninfected women: Prospective short-term study of antiretroviral excretion in breast milk and infant absorption .PLoS Med 13:e1002132.

Nachega JB, Uthman OA, Mofenson LM, et al. Safety of tenofovir disoproxil fumarate-based antiretroviral therapy regimens in pregnancy for HIV-infected women and their infants: a systematic review and meta-analysis. J Aquir Immune Defic Syndr 2017; 76: 1-12

Neubert J, Pfeffer M, Borkhardt A, et al. Risk adapted transmission prophylaxis to prevent vertical HIV-1 transmission: Efectiveness and safety of an abbreviated regimen of postnatal oral zidovudine. BMC Pregnancy Childbirth 2013 Jan 24; 13:22

Patel P, Ford SL, Baker M, et al. Pregnancy outcomes and Pharmocokinetics in pregnant womes living with HIV exposed to long-acting cabotegravir and rilpivirine in clinical trials. HIV Med 2023;24: 568-79

Pencolé L, Lê MP, Bouchet-Crivat F, et al. Placental transfer of the integrase strand inhibitors cabotegravir and bictegravir in the ex-vivo human cotyledon perfusion model. AIDS. 2020; 34: 2145-9

Peyronnet V, Warszawski J, Sibiude J, et al. Does changing antiretroviral therapy in the first trimester of pregnancy for safety concerns have an impact on viral suppression? J Acquir Immune Defic Syndr 2019; 80: 574-84

Poirier MC, Gibbons AT, Rugeles MT, et al. Fetal consequences of maternal antiretroviral nucleoside reverse transcriptase inhibitor use in human an nonhuman primate pregnancy. Curr Opin Pediatr 2015; 27: 233-9

Powis KM, Kitch D, Ogwu A, et al. Increased risk of preterm delivery among HIV-infected women randomized to protease versus nucleoside reverse transcriptase inhibitor-based HAART during pregnancy. J Infect Dis 2011; 15: 506-14

Rachas A, Warszawski J, Le Chenadec J, et al. Does pregnancy affect the early response to cART? AIDS 2013; 27: 357-67

Rough K, Seage GR 3rd, Williams PL, et al. Birth outcomes for pregnant women with HIV using tenofovir-emtricabine. NEJM 2018, 378: 1593-1603.

Schalkwijk S, Colbers A, Konopnicki D, et al. Lowered rilpivirine exposure during the third trimester of pregnancy in HIV type 1-infected women. Pharmacokinetics of newly developed antiretroviral agents in HIV-infected pregnant women (PANNA) network. Clin Infect Dis 2017, 65: 1335-41

Schalkwijk S, Ter Heine R, Colbers A, et al. Evaluating darunavir/ritonavir dosing regimens for HIV-positive pregnant women using semi-mechanistic pharmacokinetic modelling. J Antimicrob Chemother 2019; 74: 1348-56.

Schneidman J, Lee T, Sauve L, et al. Type and timing of antiretroviral therapy during pregnancy: Impact on risk of preterm delivery and small-for-gestational age births in Canada, a retrospective cohort study. Int J Gynecol Obstet 2023 Jan 27 doi: 10/1002/ijgo.

Sibiude J, Warszawski J, Tubiana R, et al. Premature delivery in HIV-infected women starting protease inhibitor therapy during pregnancy: role of the ritonavir boost. Clin Infect Dis 2012; 54: 1348-60.

Slogrove AL, Esser MM, Cotton MF, et al. A prospective cohort study of common childhood infections in South African HIV-exposed infants. Pediat Infect Dis 2017; 26: e38-e44.

Stek AM, Best BM, Luo W, et al. Effect of pregnancy on emtricitabine pharmacokinetics. HIV Med 2012, 13:226-35.

Stek A, Best BM, Wang J, et al. Pharmacokinetics of once versus twice daily darunavir in pregnant HIV-infected women. J AIDS 2015; 70: 33-44

Sudfeld CR, Lei Q, Chinyanga Y, et al. Linear growth faltering among HIV-exposed uninfected children. J AIDS 2016; 73:182-9

The Perinatal Safety Review Working Group. Nucleoside exposure in the children of HIV-infected women receiving antiviral drugs: absence of clear evidence for mitochondrial disease in children who died before 5 years of age in five united states cohorts. J AIDS Hum Retrovirol 2000; 15: 261-8.

Townsend C, Schulte J, Thorne C, et al. Antiretroviral therapy and preterm delivery – a pooled analysis of data from the United States and Europe. BJOG 2010; 117: 1399-40

Townsend CL, Byrne L, Cortina-Borja M, et al. Earlier initiation of ART and further decline in mother to child transmission rates 2000-2011. AIDS 2014;28: 1049-57

Van De Ven NS, Pozniak AL, Levi JA, et al. Analysis of pharmacovigilance databases for dolutegravir safety in pregnancy. Clin Infect Dis 2019; doi:10.1093/cid/ciz684

Venkatesh KK, Edmonds A, Westreich D, et al. Associations between HIV, antiretroviral therapy and preterm birth in the US Women's Interagency HIV Study, 1995-2018: a prospective cohort. HIV Med. 2022; 23: 406-16

Vitoria M, Ford N, Claydon P, et al. When could new antiretrovirals be recommended in low-income and middle-income countries: results of a WHO think tank. Curr opinion HIV AIDS: 2017: 414-22.

Vocks-Hauck M. HIV-Infektion und AIDS bei Neugeborenen, Kindern und Jugendlichen. In L'Age-Stehr J, Helm EB (Hrsg). AIDS und die Vorstadien. Ein Leitfaden für Klinik und Praxis. Springer Verlag 2001; Bd 1: 1-49.

Wade NA, Bearkhead GS, Warren BL, et al. Abbreviated regiments of zidovudine prophylaxis and perinatal transmission of the HIV. NEJM 1998; 339: 1409-14.

Wade NA, Unadkad JD, Huang S, et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: Pediatric AIDS Clinical Trials Group protocol 332. J Infect Dis 2004; 190: 2167-74.

Waitt C, Orrell C, Walimbwa S, et al. Safety and pharmacokinetics of dolutegravir in pregnant mothers with HIV infection and their neonates: A randomized study trial (DolPHIN-1 study). PLoS Med 2019; 16: doi:10.1371/journal.pmed.1002895

Watts DH, Williams PL, Kacanek D, et al. Combination antiretroviral use and preterm birth. J Infect Dis 2013, 207:612-621.

Wedderburn CJ, Yeung S, Rehman AM, et al. Neurodevelopment of HIV-exposed uninfected children in South Africa: outcomes from an observational birth cihort study. Lancet Child Adolesc. Health 2019; 11:803-13.

Wensing AM, Boucher CA, van Kasteren M, et al. Prevention of mother–to-child transmission of multi-drug resistant HIV-1 using maternal therapy with both enfuvirtide and tipranavir. AIDS 2006; 26: 1465-7.

Williams PL, Crain MJ, Yildirim C, et al. Congenital anomalies and in utero antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants, JAMA Pediatr 2015: 169: 48-55.

Williams PL, Hazra R, Van Dyke RB, et al. Antiretroviral exposure during pregnancy and adverse outcomes in HIV-exposed uninfected infants and children using a trigger-based design. AIDS 2016; 30; 133-44

Williams PL, Yildirim C, Chadwick EG, et al. Association of maternal antiretroviral use with microcephaly in children who are HIV-exposed but uninfected (SMARTT): a prospective cohort study. Lancet HIV 2020; 7: 49-58.

Weyland C, Mirani G, Gillespie SL, Paul ME. A Case of in utero Transmission of Drug-resistant HIV in the US. Pediatr Infect Dis J 2022 41:57-9.

Young JM, Bitnun A, Read SE, Smith ML. Neurodevelopment of HIV-exposed uninfected children compared with HIV-unexposed uninfected children during early childhood. Dev Psychol 2022; 58: 551-9.

Yuhin MH, Kennedy VL, MacGillivray SJ. HIV and infant feeding in resource-rich settings: considering the clinical significance of a complicated dilemma. AIDS Care 2016; 28:1023-6.

20. Antiretroviral therapy in children

TIM NIEHUES, CHRISTOPH KÖNIGS

Viral dynamics, clinical course, transmission routes

The clinical course of natural untreated HIV infection in infants and young children is more aggressive than in adults. The viral load in untreated children often rises to over 1,000,000 copies/mL and then decreases only hesitantly over 4–5 years. Possible reasons are the developing lymphatic system and the inability of the somewhat naive, immature immune system to develop an adequate HIV-specific immune response.
Typically, there are specific clinical manifestations that are included in the CDC classification of HIV infection in childhood (Table 1). Infants without ART show rapid progression with AIDS-defining symptoms in about 10–25% (see below). The infection is fatal if untreated: an infant at six months of age with 15% CD4 T-cells has a 20% risk of dying within 12 months (Dunn 2013). A particularly feared complication in infancy is HIV-related encephalopathy with opisthotonos, cognitive defects, loss of milestones, and hyperreflexia. National and international guidelines recommend starting ART immediately after diagnosis in all children and adolescents, regardless of CD4 T-cell count and viral load.
Perinatal HIV infections occur mainly when the mother's HIV status remains unknown during pregnancy, transmission prevention is incomplete, or the mother has no access to healthcare. Over 95% of children are infected *vertically* through the mother. *Horizontal* routes of transmission (sexual intercourse, sexual abuse, drug use) are exceptions. The transmission rate in children of untreated mothers was approximately 20–30% in Europe. These infections are considered 35–45% *peri- or intrapartum* and 10–25% *in utero*. Breastfeeding transmits HIV in another 35–40%, depending on duration. In suppressed maternal viral load cases, transmission during pregnancy, childbirth, or breastfeeding occurs rarely.

Diagnosis

The diagnosis of HIV infection is critical to enable a prompt start of treatment, particularly in infants. PCR is a highly sensitive and specific method for detecting HIV-specific DNA in lymphocytes and/or HIV-RNA in plasma. The methods for confirming the diagnosis are adapted to the child's age.
In children **under 24 months of age** with peri- and postnatal exposure, HIV detection must be performed by PCR. Maternal IgG HIV antibodies are actively transmitted to the child transplacentally. They persist into the second year of life due to the high titers in infected mothers. Consequently, the antibody test is always positive in mature, exposed children – even HIV-negative ones. Umbilical cord blood is of limited use for diagnosis, as maternal cells or contamination may give a false positive result. Early postnatal testing is helpful if there is a high risk of transmission (e.g., untreated HIV infection during pregnancy) or if breastfeeding is desired. A positive PCR should be confirmed immediately in a second blood sample. However, within 48 hours after birth, PCR remains negative in 62% of all HIV-infected infants and 11% after four weeks (Burgard 2012).
To exclude HIV infection, at least two PCR tests from independent samples should be available in breastfed children at one month and three months of age. The control after three months is necessary because the PCR can be negative even longer after the end of the transmission prophylaxis. In breastfed infants, further testing is required every eight weeks and one and three months after cessation of breastfeeding due to the potential exposure to HIV during breastfeeding.

In children **of at least 24 months of age** and with perinatal HIV exposure or suspected horizontal infection, a combined HIV antigen/antibody test should be performed. See also the chapter on *HIV testing*.

Indication for antiretroviral therapy

Updated recommendations of the European PENTA group (Paediatric European Network for Treatment of AIDS) within EACS (European AIDS Clinical Society) and WHO are freely available online. The recommendations include the approach for adolescents and hepatitis B, hepatitis C, and tuberculosis co-infections.

- Europe (EACS): https://www.eacsociety.org/guidelines/eacs-guidelines/
- US: https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/whats-new-guidelines
- WHO: https://www.who.int/publications/i/item/9789240022232

Premature infants (< 37th week of gestation)

The limited data on dosages and safety are based on case reports. Some toxicities have been described. For example, lopinavir/r can lead to metabolic derailment and cardiac or endocrinologic problems, and raltegravir can exacerbate hyperbilirubinemia.

Children < 3 years

In infancy, the risk of dying from AIDS is exceptionally high if the start of therapy is delayed (Violari 2008, Judd 2011). This is due to poorer control of HIV infection up to the age of 3. Therefore, initiation of therapy is always recommended in the first three years of life, regardless of virologic, immunologic, and clinical criteria.

Children ≥ 3 years

Starting ART in older children is not an emergency. Given the presumably lifelong treatment, limited options, and potential side effects, premature "consumption" of effective therapies makes little sense. However, starting therapy too late could result in a larger reservoir of latent HIV-infected cells in the body and irreversible damage to the immune system and CNS due to continuous, subclinical inflammation. The START trial in adults showed that early initiation of therapy above 500 CD4 T-cells/µl is superior to later initiation at 350 cells/µl (Insight 2015).

Although such data is lacking for children > 3 years of age, European and American guidelines recommend treatment for all children and adolescents, regardless of clinical, virologic, and immunologic status. Priority for a rapid treatment start is given to children < 3 years, adolescents, and children and adolescents with symptoms or low CD4 T-cells (American guidelines: "treat" and "urgent treatment").

In older asymptomatic children (37 months to the end of 12 years of age), the German guidelines do *not advocate* a general therapy recommendation in the *absence of* clinical, immunological, or virological indications (see below). At this age, a lower disease progression can be assumed. In the PREDICT trial, in which children aged > 1 year (mean age 6.4 years) were treated either immediately or delayed (CD4 T-cell-based decision), no clear clinical difference was demonstrated (Puthanakit 2012). To the extent that initiation of therapy is delayed in this age group, ART should be started immediately if clinical symptoms, immunodeficiency, and viral loads >100,000 copies/mL are present.

From the age of 12, the guidelines also advocate an immediate start of therapy. In addition to the individual clinical benefit, another benefit is the prevention of further infections since people with a negative viral load do not transmit the virus (U = U, undetectable = untransmittable).

Immunological and clinical criteria

In infancy, there is an age-dependent interpretation of the CD4 T-cell count (Table 1). Example: A value of 700 CD4 T-cells/µl, which appears normal in adults, is highly pathological in infants and indicates a severe immunodeficiency. Therefore, percentages should also be considered. The predictive value of viral load for AIDS and mortality is less significant than the combination of viral load and CD4 T-cells. For older adolescents, the recommendations for adults apply (see chapter *ART*).

Table 1: Immunological stages according to the 2014 CDC classification for childhood HIV infection, based on absolute or relative CD4 T-cell counts.

Immunological stage*	<1 year		1 to <6 years		≥6 years	
	Cell count/µl	(%)	Cell count/µl	(%)	Cell count/µl	(%)
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750–1,499	26–33	500–999	22–29	200–499	14–25
3	<750	<26	<500	<22	<200	<14

* Centers for Disease Control and Prevention. MMWR 2014; 63(Rr-03):1-10.

Table 2: Clinical stages according to the CDC classification for childhood HIV infection (http://www.cdc.gov/mmwr/preview/mmwrhtml/00032890.htm).

CDC stage	Clinical symptoms
Stage N:	Children who have no symptoms or clinical signs of HIV infection or only one of the symptoms listed under stage A
Stage A: Early symptoms	Children with two or more of the following symptoms but none of the symptoms listed in stages B and C. • Lymphadenopathy, hepatomegaly, splenomegaly • Dermatitis • Parotitis • Recurrent upper respiratory tract infections, sinusitis or otitis
Stage B: Moderately severe symptoms	Children who have symptoms other than those listed in stage A and C. Examples of stage B symptoms are: • Anemia (Hb <8 g/dL), neutropenia (<1,000/µL), thrombocytopenia (<100,000/µL) for >30 days • Bacterial meningitis, pneumonia, sepsis (one episode) • Oropharyngeal candidiasis, persistent for >6 months in children • Cardiomyopathy • CMV infection with onset in the first month of life • Diarrhea, recurrent or chronic • Hepatitis • Herpes simplex (HSV) stomatitis, more than two episodes per year • HSV bronchitis, pneumonitis, or esophagitis in the first month of life • Herpes zoster (>2 episodes on >1 dermatoma), dissemin. Varicella • Leiomyosarcoma • Lymphoid interstitial pneumonia (LIP)*. • Nephropathy • Persistent fever >1 month duration • Toxoplasmosis in the first month of life; nocardiosis

Table 2: Continuation

CDC stage	Clinical symptoms
Stage C: Severe symptoms, AIDS	• More than one severe culturally proven infection with common bacteria within two years • HIV encephalopathy • Wasting syndrome, cachexia • Pneumocystis jiroveci (formerly "carinii") pneumonia (PCP) • Cerebral toxoplasmosis in children >1 month of age. • Cryptosporidiosis with diarrhea >1 month duration • Isosporidiasis with diarrhea >1 month duration • Various lymphomas, including CNS lymphomas • Kaposi's sarcoma • Progressive multifocal leukoencephalopathy • HSV-related mucocutaneous ulcers (duration >1 month) or bronchitis, pneumonia, or esophagitis due to HSV in children aged >1 month • Lymphoid interstitial pneumonia caused by EBV • CMV: retinitis, esophagitis, and colitis in children >1 month of age • Candidiasis of the esophagus, the tracheobronchial system • Extrapulmonary cryptococcosis • Disseminated or extrapulmonary histoplasmosis • Tuberculosis, atypical mycobacterioses

* LIP is classified as B but is still considered an AIDS-defining condition when reported.

Therapy requirements and practical procedures

HIV infection in childhood is very rare. It is recommended to cooperate with an experienced center. The most essential prerequisite for successful therapy is sufficient adherence, i.e., adherence to jointly defined therapy goals. Depending on the child's age, this is only achieved in 70% of cases (MacDonell 2013). The GEPIC cohort showed treatment success (<50 copies/mL) in 91% of children and adolescents treated in Germany. Adherence of pubescent adolescents is described as problematic. Even in this age group, the viral load in the GEPIC cohort was below 50 copies/mL in 92%. Nevertheless, more individualized therapeutic approaches are needed. In adolescents and young adults, the BREATHER study of the PENTA group compared reduced administration to 5 intakes/week (break on weekends) of efavirenz-based ART with administration on 7 days/week: There was no increased risk for the reduced administration (Butler 2015). The extent to which this strategy holds outside of strictly controlled trial conditions is unclear and is currently not recommended.

Because of the stigmatization, the high burden of the family with the diagnosis of HIV, and the constant need to improve therapy adherence, intensive, multidisciplinary team care with personnel from nursing, psychology, and social work would be indispensable but is often not implemented in clinics due to a lack of funding for human resources.

Establishing a peer group, if possible, or contact with other affected adolescents is beneficial. ART should be optimally integrated into the daily routine of children and adolescents. Taking the medication in the evening before going to bed can be useful to place peak levels and thus undesirable drug effects in the sleep phase. Morning intake may be more beneficial for medications with frequent sleep disturbances or nightmares, such as efavirenz or dolutegravir. The morning routine is often more regular than the evening for school-aged adolescents. Apps, phone alarms, or electronic pill boxes can be helpful. Taking tablets/bad-tasting suspensions (e.g.,

lopinavir/r) can be difficult, especially in young children; mixing them into some milk, syrup, juice, or similar may help. There are several resources with practical tips that can help with difficulties (https://www.e-lfh.org.uk/programmes/kidzmed/; https:// www.rcpch.ac.uk/resources/pill-swallowing-podcasts).
Inpatient admission at the start or change of therapy may be necessary to monitor intake by trained nurses and to manage side effects. Critical prerequisites for successful ART are knowledge of adverse drug reactions and an understanding of pharmacology in children (Waalewijn 2019). Pharmacokinetics can vary significantly from child to child (Kearns 2003). As in adults, interactions should be considered (see below). Determining plasma levels at longer intervals may be useful to document poor adherence, ingestion errors, and underdosing. Care should be taken to ensure that children do not "outgrow" their dose and that the dose is adjusted regularly (Menson 2006).

Treatment strategies

HIV eradication in children and adolescents is currently not possible. In some children, sero-reversion may occur after early treatment – HIV-specific antibodies are no longer found after early therapy initiation. However, with ultrasensitive RNA or cDNA assays, HIV can usually still be detected in the end – when ART is discontinued, viral load increases regularly (Butler 2015). In difficult situations (e.g., treatment failure), it is highly advisable to discuss cases in a multidisciplinary team virtual clinic (link see EACS guideline (PVC))
A combination with a so-called "backbone" of two NRTIs plus an NNRTI, PI, or INSTI is recommended as first-line therapy (Table 3). Due to the small number of cases, all children should be included in clinical registries if possible. Resistance testing should be performed before starting antiviral therapy.

Classes of Drugs

Drugs are presented with regard to indication, mode of administration, and dose. Adverse effects such as headache, fatigue, gastrointestinal complaints, or skin rash are known for all. In children and adolescents, it should be noted that both infection and therapies can affect growth and development. In the following, toxicities are listed only if they are particularly relevant in childhood and adolescence. Dyslipidemias are observed in a proportion of children (Jacobson 2011). In some adolescents and young adults on long-term ART, changes in coronary vessels have been found on MR angiography (Mikhail 2011); the long-term consequences are unknown.
Dosing is mainly by body weight, partly by body surface area, and increasingly by weight ranges (so-called "weight bands") www.who.int/hiv/paediatric/generictool/en. The dosing intervals commonly used in Anglo-Saxon countries (QD = 1 x daily, BID = 2 x daily, TID = 3 x daily) are adopted here for reasons of space.

NRTIs

The combination of two NRTIs as part of ART ("backbone") is usually well tolerated. The preferred combination initially is ABC+3TC, once daily from the age of 3 months. Fixed dose combinations exist, some of which can be used in older children (see Table 4). Substance class-sparing regimens or regimens of two substances (dolutegravir/3TC or dolutegravir/rilpivirine) are now approved from 12 years of age; clinical trials are ongoing "D3" study, PENTA 21 or published (Compagnucci 2023),

Table 3: Preferred and Alternative First-Line Options in Children and Adolescents (Pediatric EACS guidelines https://www.eacsociety.org/guidelines/eacs-guidelines/).

	Backbone		3rd Agent (in alphabetical order)	
Age	**Preferred**	**Alternative**	**Preferred**	**Alternative**
0 – 4 weeks	AZT[1] + 3TC	–	LPV/r[2,3] NVP[3] RAL[3]	–
4 weeks – 3 years	ABC[4] + 3TC[5]	AZT[1] + 3TC[6] TDF[7] + 3TC	DTG[8]	LPV/r NVP RAL
3 – 6 years	ABC[4] + 3TC[5]	TDF[7] + XTC[9] AZT + XTC[9]	DTG[8]	DRV/r EFV LPV/r NVP RAL
6 – 12 years	ABC[4] + 3TC[5] TAF[10]+ XTC[9]	TDF[7] + XTC[9]	DTG[8]	DRV/r EFV EVG/c RAL
> 12 years	ABC[4] + 3TC[5] TAF[10] + XTC[9]	TDF[7] + XTC[9]	BIC[11] DTG[8]	DRV/b EFV[12] RAL[12] RPV[12]

Notes

1. Given potential long-term toxicity, any child on AZT should be switched to ABC (preferred for younger children) or TAF/TDF (alternative for younger children, with renal/bone toxicity monitoring with TDF) once age and/or weight increase makes licensed formulations available. When ABC is contraindicated in young children, it is recommended that treatment options are discussed on a case-by-case basis
2. LPV/r should not be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days. However, it may be considered if there is a risk of transmitted NVP resistance and appropriate INSTI formulations are unavailable. In these circumstances, the neonate should be monitored closely for LPV/r-related toxicity (e.g., metabolic, endocrine, cardiac)
3. If starting a non-DTG third agent in the neonatal period, it is acceptable to continue this option. However, when over 4 weeks and 3 kg, a switch to DTG is recommended if and when an appropriate formulation is available
4. ABC should NOT be prescribed to HLA-B*57:01 positive individuals (where screening is available). ABC is not licensed for children under 3 months of age, but dosing data for younger children are available from the WHO and DHHS
5. At HIV-VL > 100,000 copies/mL, ABC + 3TC should not be combined with EFV as third agent
6. If using NVP as a third agent in children aged 2 weeks to 3 years, consider using 3 NRTI backbone (ABC + AZT + 3TC) until VL consistently < 50 copies/mL
7. TDF is only licensed from 2 years of age. Given concerns about the potential impact on bone development and renal toxicity, TAF is preferred to TDF at all ages (if available)
8. DTG is licensed from 4 weeks and 3 kg. DTG has been associated with excessive weight gain in adults, especially with TAF. This has not yet been demonstrated in pediatric and adolescent observational studies or trials. However, the possibility of this should be considered when DTG is used. Families and young people should be counseled regarding this, and weight should be monitored
9. XTC indicates circumstances when FTC or 3TC may be used interchangeably
10. TAF is only licensed in Europe for the treatment of HIV in combination with FTC from 12 years of age and 35 kg in TAF/FTC and from 6 years of age and 25 kg in TAF/FTC/EVG/c. TAF is licensed for younger ages and weights, so that it can be included as a preferred option. TAF has been associated with excessive weight gain in adults, especially in combination with DTG. This has not yet been demonstrated in pediatric and adolescent observational studies or trials. However, the possibility of this should be considered when TAF is used. Families and young people should be counseled regarding this, and weight should be monitored
11. BIC is a preferred first-line option in adults. It is not licensed under 18 years of age but may be considered in those aged less than 18 years following discussion at MDT/PVC
12. Due to predicted poor adherence in adolescence, if preferred third agents (BIC or DTG) are not available, DRV/b is favored due to a higher resistance barrier compared to EFV, RAL or RPV

Lamivudine (3TC) is available as tablets and suspension or generics. Child dosing (≥3 months) for suspension is 4 mg/kg BID or 8 mg/kg QD (max dose 300 mg per day). Child dosing for tablets (150 mg) is (≥3 years): (14-21 kg): ½ tablet BID or 1 tablet QD; (>21-30 kg): ½ tablet morning + 1 tablet afternoon or 1½ tablet QD; (>30 kg): 1 tablet BID or 2 tablets QD; Dosage for adults is: (≥12 years): 150 mg BID or 300 mg QD. Given HBV activity, it may be appropriate to add 3TC to ART for chronic hepatitis B. In HIV-negative children with chronic hepatitis B (especially <7 years of age), early use of 3TC achieves a high HBe/HBs seroconversion rate (Choe 2007). No systematic data are available on HBV/HIV-coinfected children. It should be kept in mind that long-term 3TC therapy carries the risk of HBV resistance. Again, combination therapy is recommended.

Abacavir (ABC) is available as a tablet and suspension. Child dosing (≥3 months) is 8 mg/kg BID or 16 mg/kg QD (maximum dose: 600 mg per day). Child dosing with the tablet of 300 mg: (14-21 kg): ½ tablet BID or 1 tablet QD; (>21-30 kg): ½ tablet in the morning + 1 tablet in the afternoon or 1½ tablet QD; (>30 kg): 1 tablet BID or 2 tablets QD; Dosage adults: (≥12 years): 300 mg BID or 600 mg QD. The disadvantage is the hypersensitivity reaction (HSR) risk associated with HLA-B57. If positive, abacavir is contraindicated. Because HSR is not entirely ruled out, even in the presence of B57 negativity, parents should be educated about HSR. If HSR is suspected, abacavir must be permanently discontinued; re-exposure can be fatal (single observations in adults).

Emtricitabine (FTC) is available as capsules and suspension. Child dosing for suspension in children: (≥4 months): 6 mg/kg QD (maximum dose 240 mg QD); Child dosing for capsules (≥33 kg): 200 mg QD; dose in adults: Capsule (≥33 kg): 200 mg QD; Suspension: 240 mg QD. FTC is equally effective against HBV.

Tenofovir disoproxil fumarate (TDF) is available as tablets (123/163/204/245 mg TDF) and as granules containing 33 mg/g TDF (1 scoop = 1 g). It is approved for children >2 years of age and 3kg of weight. All of the following dosages are based on TDF. Child dosing for granules is (≥2 years) 6.5 mg/kg QD. Dosage for tablets in children is: (≥2 years) (17-22 kg): 123 mg QD; (22-28 kg): 163 mg QD; (28-35 kg): 204 mg QD; (≥35 kg): 245 mg QD; Dose in adults is: (≥35 kg) 245 mg QD. Intake of meals is required. Tenofovir may significantly affect renal and bone metabolism in children (Gafni 2006, Purdy 2008). It is also effective against HBV and can be used in coinfected children.

Tenofovir alafenamide (TAF) is available as 25 mg (without a booster) and as 10 mg tablets (in combination with cobicistat or ritonavir). It is approved for children 12 years of age and older and >35 kg body weight. TAF is found in coformulations with FTC and elvitegravir/c, bictegravir, rilpivirine, or darunavir/c. Ingestion with food is required. TAF appears to be somewhat better tolerated than TDF and should be preferred when possible. A slightly higher virologic potency is discussed.

Zidovudine (AZT) is available as capsules, suspensions, tablets, and ampoules. Given potential long-term toxicity, AZT should be switched to ABC or TAF/TDF if possible. Dosage (caveat: transmission prophylaxis: other dosages!): Child dosing for suspension is: (4-9 kg): 12 mg/kg BID; (9-30 kg): 9 mg/kg BID; (≥30 kg): 300 mg BID; Child dosing for capsules is: (8-13 kg): 100 mg BID; (14-21 kg): 100 mg morning + 200 mg afternoon/evening (22-30 kg): 200 mg BID; (≥30 kg): 300 mg BID; adults: 300 mg BID; intravenous dosing of 120 mg/m^2 QD may be considered for very sick children with intestinal failure.

NNRTIs

Within a few weeks, cross-class resistance may occur. However, newer substances have a higher resistance barrier. Children usually prefer the liquid preparations of the NNRTIs in terms of taste over the liquid PI solutions. Nevirapine is the preferred NNRTI in children <3 years of age, and efavirenz is the preferred NNRTI in ≥3 years. NNRTIs are contraindicated in patients with hepatic dysfunction.

Efavirenz (EFV) is approved for use from 3 years of age. At HIV-RNA >100,000 copies/mL, EFV should not be combined with ABC+XTC (Table 3). Capsules, suspensions, and sprinkles are available. Under standard dosing, levels are highly variable, and children are sometimes underdosed. Child dosing is QD: ≥3-5 years: (13-15 kg): 360 mg; (15-20 kg): 390 mg; (20-25 kg): 450 mg; (25-32 kg): 510 mg; ≥5 years: (13-15 kg): 270 mg; (15-20 kg): 300 mg; (20-25 kg): 360 mg; (25-32.5 kg): 450 mg; (32.5-40 kg); 510 mg; (≥40 kg): 720 mg.

Child dosing for capsules: ≥3 years (13-15 kg): 200 mg; (15-20 kg): 250 mg; (20-25 kg): 300 mg; (25-32.5 kg): 350 mg; (32.5-40 kg): 400 mg; (≥40 kg): 600 mg; adults: (≥40 kg): 600 mg (suspension: 720 mg). It should be taken in the evening on an empty stomach. High-fat meals should be avoided; in some cases, increases in serum lipids have been observed. The suspension must be dosed 20% higher than the capsules.

Nevirapine (NVP) is available as "immediate" and "extended-release" tablets (IR, XR) and solutions. In children aged > 2 months to 3 years, using a backbone with 3 NRTIs may be considered. The dosage for the IR formulation *by body weight* is 4 mg/kg QD for 14 days (max. 200 mg/day), then (<8 years) 7 mg/kg BID or (≥8 years) 4 mg/kg BID (max. 400 mg/day) in the absence of exanthema or hepatic dysfunction; dosing for XR formulation ≥3 years is: 0.58-0.83 m^2 body surface area: 200 mg QD; 0.84-1.16 m^2: 300 mg QD; ≥1.17m^2: 400 mg QD. All patients must start IR formulation for 14 days;

Etravirine (ETV) is approved for use from ≥2 years of age and is available as tablets (25 mg, 100 mg, and 200 mg). Child dosing is ≥10-<20 kg: 100 mg BID; ≥20-<25 kg: 125 mg BID; ≥25-<30 kg: 150 mg BID; ≥30 kg: 200 mg BID (same as adults).

Rilpivirine (RPV) is approved in adolescents >12 years of age as a single agent and in combinations and is available as a 25 mg tablet. The dosage is 25 mg QD.

Doravirine (DOR) is approved in adolescents >12 years of age and ≥35 kg as a single agent and part of combination therapies at 100 mg QD.

Protease inhibitors

Compared to NNRTIs, resistance develops less rapidly with boosted PIs. To achieve adequate plasma levels, PIs are boosted with ritonavir (/r) or cobicistat (/c). Lopinavir and atazanavir are the only PIs approved under 2 years of age. QD doses are available from 6 years of age for atazanavir and 3 years for darunavir. A study in children and adolescents showed the inferiority of QD vs. BID for lopinavir/r.

Lopinavir/r (LPV/r) is available as tablets containing 200 mg lopinavir/50 mg ritonavir tablets and 100 mg/25 mg as a suspension. The suspension tastes foul, must be refrigerated, contains 42% alcohol (153 mg/mL) and propylene glycol, and is contraindicated for premature infants and newborns. Lopinavir/r is approved from 2 weeks of age (Simon 2011). The suspension is taken with meals; this is not necessary for the tablets. Comedication with efavirenz or nevirapine requires approximately 30% higher dosing of lopinavir/r. Lopinavir/r is very effective in treatment-naive and intensively pretreated children and infants under 6 months of age (Saez-Llorens 2003,

Fraaij 2004, Resino 2005, Chadwick 2011). LPV should not be given to neonates before 14 days of age, as endocrine, metabolic, and cardiac toxicity has been reported in this age group. Child dosing is: (≥14 days to 6 months) 300/75 mg/m² BID or 16/4 mg/kg body weight; (≥6 months to 18 years) 230/57.5 mg/m² BID or (<15 kg) 12/3 mg/kg BID; (≥15-40 kg) 10/2.5 mg/kg BID (max 400/100 mg BID). Dosage for tablets is: (15-25 kg or 0.5-0.9 m²): 200/50 mg BID; (25-35 kg or 0.9-1.4 m²): 300/75 mg BID; (>35 kg or ≥1.4 m²): 400/100 mg BID; in neonates and infants ≥6 weeks, dosing is probably even higher than 2 x 300 mg/m² (Chadwick 2011). QD administration was inferior to BID administration in children and adolescents (KONCERT study, PENTA 18).

Fosamprenavir (FPV) is approved for patients 6 years of age and older, weighing 25 kg in combination with ritonavir, and is available as a suspension (50 mg/mL) and 700 mg tablets. The combined dose is given at mealtimes. Dosage for suspension in children is: (≥6 years) (25-32 kg): 18 mg/kg BID+RTV 3 mg/kg BID; (33-38 kg): 18 mg/kg BID+RTV 100 mg BID; (≥39 kg) 700 mg BID+RTV 100 mg BID; dosage for tablets is: (≥39 kg) 700 mg BID+RTV 100 mg BID; (≥18 years or ≥39 kg): 700 mg BID+RTV 100 mg BID.

Atazanavir (ATV) is available as a powder in 100, 150, 200, and 300 mg capsules. It is recommended once daily with meals. ATV is approved starting at 3 months of age and 5 kg body weight in combination with ritonavir. Dosage powder: (5-<15 kg) 200 mg and 80 mg ritonavir; (15-<35 kg) 250 mg and 80 mg ritonavir, (>35 kg) 300 mg and 100 mg ritonavir. Dosage capsules: (≥15-<20 kg) 150 mg and 100 mg ritonavir QD; (≥20-<40 kg) 200 mg and 100 mg ritonavir QD; (≥40 kg) 300 mg and 100 mg ritonavir QD. Administration of proton pump inhibitors is contraindicated. The option of once-daily administration is attractive. Since late 2015, atazanavir can be used without a booster in adults under certain conditions (e.g., >6 months viral load below detection limit).

Darunavir (DRV) is available as 75, 150, 400, 600, 800 mg tablets and as a suspension (100 mg/mL). It is recommended to be taken with food. Darunavir is approved for >3 years of age and a body weight of at least 15 kg in combination with ritonavir or cobicistat (12 years and older). Dosage for therapy-naive or therapy-experienced children is QD: (≥15-30 kg) 600 mg+ritonavir 100 mg; (≥30-<40 kg): 675 mg+ritonavir 100 mg; (≥40 kg): 800 mg+ritonavir 100 mg or cobicistat 150 mg. Dosage for treatment-experienced children with darunavir resistance is BID: (≥15-30 kg) 380 mg BID+ritonavir 50 mg BID; (≥30-<40 kg): 460 mg BID+ritonavir 60 mg BID, (≥40 kg): 600 mg BID+ritonavir 100 mg BID or QD is: (≥15-30 kg) 600 mg BID+ritonavir 100 mg BID; (≥30-<40 kg): 675 mg BID+ritonavir 100 mg BID, (≥40 kg): 800 mg BID+ritonavir 100 mg BID or cobicistat 150 mg BID.

Integrase inhibitors

More frequent CNS side effects have been described for some INSTIs than other antiretroviral drugs. In addition, there have been case reports of myocarditis. A meta-analysis found an increased risk of insomnia with dolutegravir (Hill 2018). Cardiovascular risks or increased rates of suicidality were not found.

Raltegravir (RAL) is available as granules and as 25 mg, 100 mg, 400 mg, and 600 mg tablets. It is approved from birth. Child dosing for granules in the first week of life (from birth): (2-<3 kg) 4 mg QD; (3-<4 kg) 5 mg QD; (4-<5 kg): 7 mg QD. Child dosing from the first to 4th week of life: (2-<3 kg) 8 mg BID; (3-<4 kg) 10 mg BID; (4-<5 kg): 15 mg BID. Dosage from 5. Week of life: (3-<4 kg) 25 mg BID; (4-<6 kg) 30 mg BID; (6-<8 kg) 40 mg BID; (8-<11 kg) 60 mg BID; (11-<14 kg) 80 mg BID;

(14-<20 kg) 100 mg BID; Dosage for chewable tablets in children: (11-<14 kg): 75 mg BID; (14-<20 kg) 100 mg BID; (20-<28 kg): 150 mg BID; (28-<40 kg): 200 mg BID; (>40 kg): 300 mg BID; Dosage for film-coated tablets in children: (≥6 years and >25 kg or ≥12 years) 400 mg BID. QD administration of the 600 mg tablet is approved for 40 kg and above.

Dolutegravir (DTG) is available as 5, 10, 25, and 50 mg tablets. It is approved from 4 weeks of age and a weight of ≥3 kg. Dosage is: (3-<6kg): 5 mg QD, (6-<10kg, under 6 months): 10 mg QD, (6-<10kg, ≥6 months): 15 mg QD, (10-<14kg): 20 mg QD, (14-<20kg): 25 mg or 40 mg film-coated tablet QD, (≥20kg): 50 mg QD. In cases of INSTI resistance, a dosage of 50 mg BID is discussed for patients weighing 40 kg or more. In the ODYSSEY trial (Penta 20), DTG-containing regimens were superior to standard regimens regarding viral load suppression (Turkova 2021). DTG has been associated with excessive weight gain in adults, especially in combination with TAF. This adverse effect may also affect children; parents should be educated accordingly.

Elvitegravir (EVG) is available in Germany only as a fixed-dose combination. EVG/c/FTC/TAF is approved from 2 years and ≥14 kg for once-daily administration and is available in doses of 150/150/200/10 mg and 90/90/120/6 mg. The latter should be used in children between 14 and 25 kg. EVG/c/FTC/TAF is approved from 12 years of age and a body weight of ≥35 kg, also for once-daily administration.

Bictegravir (BIC) is approved only in a fixed combination for adults and is a preferred first-line option. However, it is not yet licensed for children <18. The combination drug has been tested in trials in children >6 years and ≥25 kg and adolescents >12 years and ≥35 kg. Bictegravir/FTC/TAF is now the preferred first-line therapy in US guidelines from 12 years and >35 kg.

Fusion and entry inhibitors

Enfuvirtide (ENF) is approved for use in children 6 years and older and administered subcutaneously. Child dosing is: (6 -16 years): 2 mg/kg BID (maximum dose 90 mg BID); (11.0-15.5 kg): 27 mg BID; (15.6-20.0 kg): 36 mg BID; (20.1-24.5 kg): 45 mg BID; (24.6-29.0 kg): 54 mg BID; (29.1-33.5 kg): 63 mg BID; (33.6-38.0): 72 mg BID; (38.1-42.5 kg): 81 mg BID, (≥42.6 kg): 90 mg BID; adult dosage is: (≥16 years): 90 mg BID. Controlled studies in children are lacking.

Maraviroc (MRV) is available as 25-, 75-, 150-, and 300-mg tablets and as a solution (20 mg/mL) and is approved for 2 years of age and >10 kg. Child dosing is: (10-<20 kg) 50 mg BID; (20-<30 kg) 75 mg BID; (30-<40 kg), 100 mg BID with potent CYP3A4 inhibitors and 300 mg without strong CYP3A4 inhibitors; (>40 kg) 150 mg BID with potent CYP3A4 inhibitors (eg., clarithromycin, itraconazole, ketoconazole, PIs) and 300 mg without potent CYP3A4 inhibitors. A tropism test to clarify efficacy should be performed before initiation of therapy.

Fixed Dose Combinations (FDC)

There are now numerous fixed combinations and, in some cases, complete ART regimens. A use for younger children is limited by size, dosage, and license.

Many drug interactions can complicate therapies and their management (see also the chapter *Interactions;* https://www.hiv-druginteractions.org/checker). A particular problem is the management of concomitant infections (TB, CMV, etc.). It is recommended to consult a center that has experience with ART in childhood.

Table 4: Antiretroviral formulations useful for pediatric and adolescent dosing and Administration https://www.eacsociety.org/guidelines/eacs-guidelines.

NRTI	
ABC	tablets (300 mg), solution (20 mg/mL)
FTC	capsules (200 mg), solution (10 mg/mL)
3TC	tablets (300, 150 mg), solution (10 mg/mL)
TDF	tablets (245, 204, 163, 123 mg), granules (33 mg/g)
ZDV	capsules (250 mg, 100 mg), solution (10 mg/mL) iv infusion: 10 mg/mL (20 mL/vial)
TAF/FTC	tablets (25/200 mg and 10/200 mg)
TDF/FTC	tablets (300/200 mg)
ABC/3TC	tablets (600/300 mg)
ZDV/3TC	tablets (300/150 mg)
NNRTI	
EFV	tablets (600 mg), capsules (200, 100, 50 mg)
NVP	tablets (200 mg), extended-release tablets (400, 100 mg), suspension (10 mg/mL)
RPV	tablets (25 mg)
TDF/FTC/EFV	tablets (300/200/600 mg)
TAF/FTC/RPV	tablets (25/200/25 mg)
TDF/FTC/RPV	tablets (300/200/25 mg)
PI	
DRV	tablets (800, 600, 400, 150, 75 mg), solution (100 mg/mL)
DRV/c	tablets (800/150 mg)
LPV/r	tablets (200/50 mg and 100/25 mg), solution (80/20 mg/mL)
RTV	tablets (100 mg), powder for oral suspension (100 mg sachet)
TAF/FTC/DRV/c	tablets (10/200/800/150 mg)
INSTI	
DTG	tablets (50, 25, 10 mg), dispersible tablets (5 mg)
RAL	tablets (600 mg, 400 mg), chewable tablets (100, 25 mg), granules for oral suspension (100 mg)
ABC/3TC/DTG	tablets (600/300/50 mg)
TAF/FTC/BIC	tablets (25/200/50 mg)
TAF/FTC/EVG/c	tablets (10/200/150/150 mg)
TDF/FTC/EVG/c	tablets (300/200/150/150 mg)

Therapy effectiveness, failure, and conversion

The effectiveness of ART is measured in children by virological and immunological response and, more importantly, by growth and development: Normalization of growth velocity can be expected approximately two years after ART initiation (Nachman 2005a). Data regarding neuropsychological status are conflicting. Infected children sometimes perform worse on neuropsychological tests despite ART and are at increased risk for psychiatric disorders (Laughton 2013). A small German study showed that early, sufficient initiation of therapy could enable normal cognitive development: the intelligence quotient in this study correlated inversely with viral loads in the first years of life (Weber 2017). Many children can be treated with the first combination for many years without complications, and the first regimen succeeds in keeping viral loads below the detection limit for more than five years. A change in therapy may be appropriate despite viral load suppression to reduce the number of tablets, simplify intake, and reduce actual or potential long-term side

effects. Therapy failure is almost always a result of inadequate adherence. It can be assessed with systematic questioning, monitoring of prescribed medications, plasma level determinations, and resistance testing. Discussing the case in a PVC can help (see link EACS guideline 2022).

The following points indicate virologic treatment failure: a repeatedly measured rebound of plasma HIV RNA or failure to reach the detection limit of <50 copies/mL after six months. In infants and young children, achievement of complete viral suppression <50 copies/mL may take longer. Despite detectable viral replication on ART, most children are usually immunologically and clinically stable. The risk of further resistance developing with viral replication must be considered. The PENPACT 1 study (see above) investigated in 263 children whether it makes a difference whether switching is already above 1,000 or only above 30,000 copies/mL (PENPACT study 2011). Interestingly, over a 5-year observation period, there was no significant difference in viral load reduction and no increased risk of PI or NNRTI resistance when therapy was switched at higher viral loads. Immunologic criteria of treatment failure are CD4 T-cells decreasing beyond physiologic levels. The guideline is a decrease of at least 30% of the absolute value in less than six months. In children with relative CD4 T-cell counts of less than 15%, a decrease of more than 5% may also be considered a treatment failure.

Clinical treatment failure is defined as drug toxicity, clinical progression, striking accumulation of trivial infections without change in the CDC stage, onset of encephalopathy, or failure to thrive.

A resistance test should be performed before each start and switch. Usually, the first regimen contains two NRTIs (e.g., ABC+3TC). It then makes sense to select new NRTIs (e.g., AZT+TDF) according to a resistance test and introduce a new substance class if possible. Integrase inhibitors offer new possibilities here. There are very few prospective data on the value of resistance testing-guided therapy in children and adolescents. For example, in the presence of an M184V mutation (3TC/FTC resistance) and the absence of alternatives, it may be justifiable to maintain ART, including 3TC/FTC, as part of treatment optimization.

Supportive therapy and prophylaxis

With timely diagnosis and treatment of perinatal HIV infection, common infections are no more frequent than in immunocompromised children. Clinically stable children on successful ART and with good immune status can receive live vaccines (Ehl 2018). Immunoglobulin substitution is usually not necessary anymore (Nachman 2005b). Antibiotic prophylaxis (e.g., PCP prophylaxis) is based on immune status. If ART is not yet effective and immune reconstitution is not yet sufficient, AIDS still occurs, especially in infants (see chapter *AIDS*, presentation of all OIs in children at www.cdc.gov/mmwr/preview/mmwrhtml/rr5314a1.htm).

Summary

Clinical management in children and adolescents differs from HIV infection in adults. Infants, in particular, are highly vulnerable and must be diagnosed and treated expeditiously. The goal is to individually manage ART for maximum effectiveness while avoiding long-term side effects in growing children and adolescents. Long-term success is achieved through

- Development of child-friendly forms of application (e.g., granules or tasteless juices for young children)

- Intersectoral and interdisciplinary collaboration (pediatrician in the practice and at the center, gynecologist in the practice and at the clinic, psychosocial team, virology, infectiology, pharmacology).
- Standardized PVCs, evidence-based approach along national guidelines, and participation in multicenter trials (e.g., German-Austrian Guideline on Antiretroviral Therapy of HIV Infection in Children and Adolescents; Pediatric European Network Trial in AIDS PENTA).
- Development of new substance classes (e.g., monoclonal antibodies, capsid inhibitors) and strategies (e.g., long-term injectables induction and continuous therapy)

In the majority of children and adolescents in Western countries, HIV has changed from a mostly fatal infection to a chronic one that allows them to lead largely normal lives.

Literature

ArrowTrialTeam, Kekitiinwa A, Cook A, et al. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. Lancet 2013, 381:1391-403.

Bamford A, Turkova A, Lyall H, et al. Paediatric European Network for Treatment of AIDS (PENTA) guidelines for treatment of paediatric HIV-1 infection 2015: optimizing health in preparation for adult life. HIV Medicine 2015.

Burgard M, Blanche S, Jasseron C, et al. Performance of HIV-1 DNA or HIV-1 RNA tests for early diagnosis of perinatal HIV-1 infection during anti-retroviral prophylaxis. J Pediatrics 2012;160:60-6 e1.

Butler K, Inshaw J, Ford D, et al. BREATHER (PENTA 16) short-cycle therapy (SCT) (5 days on/2 days off) in young people with chronic human immunodeficiency virus infection: an open, randomised, parallel-group Phase II/III trial. Health Technol Assess 2016, 20:1-108.

Butler KM, Gavin P, Coughlan S et al. Rapid viral rebound after 4 years of suppressive therapy in a seronegative HIV-1 infected infant treated from birth. Pediatr Infect Dis J 2015, 34:e48-51

Chadwick EG, Yogev R, Alvero CG, et al. Long-term outcomes for HIV-infected infants less than 6 months of age at initiation of lopinavir/ritonavir combination antiretroviral therapy. AIDS 2011, 25:643-9.

Choe BH, Lee JH, Jang YC, et al. Long-term therapeutic efficacy of lamivudine compared with interferon-alpha in children with chronic hepatitis B: the younger the better. J Ped Gastroenterol Nutri 2007, 44:92-8.

Compagnucci A, Chan MK, Saïdi Y, et al. Nucleoside/nucleotide reverse transcriptase inhibitor sparing regimen with once-daily integrase inhibitor plus boosted darunavir is non-inferior to standard of care in virologically-suppressed children and adolescents living with HIV – Week 48 results of the randomised SMILE Penta-17-ANRS 152 clinical trial. EClinicalMedicine 2023, 60:102025. Dunn D, Group HIVPPMCS. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. Lancet 2003, 362:1605-11.

Ehl S, Bogdan C, Niehues T, et al. Impfen bei Immundefizienz : Anwendungshinweise zu den von der Ständigen Impfkommission empfohlenen Impfungen.(II) Impfen bei 1. Primären Immundefekterkrankungen und 2. HIV-Infektion. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2018, 61:1034-1051.

Fillekes Q, Natukunda E, Balungi J, et al. Pediatric underdosing of efavirenz: a pharmacokinetic study in Uganda. Journal of Acquired Immune Deficiency Syndromes 2011;58:392-8.

Fletcher CV. Antiretroviral drug-drug interaction considerations for HIV-infected children. Ped Inf Dis J 2009; 28:429-30.

Fraaij PL, Neubert J, Bergshoeff AS, et al. Safety and efficacy of a NRTI-sparing HAART regimen of efavirenz and lopinavir/ritonavir in HIV-1-infected children. Antiviral Ther 2004, 9:297-9.

Gafni RI, Hazra R, Reynolds JC, et al. Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. Pediatrics 2006;118:e711-8.

INSIGHT START Study Group, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. NEJM 2015, 373:795-807.

Johnson SR, Marion AA, Vrchoticky T, et al. Cushing syndrome with secondary adrenal insufficiency from concomitant therapy with ritonavir and fluticasone. J Ped 2006;148:386-8.

Judd A, EuroCoord HIVCCsgi. Early antiretroviral therapy in HIV-1-infected infants, 1996-2008: treatment response and duration of first-line regimens. AIDS 2011, 25:2279-87.

Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology—drug disposition, action, and therapy in infants and children. N Engl J Med 2003, 349:1157-67.

Kinabo GD, Sprengers M, Msuya LJ, et al. Prevalence of lipodystrophy in HIV-infected children in Tanzania on HAART. Ped Inf Dis J 2013;32:39-44.

Laughton B, Cornell M, Boivin M, Van Rie A. Neurodevelopment in perinatally HIV-infected children: a concern for adolescence. J IAS 2013;16:18603.

Lipshultz SE, Williams PL, Wilkinson JD, et al. Cardiac status of children infected with HIV who are receiving long-term combination antiretroviral therapy: results from the Adolescent Master Protocol of the Multicenter Pediatric HIV/AIDS Cohort Study. JAMA pediatrics 2013;167:520-7.

MacDonell K, Naar-King S, Huszti H, et al. Barriers to medication adherence in behaviorally and perinatally infected youth living with HIV. AIDS Behavior 2013, 17:86-93.

Menson EN, Walker AS, Sharland M, et al. Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study. BMJ 2006;332:1183-7.

Mikhail IJ, Purdy JB, Dimock DS, et al. High rate of coronary artery abnormalities in adolescents and young adults infected with human immunodeficiency virus early in life. Ped Inf Dis J 2011;30:710-2.

Nachman SA, Lindsey JC, Moye J, et al. Growth of human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. Ped Inf Dis J 2005;24:352-7.

Nachman S, Gona P, Dankner W, et al. The rate of serious bacterial infections among HIV-infected children with immune reconstitution who have discontinued opportunistic infection prophylaxis. Pediatrics 2005;115:e488-94.

Patni N, Diaz EG, Cabral MD, et al. Worsening hypertriglyceridemia with oral contraceptive pills in an adolescent with HIV-associated lipodystrophy: a case report and review of the literature. JPEM 2014, 27:1247-51.

Penpact StudyTeam. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. Lancet Infect Dis 2011;11:273-83.

Paediatric European Network for Treatment of AIDS (PENTA). Once vs. twice-daily lopinavir/ritonavir in HIV-1-infected children. AIDS 2015, 29:2447-57.

Piloya T, Bakeera-Kitaka S, Kekitiinwa A, et al. Lipodystrophy among HIV-infected children and adolescents on highly active antiretroviral therapy in Uganda: a cross sectional study. J IAS 2012;15:17427.

Purdy JB, Gafni RI, Reynolds JC, et al. Decreased bone mineral density with off-label use of tenofovir in children and adolescents infected with human immunodeficiency virus. J Ped 2008;152:582-4.

Puthanakit T, Saphonn V,Vonthanak S, et al. Early versus deferred antiretroviral therapy for children older than 1 year infected with HIV (PREDICT): a multicentre, randomised, open-label trial. Lancet Infect Dis 2012, 12: 933-41.

Read JS; American Academy of Pediatrics Committee on Pediatric AIDS. Human milk, breastfeeding, and transmission of human immunodeficiency virus type 1 in the United States. Pediatrics 2003, 112:1196-205.

Resino S, Galan I, Perez A, et al. Immunological changes after highly active antiretroviral therapy with lopinavir-ritonavir in heavily pretreated HIV-infected children. AIDS Res Hum Retrovir 2005;21:398-406.

Rossi P, et al. Early diagnosis of HIV infection in infants – Report of a consensus workshop, Siena, Italy, January 17-18, 1992. JAIDS 1992; 5:1168-78.

Saez-Llorens X, Violari A, Deetz CO, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. Ped Inf Dis J 2003, 22:216-24.

Schomaker M, Leroy V, Wolfs T, et al. Optimal timing of antiretroviral treatment initiation in HIV-positive children and adolescents: a multiregional analysis from Southern Africa, West Africa and Europe. Int J Epidemiol 2017, 46:453-465.

Simon A, Warszawski J, Kariyawasam D, et al. Association of prenatal and postnatal exposure to lopinavir-ritonavir and adrenal dysfunction among uninfected infants of HIV-infected mothers. JAMA 2011;306:70-8.

Taweesith W, Puthanakit T, Kowitdamrong E, et al. The immunogenicity and safety of live attenuated varicella-zoster virus vaccine in human immunodeficiency virus-infected children. Ped Inf Dis J 2011;30:320-4.

Turkova A, White E, Mujuru HA, et al. Dolutegravir as First- or Second-Line Treatment for HIV-1 Infection in Children. NEJM 2021; 385:2531-43

Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. NEJM 2008;359:2233-44.

von Hentig N, Koenigs C, Elanjikal S, et al. Need for therapeutic drug monitoring in HIV-1 infected children receiving efavirenz doses according to international guidelines. Eur J Med Res 2006;11:377-80.

Waalewijn H, Turkova A, Rakhmanina N, et al. Optimizing Pediatric Dosing Recommendations and Treatment Management of Antiretroviral Drugs Using Therapeutic Drug Monitoring Data in Children Living With HIV. Ther Drug Monit 2019, 41:431-443.

Weber V, Radeloff D, Reimers B, et al. Neurocognitive development in HIV-positive children is correlated with plasma viral loads in early childhood. Medicine (Baltimore) 2017, 96:e6867.

SECTION 6

Organs · Interdisciplinary Medicine

21. Checklist: the new patient

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One aim of the initial contact with a new patient is to gain a comprehensive overview of the health and social situation of the patient to assess whether and how urgently opportunistic infections, concomitant diseases, and the HIV infection itself need to be treated. Furthermore, these first encounters include general information about the disease and establishing a trusting relationship. Nowadays, starting treatment immediately at the first presentation can be considered.

What the patient should know after the first consultation

- How HIV destroys the immune system.
- The difference between HIV infection and AIDS disease.
- The significance of CD4 T-cells and viral load.
- The risk of infecting other persons and how to avoid transmission.
- The efficacy, effectiveness, and success of the HIV treatment.
- The need to take tablets (or injections) regularly.
- Good prognosis: with ART, everyday life is quite possible.
- Aspects of partnership, family planning, and professional activities.
- The risk of additional sexually transmitted infections (STIs) and viral hepatitis. Both can worsen the course of HIV infection.
- The patient should be able to speak freely about the symptoms of an STI.
- It is possible to become infected again with a different, more pathogenic, or resistant HIV strain.
- A healthy diet and physical exercise can improve prognosis.
- Smoking increases the risk of a variety of complications markedly.
- Information sources, support groups, NGOs, community-based organizations, and other facilities for the support of people with HIV.
- Other diagnostic tests and why they may need to happen.

What the doctor should know after the first consultation

Infection and risk

- What are the circumstances of the initial diagnosis? Are there additional diagnoses at the time of the initial diagnosis? Are there any current complaints?
- When, where, and why was the HIV test performed? (When) Was there a negative test before? What risks have been taken since then?
- Are stimulants being used? Are there any sexual function disorders? A sexual history is essential to detect STIs and advise on prevention.
- Are there any sexual partners who should be tested and treated for STIs?
- Has the patient traveled recently, and what is his geographical background (prevalence of infections may vary by region)?
- Use of legal and illegal drugs (including oral, inhalation, intravenous).
- Smoking status and the cumulative amount of smoking (pack-years).
- Family history, including diabetes mellitus, heart disease, cancer, tuberculosis (-contact), and other infections.

Concomitant illnesses

- Illnesses other than HIV.
- Previous infections such as STIs, viral hepatitis, pneumonia, TB, zoster, and candidiasis.
- Any medication, including painkillers and sleeping pills, injections, inhaled agents, dietary supplements, and ovulation inhibitors.
- Was PREP or PEP (HIV pre/post-exposure prophylaxis) used?
- Allergies or intolerances.
- Participation in disease screening programs and vaccination status (vaccination certificate).

Social

- What is the patient's social background? Is there a partnership? Is there a partner test? Are there children, or is there a wish to have children?
- What is the patient's (former) profession? Shift work?
- How is the financial situation? Are there any economic or social obligations? Can payments for prescriptions or medications happen?
- Re: migration issues: residency and legal status, health care insurance.
- Is there a relevant religious background? Will this affect medication use, sexual orientation, or risk behavior?
- Who knows about the infection? Who can help if necessary? With whom can concerns be discussed? Are there infected persons in the circle of friends? Is the patient interested in contacting social workers or support groups?
- How will the patient cope with the diagnosis? Is psychiatric/psychotherapeutic support necessary?
- Is there a legal guardianship?

Laboratory tests

Reasonable baseline testing for all PLWH

- Confirmation of the HIV infection in a second blood sample.
- Full blood count (30–40% of untreated patients have anemia, neutropenia, thrombocytopenia).
- Total lymphocyte count, CD4 T-cell count, percentage, and CD4/CD8 ratio (less variable).
- Plasma HIV RNA (viral load) and resistance test (genotype).
- HLA-B*5701 test before starting abacavir treatment.
- Tropism testing before starting maraviroc treatment.
- Electrolytes, creatinine, calculated creatinine clearance, urine test, AST (GOT), ALT (GPT), γGT, lipase, total protein and protein electrophoresis.
- Fasting blood glucose and lipid profile (total cholesterol, LDL, HDL, triglycerides)
- Hepatitis serology: A, B (if B positive, then D), C, (E). Take vaccinations into account. Consider PCR test in case of acute infections.
- Lues serology: TPHA test, VDRL if necessary, FTA abs IgM, IgG (depending on the laboratory).
- STI screening with (pooled) tissue swabs (gonorrhea, chlamydia, and Mycoplasma genitalium if applicable).
- Toxoplasmosis: IgG serology. If negative: prevention (avoid raw meats and contact with cats). If positive and < 200 CD4 T-cells/µl: prophylaxis.
- Varicella, measles, rubella IgG serology (immunity?).
- Tuberculosis: interferon-gamma assay (IGRA test). Caveat: False-negative results are possible in case of severe immunodeficiency. Mendel-Mantoux skin test is less sensitive and specific.

Additional examinations in case of suspicion or low CD4 T-cell count

- CMV: IgG serology. If positive and < 100 CD4 T-cells/µl: fundoscopy, CMV-PCR as activity marker.
- Cryptococcus: Antigen test for neurological symptoms.
- Folic acid, vitamins B12 and D (often low).
- Blood cultures in case of acute infections.
- Sputum diagnostics for mycobacteria.

Further investigations

- Physical examination (general condition, lungs, heart, skin, lymph nodes), height, weight, BMI, exploratory neurological examination, vibration sensitivity, and cognitive test (e.g., MiniMental, DemTect, clock drawing test).
- Neurological impairment should prompt a CT or MRI scan of the brain to check for cerebral infections or malignancies.
- Chest X-ray, if IGRA is positive, and in case of suspicion of diseases of the thoracic organs (in smokers, also low-dose CT should be considered).
- Sonography of the abdomen if necessary. It also serves as a baseline examination of the liver, spleen, kidney, and lymph nodes.
- ECG and pulmonary function test (especially in smokers) in case of suspected or existing diseases. Nt-pro-BNP and/or echocardiography for cardiac assessment; risk score for CHD; baseline QTc interval before starting ART.
- In female patients: cervical PAP smear for CIN at initial HIV diagnosis, after six months, then once a year if negative.
- In all patients: anal PAP smear. Proctological examination (condylomata acuminata, genitoanal dys-/neoplasia) is recommended.
- Ophthalmic fundoscopy: Especially when < 100 CD4 T-cells/µl and/or visual impairment.
- Estimate osteoporosis risk by obtaining vitamin D levels and, if necessary, bone density measurement.
- Check vaccinations and vaccination counseling.

22. HIV and cardiopulmonary disease

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Lung diseases

The lung is one of the major organs of manifestation of HIV. The spectrum of possible disease includes HIV-typical complications such as tuberculosis (TB), *Pneumocystis jirovecii* (PCP), bacterial pneumonia, lymphoma and pulmonary hypertension (PH), but also acute bronchitis, bronchial asthma, chronic obstructive pulmonary disease (COPD), bronchial carcinoma (BC) and pulmonary fibrosis (Table 1). COPD and lung cancer increase with age (Staitieh 2014, Maitre 2018), whereas PCP and TB have become less common in industrialized countries.

Table 1: Pulmonary complications in people living with HIV.

Infections	Neoplasia	Other
Pneumocystis jiroveci (PCP)	Kaposi's sarcoma	Bronchial hyperresponsiveness / Asthma / COPD
Bacteria	Non-Hodgkin's lymphoma	Lymphocytic interstitial pneumonia (LIP)
S. pneumoniae	Hodgkin's lymphoma	Non-specific interstitial pneumonia (NSIP)
S. aureus	Bronchial carcinoma	Cryptogenic organizing pneumonia (COP)
H. influenzae		Pulmonary arterial hypertension (PAH)
B. catarrhalis		
P. aeruginosa		**Complications under ART**
Rhodococcus equi		Dyspnea + cough as hypersensitivity reaction (ABC)
Nocardia asteroides		Dyspnea + tachypnea in lactic acidosis
Mycobacteria		Pneumonia while on T-20
M. tuberculosis		Infiltrates lymph nodes and/or fever as immune reconstitution syndrome (IRIS)
Atypical mycobacteria		
Other		
Cytomegalovirus		
Aspergillus spp.		
Cryptococcus neoformans		
Histoplasma capsulatum		
Toxoplasma gondii		

HIV has a particular affinity for the lung. The pathogenesis is probably multifactorial (Cribbs 2020): latent persistent virus in bronchopulmonary lymphoid tissue reduces antimicrobial cytokines. A possible synergy exists between smoking, cytotoxic T-cells, and activated HIV-infected alveolar macrophages. In addition, increased senescence of lung tissue is probably pathogenetically relevant (Neri 2018).
Especially in advanced immunodeficiency, many differential diagnoses of respiratory symptoms must be considered. History and clinical clues often point the way. This chapter provides an overview; further chapters are on PCP, mycobacterioses, aspergillosis, CMV, and PH.

Medical history

The most important question: What is the immune status? The CD4 T-cell count is the most critical indicator of the patient's risk of opportunistic infections (OI). The current value is more essential than the nadir. Above 200 cells/µl, acute bronchitis, and bacterial pneumonia are typical and OIs are very unlikely. Below 200 CD4 T-cells/µl, PCP is *the* typical complication, although bacterial pneumonia is also more common in PLWH.
TB is the exception to this rule: while the risk increases with decreasing CD4 T-cell counts, most TB infections are seen in patients with CD4 T-cells above 200/µl, due to the larger numbers of these patients.
Pulmonary Kaposi's sarcoma and *Toxoplasma gondii* infections are rarely seen and are usually diagnosed below 100 CD4+ T cells/µl. Below 50 CD4 T-cells/µl, CMV infections (usually in combination with PCP), invasive pulmonary aspergilloses (usually by hematogenous spread), atypical mycobacterioses and endemic fungal infections (*Histoplasma capsulatum, Coccidioides immitis*) occur.

What are the symptoms? In PCP, dyspnea and unproductive, dry cough are typical. Yellow or green sputum suggests a bacterial etiology, possibly a co-infection like an OI. Bacterial pneumonia typically begins acutely, and patients present after 1–5 days, whereas individuals with PCP are symptomatic on average 28 days before medical attention is sought (Cilloniz 2014).

What are the pre-existing conditions? Those with PCP previously have a higher risk of getting one again. PLWH with concurrent COPD have "normal" exacerbations.

Is the patient under prophylaxis? The use of cotrimoxazole makes PCP unlikely. It may also reduce the risk of bacterial pneumonia. Pentamidine inhalation is likely to cause atypical, often apically accentuated manifestations of PCP.

Has ART been started recently? Pulmonary symptoms and fever are possible in the setting of IRIS; PCP- or TB-IRIS also occur. Hypersensitivity reaction (HSR) due to abacavir is rare nowadays because of HLA testing. It often manifests with dyspnea (13%), cough (27%), and pharyngitis (13%). Sometimes even pulmonary infiltrates are found. T-20 appears to increase the risk of bacterial pneumonia, at least with cigarette smoking.

Does the patient smoke cigarettes? PLWH are about twice as likely to smoke as HIV-negative individuals and die significantly earlier (Helleberg 2013, Park 2016). Smoking promotes a local immune deficit in the lungs. Bacterial pneumonia and PCP as well as asthma, COPD, and lung cancer, are more common in HIV+ smokers. Motivation to abstain from smoking is, therefore, an essential medical task. Study-proven benefits can come from brief verbal interventions, motivational groups, nicotine replacement therapy, bupropion (caveat: interactions, e.g., with ritonavir), and varenicline (caveat: psychic disorders/suicidal tendencies). For practical help, see the HIV Provider Smoking Cessation Handbook (VA 2012).

What is the patient's geographical background? Histoplasmosis and coccidioidomycosis are more common than PCP in some parts of the US but are rarely seen in Europe. In Southeast Asia, cryptococci are very common. Among African migrants and people from the former Soviet Union, (resistant) tuberculosis plays a more significant role.

What is the route of HIV infection? People with intravenous drug use are more likely to have bacterial pneumonia, pulmonary abscesses, endocarditis due to *Staphylococcus aureus*, and TB. Pulmonary Kaposi's sarcomas are found almost exclusively in MSM.

What does the X-ray image look like? See Table 2.

Table 2: What does the X-ray image look like?

Chest X-ray	Typical differential diagnosis
Without pathological findings	PCP, asthma, KS of the large airways, TB in case of low CD4 counts
Localized infiltrates	Bacterial pneumonia, mycobacteriosis, lymphoma, fungi, BC
Multifocal infiltrates	Bacterial pneumonia, mycobacteriosis, PCP, KS
Diffuse infiltrates	Bacterial pneumonia (in low CD4+ counts) PCP (centrally accentuated), CMV, KS, LIP, heart failure, fungal infections
Miliary pattern	Bacterial pneumonia (in low CD4 count), mycobacterial and fungal infections
Pneumothorax	PCP, COPD/emphysema
Cavernous lesions	Mycobacteriosis (CD4 T-cells > 200), bacterial abscess (staphylococcus, pseudomonas), lung cancer, pulmonary embolus
Cystic lesions	PCP, fungal infections
Pleural effusion	Bacterial pneumonia, mycobacteriosis, KS, lymphoma, heart failure, malignoma
(Bihilary) lymphadenopathy	Mycobacteriosis, KS, sarcoidosis, lymphoma

KS = Kaposi's sarcoma, PCP = Pneumocystis jirovecii, LIP = lymphoid interstitial pneumonia, BC = bronchial carcinoma.

Diagnostic strategy in pulmonary infiltrates

Diagnostics depend on the HIV stage and the expected pathogen spectrum. For CD4 T-cells above 200/µl, basic non-invasive diagnostics, and an empirical antibiotic therapy are reasonable. In hospitalized patients, two blood cultures (the rate of bacteremia is higher than in immunocompetent patients), a microscopic and cultural sputum examination (including mycobacteria), and pneumococcal and legionella antigen urine tests are recommended. In most immunodeficiency situations, broad antibacterial treatment should be started immediately after obtaining blood cultures and sputum. Multiplex PCR for several pathogens can be an additional option. Cryptococcal and Histoplasma antigen tests have a high positive predictive value; however, these diseases are rare in European countries.

Bronchoscopy is indicated if CD4 T-cells are below 200/µl and PCP, CMV, and TB are suspected but must not delay therapy. Antibiotics do not alter the PCR results initially. The sensitivity of BAL is 60–70% for bacterial pneumonia without pretreatment and 85–100% for PCP with modern PCR methods (Unnewehr 2016).

A high-resolution chest CT should be done early and with a low threshold, especially in patients with a CD4 T-cell count lower than 200/µl. For example, PCP can be visualized much better on CT than on usual radiography. A second bronchoscopy with transbronchial biopsies, CT-guided biopsy, and thoracoscopic/open biopsies are rarely necessary.

Pulmonary complications and co-morbidities

Asthma, COPD, BC, PH, pulmonary fibrosis, and pulmonary infections are more common in PLWH (Cribbs 2020). In patients on ART, non-infectious co-morbidities become more critical. However, it should be considered that the prevalence of co-morbidities, especially BC, COPD, and pulmonary fibrosis is increased due to the more intensive diagnostic efforts in PLWH and the much higher prevalence of cigarette smoking.

Bacterial pneumonias: are more common and lead to persistent limitation of lung function and worsen the long-term prognosis due to scarring. The incidence increases with increasing immunosuppression and age. Two or more pneumonias per year define AIDS. In addition to the risk calculated by the CRB-65 score (confusion, respiratory rate, blood pressure, > 65 years), SpO_2 <= 90%, and co-morbidities, the CD4 T-cell count is essential. Below 200 cells/µl, the pneumonia can be more multifocal and interstitial. Even those supposedly mildly ill with less than 100 CD4 T-cells/µl have a more than six-fold increased mortality and should be hospitalized. As prevention, the standard vaccinations should be done (see *Vaccinations*).

COPD and emphysema: Next to pneumonia, COPD is the most common pulmonary complication of an HIV infection. Patients suffer more severely from this pulmonary co-morbidity: obstruction is more pronounced, emphysema is more common, and quality of life is worse (Neri 2018). COPD symptoms should always be asked about, and a pulmonary function test should be performed, especially in all smokers.

Bronchial asthma: Besides COPD, asthma is the most common (non-infectious) pulmonary co-morbidity and probably somewhat more common than HIV-negative individuals. Therefore, a hyperresponsive bronchial system or asthma should be considered in case of unexplained cough, dyspnea, or recurrent bronchitis. Whether HIV-related immunosuppression protects against or even increases the incidence of an exaggerated immune response, like in allergy and asthma, is controversial.

Pulmonary fibrosis and lymphoid interstitial pneumonia: Lymphoid interstitial pneumonia (LIP) is a rare chronic or subacute pneumonia in adults, clinically and radiologically similar to PCP. It is characterized by CD8-dominant lymphocytic alveolitis without evidence of pathogen, with CD4 T-cells above 200/µl and normal LDH (differential diagnosis to PCP). The definitive diagnosis often requires lung biopsy or, nowadays, bronchoscopic cryo-biopsy. LIP is considered to be steroid-sensitive. The role of ART is unclear, mainly since LIP is also observed in the context of immune reconstitution (Van Zyl-Smit 2015). PLWH are more likely to have pulmonary fibrosis (Leader 2016). Various manifestations (including COP, NSIP, IPF/UIP) have been described, including alveolar proteinosis in individuals.

Lung cancer (LC): Studies show a 2- to 8-fold increased incidence of LC in HIV infection (see *Non-AIDS-defining malignancies*). By now, more PLWH die from LC than from many AIDS-defining malignancies. A low dose chest CT is reasonable in case of suspicion or high risk (smoking > 20 pack years, age 50 to 80 years).

Rare opportunistic infections

In children, CMV pneumonia is more common than PCP, but rare in adults. However, pulmonary CMV infections have been frequently detected in autopsy series – the importance of the pathogen may be underestimated in the late stages. Especially in cases of severe respiratory failure in the setting of PCP, CMV pneumonia should be considered and treated in case of doubt, since co-infection increases mortality.
CMV pneumonia is unlikely if CMV PCR in BAL is negative. If positive, this does not prove CMV infection because of the frequent CMV colonization of the airways. This is why serologic markers are of little help. On the other hand, a high CMV viral load (or antigen) in the blood and within the appropriate context is a strong indication of a relevant infection; the probability of infection increases with the level of viremia. Invasive pulmonary aspergillosis is also rare but occurs in the late stages, sometimes in combination with other OIs and with additional risk factors such as neutropenia or steroid therapy. Blood cultures, fungal cultures, galactomannan antigen tests in BAL, and CT are helpful diagnostic tools.

Literature

Cilloniz C, Torres A, Polverino E, et al. Community-acquired lung respiratory infections in HIV-infected patients. Eur Respir J 2014, 43:1698-1708.

Cribbs SK, Crothers K, Morris A. Pathogenesis of HIV-related lung disease: Immunity, infection, and inflammation. Phys Rev 2020, 100:603-32.

Helleberg M, Afzal S, Kronborg G, et al. Mortality attributable to smoking among HIV-1-infected individuals: a nationwide, population-based cohort study. Clin Infect Dis Off Publ Infect Dis Soc Am 2013, 56:727-734.

Kynyk JA, Parsons JP, Para MF et al. HIV and asthma, is there an association? Respir Med 2012, 106:493-9.

Leader JK, Crothers K, Huang L, et al. Risk factors associated with quantitative evidence of lung emphysema and fibrosis in an HIV-infected cohort. J Acquir Immune Defic Syndr 2016, 71:420-427.

Neri S, Leung J, Besutti G, et al. Chronic Lung Disease in HIV Patients. Aids Reviews 2018, 20: 150-7

Maitre T, Cottenet J, Beltramo G, et al. Increasing burden of non-infectious lung disease in persons living with HIV: a 7-year study using the French nationwide hospital administrative database. ERJ 2018 52 (3).

Park LS, Hernández-Ramírez RU, Silverberg MJ, et al. Prevalence of non-HIV cancer risk factors in persons living with HIV/AIDS: a meta-analysis. AIDS Lond Engl 2016, 30:273-291.

Sigel K, Wisnivesky J, Gordon K, et al. HIV as an independent risk factor for incident lung cancer. AIDS 2012, 26:1017-25.

Staitieh B, Guidot DM. Noninfectious pulmonary complications of human immunodeficiency virus infection. Am J Med Sci 2014, 348:502-511.

Unnewehr M, Friederichs H, Bartsch P, Schaaf B. High Diagnostic Value of a New Real-Time Pneumocystis PCR from Bronchoalveolar Lavage in a Real-Life Clinical Setting. Respir Int Rev Thorac Dis 2016, 92:144-149.

U.S. Department of Veterans Affairs, Veterans Health Administration, Washington, DC 20420. HIV Provider Smoking Cessation Handbook: A Resource for Providers, 2012. https://www.mentalhealth.va.gov/quit-tobacco/docs/IB_10-432-HIV_Provider_Smoking_Cessation_Handbook.pdf

Van Zyl-Smit RN, Naidoo J, Wainwright H, et al. HIV-associated Lymphocytic Interstitial Pneumonia: a clinical, histological and radiographic study from an HIV endemic resource-poor setting. BMC Pulm Med 2015,15:38.

Cardiovascular diseases

The prevalence of cardiovascular disease increases with age and the duration of the HIV infection (Bloomfield 2017). Cardiovascular morbidity with HIV is higher because of vascular and myocardial diseases (Manga 2017).

Coronary heart disease (CHD)

The prevalence of CHD and the incidence of acute coronary syndromes (ACS) are increased, often at younger ages. Reasons or risk factors are:

1. Increased cardiovascular risk profile: Smoking is about twice as common, hypertension is often not controlled, and risk factors are not always adequately treated (Reinsch 2012).
2. Negative effects of ART: Until now, ART was considered a risk factor for ACS due to inflammatory influences on the endothelium and concomitant dyslipidemias. However, a beneficial effect on myocardial inflammation is also conceivable. It is not sure whether antiretroviral agents impact cardiovascular morbidity differently (see *ART*).
3. Direct consequences of HIV: progression of atherosclerosis is promoted by chronic inflammation, possibly depending on the extent of immunodeficiency.
4. Comparatively more intense diagnostic workup in HIV+ individuals.

Due to increased cardiovascular morbidity, detection and treatment of risk factors are essential to HIV care. Relevant guidelines, including those for secondary prevention and indication for coronary angiography, also apply to HIV (Perk 2012). In treating hyperlipoproteinemia, attention should be paid to potential interactions between CSE inhibitors and ART (especially boosted regimens). If risk factors are present, ECG and risk assessment using common scores (e.g., PROCAM, ESC) are recommended once a year. Symptomatic individuals require the usual further diagnostic workup.

Cardiomyopathy

The prevalence of HIV cardiomyopathy has decreased since the pre-ART era (ranging from 9% to 52%, Manga 2017) to 1.8%. The mortality remains slightly elevated today (Whiteside 2015). Causes include direct myocardial injury from HIV and autoimmune-mediated myocardial injury (Choi 2021).

Whereas some older antiretroviral drugs were previously thought to have cardiotoxic effects, tenofovir, for example, appears to have more of a beneficial effect on heart failure (Hsue 2017). Heart failure is diagnosed and treated the same way as HIV-negative people, focusing on the underlying cause. People with HIV should be asked once a year for symptoms and signs of heart failure and examined (ECG, echocardiography, serum pro-BNP).

Pericardial effusion

Pericardial effusion is rare in Europe in PLWH, but much more common in Africa (Lind 2011). The pathogenesis is diverse: infections (mainly TB, but also other bacteria), neoplasms, and capillary defects due to HIV (Manga 2017). TB is by far the most common in people from high-prevalence areas, often with chronic courses and pericarditis constrictiva.

Cardiac arrhythmias

HIV can lead to autonomic nervous system changes with reduced heart rate variability (Chow 2011). A structural heart disease may promote arrhythmias. Sudden cardiac death is generally more common in PLWH (Manga 2017). Antiretroviral drugs usually do not cause relevant arrhythmias. However, PIs, particularly ritonavir, lopinavir, and atazanavir, can asymptomatically prolong the PR interval on ECG and occasionally cause block images and conduction disturbances. They should therefore be avoided in the presence of pre-existing conditions affecting the conduction system and co-medications affecting conduction. Ventricular arrhythmias have also been reported in IRIS (Rogers 2008).
In clinical practice, arrhythmias caused by a combination of ART with other drugs are far more common. Antiarrhythmic medicines such as amiodarone, quinidine, flecainide, and propafenone can interact with NNRTIs and should, therefore, be avoided or dosed lower. Combinations with PIs should be avoided because PIs increase antiarrhythmic drug levels. NRTIs are less problematic. No interactions are expected for un-boosted INSTIs.

Diseases of the heart valves

It has not been proven that people living with HIV are more likely to develop endocarditis. Specific risk groups, such as intravenous drug users, have a 10- to 12-fold increased risk, especially for tricuspid valve endocarditis. The bacterial spectrum differs in HIV: the most common pathogen (40%) is *Staphylococcus aureus*; other typical pathogens are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Diagnosis, therapy, and prognosis do not differ from those of the HIV-negative population. There is no general recommendation for endocarditis prophylaxis in HIV infection.

HIV-associated pulmonary arterial hypertension (HIV PAH)

The most common causes of high pulmonary arterial pressure (pulmonary hypertension, PH) are cardiac and pulmonary diseases. Hereditary and idiopathic forms of pulmonary hypertension, and those occurring in association with certain diseases ("associated PH"), are sporadic and are referred to as "pulmonary arterial hypertension" (PAH). These include HIV PAH. In 2018, PAH was redefined – not without controversies – by a mean pulmonary arterial pressure measured by right heart catheterization of > 20 mmHg at rest (previously > 25 mmHg) in combination with other measurements (Hon 2022).
The cause of HIV PAH is unclear; the histology is indistinguishable from other forms of PAH. An inflammatory response of the pulmonary arterial vessel wall mediated by the viral proteins *tat*, gp120, and *nef* with vasoconstriction and vascular remodeling with the proliferation of endothelial cells and smooth muscle cells ("plexiform vasculopathy") is discussed. PAH causes reactive hypertrophy of the right ventricular myocardium with dilatation and right heart failure. The prognosis of HIV PAH is poor (Manga 2017, Hon 2022).
The prevalence of HIV PAH is not precisely known; it was probably at most 0.5% before the new definition (Staitieh 2014). Thus, it is increased about 1,000-fold compared to the general population. Echocardiography should therefore be performed in cases of unclear dyspnea. Although general screening of all people with HIV is not recommended, echocardiography is recommended for the following PAH risk factors, regardless of symptoms: women, intravenous drug use, hepatitis C co-infection, origin from a high-prevalence country (Africa), or known *nef* or *tat* protein expression. The further work-up is the same as for the other forms of PAH.

Generally, HIV PAH is treated like the other forms of PAH, but interactions with ART must be considered. Although no precise data exists, ART and specific PAH medications are likely beneficial for disease progression. ART does not appear to induce PAH. PAH medication always requires individualized assessment by experts.

Literature

Bloomfield GS, Leung C. Cardiac Disease Associated with Human Immunodeficiency Virus Infection. Cardiol Clin 2017, 35:59-70.

Choi H, Dey AK, Sharma G, et al. Etiology and pathophysiology of heart failure in people with HIV. Heart Fail Rev 2021, 26:497-505.

Chow DC, Wood R, Choi J, et al. Cardiovagal autonomic function in HIV-infected patients with unsuppressed HIV viremia. HIV Clin Trials 2011,12:141–50

Hon SM, Alpizar-Rivas RM, Farber HW. Pulmonary Arterial Hypertension in Patients Infected with the HIV. Cardiol Clin 2022, 40:45-54.

Hsue PY, Waters DD. Heart failure in persons living with HIV infection. Curr Op HIV AIDS 2017, 12: 534–539.

Lind A, Reinsch N, Neuhaus K, et al. Pericardial effusion of HIV-infected patients? Results of a prospective multicenter cohort study in the era of antiretroviral therapy. Eur J Med Res 2011, 16:480-483.

Manga P, MacCutcheon K, Tsabedze N, et al. HIV and ischemic heart disease. JACC 2017, 69:83-91

Perk J, De BG, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2012, 33:1635-1701.

Reinsch N, Neuhaus K, Esser S, et al. Are HIV patients undertreated? Cardiovascular risk factors in HIV: results of the HIV-HEART study. Eur J Prev Cardiolog 2012, 19:267-274.

Rogers JS, Zakaria S, Thom KA, et al. Immune reconstitution inflammatory syndrome and human immunodeficiency virus-associated myocarditis. Mayo Clin Proc 2008, 83:1275-1279.

Staitieh B, Guidot DM. Noninfectious pulmonary complications of human immunodeficiency virus infection. Am J Med Sci 2014, 348:502-11.

Whiteside YO, Selik R, An Q, et al. Comparison of rates of death having any death-certificate mention of heart, kidney, or liver disease among persons diagnosed with HIV infection with those in the general US population, 2009-2011. Open AIDS J 2015, 9: 14–22.

23. HIV and nephrology

ANSGAR RIEKE

As renal function decreases with age, its preservation is a key requirement of long-term ART. Co-morbidities in HIV are more frequent and occur earlier (Guaraldi 2011, Bonnet 2016). Arterial hypertension, diabetes mellitus, dyslipidemia, older age, nicotine use, and chronic inflammation from HIV worsen renal function. Every effort should, therefore, be made to eliminate renal risks. The START trial has shown that early ART can prevent renal events. When selecting agents, renal-friendly ART, avoiding TDF, should always be requested when additional renal risks exist: these are present in degenerative skeletal diseases and often uncontrolled NSAID use, drug use, chemsex practices, chemotherapy, diabetes, or hypertension, where acute renal failure should always be expected. Proteinuria and loss of GFR regularly imply increased cardiovascular risk, which directly correlates with the extent of proteinuria (CKD Consortium 2010). Acute renal failure and adjusted mortality are still significantly more common in PLWH. Cohort analyses show significantly increased renal vulnerability compared with non-HIV-infected individuals (Schulz 2020). There has also been no decrease in renal replacement therapy. People of African-American descent are particularly affected, with a 10-fold higher risk of renal failure than uninfected individuals (Lucas 2007).
In addition to the treatment of HIV infection, the most important measures to prevent the progression of renal failure are normalization of body weight, adjustment of blood pressure to values < 130/80 mmHg, treatment of dyslipidemia according to cardiological guidelines, abstinence from nicotine and, in people with diabetes, reasonable blood glucose control. Early RAAS blockade with ACE inhibitors or AT 1/2 inhibitors is recommended in proteinuria. The use of contrast media in diagnostics should be viewed critically.

The clinic and diagnosis of nephropathy

The clinical picture is often non-specific, with fatigue, poor concentration, loss of appetite, hypertension, and possibly edema. Prerenal, intrarenal (glomerular, tubular, interstitial), and postrenal damage must be differentiated. Anamnesis might provide evidence of a renal cause (NSAIDs, infections, sepsis, contrast media?). Sonography identifies a possible post-renal outflow obstruction (renal congestion, prostatic hypertrophy?), and renal size (reduced with narrow parenchyma) may give clues for chronic renal failure. The diagnosis is supplemented by a urine dipstick or sediment and the determination of creatinine, electrolytes, and phosphate. Anemia, metabolic acidosis (blood gas analysis), calcium-phosphate metabolism disorders, venous thrombi, and newly diagnosed arterial hypertension help distinguish between acute and chronic renal failure.

Creatinine, Cystatin C, GFR

Elevated serum creatinine is only to be expected from a GFR restricted by more than 50%. It is dependent on muscle mass and gender and is, therefore, not a good marker of renal function on its own. Creatinine is predominantly glomerular filtered and secreted in the proximal tubule via transporters. Partial blockade of tubular excretion by dolutegravir, bictegravir, cobicistat, and ritonavir (see below) causes a creatinine increase of approximately 0,14 mg/mL. This does not indicate a worsening of the actual GFR ("Cobi effect").

The alternative cystatin C is constantly produced by all nucleus-bearing cells and is not subject to the effect above at the tubule – its clinical value is questionable in view of chronic inflammation, and the determination is more expensive. Clearance measurements are necessary because they detect the "creatinine-blind" region of renal insufficiency earlier, especially if the renal function is over-estimated by lower muscle mass (in older age). The CKD-Epi formula is widely accepted among the four methods for GFR determination, but it has only been evaluated in moderately impaired renal insufficiency. In EuroSIDA, CKD-Epi and the Cockroft and Gault formula indicated renal insufficiency well in more than 9000 PLWH (Mocroft 2013). Follow-up controls should be performed using the same GFR formula in each case.

Proteinuria

The extent of proteinuria with protein loss, the imbalance of serum protein fractions, and residual renal function with possible overhydration determine edema, decreased performance, susceptibility to infection, and hyperlipidemia. As with diabetes mellitus, microalbuminuria (urinary micral test) is an essential indicator of renal and cardiovascular mortality (Wyatt 2010). PLWH with confirmed microalbuminuria are 25 times more likely to develop proteinuria (Szczech, 2010), doubling the mortality risk if it persists despite ART (Wyatt 2010). They should, therefore, be screened for renal disease as carefully as people with diabetes. The extent of proteinuria (UP/C = urinary protein/creatinine in urine) can be graduated using the three ranges < 50, 50–100, and > 100. For albumin in urine (= UA/C), ranges of < 30, 30–70, and > 70 are considered graduations for the extent of glomerular proteinuria. If the value for UP/C is greater than UA/C, the difference indicates the extent of tubular proteinuria. The urine dipstick only detects albumin in the urine! Tubular markers such as beta-2-microglobulin are mainly used in clinical studies.
Proteinuria and "nephritic sediment" are the leading symptoms of glomerulonephritis (GN) and should be quantified. Clinical distinctions are made between nephrotic syndrome (protein loss, edema), acute nephritic syndrome (acanthocytes in the urine as a sign of GN), rapid-progressive GN (renal function loss within a few days), asymptomatic proteinuria or hematuria, and chronic GN. These entities are managed differently and require nephrology consultation. HIV-associated nephropathy (HIVAN, see below) is a specific glomerulonephritis. Although mild courses are possible, it most commonly presents as a nephrotic syndrome with edema, hypoalbuminemia, hyperlipidemia, and proteinuria greater than 3.5 g/day.

Urine sediment and dipsticks

In addition to salts, crystals (formerly with indinavir, but also other PIs), and epithelia, ***erythrocyturia*** (number and shape of erythrocytes?) is differential diagnostically significant: coincidence with proteinuria is pathognomonic for GN and usually secures the diagnosis together with nephritic sediment. Under a polarized light microscope, the glomerular origin of the erythrocytes can be identified quite reliably by glomerular deformed acanthocytes. More than five acanthocytes per field of view is a definite indication. If there is significant erythrocyturia, bleeding below the renal pelvis (tumors of the urinary tract?) should be excluded by sonography and cystoscopy, especially if there is no proteinuria as a sign of GN. ***Leukocyturia*** must be clarified microbiologically/culturally (uricult: midstream urine); bacterial interstitial nephritis may also be present. Sterile leukocyturia may indicate urogenital tuberculosis but may also express interstitial renal disease (e.g., earlier if on indinavir). ***Glucosuria*** (with normal blood glucose levels/lowering of the normal glucose threshold)) or ***phosphaturia*** are signs of tubular dysfunction, such as may occur with TDF.

Routine tests for kidney damage

As a routine examination in PLWH, sodium, potassium, calcium, phosphate, serum creatinine, and GFR are determined. Every 3–6 months, urinalysis should be performed as a strip test semi-quantitatively for proteinuria, erythrocyturia, urine sugar, and signs of urinary tract infection. If proteinuria in the urine stix is greater than 1, it is better to measure the protein/creatinine ratio (UP/C) quantitatively in spontaneous urine or the albumin/creatinine ratio (UA/C) for the glomerulus for the course (see above).

If there is a significant increase in proteinuria, serum creatinine, or a drop in GFR below 60, a nephrological consultation should be obtained (renal biopsy if necessary). This is necessary without delay in the case of a rapid creatinine increase (rapid-progressive GN?), LDH elevation in conjunction with hyperbilirubinemia and thrombocytopenia (hemolytic uremic syndrome in HIV?), or electrolyte imbalances (especially hyperkalemia), or an acidosis that can no longer be controlled, as can also occur as lactic acidosis under ART and metformin, for example.

Asymptomatic, mild proteinuria without creatinine elevation is observed in more than 50% of patients on ART (Zeder 2016). It should be monitored every three months. The extent of proteinuria can be estimated with the urine protein/creatinine quotient from spontaneous urine, which should be < 1 (example: urine protein 120 mg/dl and urine creatinine 30: proteinuria of 4 g/day).

Determination of parathyroid hormone and vitamin D can detect the interaction of kidney and bone and risks for osteoporosis.

Renal function decline is also a symptom of HIV infection and an indication for ART.

In imaging studies, contrast agents should be avoided to prevent renal failure, especially in renal function impairment, proteinuria, and all forms of intravascular fluid deficit (including liver cirrhosis). Any change in renal function is cause for sonography.

HIV-associated nephropathy (HIVAN)

HIVAN refers to a rapid loss of renal function that is particularly prevalent in African-American patients. In this group of individuals, HIVAN is the third most common reason for dialysis between the ages of 20–64. A genetic predisposition is likely due to the interaction of the human gene MYH9 (non-muscle myosin heavy chain 9) with HIV and an adjacent apolipoprotein L1 gene as a promoter of HIVAN. Because mutations of the ApoL-1 gene confer an evolutionary advantage in sleeping sickness, HIVAN is found almost exclusively in people of black African origin (Kao 2008, Kopp 2008, Soleiman 2011). Despite hemodialysis, one-year mortality without ART is about 50%; ART has reduced the risk of dialysis from HIVAN by 40%; moreover, one-year survival on dialysis has increased from 25% to 75% with ART (Winston 2008).

There is usually a poor immune status with < 100 CD4 T-cells/µl; only in 20% does the clinical picture occur with higher values. Isolated cases of acute retroviral syndrome have been reported. However, there seems to be no correlation between the level of viremia and the duration of HIV infection.

The clinical manifestation is usually nephrotic proteinuria of more than 3,5 g/day, but less is also possible. Progression is rapid and can lead to dialysis requirement in a few months (Szczech 2001). Blood pressure is normotensive or only moderately elevated, and the kidneys tend to be normal in size on a sonograph.

In about 70% of patients, the histological picture corresponds to a focal segmental sclerosing glomerulonephritis (FSGN) and cystic tubular changes and degeneration.

However, other GN forms up to amyloid kidney are also possible in PLWH (Daugas 2005). Case reports proved direct infection of the glomerular basement membrane with HIV and an impressively positive effect of ART on histological changes (Bruggemann 1997, Winston 2001).
Only early ART – even before scarring of the glomeruli! – offers the prospect of success (Lucas 2004). There are no recommendations for the selection – however, renal elimination (dose adjustment from < 60 mL GFR for NRTIs) must be considered. TDF-containing regimens are generally not suitable, but TAF is. ART should be supplemented with ACE inhibitors or angiotensin receptor blockers for blood pressure control. The use of steroids is controversial (1 mg/kg/day for 2 to 11 weeks). It is favored in the US, especially in the lupus-like course of HIVAN (Gupta 2005, Haas 2005, Choi 2009).
Controversy surrounds the question of whether HIVAN needs to be confirmed by renal biopsy. If ethnicity suggests the diagnosis, it is justified to start ART immediately and wait for therapy's success over three months. During this period, the viral load should be entirely suppressed, blood pressure should be well-controlled, diabetes mellitus should be treated if necessary, and the therapy should be supplemented with a lipid-lowering agent (e.g., pravastatin, analogous to the recommendations of post-infarction cardiology) (Szczech 2009). Often, renal function improves, and proteinuria regresses. The decision to biopsy belongs in nephrological hands. Depending on the extent of proteinuria and limitation of GFR (< 60 mL/min/1.73 m^2), nephrologists should be consulted. Renal biopsy can clarify the multiple causes of renal damage, prognosis, and therapy by a triple diagnosis of light and electron microscopy and immunohistochemistry.

Other glomerulonephritides (GN) in HIV

In Caucasian patients, IgA nephropathy, membranous, and membranoproliferative GN are particularly associated with HIV. Even without typical HIVAN, there is a significantly higher prevalence of proteinuria in PLWH, 6–32% (Soleiman 2011). The odds ratio for developing renal failure was increased dramatically in cohort analyses at 3.85 compared with people without HIV (Islam 2012). Many other pathogens can cause or maintain post-infectious GN or other forms of chronic GN. Viruses such as HBV, HCV, CMV, EBV, and VZV can do so, as are influenza viruses, adenoviruses, hantaviruses, and parvovirus B19. However, acute postinfectious GN can also occur after malaria, syphilis, and infections with staphylococci, pneumococci, legionella, salmonella, and other pathogens. In addition, there is a risk of circulatory renal failure in profuse diarrhea associated with infectious bowel disease or traveler's diarrhea.
In ***membranous glomerulonephritis,*** malignancy, and viral hepatitis must be excluded as classic "secondary GN". Chronic hepatitis C usually leads to ***membranoproliferative GN*** or vasculitis and renal involvement via cryoglobulinemia.
One of the most common kidney diseases is ***IgA nephropathy***, which can also be triggered or induced by HIV infection, respiratory infections, or hepatitis. An imbalance of the microbiome in the axis of the intestine and kidney is discussed. In post-infectious GN, the underlying infection is treated first. Depending on the course, additional immunosuppression may need to be considered on an interdisciplinary basis.
Hepatitis C-associated GN should always be treated by eliminating HCV (see below), especially if cryoglobulin-associated vasculitis is present.
As a complication of acute infection and untreated PLWH, ***hemolytic uremic syndrome (HUS)*** or thrombotic thrombocytopenic microangiopathy syndrome ***(TTP)***

may occur. This is characterized by the combination of creatinine elevation, hemolysis (LDH elevated, thrombocytopenia), and neurologic symptoms with renal failure. The pathomechanism is probably based on the induction of procoagulant effects of the HIV surface glycoprotein gp120 on endothelial cells with activation of the complement system (Mikulak 2010). In these cases, plasma separation, immune absorption, or even drug complement inhibition is necessary after nephrologic consultation to halt the progression to dialysis dependency. Such forms of renal failure can also be observed with COVID-19.

Therapeutic principles in glomerulonephritis

In post-infectious GN, the underlying disease is treated first. This also applies to hepatitis B or C, but also to HIV infection. In the case of kidney failure caused by hantaviruses (transmitted by mouse or rat feces), the spontaneous course can be waited for, given the excellent prognosis in Europe but not in South America.
It is crucial to adjust blood pressure to target values below 140/80 mmHg or below 130/80 mmHg in the case of proteinuria. This is achieved primarily with ACE inhibitors or AT-1 blockers, often in combination with diuretics. Proteinuria should be treated independently of blood pressure with a blockade of the renin-angiotensin-aldosterone system (RAAS), e.g., with ACE inhibitors, if necessary, also in high doses; if proteinuria exceeds 0.5 to 1 g/day, an AT-1 blocker is recommended. Protein intake is reduced to 0.6 to 0.8 g/kg/day; a "Mediterranean diet" with little meat is recommended pragmatically. Significant proteinuria (> 3.5 g/24 h) requires anti-coagulation if serum albumin concentration drops to values below 25 g/l – renal loss of clotting factors causes hypercoagulability and risk of thrombosis (if so, then phenprocoumon (Marcumar in Germany) up to INR 2–3, low molecular weight heparins if necessary, after factor Xa determination or NOACs dosed according to renal function). The drinking quantity is limited to 1.5–2 liters/day based on body weight and edema tendency. Nicotine abstinence is crucial since an increased risk of progression of GN due to nicotine is ensured "dose-dependently".
Hyperlipidemia should be treated with medication after dietary measures have been exhausted. HMG-CoA reductase inhibitors are suitable for this purpose, but interactions must be considered (see *Interactions*). Fibrates or fibrate-statin combinations should be used cautiously in patients with impaired renal function (accumulation).
Analgesics should be avoided; this applies especially to the "minor" analgesics such as NSAIDs. When creatinine clearance is reduced below 60 mL/min/1,73 m², nephrological co-care is required, especially when renal biopsy and immunosuppressive therapy are indicated.

Table 1: Blood pressure setting.

Active ingredient class	Medication	Dosage (examples)
ACE inhibitors	Lisinopril, benazepril-HCL, fosinopril sodium, enalapril, etc.	Enalapril® 5 mg /1x morning, slowly increase to 20 mg/day
Beta-blocker	Metoprolol, bisoprolol	Beloc-Zok® (mite) 1 x 1
AT II receptor	Valsartan, candesartan, telmisartan etc.	Candesartan® initially 2–4 mg/day, increase cautiously to 32 mg/day
Diuretics	Torasemide	Torasemide® 5 mg 1 x 1
Ca antagonists	Amlodipine	Amlodipine® 5 mg 1 x 1, increase to 2 x 1 after at least 1 week if necessary

Blood pressure control in PLWH

Drug-specific side effects should be considered. Caution hyperkalemia with ACE inhibitors! Potassium-sparing diuretics should not be used above a creatinine of 1,4 mg/dl; loop diuretics such as Lasix® or torasemide should be used at a creatinine > 1,8 mg/dl.

Renal toxicity of drugs

The spectrum of drug-allergic or autoimmune reactions in the kidney is not different from that in the skin or other internal organs. Reactions can be humoral or T-cell-mediated and can lead to renal failure. Even a single use of an analgesic (ibuprofen) can lead to renal failure. This is also conceivable with any antiretroviral therapy. Therefore, renal function should always be monitored when changing treatment. In case of renal abnormalities and risk factors (diabetes, hypertension, hepatitis, black skin color, poor immune status), this should be done at short notice, especially with TDF (even when given as PrEP). Acute renal failure or acute tubular necrosis is also possible with acyclovir, ganciclovir, adefovir, aminoglycosides, or pentamidine. Acute allergic interstitial nephritis may develop as part of the hypersensitivity reaction under abacavir. Membranoproliferative GN has been described with atazanavir and T-20. Ritonavir or efavirenz can also cause renal damage (Winston 2008). The specific drug-toxic renal impairment will be presented separately.

Interstitial nephritis, crystalluria, nephrolithiasis

Various drugs such as NSAIDs, indinavir (withdrawn from the market), and atazanavir (generics available) can cause interstitial nephritis with a decrease in eGFR and tubular proteinuria; hematuria and leukocyturia (sterile) are indicative of such nephritis. Antibiotics (ciprofloxacin, ampicillin), acyclovir, vitamin C, aspirin, and also PIs such as indinavir, atazanavir, and (to a limited extent) darunavir can lead to increased crystalluria, which, in combination with other factors (e.g., increased uric acid), can cause nephrolithiasis. Previously common kidney stones under indinavir are not radiopaque until combined with calcium, which can be confused with a calcium oxalate stone. In contrast, urate stones are radiolucent. With forced fluid administration, Buscopan®, and analgesics, the acute situation of renal colic can usually be resolved on an outpatient basis. If urologic presentation is necessary, risks for contrast administration must be communicated. ART history is essential because any crystal-inducing substance can leave interstitial tubular damage over time.
Atazanavir has been associated with possible (mostly interstitial) renal changes in cohort analyses. For example, a 21% higher risk of renal failure was seen in EuroSIDA compared with atazanavir-free combinations, which was reversible (Mocroft 2015, Dauchy 2011). The incidence of nephrolithiasis is also controversial, ranging from "rare" (Calza 2012) to an FDA case analysis of 30 cases that fully recovered in renal function after discontinuation (Chan-Tack 2007). However, if there is a known history of nephrolithiasis, renal colic, or hematuria, atazanavir is undoubtedly not a preferred agent (EACS 2018).

Tubular transport mechanisms and tubular-toxic damage, Fanconi syndrome

In addition to glomerular filtration of substances such as creatinine, they are also secreted alternatively by transporters in the tubule. In the proximal tubule, the transporter OCT2 leads to the uptake of creatinine from the blood into the tubule cell, which is then secreted into the urine via MATE 1. Some integrase inhibitors inhibit OCT 2, dolutegravir (more strongly), and bictegravir (less strongly), whereas the pharmacoenhancer cobicistat inhibits MATE 1. Thus, these agents block the alter-

native excretory pathway via the tubule cell, resulting in a mild increase in creatinine (approximately 0,14 mg/dl) or a decrease in estimated eGFR of approximately 15 mL. This may also be important for eliminating metformin, although clinically relevant descriptions are still lacking. Of course, the creatinine increase does not change the true GFR, so it does not affect glomerular filtration efficiency or renal function. Thus, the agents above can be used to their full potential even in impaired renal function. However, caution should be exercised when combining them with TDF because, in this case, it may be more challenging to distinguish a true deterioration in renal function, and TDF must be reduced below a GFR of 60 mL. In these cases, TAF should always be given instead of TDF.

Tenofovir is taken up into the tubule cell via the transporter OAT 1 and glomerular filtration. It is then actively secreted (ATP-dependent) into the urine of the proximal tubule via the transporters MRP 2 and 4. If the true filtration in the glomerulus drops (for example, in acute renal failure), an attempt is made to eliminate more TDF via the tubule cell (increased activity of OAT 1). The consequence is an increased concentration of TDF in the tubule cell, which can lead to a decrease in energy-dependent MRP 2 and 4 transport capacity and, thus, tubule damage (Perazella 2010). Indeed, the concentration-dependent damage of TDF to the tubule cell has been shown people with low body weight are vulnerable (Nishijirna 2012).

Suppose the substances filtered from the glomerulus in the primary urine exceed the transport capacity of the reabsorbing tubule cells (for example, in the case of tubule damage). In that case, they are excreted in the urine. A prominent example is glucosuria. However, transport dysfunction of the tubule system can also be caused by drugs such as cidofovir and tenofovir. This is called secondary (drug-induced) Fanconi syndrome. It is characterized by a dysfunction of the tubular system without impaired GFR: phosphate, amino acids, and glucose are increased in the urine, and phosphate is decreased in the blood. The loss of amino acids, phosphate, glucose, bicarbonate, and other organic and inorganic substances, as well as water, may manifest clinically with increased urination, thirst, fatigue, bone pain, and weakness and may lead to secondary changes in bone metabolism and osteoporosis/reduced bone density.

But beware: not every **hypophosphatemia** (< 0,8 mmol/l) is immediately Fanconi syndrome. Hypophosphatemia also occurs under the influence of alcohol, diabetes, cachexia, diarrhea, a disorder of vitamin D metabolism, or hyperparathyroidism. In untreated PLWH, it is found in about 10%, while on ART in 23%, and on tenofovir in up to 31% of cases (Day 2005). The reasons may be multiple, including inadequate phosphate intake (normal about 1,200 mg/day). Abnormal values (< 0.8 or 0.6 mmol/L) should be monitored, and start looking for other signs of Fanconi syndrome. Determination of intact parathyroid hormone, vitamin D, or a history of diuretics, vomiting, or tumor disease may indicate other causes of hypophosphatemia. The excretion ratio of phosphate to creatinine may indicate tubular damage if more than 10% of filtered phosphate is excreted despite hypophosphatemia (Jamison 1982).

$$\text{Excretion Ratio:} \quad \frac{(\text{urine phosphate mg/dl}) \times (\text{serum creatinine mg/dl})}{(\text{serum phosphate mg/dl}) \times (\text{urine creatinine mg/dl})}$$

Case reports describe renal failure in pre-damaged kidneys, mainly in combinations of boosted PIs plus TDF, but also in concomitant diseases such as liver cirrhosis or hepatitis. From a nephrological point of view, ART should be chosen carefully in cases of proteinuria, nephrotic syndrome, liver cirrhosis, and/or dyslipoproteinemia; one is well advised to avoid then potentially nephrotoxic substances such as cidofovir, adefovir or TDF (including fixed combinations containing TDF); the use of TAF is possible up to a GFR of 30 mL.

Tenofovir-DF (TDF) and Tenofovir-AF (TAF)

Given the widespread use of TDF and its current generic availability, interest is mainly focused on long-term renal toxicity. In cohort studies, a gradual GFR loss has been observed in recent years with TDF regimens (Casado 2016). There is an increased tubular risk (Dauchy 2011), which is higher than under ABC + 3TC (Moyle 2010). Although a meta-analysis of 17 studies showed only a small decrease in GFR (–3.92 mL/min) and a small increased risk of renal failure (+ 0.7%), TDF should not be used uncritically and without regular testing of renal function (Cooper 2010). In the large D:A:D cohort of 22.603 patients, a drop in GFR of more than 20 mL to below 70 mL/min correlated with the use of TDF, boosted atazanavir, and lopinavir (Derek 2013). Similarly, in the EuroSIDA cohort, the incidence of renal failure was 1.05/100 person-years. Again, there was a correlation with TDF, atazanavir/r, and lopinavir/r. In EuroSIDA, unlike the D:A:D cohort, patients with renal insufficiency were not excluded (Derek 2013). GFR under TDF falls more rapidly in combination with PIs than with NNRTIs (Goicoechea 2008, Winston 2008, Casado 2016). In pregnancy, TDF does not appear to cause renal injury in the newborn (Linde 2010, personal communication). The incidence of renal events reported to the manufacturer with TDF was 29.2 per 100,000 person-years (Nelson 2006). In the GS903E/934 prospective studies in renally healthy patients, creatinine increases to greater than 1.5 mg/dl in 144 weeks was observed in less than 1%, and proteinuria more significant than 100 mg/dl was observed in 5% (Gallant 2008). In a meta-analysis of 11 studies, no advantage of TAF over TDF was seen concerning renal events when boosters or PIs were omitted (Hill 2018). Another meta-analysis with 26 studies and > 12.000 person-years on TDF or TAF showed a benefit of TAF in initial therapy or at switch related to more sensitive biomarkers of renal events: renal events, functional decline, or tubule damage were significantly lower under TAF than under TDF (Gupta 2018).

The leading renal event of TDF is Fanconi syndrome (incidence 22,4/100.000 person-years). This renal dysfunction manifests as **hypophosphatemia** in association with normoglycemic glucosuria and moderate proteinuria (see above) and occurs on average seven to nine months after the start of therapy (Izzedine 2004). Complete regression after discontinuation may be expected in 42%, after a mean of 5 months (Wever 2010). A rapid response with early switching is beneficial for outcomes (Verwiys 2019). The risk of renal damage increases in combination with nephrotoxic agents, renal disease or renal insufficiency in history, sepsis, dehydration, or severe hypertension (Nelson 2006). In cohort analyses, this was also the case with CD4 T-cells below 50/µl, age over 45 years, diabetes mellitus, and long antiretroviral treatment exposure (Moore 2007).

TDF is eliminated renally and must be dose-adjusted in renal insufficiency. Combination with boosted PIs is possible, but ritonavir increases the Cmax and AUC of tenofovir by approximately 30% (Izzedine 2005). In cohort studies, a decrease in GFR of 7–10 mL/min per year was observed, although total GFR remained within normal ranges. Therefore, using a boosted PI today should only be with TAF, not TDF.

In renally healthy people on PrEP, creatinine, eGFR (calculated), serum phosphate and glucose, and urine tix (proteinuria, glucosuria, and erythrocyturia) should be monitored at least every three months during the first year on TDF. Check more frequently in cases of renal dysfunction. This is especially true with additional nephrotoxic substances or drugs that are also excreted via the renal transporter OAT1 (aminoglycosides, amphotericin B, famciclovir, ganciclovir, pentamidine, vancomycin, cidofovir, IL-2).

Particular caution applies to the TDF-containing fixed combination Stribild®: its use is only considered for healthy kidney patients with a GFR > 90 mL. After the approval

of Genvoya®, there is no longer any reason to accept these risks, and one is well advised to switch.

The prodrug tenofovir-AF (TAF) achieves comparable concentrations in the target cell. However, the dose is lower, and the plasma concentration is reduced by 90%. As a result, the risk of accumulation in the tubule cell is reduced because significantly less substance must be alternatively excreted. Therefore, TAF can be used up to a GFR of 30 mL. In pivotal trials and renal insufficiency, proteinuria and tubular protein excretion improved when switched from TDF to TAF (Gupta 2015). Renal events such as Fanconi syndrome no longer occurred in pivotal trials. In cohorts, patients with impaired renal function particularly benefited from switching from TDF to TAF (Rieke 2018, Surial 2019). The effects on phosphate metabolism are lower – there is probably also help in terms of bone density as a result. In sub-analyses, largely stable renal function while on TAF was also observed for renally vulnerable groups (older age or diabetes) (Gupta 2019). Patients with true Fanconi syndrome on TDF may switch to TAF, as may those with proteinuria or renal insufficiency up to 30 mL. From a nephrology perspective, TDF should be replaced with TAF, especially in all renally vulnerable patients. Only in pregnant women and people with TBC (interaction) does this not apply.

Renal function and PrEP

A meta-analysis of 11 controlled trials with 3523 participants of PrEP with TDF (either alone or combined with FTC/3TC) found only infrequent or mild impairment of renal function during follow-up. In another cohort of 18,676 participants, GFR fell primarily in older users and those with previously impaired renal function but not in young, renally healthy individuals (Schäfer 2022). Nevertheless, because of renal risks from STIs or substance use, the kidney should be regularly monitored with creatinine, GFR, and dipstick.

Advanced renal failure, dialysis, and ART

In advanced renal failure, "renal neutral solutions" can be considered if the resistance situation allows. These are, for example, combinations of boosted PIs and dolutegravir or raltegravir, but also two boosted PIs, a combination of NNRTI/PI, or combinations with dolutegravir or maraviroc. TDF should be avoided at a GFR < 60 mL/min! In case of progressive renal insufficiency, dual ART should also be considered: Dovato® (dolutegravir/3TC), 3TC is the limiting factor; from a GFR < 50, the 3TC dose should be adjusted. If dialysis is required, all INSTIs, all PIs, and NNRTIs are available in principle. For NRTIs, the dose must be adapted. The studies on dual therapy with darunavir plus dolutegravir, dolutegravir plus rilpivirine, and with the long-acting depot preparations cabotegravir plus rilpivirine or doravirine plus islatravir (in the future) show possibilities for use, even if there are no data on dialysis so far. In Europe and the US, about 1,500–2,500 PLWH and on dialysis are to be assumed. However, data on adequate ART on hemodialysis remains sparse. A single-arm study in 26 centers in the US and Europe (Eron 2019) demonstrated safety and efficacy for elvitegravir/c plus TAF/FTC (Genvoya®) for 48 weeks in 55 patients (Joseph 2018). Viral response and tolerability persisted after switching to Biktarvy® (Rieke 2021). TAF/FTC/darunavir/c (Symtuza®) should also be possible, but no studies or approval exist. It is recommended that STRs be taken after hemodialysis each time. Odefsey®, Descovy®, Genvoya®, and Biktarvy® are also approved for hemodialysis, but EMA does not recommend use in the SmPC and remains a case-by-case consideration. Because of the abundance of concomitant medications and potential interactions, therapy without cobicistat is desirable. Abacavir is not appropriate because

of increased cardiovascular morbidity. Careful monitoring of serum creatinine, proteinuria, erythrocyturia, glucosuria, and serum phosphate is advised if there is residual diuresis.

Hepatitis C and kidney

The renal parenchyma expresses CD81 and FR-B1 receptors, which allow hepatitis C viruses to bind to the cell surface and infect the kidney's cells through endocytosis. Indeed, HCV RNA can be detected in mesangial cells, tubular epithelium, endothelial cells of the glomerulus, and the tubular apparatus of the kidney. The immune response of the body is likely triggered via Toll-like receptors (TLRS) and via the formation of protein molecules, which can trigger a highly variable histopathological picture: microdissections in the glomerular loop volume as TLR3 specificity and forms of membranoproliferative glomerulonephritis (MPGN) are typically found in renal biopsies in hepatitis C. If there is HCV-triggered cryoglobulinemia (circulating proteins that precipitate in cold), this can induce ulcers as vasculitis on the skin, especially in the extremities. The proteins are attached to the kidney, mesangial matrix area, or glomerular capillaries and induce an immune response. Hepatitis C and cryoglobulins can thus induce "endotheliitis" and cause renal damage through anti-endothelial antibodies and complement activation, which can result in all forms of glomerulonephritis: in addition to immune complex glomerulonephritis, these include membrano-proliferative glomerulonephritis (MPGN), membranous GN, focal segmental glomerulosclerosis (FSGS), IgA nephritis, forms of fibrillary or immuno-tactoid glomerulonephritis, and renal involvement in the setting of polyarteritis nodosa (PAN). In a compilation of renal damage (Kidder 2015), the cause of renal impairment in HCV was seen to be chronic tubulointerstitial damage in the majority (46%) (acute in 25%), while glomerulonephritis was distributed as membrano-proliferative in 8%, minimal change GN in 4%, and membranous GN in 4%. With today's drugs, it is possible to treat hepatitis C even in ESRD: The combination of glecaprevir/pibrentasvir (Maviret®) as a pan-genotypic combination and elbasvir/grazoprevir (Zepatier®) for genotypes 1 and 4 are also available in dialysis. No agent is renally eliminated or removed by hemodialysis; they can be dosed normally (Kosloski 2016). Ribavirin, on the other hand, which has repeatedly led to severe anemia, now has no place in renal failure. Sofosbuvir (such as in Epclusa®) can only be used up to a GFR of 30 mL and may worsen renal function. The fixed pan-genotypic salvage combination of sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) is therefore only possible up to a GFR of 30 mL. Below that; the use must be decided upon individually.

Dosage of ART in renal failure

The professional information applies. Since NNRTIs, PIs, and INSTIs (including dolutegravir, bictegravir, cabotegravir, and islatravir) and maraviroc are almost exclusively hepatically eliminated, dose adjustment is necessary only for NRTIs unless there is concomitant hepatic insufficiency. Maraviroc should be dosed differently in the presence of impaired renal function and in combination with a CYP3A4 inhibitor, depending on the specific agent and GFR (see *ART*). The most cumulative substance for fixed-dose combinations (FDCs) is decisive; TAF-containing FDCs can only be used up to a GFR of 30 mL but are now approved on HD on a case-by-case decision (see Table 2). The substances fostemsavir and ibalizumab do not need to be dose-adapted in renal insufficiency (cf. SmPC). A good overview is also provided by the EACS guideline: https://eacs.sanfordguide.com/EACS/drug-drug-interactions-other-prescribing-issues/other-prescribing-issues/arv-dosing-renal-impairment

Table 2: Dosage of NRTI-containing agents adapted to renal function.

Drug	Standard dose	CrCl (mL/min)	Dosage
AZT (Retrovir®)	2 x 250 or 300 mg	>50 30–10 <10 HD	300 mg BID No dose adjustment 100 mg TID 100 mg TID
3TC (Epivir®)	1 x 300 mg or 2 x 150 mg	>50 30–49 10–29 <10 + HD	300 mg QD 150 mg QD 100 mg QD 50–25 mg QD
AZT/3TC (Combivir®)	2 x 1 tbl	>50 <50	Standard dose Not recommended
ABC (Ziagen®)	2 x 300 mg	>50 <30	300 mg BID No dose adjustment
AZT/3TC/ABC (Trizivir®)	2 x 1 tbl	>50 49–<10 +HD	300/150/300 mg BID Use single preparations
TDF (Viread®)	1 x 245 mg	>50 30–49 10–29 <10 HD	300 mg QD 300 mg every 48 hours Not recommended (300 mg alle 72–96 hours, if no alternative) Not recommended (300 mg every seven days if there is no alternative) 300 mg every seven days
FTC (Emtriva®)	1 x 200 mg	>50 30–49 10–29 <10 (incl. HD)	200 mg QD 200 mg every 48 hours 200 mg every 72 hours 200 mg every 96 hours
ABC/3TC (Kivexa®)	1 x 1 tbl	>50 49–<10 +HD	600/300 mg QD Use single preparations
TDF/FTC (Truvada®)	1 x 1 tbl	>50 30–49 <30 and HD	300/200 mg QD 300/200 mg every 48 hours Use single preparations
RPV/DTG (Juluca®)	1 x 1 tbl	>50 – HD	Standard dose
TAF/FTC (Descovy®)	1 x 1 tbl	up to 30 29–<10 +HD	Standard dose Standard dose, given after HD
EVG/c/TDF/FTC (Stribild®)	1 x 1 tbl	>50 49–<10+HD	Standard dose (do not start if eGFR < 70) Do not use
EVG/c/TAF/FTC (Genvoya®)	1 x 1 tbl	>50–30 29–<10 +HD	Standard dose Standard dose, given after HD
RPV/TAF/FTC (Odefsey®)	1 x 1 tbl	>50–30 29–<10 +HD	Standard dose Standard dose, given after HD
RPV/TDF/FTC (Eviplera®)	1 x 1 tbl	>50 49–<10 +HD	Standard dose Do not use
DTG/ABC/3TC (Triumeq®)	1 x 1 tbl	>50 49–<10 +HD	Standard dose Use single preparations

Table 2: Continuation

Drug	Standard dose	CrCl (mL/min)	Dosage
BIC/TAF/FTC (Biktarvy®)	1 x 1 tbl	>50–30 <30 + HD	Standard dose No dose adjustment, given after HD (individual consideration)
DOR/TDF/3TC (Delstrigo®)	1 x 1 tbl	>50 49–<10	Standard dose Not recommended
DTG/3TC (Dovato®)	1 x 1 tbl	>50 49–<10	Standard dose Not recommended
DRV/c/TAF/FTC (Symtuza®)	1 x 1 tbl	>30 29–<10	Standard dose Not recommended

Daily doses, unless otherwise stated. HD = hemodialysis

OIs and renal insufficiency

The following tables depict the treatment of the most important OIs in renal failure.

Table 3: Treatment of PCP in renal failure based on 80 kg patient.

Drug	GFR normal	GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min	Dose adjustment for HD/CAPD/cont. dialysis
Cotrimoxazole	3 x 3 or 4 x 2 tbl at 960 mg p.o. or 3 x 5–6 Amp of 480 mg i.v	5–6 Amp of 480 mg IV every 8 h	5–6 Amp at 480 mg i.v. all 12 h	5–6 Amp of 480 mg IV all 24 h	HD:+ as GFR <10: half-dose after dialysis CAPD: no adjustment CAVH: like GFR 10–50 CVVHD: like GFR <10***
Dapsone	100 mg every 24 h	50–100%	50%	avoid	avoid
Atovaquone	750 mg every 12 h	100%**	100%**	100%**	HD: no adjustment CAPD: no adjustment* CAVH: (GFR <10)**
Pentamidine	4 mg/kg every 24 h	100%	100% all 24–36 h	100% every 48 h *see text!*	HD: (GFR <10)** CAPD: (GFR <10)** CAVH: (GFR <10)**

***For cotrimoxazole high-dose in PCP specifically: in HD 3x/week: 15–20 mg/kg before HD and 7–10 mg/kg after HD – based on the trimethoprim content in cotrimoxazole. For continuous renal replacement therapy (CVVH): usual dosage if necessary.

A specific example for 80 kg: normal renal function 5 ampoules (400/80 mg each) every 6–8 hours. For GFR < 30 mL/min, 5–6 ampoules (400/80 mg each) every 12 hours. In HD 3x/week, 5–8 ampoules (400/80 mg each) every 24 hours (give at least half after dialysis on dialysis day). In CVVH(DF): 5–10 ampoules (400/80 mg each) every 12 h.

Dose-finding studies are not available, *regular dosing recommended, **dosing as it is recommended for GFR < 10 mL/min.

HD = intermittent hemodialysis, CAPD = continuous peritoneal dialysis, CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-venous hemodiafiltration.

Caution: Cotrimoxazole is nephrotoxic in high doses; its use should be critically evaluated and requires close monitoring.

Table 4: Treatment of cerebral toxoplasmosis in renal failure.

Drug	GFR normal	GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min	Dose adjustment for HD/CAPD/cont. dialysis
Pyrimethamine	50 mg/12 h for 2 days, then halve	100%	100%	100%	HD, CAPD or CAVH: no adjustment
Clindamycin	600 mg every 6 h	100%	100%	100%	HD: no adjustment CAPD: (GFR <10)* CAVH: (GFR <10)* CVVHD: GFR normal
Sulfadiazine	2 g every 6 h	avoid	avoid	avoid	avoid

* Dose-finding studies do not exist; dosing as recommended for GFR < 10 mL/min.
HD = intermittent hemodialysis, CAPD = continuous peritoneal dialysis, CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-venous hemodiafiltration.

Table 5: Treatment of viral infections such as CMV, HSV, and VZV in renal failure.

Drug	GFR normal	GFR >50 mL/min	GFR 10–50 mL/min	GFR <10 mL/min	Dose adjustment for HD/CAPD/cont. dialysis
Acyclovir	5–10 mg/kg every 8 h	5 mg/kg every 8–12 h	5 mg/kg every 12-24 h	2,5 mg/kg every 24 h	HD: Dose after dialysis CAPD: GFR <10 CAVH: 6.5 mg/kg every 24 h CVVHD: 6.5–15 mg/kg every 24 h
Ganciclovir	5 mg/kg every 12 h	3 mg/kg every 12 h at GFR 25-50 mL	3 mg/kg every 24 h at GFR 10–25 mL	15 mg/kg every 24 h	HD: Dose after dialysis CAPD: GFR <10 CAVH: 3.5 mg/kg every 24h CVVHD: 2.5 mg/kg every 24h
Valganciclovir	900 mg every 12 h for induction therapy	GFR 40–59 mL/min: 450 mg every 12 h (25–39: every 24 h 10–24: every 48 h)		unknown	unknown
Foscavir	90 mg/kg every 12 h	50–100%	10–50%	avoid	HD: Dose after dialysis CAPD: 60 mg/kg every 48–72h CAVH: GFR 10–50
Cidofovir	5 mg/kg every 7 days	100%	0,5–2 mg/kg every 7 days	avoid	HD: GFR 10–50 CAPD: GFR 10–50 CAVH: avoid
Famciclovir	250 mg every 8 h orally	every 12 h	every 48 h	50% every 48 h	HD: Dose after dialysis CAPD: ? CAVH: GFR 10–50

* Dose-finding studies do not exist; dosing as recommended for GFR <10 mL/min.
HD = intermittent hemodialysis, CAPD = continuous peritoneal dialysis, CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-venous hemodiafiltration.

A reasonable overview of drug use in renal insufficiency can also be found in the EACS guidelines in the chapter on dose adjustment of ARVs, as amended: https://eacs.sanfordguide.com/EACS/drug-drug-interactions-other-prescribing-issues/other-prescribing-issues/arv-dosing-renal-impairment; https://dosing.de/nierelst.php

Literature

Ando M, Tsuchiya K, Nitta K. How to manage HIV-infected patients with chronic kidney disease in the HAART era. Clin Exp Nephrol 2012,16:363–372.

Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine and efavirenz compared with zidovudine/ lamivudine and efavirenz in treatment-naive patients: 144-week analysis. J AIDS 2008, 47: 74-78.

Bickel M, Khaykin P, Stephan C, et al. Acute kidney injury caused by tenofovir disoproxil fumarate and diclofenac co-administration. HIV Med 2013;14:633–8.

Bonjoch A, Echeverría P, et al. High rate of reversibility of renal damage in a cohort of HIV-infected patients receiving tenofovir-containing antiretroviral therapy. Antiviral Res 2012, 96:65–69.

Bonnet F, Le Marec F, Leleux O, et al. HIV patients today and 10 years ago: do they have the same needs? Results from cross-sectional analysis of ANRS CO3 Aquitaine cohort. Abstract O212, HIV Drug Therapy, Glasgow 2016.

Calza L. Renal toxicity associated with antiretroviral therapy. HIV Clin Trials 2012, 13:189–211.

Casado JL, Bañón S, Santiuste C, et al. Prevalence and significance of proximal renal tubular abnormalities in HIV-infected patients receiving tenofovir. AIDS 2016, 30: 231- 239

Chan-Tack KM, Truffa MM, Struble KA, Birnkrant DB. Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's Adverse Event Reporting System. AIDS 2007;21:1215–1218.

Carr DR, Johnson J, Wilki A, et al. Outcomes of tenofovir discontinuation among human immunodeficiency virus (HIV)-infected patients with suspected tenofovir-associated nephrotoxicity. ID Week 2016. New Orleans, LA, USA. Poster 2183.

Choi A, Shlipak MG, Hunt P, et al. HIV-infected persons continue to lose kidney function despite successful ART. AIDS 2009, 23: 2143-9.

Cihlar T, Ho ES, et al. Human renal organic anion transporter (hOAT 1) and its role in nephrotoxicity of antiviral nucleoside analogs. Nucleos Nucleot Nucleic Acids 2001; 20: 641-648.

Cooper RD, Wiebe N, Smith N, et al. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV- infected patients. Clin Infect Dis 2010,51: 496- 505

Crum-Cianflone N, Ganesan A, et al. Prevalence and factors associated with renal dysfunction among HIV-infected patients. AIDS Pat Care STD 2010, 24:353–360.

Daar E. et al. Phase 3 Randomized, Controlled Trial of Switching to Fixed-Dose Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) from Boosted Protease Inhibitor-Based Regimens in Virologically Suppressed Adults: Week 48 Results. Abstract # 67504 ID Week 2017, San Diego US.

Dauchy FA, Lawson-Ayayi S, de La Faille R, et al. Increased risk of abnormal proximal renal tubular function with HIV infection and antiretroviral therapy. Kidney Int 2011, 80:302–309.

Day SL, Leake Date HA, Bannister A, et al. Serum hypophosphatemia in tenofovir disoproxil fumarate recipients is multifactorial in origin, questioning the utility of its monitoring in clinical practice. J AIDS 2005; 38: 301- 4.

Del Palacio M, Romero S, Casado JL. Proximal tubular renal dysfunction or damage in HIV-infected patients. AIDS Rev 2012, 14:179–187.

DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection. Lancet 2012, 379:2429-38.

Derek M, Gallant JE. Nephrotoxicity of Antiretroviral Agents: Is the List getting longer? J Infect Dis 2013, 207:1349-51.

Eron J, Lelievre JD, Kalaylian R, et al. Safety of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in HIV-1-infected adults with end-stage renal disease on chronic haemodialysis: an open-label, single-arm, multicentre, phase 3b trial. Lancet HIV 2019; 6: e15–24.

Eron JJ, et al. ID Week 2020. Virtual Conference. Poster 1002.

Franceschini N, Napravnik S, Eron JJ, et al. Incidence and etiology of acute renal failure among ambulatory HIV-infected patients. Kidn Int 2005;67:393-403.

Gagliardini R, et al. CROI 2019. Seattle, WA, USA. Poster 693.

Gaillant JE, Brunetta J, Crofoot G, et al. Efficacy and Safety of Switching to a Single-Tablet Regimen of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide in HIV-1/Hepatitis B-Coinfected Adults. J AIDS 2016; 73-294-298

Gaspar G, Monereo A, García-Reyne A, et al. Fanconi syndrome and acute renal failure in a patient treated with Tenofovir. AIDS 2004, 18: 351-352.

Gaur AH, Kizito H, Prasitsueubsai W, et al. Safety, efficacy, and pharmacokinetics of a single-tablet regimen containing elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide in treatment-naïve, HIV-infected adolescents: a single-arm, open-label trial. Lancet HIV 2016, 3:e561-e568.

Goicoechea M, Liu S, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside transcriptase inhibitor-based therapy. J Infect Dis 2008; 197:102-108.

Guaraldi G, Orlando G, Zona S, et al. Premature Age-Related Comorbidities Among HIV-Infected Persons Compared With the General Population. Clin Inf Dis 2011;53:1120-1126.

Gupta S, et al. Renal Safety of TAF vs. TDF and ABC in a Pooled Analysis of 26 Phase 2/3 Clinical Trials. AIDS 2018. Amsterdam, NL. Poster TUPEB113.

Gupta S, Milla A, Brinson C, et al. 96 Week Efficacy and Safety of B/F/TAF in Treatment-Naive Adults and Adults ≥50 Years. Abstract502, CROI 2019, Boston US.

Guy M, Borzomato JK, Newall RG, et al. Protein and albumin-to-creatinine ratios in random urines accurately predict 24 h protein and albumin loss in patients with kidney disease. Ann Clin Biochem 2009;46:468-76.

Hill A, Hughes SL, Gotham D, et al. Tenofovir Alafenamide versus Tenofovir Disoproxyl fumarate: Is there a true difference in efficacy and safety? J Viral Erad 2018 4: 72-79.

Huhn GD, Tebas P, Galland J, et al. A Randomized, Opel-Label Trial to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Plus Darunavir in Treatment-Experienced HIV-1-Infected Adults. J AIDS 2017, 74:193-200.

Islam F et al. HIV-infected individuals are at increased risk of renal complications over time. BMC Public Health 2012;234:1–15

Izzedine H, Hulot JS, Vittecoq D, et al. Long-term renal safety of tenofovir disoproxil fumarate in antiretroviral-naive HIV-1-infected patients data from a double-blind randomized active-controlled multicentre study. Nephrol Dial Transplant 2005, 20:743-746.

Izzedine H, Isnard-Bagnis C, Hulot JS, et al. Renal safety of tenofovir in HIV treatment-experienced patients. AIDS 2004, 18: 1074- 76.

Izzedine H, Launday-Vacher V, Deray J. Renal tubular transporters and antiviral drugs: an update. AIDS 2005, 19: 455-62.

Izzedine H, Hulot JS, Vittecoq D, et al. Long-term renal safety of tenofovir disoproxil fumarate in antiretroviral-naive HIV-1-infected patients data from a double-blind randomized active-controlled multicentre study. Nephrol Dial Transplant 2005, 20:743-746.

Kidney disease: Improving global outcomes (KDIGO). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013, 3:1–150.

Kinai E, Hanabusa H, et al. Renal tubular toxicity associated with tenofovir assessed using urine-beta 2 microglobulin, percentage of tubular reabsorption of phosphate and alcaline phosphatase levels. AIDS 2005 19:2031-2041.

Kopp JB, Smith MW, Nelson GW, et al. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. Nat Genet 2008, 40:1175-1184.

Lucas GM, Metha SH, Atta MG, et al. End stage renal disease and chronic kidney disease in a cohort of african-american hiv-infected and at risk- seronegative participants followed between 1988 and 2004. AIDS 2007, 2435-2443.

Malik A, Abraham P, Malik N. Acute renal failure and Fanconi syndrome in an AIDS patient on tenofovir treatment-case report and review of literature; J Infect 2005; 51: E61-65.

Mills, A, Arribas JR, Andrade-Villanueva J, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection. Lancet Infect Dis 2016, 16:43-52.

Miro JM, Cofan F, Trullas JC, et al. Renal dysfunction in the setting of HIV/AIDS. Curr HIV/AIDS Rep 2012;9:187-99.

Mocroft A, Kirk O, Gatell J, et al. Chronic renal failure among HIV-1-infected patients. AIDS 2007;21:1119-27.

Mocroft A, et al. Incidence rates of CKD and cumulative exposure to ARVs Abstract 142, CROI 2015, Seattle.

Moreno S, Domingo P, et al. Renal safety of tenofovir disoproxil fumarate in HIV-1 treatment-experienced patients with adverse events related to prior NRTI use. J AIDS 2006; 42: 385- 387

Moyle G, et al. Assessment of safety and efficacy of abacavir/lamivudine and tenofovir/emtricitabine in treatment-naive HIV-1 infected subjects. ASSERT: 96-week results. 12th IWADR 2010

Nelson M, Katlama C, Montaner JS, et al. The safety of TDF for the treatment of HIV infection in adults: the first 4 years. AIDS 2007; 21:1273-81.

Odden MC, Scherzer R, Bacchetti P, et al. Cystatin C level as a marker of kidney function in human immunodeficiency virus infection: the FRAM study. Arch Intern Med 2007;167:2213-9.

Peyriere H, Reynes J, Rouanet I, et al. Renal tubular dysfunction associated with tenofovir therapy: report of 7 cases. J AIDS 2004; 35: 269-273.

Post F, Tebas P, Clarke A, et al. Switching to Tenofovir Alafenamide, Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, in HIV-Infected Adults With Renal Impairment: 96-Week Results From a Single-Arm, Multicenter, Open-Label Phase 3 Study. J AIDS 2017, 74:180-184.

Post F, Molina JM, Mills AM, et al. Renal safety parameters after switch to doravirine/islatravir once daily: week 48 results from two randomized, active-controlled Phase 3 studies, MK 8591A-017 and MK 8591A-018. Abstract. 12th IAS, Brisbane 2023.

Rieke A, Jessen H, Pauli R, et al. Real-world effects with emtricitabine/TAF versus emtricitabine/TDF based regimens in people living with HIV in a clinical cohort in Germany. Abstract P206 HIV Drug Ther Glasgow 2018.

Rieke A. et al. A daily single Tablet Regimen of Bictegravir, Tenofovir-alafenamide and Emtricitabine in virologically suppressed adults living with HIV and end-stage renal disease on hemodialysis. DÖAK 2021, Poster 46813.

Rieke A, et al. SFLS 2021. Hybrid Conference, Grenoble, France. Poster 44.

Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet 2013;381:735-743.

Sax P, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet 2012, 379:2439-2448.

Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomized, double-blind, phase 3, noninferiority trials. Lancet 2015, 385:2606-15.

Schaefer R, Amparo da Costa Leite PH, Silva R, et al. Kidney function in tenofovir disoproxil fumarate-based oral pre-exposure prophylaxis users. Lancet HIV 2022; 9:e242-253.

Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS 2012, 26:867-75.

Schooley RT, Ruane P, Myers RA, et al. Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. AIDS 2002; 16:1257-63.

Schulz CA, et al. EACS 2019. Basel, Switzerland. Poster PE9-55.

Surial B, Ledergerber B, Calmy A, et al. Renal function trajectories after switching from TDF to TAF, a nationwide cohort study, Abstract MOAB0205,10th IAS 2019, Mexico City MX.

Soleiman AF. Pathophysiologie und Pathodiagnostik HIV assoziierter Nierenerkrankungen, Nephro Script 2011;14: 21–24.

Szczech LA, Gange SJ, van der Horst C, et al. Predictors of proteinuria and renal failure among women with HIV infection. Kidney Int 2002;61:195-202.

Szczech LA. Renal diseases associated with HIV infection: epidemiology, clinical course, and management. Clin Infect Dis 2001;33:115-9.

Szczech LA. HIV-related renal disease and the utility of empiric therapy: Not everyone needs to be biopsied. Nat Clin Pract Nephrol 2009; 5: 20–21.

Szczech LA. HIV–Management of Renal Disease 2013 available in CCO: www.clinicaloptions.com/inPractice/HIV/Management.

Verwijs R, et al. Switch to TAF or ABC Following TDF-Associated eGFR Decline. CROI 2019. Seattle, WA. Poster 694.

Wever K, van Agtmael MA, Carr A. Incomplete reversibility of tenofovir-related renal toxicity in HIV-infected men. J AIDS 2010, 55:78-81.

Winston JA, Bruggeman LA, Ross MD, et al. Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. N Engl J Med 2001; 344: 1979-1984.

Winston A, Amin J, Mallon P, et al. Minor changes in calculated creatinine clearance and anion-gap are associated with tenofovir disoproxil fumarate-containing highly active antiretroviral therapy. HIV Med 2006;7:105-11.

Winston J, Deray G, Hawkins T, et al. Kidney disease in patients with HIV Infection and AIDS. Clin Infect Dis 2008; 47: 1449-1457.

Wohl D, Oka S, Clumeck N, et al. A Randomized, Double-Blind Comparison of Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate, Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine for Initial HIV-1 Treatment: Week 96 Results. J Acquir Immune Defic Syndr 2016; 72:58-64.

Wyatt CM, Arons RR, Klotman PE, Klotman ME. Acute renal failure in hospitalized patients with HIV: risk factors and impact on in-hospital mortality. AIDS 2006;20:561-5.

Wyatt CM, Hoover DR, Shi Q, et al. Microalbuminuria. is associated with all-cause and AIDS mortality in women with HIV infection. J AIDS 2010, 55:73-7.

Zeder A, Hilge R, Schrader S, et al. Medium-grade tubular proteinuria is common in HIV-positive patients and specifically associated with exposure to tenofovir disoproxil Fumarate. Infection 2016, 44:641–649.

24. Organ transplantation in HIV infection

CHRISTIAN HOFFMANN

Due to living longer with HIV, the number of needed transplants is growing; especially livers (hepatitis C) and kidneys (nephropathies) are needed. According to national guidelines, PLWH can be included on waiting lists in many countries. However, there are still many issues and questions to consider.

Worse survival rates of PLWH?

One argument still occasionally used today against organ transplantation in PLWH is the supposedly poorer survival rates. Large studies and meta-analyses have now shown that success rates, if any, are barely worse than in HIV-negative individuals (Roland 2016, Zheng 2019). In 510 HIV-positive kidney transplant recipients, neither overall survival nor graft survival was worse in the absence of HCV co-infection (Locke 2015). Outcomes were also good in 180 liver transplants, although HCV co-infection did remain a risk factor (Locke 2016). This will likely continue to improve with DAAs and the resulting significant improvement in hepatitis C therapy (Manzardo 2018, Werbel 2019). Simultaneous kidney and liver transplants (Ballarin 2008, Di Benedetto 2011) have now been described, as have numerous re-transplants (Agüero 2016). Individuals with hepatocellular carcinoma can also be transplanted – their prospects are not significantly worse than for HIV-negative HCC.
Exclusion criteria for transplantation in most countries are CD4 T-cell counts below 200/µl for kidney or below 100/µl for liver and a non-controlled viral load (Trullas 2011). AIDS is usually not considered an exclusion criterion, except for PML.

Reinfection of the graft with HBV and HCV

HCV co-infection has long remained an independent factor for poorer survival after liver transplantation (Locke 2016). This is changing with DAAs, which can be used successfully and efficiently after transplantation – response rates are just as reasonable, and there is a larger prospective study for glecaprevir/pibrentasvir (Reau 2018). There is also data for co-infected individuals (Campos-Varela 2016, Manzardo 2018, Werbel 2019).
HBV is usually treated with immunoglobulins and 3TC. As a rule, re-infection can be prevented in this way – unlike with HCV. Any 3TC resistance can generally be treated adequately with nucleos(t)id analogs such as tenofovir or entecavir (Tateo 2009, Coffin 2010).

Do immunosuppressants worsen the immune situation?

The rates and outcomes of surgical complications are similar to those observed in the non-HIV setting in carefully selected HIV-infected liver and kidney transplant recipients (Harbell 2012). However, the risks of immunosuppressive therapy are often emphasized. Concerns are mainly directed at herpesviruses (CMV, EBV, HSV, HHV-8), as these pathogens or their reactivations can be dangerous to HIV-positive and transplanted patients. This has not yet been confirmed in more recent cohorts (Teicher 2015). Moreover, laboratory studies show that immunosuppressants are well tolerated. In a placebo-controlled study of low-dose cyclosporin A (2 x 2 mg/kg CsA/die) in asymptomatic PLWH, there was no adverse effect on CD4 and CD8 T-cells or antigen-specific immune responses (Calabrese 2002). Mycophenol (Cellcept®), used

in kidney, heart, or liver transplantation, is also well tolerated by people living with HIV. If a rejection reaction occurs, thymoglobulin can be tried to suppress the reaction, as in HIV-negative individuals. However, in one small study, prolonged CD4 T-cell depletion occurs with thymoglobulin, leading to increased infections (Carter 2006). CTLs are also likely reduced, which could result in reactivations of EBV infections (Gasser 2009).

Immunosuppressants and ART – interactions?

Interactions between immunosuppressants and antiretroviral therapy are a manageable problem. The calcineurin inhibitors cyclosporine and tacrolimus are metabolized via the cytochrome p450 enzyme CYP 3A4, which is why significant level changes (mainly increases) are possible, especially with PIs. Relevant interactions are also likely with rapamycin (Krown 2012).
An INSTI-based regimen without a booster should be used; most data are available for raltegravir (Azar 2016). ART may only be discontinued, switched, or restarted under close monitoring of levels and in interdisciplinary cooperation!

Other organs: heart, lung, pancreas, cornea

In June 2003, an article in the New England Journal of Medicine caused a sensation (Calabrese 2003). The list of authors was unusual: the last author was Dr. Zackin, who, together with a team from Cleveland, US, described the world's first successful heart transplantation in an AIDS patient, namely his own. Various other successful heart transplants have since been published, although there is still a need for education among heart transplant professionals (Uriel 201, Agüero 2016). There are also case reports of corneal transplantation (Vincenti 2002), lung transplantation (Bertani 2009, Kern 2014), or combined kidney-pancreas transplantation (Toso 2003, Morabito 2016). Although data are sparse in each case, PLWH are not thought to have worse prospects than HIV-negative individuals for organ transplantation (Blumberg 2019).

HIV to HIV

Given the shortage of organs, an "HIV-to-HIV" approach, where PLWH receive organs from other PLWH, has also been increasingly explored, particularly recently (Fulco 2015, Boyarsky 2019, Lushniak 2022). In a prospective, multicenter pilot study, 24 transplants were performed between 2016 and 2019. The one-year survival rate was 83%. Affected and graft survival rates were better than in previous cohorts, but some infections and cancers were observed (Durand 2022).

Literature

Agüero F, Castel MA, Cocchi S, et al. An Update on Heart Transplantation in Human Immunodeficiency Virus-Infected Patients. Am J Transplant 2016, 16:21-8.

Agüero F, Forner A, Manzardo C, et al. Human immunodeficiency virus infection does not worsen prognosis of liver transplantation for hepatocellular carcinoma. Hepatology 2016, 63:488-98.

Agüero F, Rimola A, Stock P, et al. Liver Retransplantation in Patients With HIV-1 Infection: An International Multicenter Cohort Study. Am J Transplant 2016, 16:679-87.

Anadol E, Beckebaum S, Radecke K, et al. Orthotopic liver transplantation in human-immunodeficiency-virus-positive patients in Germany. AIDS Res Treat. 2012;2012:197501.

Azar MM, Malinis MF, Moss J, et al. Integrase strand transferase inhibitors: the preferred antiretroviral regimen in HIV-positive renal transplantation. Int J STD AIDS. 2016 May 18.

Bertani A, Grossi P, Vitulo P, et al. Successful lung transplantation in an HIV- and HBV-positive patient with cystic fibrosis. Am J Transplant 2009, 9:2190-6.

Blumberg EA, Rogers CC, et al. Solid organ transplantation in the HIV-infected patient: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019, 33:e13499.

Boyarsky BJ, Bowring MG, Shaffer AA, et al. The future of HIV Organ Policy Equity Act is now: the state of HIV+ to HIV+ kidney transplantation in the United States. Curr Opin Organ Transplant 2019, 24:434-440.

Calabrese LH, Albrecht M, Young J, et al. Successful cardiac transplantation in an HIV-1-infected patient with advanced disease. N Engl J Med 2003, 348:2323-8.

Calabrese LH, Lederman MM, Spritzler J, et al. Placebo-controlled trial of cyclosporin-A in HIV-1 disease: Implications for solid organ transplantation. J Acquir Immune Defic Syndr 2002, 29:359-362.

Campos-Varela I, Moreno A, Morbey A, et al. Treatment of severe recurrent hepatitis C after liver transplantation in HIV infected patients using sofosbuvir-based therapy. Aliment Pharmacol Ther. 2016; 43:1319-29.

Carter JT, Melcher ML, Carlson LL, Roland ME, Stock PG. Thymoglobulin-associated Cd4+ T-cell depletion and infection risk in HIV-infected renal transplant recipients. Am J Transplant 2006; 6: 753-60.

Coffin CS, Stock PG, Dove LM, et al. Virologic and clinical outcomes of hepatitis B virus infection in HIV-HBV coinfected transplant recipients. Am J Transplant 2010, 10:1268-75.

Di Benedetto F, D'Amico G, De Ruvo N, et al. Combined liver-kidney transplantation in patients infected with human immunodeficiency virus.Transpl Infect Dis 2011,13:501-6.

Durand CM, Florman S, Motter JD, et al. HOPE in action: A prospective multicenter pilot study of liver transplantation from donors with HIV to recipients with HIV. Am J Transplant 2022, 22:853-864.

Fulco PP. HIV-positive-to-HIV-positive kidney transplantation. N Engl J Med 2015;372:2069-70.

Gasser O, Bihl F, Sanghavi S, et al. Treatment-dependent loss of polyfunctional CD8+ T-cell responses in HIV-infected kidney transplant recipients is associated with herpesvirus reactivation. Am J Transplant 2009, 9:794-803.

Harbell J, Fung J, Nissen N, et al. Surgical complications in 275 HIV-infected liver and/or kidney transplantation recipients. Surgery 2012, 152:376-81.

Kern RM, Seethamraju H, Blanc PD, et al. The Feasibility of Lung Transplantation in HIV-Seropositive Patients. Ann Am Thorac Soc 2014, 11:882-9.

Krown SE, Roy D, Lee JY, et al. Rapamycin with antiretroviral therapy in AIDS-associated Kaposi sarcoma: an AIDS Malignancy Consortium study. J Acquir Immune Defic Syndr. 2012, 59:447-54.

Locke JE, Durand C, Reed RD, et al. Long-term Outcomes After Liver Transplantation Among Human Immunodeficiency Virus-Infected Recipients. Transplantation 2016, 100:141-6.

Locke JE, Mehta S, Reed RD, et al. A National Study of Outcomes among HIV-Infected Kidney Transplant Recipients. J Am Soc Nephrol 2015, 26:2222-9.

Lushniak SA, Durand CM. Donors with human immunodeficiency virus and hepatitis C virus for solid organ transplantation: what's new. Curr Opin Infect Dis 2022, 35:321-329.

Manzardo C, Londoño MC, Castells L, et al. Direct-acting antivirals are effective and safe in HCV/HIV-coinfected liver transplant recipients who experience recurrence of hepatitis C: A prospective nationwide cohort study. Am J Transplant 2018, 18:2513-2522.

Mindikoglu AL, Regev A, Magder LS. Impact of human immunodeficiency virus on survival after liver transplantation: analysis of United Network for Organ Sharing database. Transplantation 2008;85:359-68.

Morabito V, Grossi P, Lombardini L, et al. Solid Organ Transplantation in HIV+ Recipients: Italian Experience. Transplant Proc 2016, 48:424-30.

Reau N, Kwo PY, Rhee S, et al. Glecaprevir/Pibrentasvir Treatment in Liver or Kidney Transplant Patients With Hepatitis C Virus Infection. Hepatology 2018 Apr 19.

Roland ME, Barin B, Huprikar S, et al. Survival in HIV-positive transplant recipients compared with transplant candidates and with HIV-negative controls. AIDS 2016, 30:435-44.

Tateo M, Roque-Afonso AM, Antonini TM, et al. Long-term follow-up of liver transplanted HIV/hepatitis B virus coinfected patients: perfect control of hepatitis B virus replication and absence of mitochondrial toxicity. AIDS 2009, 23:1069-76.

Teicher E, Boufassa F, Vittecoq D, et al. Infectious complications after liver transplantation in human immunodeficiency virus-infected recipients. Transpl Infect Dis 2015, 17:662-70.

Toso C, Berney T, Oberholzer J, et al. Kidney-pancreas transplantation in a long-term non-progressor HIV-infected recipient. Am J Transplant 2003, 3:631-3.

Trullàs JC, Barril G, Cofan F, et al. Prevalence and clinical characteristics of HIV type 1-infected patients receiving dialysis in Spain: results of a Spanish survey in 2006: GESIDA 48/05 study. AIDS Res Hum Retroviruses 2008, 24:1229-35.

Uriel N, Nahumi N, Colombo PC, et al. Advanced heart failure in patients infected with human immunodeficiency virus: Is there equal access to care? J Heart Lung Transplant. 2014 May 9.

Vincenti A, Meini M, Donati D, et al. Corneal transplantation in a patient with AIDS. Abstract A10163, XIV Int AIDS Conf 2002, Barcelona.

Werbel WA, Durand CM. Solid Organ Transplantation in HIV-Infected Recipients: History, Progress, and Frontiers. Curr HIV/AIDS Rep 2019, 16:191-203.

Zheng X, Gong L, Xue W, et al. Kidney transplant outcomes in HIV-positive patients: a systematic review and meta-analysis. AIDS Res Ther 2019, 16:37.

25. HIV-associated thrombocytopenia

HEINZ-AUGUST HORST

Thrombocytopenia is one of the most common hematologic complications of HIV infection. Before ART, the incidence increases markedly with the duration of infection (Heyward 1988), and cumulative incidences over ten years of up to 45% have been described (Eyster 1993). A significant incidence of thrombocytopenia also occurs during breaks in therapy, even with previously normal platelet counts (Bouldouyre 2009). Thrombocytopenias in HIV are mostly mild – levels below 30,000/µl have been observed in less than 10% of all cases (Vannappagari 2011). An initial manifestation may also occur in isolated cases during immune reconstitution (Quach 2012). HIV-related thrombocytopenia has been generally attributed to two different mechanisms: first, an immunologically driven destruction of the platelets, and second, an insufficient platelet production by the megakaryocytes. While in early HIV infection, increased platelet destruction appears to be predominant, in advanced HIV infection, it is the combination of both mechanisms (Najean 1994, Cines 2009).

Clinic

Usually, only mild mucosal bleeding occurs, such as petechiae, ecchymosis, gingival hemorrhage, or epistaxis. Severe gastrointestinal or intracerebral bleeding is rare and is only observed with platelet counts below 30,000/µl. However, platelet count and function may play an essential role in bleeding risk (Middelburg 2016). In contrast to patients with immune thrombocytopenia (ITP), patients with HIV-associated thrombocytopenia often present with moderate splenomegaly and enlarged lymph nodes. Spontaneous remissions of HIV-associated thrombocytopenia have been described in 10–20%, mainly in mild cases (Walsh 1985, Abrams 1986).

Diagnosis

HIV-associated thrombocytopenia is a repeatedly confirmed isolated thrombocytopenia with platelet counts less than 100,000/µl. The platelets often show increased variability in size. In the bone marrow, the frequency of megakaryocytes is normal to increased. Differential diagnoses include ruling out EDTA-induced pseudothrombocytopenia as well as bone marrow injury caused by drugs, narcotics, CMV, or atypical mycobacteria (MAC). For a review of drugs that can trigger associated thrombocytopenias, see https://ouhsc.edu/platelets/ditp.html. The risk of heparin-induced thrombocytopenia is likely increased with HIV (Thompson 2007). In isolated cases, thrombocytopenias also occur with ART (Lebensztejn 2002, Camino 2003). Table 1 gives an overview of the leading causes of thrombocytopenia. It is essential to distinguish them from thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), two life-threatening diseases that occur more frequently with HIV and are associated with non-immunologically caused peripheral platelet destruction. Platelets are also commonly reduced in liver insufficiency (hepatitis C!).

Table 1: Causes of thrombocytopenias (except HIV, selected from Matzdorff 2021).

Pseudo-thrombocytopenia
Toxic bone marrow injury caused by drugs (e.g., TMP-SMX, rifampicin, or ethambutol), radiation.
infections such as HCV, *Helicobacter pylori,* CMV, MAC, COVID-19
Malignancies such as chronic lymphocytic leukemia, high-grade malignant lymphomas
Immunologic: lupus erythematosus, immune thyroiditis, Evans syndrome, heparin
Other causes: HUS, TTP, hypersplenism, vaccinations.

Therapy

First-line therapy is based on two principles: ART and, in severe forms, additional immunosuppression with steroids. The treatment besides ART is based on recent international consensus reports and the guidelines of the American Society of Hematology (Neunert 2018, 2019, Matzdorff 2018, 2021). If first-line therapy fails, thrombopoietin receptor agonists (TRAs), splenectomy, or rituximab may be indicated. After successful treatment for HIV-associated thrombocytopenia, recurrences requiring therapy are expected in more than half of cases (Ambler 2012).

Table 2: Therapy of HIV-associated thrombocytopenia.

Clinical situation	Therapy
Asymptomatic and platelets > 30,000/µl	ART
Platelets < 30,000/µl or Platelets < 50,000/µl and significant mucosal bleeding	ART plus first-line therapy: corticosteroids Subsequent therapy(s)*: immunoglobulins, splenectomy, rituximab, TRAs, azathioprine
Severe bleeding	Platelet transfusions and corticosteroids possibly additional immunoglobulins

* Subsequent therapies after failure of corticosteroids should be given according to the experience of the treating physician since only a few prospective randomized studies are available (Vesely 2004).

ART usually leads to a recovery of the platelet count within three months (Arranz Caso 1999). The effect is independent of the antiretrovirals used and the level of platelets at the start of therapy (Arranz Caso 1999). It should be noted that thrombocytopenias frequently occur during antiretroviral therapy breaks, especially in the presence of previous thrombocytopenia (Ananworanich 2003). Therapy beyond ART is indicated in cases of less than 30,000 platelets/µl and less than 50,000 platelets/µl with concomitant marked mucosal bleeding or risk factors such as arterial hypertension or peptic ulcers (George 1996).

Corticosteroids: are the standard for initial therapy. A dose of 0.5–1.0 mg/kg/day predniso(lo)ne results in a substantial platelet increase in 60–90% of patients (Abrams 1986). After a response, which can be expected within a few days, the initial dose should be continued for 2–4 weeks and then phased out rapidly depending on the platelet count, preferably above 60,000/µl. Therapy should not exceed six weeks (Provan 2019, Matzdorff 2021). In cases of life-threatening bleeding, we recommend higher doses (1 g methylprednisolone/day for three days, then gradual dose reduction). An alternative, especially in poor immune status, is the short-term administration of high-dose dexamethasone. After four days of 40 mg dexamethasone/day, a response is achieved in 85% of non-HIV-infected patients with thrombocytopenia. Only 50% had a relapse within six months (Cheng 2003). After four cycles of this

dexamethasone therapy given at 14-day intervals, a response was achieved in 74% for at least eight months (Mazzucconi 2007). Retrospective studies of HIV-negative patients with ITP indicate an increased rate of fatal infections with prolonged steroid administration (Godeau 2007).

Intravenous immunoglobulins: used at a dose of 1 g/kg/day for 1–2 days without response or contraindications to corticosteroids or in the presence of threatening bleeding. The response rate is approximately 60%. However, without maintenance therapy, platelets usually drop again after a few weeks and reach baseline levels after about one month (Godeau 2007).

Splenectomy: is effective, even after failure of corticosteroid and immunoglobulin therapy. Platelet count usually increases within the first postoperative week, often to normal values (Ravikumar 1989). The feared additional weakening of the immune system leading to an acceleration of the HIV infection was not observed in long-term follow-up (Oksenhendler 1993). However, long-term complication risks are well documented and may be one of the reasons for the overall low acceptance of this procedure (Lambert 2017). For prophylaxis of life-threatening bacterial infections, vaccination against pneumococcus, *Haemophilus influenzae*, and meningococcus is recommended at least two weeks before splenectomy (George 1996). However, vaccine response is uncertain with CD4 T-cell counts below 400/µl (Greub 1996). Splenectomy should therefore be performed only in individual cases of therapy-resistant severe thrombocytopenia and after an observation period of preferably not less than 12 months (Provan 2019).

Rituximab: The CD20 antibody rituximab has also been used successfully in HIV-associated thrombocytopenia (Ahmad 2004) and is an alternative to splenectomy. Especially in cases of low CD4 T-cell count (< 100/µl), its use should be carefully considered because rituximab may increase susceptibility to infection. Fatal progressive multifocal leukoencephalopathies have been observed in HIV-negative patients (Carson 2009). A literature review of clinical efficacy in HIV-negative patients (age over 15 years) with ITP revealed a response rate (platelets > 50,000/µl) of over 60%. The platelet increases usually occurred after 3–8 weeks and lasted 2–48 months (Arnold 2007). However, a long-term effect is questioned in other studies (Ghanima 2015).

Platelet substitution: Since increased platelet destruction is an essential mechanism in HIV-associated thrombocytopenia, platelet transfusions are only useful in rare situations with life-threatening bleeding. Platelet transfusions are combined with corticosteroids and/or immunoglobulins in this situation. Platelet transfusions are also recommended before splenectomy if the platelet count is below 10,000/µl despite adequate therapy.

Thrombopoietin receptor agonists (TRAs): TRAs offer an essential treatment option in the event of failure or inadequate response to steroids and are characterized by a relatively favorable safety profile with a lack of immunosuppressive effect (Neunert 2018). They show efficacy even after splenectomy. When on TRAs, a platelet count of 50–150/µl is targeted (Matzdorff 2021). Subcutaneous administration of the peptide romiplostim has been shown to increase platelet counts in 88% (non-splenectomized) and 79% (splenectomized) in Phase III trials in HIV-negative patients. A permanent increase was observed in 56% and 38%, respectively (Kuter 2008). Dosage is initially 1 µg/kg SC once weekly, then 1–10 µg/kg SC once weekly, adjusted for platelet count. An increment can be expected after 7–10 days. A response rate of over 80% has also been seen with the small molecule eltrombopag, which has the advantage of oral administration (Bussel 2007). However, intake restrictions should be considered with antacids, dairy products, and polyvalent cations (Fe, Ca, Mg). The recommended starting dose is 50 mg once daily PO (while for ITP associated

with hepatitis C and for Asian ancestry, 25 mg once daily). It needs to be adjusted up to 75 mg daily according to the platelet count. A platelet response can be expected after 7–10 days. After the failure of other therapies, both molecules have been shown to positively affect HIV-associated thrombocytopenias (Quach 2012, Vishnu 2015). In the case of concomitant administration of protease inhibitors, it should be noted that a 17% decrease in plasma AUC has been described for eltrombopag (Wire 2012). Systematic studies in HIV-associated thrombocytopenias are pending. Side effects reported for eltrombopag include an increased risk of thromboembolism and possible liver damage in chronic liver disease (Vishnu 2015). An increase in bone marrow reticulin has also been observed with TRAs (Lambert 2017). Sustained responses of the platelet count after discontinuation of TRAs have been reported. After an adequate treatment response (e.g., platelet count > 50,000/µl) has been achieved for several months, discontinuation of TRAs was suggested in a stepwise fashion (abruptly stopping treatment can lead to a rebound of thrombocytopenia). Platelet counts should be monitored during tapering and thereafter (Cooper 2021, Matzdorff 2021).

Avatrombopag, another TRA, has been approved for treating chronic ITP by the FDA (2019) and the EMA (2021). However, there is insufficient data on its efficacy in HIV-associated thrombocytopenia.

SYK inhibitors: Fostamatinib is the first approved SYK (spleen tyrosine kinase) inhibitor. It was approved for treating chronic ITP in adults refractory to other treatment modalities. Adequate data on HIV-associated thrombocytopenias are lacking to date.

Interferon-α: Efficacy over placebo (dose 3 million IU 3x/week) was demonstrated in a small, double-blind, randomized trial in 15 patients with HIV-associated thrombocytopenia (Marroni 1994). A significant platelet response was observed after three weeks. However, platelet levels dropped back to baseline after the end of therapy. Side effects include flu-like symptoms and, less frequently, cytopenias.

Other options: Various other treatment options for ITP, such as danazol and mycophenolate, have been reported (review in Matzdorff 2021). However, the case numbers are mostly small, and the effect is not proven.

Literature

Abrams DI, Kiprov D, Goedert JJ, et al. Antibodies to human T-lymphotropic virus type III and development of the AIDS in homosexual men presenting with immune thrombocytopenia. Ann Intern Med 1986; 104: 47-50.

Ahmad HN, Ball C, Height SE, Rees DC. Rituximab in chronic, recurrent HIV-associated immune thrombocytopenia. Br J Heamatol 2004; 127: 607-608.

Ananworanich J, Phanuphak N, Nuesch R, et al. Recurring thrombocytopenia associated with structured treatment interruption in patients with HIV infection. Clin Infect Dis 2003; 37: 723-5.

Ambler KLS, Vickars LM, Leger CS, et al. Clinical Features, Treatment, and Outcome of HIV-Associated Immune Thrombocytopenia in the HAART Era. Adv Hematol 2012; 2012: 1-6.

Arnold DM, Dentali F, Crowther MA, et al. Systematic review: Efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med 2007; 146: 25-33.

Arranz Caso JA, Sanchez Mingo C, Garcia Tena J. Effect of highly active antiretroviral therapy HAART on thrombocytopenia in patients with HIV infection. N Engl J Med 1999; 341: 1239-40.

Bouldouyre MA, Charreau I, Marchou B, et al. Incidence and risk factors of thrombocytopenia in patients receiving intermittent antiretroviral therapy: a substudy of the ANRS 106-window trial. J Acquir Immune Defic Syndr 2009; 52: 531-7.

Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med 2007; 357: 2237-47.

Camino N, Núñez M, Blanco F, et al. Indinavir-induced thrombocytopenia. AIDS Patient Care STD 2003; 17: 103-4.

Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009; 113: 4834-40.

Cheng Y, Wong RS, Soo YO, et al. Initial treatment of immune thrombocytopenic purpura with high-dose dexamethasone. NEJM 2003; 349: 831-6.

Cines DB, Liebman H, Stasic R. Pathobiology of secondary immune thrombocytopenia. Semin Hematol 2009;46, Suppl 2: 2-14.

Cooper N, Hill QA, Grainger J, et al. Tapering and discontinuation of thrombopoietin receptor agonist therapy in patients with immune thrombocytopenia: Results from a modified Delphi panel. Acta Haematol 2021; 144: 418–426.

Eyster ME, Rabkin CS, Hilgartner MW, et al. HIV-related conditions in children and adults with hemophilia: rates, relationship to CD4 counts, and predictive value. Blood 1993; 81: 828-34.

George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: A practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996; 88: 3-40.

Ghanima W, Khelif A, Waage A, et al. RITP study group. Rituximab as second-line treatment for adult immune thrombocytopenia (the RITP trial): a multicentre, randomised, double-blind, placebocontrolled trial. Lancet 2015; 385: 1653-61.

Godeau B, Provan D, Bussel J. Immune thrombocytopenic purpura. Curr Opin Hematol 2007; 14: 535-56.

Greub G, Erard P, von Overbeck J. HIV infection and splenectomy: 3 cases and literature review. Schweiz Med Wochschr 1996; 126: 1524-9.

Heyward WL, Curran JW: The epidemiology of AIDS in the US. Sci Am 1988; 259: 72-81.

Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet 2008; 371: 395-403.

Lambert MP, Gernsheimer TB. Clinical updates in adult immune thrombocytopenia. Blood 2017; 129: 2829-35.

Lebensztejn DM, Kaczmarski M. Lamivudine-associated thrombocytopenia. AJG 2002; 97: 2687-8.

Matzdorff A, Meyer O, Ostermann H, et al. Immune thrombocytopenia—current diagnostics and therapy: Recommendations of a joint working group of DGHO, OGHO, SGH, GPOH, and DGTI. Oncol Res Treat 2018; 41 (Suppl 5): 1–30.

Matzdorff A, Holzhauer S, Kühne T, et al. Immunthrombozytopenie (ITP). https://www.onkopedia.com/de/onkopedia/guidelines/immunthrombozytopenie-itp/@@guideline/html/index.html

Marroni M, Gresele P, Landonio G, et al. Interferon-a is effective in the treatment of HIV-1-related, severe, zidovudine-resistant thrombocytopenia. A prospective placebo-controlled double-blind trial. Ann Intern Med 1994; 121: 423-9.

Mazzucconi MG, Fazi P, Bernasconi S, et al. Therapy with high-dose dexamethasone (HD-DXM) in previously untreated patients affected by idiopathic thrombocytopenic purpura: a GIMEMA experience. Blood 2007; 109: 1401-7.

Middelburg RA, Carbaat-Ham JC, Hesam H, Ragusi MA, Zwaginga JJ. Platelet function in adult ITP patients can be either increased or decreased, compared to healthy controls, and is associated with bleeding risk. Hematology. 2016; 21: 549-51.

Najean Y, Rain JD. The mechanism of thrombocytopenia in patients with HIV. J Lab Clin Med 1994; 123: 415-20.

Neunert CE, Cooper N. Evidence-based management of immune thrombocytopenia: ASH guideline update: Hematology Am Soc Hematol Educ Program 2018; 30: 568-75.

Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv 2019; 3: 3829–3866.

Oksenhendler E, Bierling P, Chevret S. Splenectomy is safe and effective in HIV-related immune thrombocytopenia. Blood 1993; 82: 29-32.

Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Advances 2019; 3: 3780-817.

Quach H, Lee LY, Smith B, Korman T, Woolley IJ. Successful use of eltrombopag without splenectomy in refractory HIV-related immune reconstitution thrombocytopenia. AIDS 2012; 26: 1977-9.

Ravikumar TS, Allen JD, Bothe A Jr, Steele G Jr. Splenectomy. The treatment of choice for HIV-related immune thrombocytopenia? Arch Surg 1989; 124: 625-8.

Thompson GR 3rd, Lawrence VA, Crawford GE. HIV infection increases the risk of heparin-induced thrombocytopenia. Clin Infect Dis 2007; 45:1393-6.

Vannappagari V, Nkhoma ET, Atashili J, Laurent SS, Zhao H. Prevalence, severity, and duration of thrombocytopenia among HIV patients in the era of highly active antiretroviral therapy. Platelets. 2011; 22: 611-8.

Vesely SK, Perdue JJ, Rizvi MA, Terrell DR, George JN. Management of adult patients with persistent idiopathic thrombocytopenic purpura following splenectomy. Ann Intern Med 2004; 140: 112-20.

Vishnu P, Aboulafia DM. Haematological manifestations of human immune deficiency virus infection. Br J Haematol 2015; 171: 695-709.

Walsh C, Krigel R, Lennette F, Karpatkin S. Thrombocytopenia in homosexual patients. Prognosis, response to therapy, and prevalence of antibody to the retrovirus associated with AIDS. Ann Intern Med 1985; 103: 542-5.

Wire MB, McLean HB, Pendry C, Theodore D, Park JW, Peng B. Assessment of the pharmacokinetic interation between eltrombopag and lopinavir-ritonavir in healthy adult subjects. Antimicrob Agents Chemother 2012; 56: 2846-51.

26. HIV-associated skin diseases

STEFAN ESSER

Compared to the general population, PLWH develop dermatoses more frequently (Tan 2018). Skin and mucosal findings are directional in the initial diagnosis of HIV infection and determination of clinical stage and manifest as a function of immunodeficiency (Schöfer 1991, Esser 2021). Diseases with skin or mucosal involvement can often be diagnosed by simple inspection. Typical marker diseases of skin and mucous membranes appear: during acute HIV infection, exanthema is often observed. In clinical CDC stage B, oral and vulvovaginal candidiasis, herpes zoster, oral hairy leukoplakia, carcinoma *in situ* of the cervix, and bacillary angiomatosis are diagnosed. Many AIDS-defining diseases also develop manifestations on the skin and mucous membranes. In untreated PLWH, Kaposi's sarcoma is the most common AIDS-defining neoplasm. Approximately 10% of initial HIV diagnoses are due to changes in the skin or mucous membranes (Itin 2008).

The HIV Indicator Diseases Across Europe Study (HIDES) showed a high prevalence of HIV in people with STDs (see *STD*) and certain skin diseases such as seborrheic dermatitis and mononucleosis-like exanthema (Chatzikokkinou 2008, Sullivan 2013). HIV testing should, therefore be offered for indicator diseases.

The spectrum has changed considerably with antiretroviral therapy: Kaposi's sarcoma and opportunistic infections such as *Candida* infections (Friedman-Kien 1981, Gottlieb 1981) have become rarer, whereas drug side effects, epithelial tumors, and STDs have increased (Hartmann 2019, Esser 2021). Especially in advanced immunodeficiency, immune reconstitution syndrome may occur after ART initiation. In this context, opportunistic infections of the skin and mucous membranes may unmask, but also dermatoses may exacerbate.

Skin and mucous membranes have an independent immune system. Immunodeficiency allows even harmless saprophytes to penetrate deeper tissue layers, causing e.g. folliculitis. Dry skin, chronic itching, exacerbation of atopic dermatitis, and prurigo nodularis are prevalent in up to 38% of people living with HIV infection (Rudikoff 2002, Coates 2019). Wound and soft tissue infections, pyoderma, and methicillin-resistant *Staphylococcus aureus* infections are frequently observed (Burkey 2008, Imaz 2010). In addition to common dermatoses (oral candidiasis, herpes zoster, seborrheic eczema), diseases that are otherwise rare are diagnosed in immunodeficiency, including cutaneous cryptococcosis, bacillary angiomatosis, oral hairy leukoplakia, or infections with *Talaromyces marneffei* (Esser 2021).

A functional cellular immune system can protect against the development of neoplasms. The longer cellular immune deficiency persists, the more likely malignant tumors will develop on the skin and mucous membranes. Cancers are more common in PLWH, even at younger ages (Yarchoan 2018). Several cohorts worldwide observe an increased risk of both basal cell carcinoma and cutaneous squamous cell carcinoma (Silverberg 2013, Omland 2018, Coates 2019), while recent data on the incidence of melanoma are conflicting (Coates 2019, Facciola 2020). Low CD4 T-cell counts increase risk. Oncogenic viruses and immunodeficiency increase the risk for Kaposi's sarcoma (HHV-8), non-Hodgkin's lymphoma (EBV, HHV-6, and HHV-8), and cervical and anal carcinomas (high-risk HPV types) (Esser 1998, Hartmann 2019, Clifford 2021). Despite ART, HPV-associated diseases continue to increase. In addition to the already established colposcopic screening of cervical carcinomas, regular proctological screening examinations are also indicated due to the increasing incidence of anal carcinomas in PLWH (Esser 2015, Clifford 2021). Pre-cancerous lesions should be removed early. Screening and early treatment of HPV-associated lesions reduce

the incidence of anal carcinoma (Revollo 2020, Palefsky 2022). Merkel cell carcinomas caused by polyomaviruses are sporadic but may also be more common (Wieland 2011). Attention should be paid to regular skin cancer screening by reflected light microscopy (Burgi 2005).

Dermatological examination and treatment

Regular inspections of the entire skin surface, the mucous membranes of the mouth, genitals and anal region, and palpations of the lymph nodes are easy to perform. Diseases of the skin and mucous membranes are often more severe, rapid, and refractory to treatment in PLWH (Ameen 2010); the germ spectrum is also unusual (Imaz 2010). Therefore, material for pathogen diagnostics should be obtained even before treatments. In the case of unclear findings and ulcerative dermatoses, a punch biopsy should always be taken.

Because standard treatments often fail due to advanced immunodeficiency and resistance, higher and longer doses must be given (note side effects!), or alternative drugs must be used (Osborne 2003). Interactions with ART must be considered. Systemic immunosuppressive therapies and biologics should be used with caution. For example, significant decreases in CD4 T-cells are observed with fumaric acid, increasing the risk of opportunistic disease even without HIV infection (Philipp 2013). Progressive multifocal leukoencephalopathies have been reported with TNF-alpha inhibitors, and they should be avoided in PLWH if possible (Kumar 2010). IL-17 blockers are associated with increased fungal infections (Siegel 2019). Viral infections can be provoked, and tumors can be induced during UV treatments (Popivanova 2010).

Diagnosis and therapy may require the entire repertoire of an infectious disease-oriented specialty clinic and the interdisciplinary cooperation of various specialist groups. Brief descriptions of selected HIV-associated dermatoses and tumors can be found in the alphabetical appendix.

ART-associated adverse reactions frequently affect the skin and mucous membranes (Esser 2007). In the case of exanthema, it is often challenging to distinguish drug reactions from immune reconstitution syndrome, syphilis, or viral exanthema (Beatty 2010). Also, the causative agent often cannot be identified with certainty. A switch of ART should be considered before symptomatic treatment of adverse events. The resistance situation, co-morbidities, and interactions must be considered (see S*ide Effects*).

Drug reactions and allergies

The risk of cutaneous drug reactions in AIDS is approximately 9-fold (Hernandez-Salazar 2006), and the risk of severe drug reactions is even more than 500-fold greater than in the general population (Ward 2002). In 86% of PLWH, these reactions occur within the first four weeks of the start of therapy (Rotunda 2003). Exanthems (rashes) (Pirmohamed 2001, Shibuyama 2006) range clinically from macular to toxic epidermal necrolysis. In principle, all drugs can be considered as triggers (Esser 2007). The type of exanthema does not usually allow conclusions to be drawn about the triggering allergen, but rather the temporal relationship with the initial ingestion (latency on average, 9 ± 2 days). Drug exanthema is particularly frequent with nevirapine and efavirenz (Van Leth 2005, Hartmann 2005), abacavir (Clay 2000), and cotrimoxazole. Prophylaxis with glucocorticoids or antihistamines is ineffective (Montaner 2003, Launay 2004). Pharmacogenetic HLA-B*57:01 testing is mandatory before abacavir administration (see *ART*; Mallal 2008). Pharmacogenetic predictors have also been studied for other drugs (Littera 2006, Wyen 2011). ART can often be

continued for mild or moderate drug reactions. Patients are monitored closely and receive glucocorticosteroids locally or systemically (up to 1 mg/kg body weight) for a short time if needed, as well as antihistamines for pruritus. Drug reactions often regress despite the continuation of therapy.

Severe drug exanthema is often accompanied by general symptoms such as fatigue, fever, and gastrointestinal complaints. Alarm signs include extensive skin detachment (TEN: Toxic epidermal necrolysis), blistering (vesicles, bullae, SJS – Stevens-Johnson Syndrome) and hemorrhage (petechiae, purpura, vasculitis) without previous trauma, generalized seeding of sterile pustules and pustules (AGEP, Acute Generalized Exanthemetous Pustulosis), dead, scabbed areas of skin (necrosis), and sudden onset and disappearance of wheals and fluid retention in tissues (edema). Mucosal involvement (eye, oral cavity, pubic region) is also classified as dangerous. Blood eosinophilia indicates a DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms). In the case of such symptoms, the affected person must be monitored as an inpatient and treated systemically; the previously taken medications, including ART, may have to be discontinued permanently.

If general symptoms co-occur with exanthema, life-threatening and even lethal courses are possible. In severe cases such as toxic epidermal necrolysis, immediate intensive medical care is necessary. After severe reactions, the responsible substance should not be used again. Different half-lives must be considered when discontinuing ART, as resistance can develop rapidly under functional monotherapy. Some patients take medications, drugs, herbal and other preparations, and dietary supplements, often without informing their healthcare provider. Many "alternative medicine" preparations have a relevant potential for allergic or toxic reactions (Witkowski 2003).

The trigger often remains open if several medications have been restarted simultaneously. In such cases, "allergological" test methods are available. In type I reactions, e.g., for penicillin, specific IgE antibodies can be detected in the blood. Lymphocyte transformation tests are not yet methodologically mature. Cutaneous prick and scratch and intracutaneous tests primarily evaluate immediate type I reactions. Epicutaneous and patch tests are used to confirm a type IV reaction and other late-type reactions. They must be read over several days. All skin tests are not able to detect reactions against possible metabolites.

If all skin tests are negative, graded systemic provocation testing under inpatient conditions (readiness for resuscitation, strict indication) can definitively clarify whether a drug reaction to a specific substance is present (Shear 2008). A diagnosed reaction or allergy should be recorded in an allergy passport, to be carried by the person at all times.

Specific dermatological side effects of antiretroviral drugs

The intragluteal administrations of modern "long-acting injectables" such as cabotegravir and rilpivirine (Landovitz 2016) cause local irritation and granulomas at the injection sites that may persist over time. Laugier-Hunziker-Baran syndrome with melanonychia striata medicamentosa (streaky brownish nail pigmentation) and endobuccal mucosal lentiginosis (pigmentation of buccal mucosa, DD melanoma!) is rarely observed with AZT (Greenberg 1990). Nearly 2% of (dark-skinned) patients experience mostly mild palmoplantar hyperpigmentation with FTC (Nelson 2004). However, there are case reports of PLWH who develop hyperpigmentation of the nails, skin, and mucous membranes even without ART (Granel 1997).

Fat distribution disorders, lipodystrophy syndrome (Potthoff 2010), and weight gain under certain substances are discussed elsewhere.

Alphabetical overview of selected HIV-associated dermatoses and their therapy

Folliculitides: Follicular bound pustular, papular efflorescences, emphasized on the upper trunk and proximal extremities. Causes include staphylococci, *Malassezia furfur*, *Acinetobacter baumanii* (Bachmeyer 2005), *Demodex folliculorum, scabies* mites (*Sarcoptes scabiei* var. hominis), drugs, or atopic dermatitis (Rudikoff 2002) (Budavari 2007). Treatment depends on the cause with staphylococcal-active antibiotics, antifungals, DADPS, isotretinoin, and ivermectin. Local therapy with topical glucocorticosteroids, calcineurin inhibitors such as pimecrolimus or tacrolimus (Toutous-Trellu 2005), low-dose UV-311nm irradiation (Holmes 2001), and discontinuation of triggering drugs. ART renders these dermatoses associated with cellular immunodeficiency less frequent; in particular, the eosinophilic variant improves on ART (Hayes 2004).

Mollusca contagiosa ("dell warts"): Benign viral dermatosis caused by poxvirus mollusci. Especially children with neurodermatitis contract the disease. In adults, it is usually an STD. Extragenital molluscs in adults are a marker of advanced HIV infection (CD4 T-cells usually below 100/µl). In addition to the characteristic "dell wart" with central expressible crumbly pulp, there are also large nodular conglomerates or endophytic growth—differential diagnoses: cutaneous cryptococcosis, penicillinosis, and histoplasmosis. Gentle procedures, as well as spontaneous healing, are possible after initiation of ART. Surgical ablation with a curette or egg skin forceps (van der Wouden 2005); topical: 5% KOH solution (Infectodell® solution). In individual cases, an attempt at treatment with imiquimod can be made in cases of high suffering pressure (Liota 2000).

Papular dermatoses: Diffuse appearance of monomorphic, skin-colored to reddish papules (2–5 mm) or the combined eruption of papules and pustules (sterile eosinophilic pustulosis, Ofuji's disease [Kanaki 2021]): Upper trunk, extremities with larger plaques that heal centrally with hyperpigmentation. Heterogeneous etiology (Ramos 2006): an autoimmune reaction against follicular antigens as eosinophilic folliculitis (See folliculitides), a variant of adult pruriginous type atopic dermatitis, hypersensitivity reaction to drugs or by microbial agents, parasites, or saprophytes. Diagnosis: drug history, histological special stains (PAS and others), mite search with dermatoscopy (mite ducts?). Therapy: pathogen-specific or sanitation of focal infections. Otherwise, symptomatic antihistamines, itraconazole (200 mg/d for two weeks), isotretinoin, dapsone, mild PUVA or UVB (311 nm) irradiation (most effective), 5% permethrin cream or topically glucocorticosteroids, calcineurin inhibitors such as pimecrolimus or tacrolimus (Ellis 2004, Kanaki 2021).

Pityriasis versicolor: One of the most common superficial skin mycoses is caused by lipophilic yeasts of the genus Malassezia and is favored by immunodeficiency, a strong tendency to sweat, and a warm, humid climate. In areas rich in sebaceous glands, white to dark brown, sometimes erythematous macules with fine, bran-like scaling, which tend to confluence like a map, appear, depending on the UV exposure. Even after successful therapy, it may take months for "repigmentation" to occur. Detection is usually made directly by clear adhesive strip tear-off preparations or by taking scale material from the marginal area of the lesion, making a potassium alkali preparation (15% KOH) while staining with methylene blue and subsequent microscopy at 400× magnification, or a calcofluorine or black phosphorous preparation for fluorescence microscopy. Wood light examinations (UV light of 365 nm wavelength) show a yellowish-green fluorescence of the affected skin areas. It is usually not necessary to perform a culture. Topically effective are azoles. Systemic therapy is indicated for frequent recurrences.

Prurigo nodularis: Cutaneous manifestation of HIV infection (Liautaud 1989, Coates 2019). Chronic persistent, massively pruritic, usually excoriated papules and nodules (0.5–3cm) mainly on the extensor sides of the extremities. Itch-scratch cycles with lesional proliferation of cutaneous nerves maintain the disease for years. Severe scratching enlarges the nodules. Hemorrhagic crusts, dark discoloration, keratotic or verrucous dirty gray overgrowth, scars, depigmentation after healing. Frequent psychiatric comorbidity and psychosocial disorders. Therapy: topical – potent corticosteroids if possible occlusive, polidocanol, calcipotriol, capsaicin; phototherapy (UVB, UVA1) or PUVA therapy. Treatment of persistent single-cell lesions: injection with triamcinolone crystal suspension, cryotherapy, excision, dermabrasion, electrocaustic or laser surgical ablation. Systemic: sedating antihistamines (*caveat:* interactions), psychotropic drugs (neuroleptics, antidepressants), corticosteroids, retinoids. Good results are obtained with thalidomide up to 400 mg/day (*caveat:* neurotoxicity, teratogenicity) (Matthews 1998). Adjunctive psychosomatic therapy. Dressings to prevent mechanical irritation.

Pruritus: Chronic, often distressing pruritus is a common clinical symptom in PLWH (Tarikci 2015, Coates 2019). Etiological clarification and therapy are complex (Singh 2003). In addition to infectious causes (follicular and non-follicular infections caused by bacteria, viruses, fungi, and parasites such as *Sarcoptes scabiei* and crabs), dryness of the skin (xeroderma, exsiccation eczema), erythrosquamous dermatoses, systemic diseases such as lymphoma, renal insufficiency, hepatitides, and hepatoses, as well as drug reactions, can also cause pruritus. Diagnosis includes exclusion of skin and systemic diseases, especially scabies. The diagnosis of "idiopathic HIV-associated pruritus" is a diagnosis of exclusion. Some authors suspect a direct connection with HIV viral load (Zancanoro 2006).

Therapeutically, there are various phototherapies (UVA, PUVA, UVB-311nm) in addition to antihistamines (cave interactions) and (primarily topical) glucocorticosteroids (Tarikci 2015) (Singh 2003). For longer-term topical treatments, calcineurin inhibitor-containing topicals are available for glucocorticosteroid sparing. Care should be taken to ensure an appropriate base for all topical therapies. In severe, refractory individual cases with pruritus, especially on the extremities, costly local treatment with capsaicin may also provide relief (Tarikci 2015). Gabapentin or neuroleptics such as promethazine are also used systemically in extreme and chronic courses, as are biologics such as dupilumab (Avallone 2021) and tralokinumab or JAK inhibitors in individual cases, especially in atopic dermatitis.

Psoriasis vulgaris is an inherited, chronic autoimmune disease (0.2–2.8% of the population) provoked by physical stimuli (including friction, lack of UV light), and endogenous factors (infections, alcohol abuse, drugs such as beta-blockers or "stress"). Psoriasis is now considered a systemic disease, as cardiovascular events, for example, are also observed more frequently due to chronic inflammation. Psoriasis occurs for the first time or as an exacerbation triggered by HIV infection in about 5.4% of PLWH (Tan 2018). The more severe the immunodeficiency, the more severe and refractory the course (Ceccarelli 2019). Clinically, psoriasis can manifest eruptive-exanthematous, chronic stationary, or atypical with an inverse pattern of involvement (involvement of groin, axillae, palms, soles, face) as erythrosquamous plaques or exudative, pustular, or erythrodermic. Involvement of the scalp and nails (spotted or crumbled nails), joint involvement, and pustular forms are possible.
First, triggering factors should be eliminated and ART initiated. Local therapy with dithranol, glucocorticosteroids, calcipotriol, tacalcitol, or a topical retinoid tazarotene is sufficient in case of circumscribed affection. For localizations on the capillitium and nails, corticosteroids can be combined, and for intertriginous areas,

calcineurin inhibitors such as pimecrolimus can be used (Gisondi 2005). In case of generalized or exudative involvement, systemic treatment is required, e.g., with acitretin = neotigason 25–75 mg/d (von Zander 2005) or fumarates with gradual dosage, in severe cases also with immunosuppressants such as methotrexate, cyclosporine or hydroxyurea (Kumar 2001). When fumaric acid esters are administered, CD4 and CD8 T-cells drop off – Kaposi's sarcomas have been observed with long-term administration even in people without HIV (Philipp 2013). Alternatives: Photo- and photochemotherapy (UVB 311, UVB, PUVA: local or systemic) are effective and have few adverse effects on HIV infection (Schoppelrey 1999). Clinical experience is now increasingly available for people with HIV with biologics that specifically inhibit factors of the inflammatory cascade (e.g., TNF-alpha, IL-12, IL-23, IL-17A, and JAK) but may also increase the overall risk of infection. In a systematic review of 25 cases published between 1985 and 2015, serious infections occurred almost exclusively in cases of ineffective ART (Nakamura 2018). Therefore, the current German psoriasis guidelines recommend systemic treatment only in severe, refractory psoriasis when HIV infection is successfully treated with antiretroviral therapy. Systemic biologics are indicated especially in cases of joint involvement but also in cases of poor response. The selection is individual, based on the dynamically changing guidelines (AWMF Psoriasis 2021). Before using biologics, co-infections with tuberculosis, hepatitis B, and other opportunistic infections should be excluded. Among some biologics, the increased incidence of PML (rare overall) should be pointed out (Kumar 2010, Bharat 2012).

Scabies: Extremely pruritic dermatosis, especially at night. Predilection sites: finger interdigitates, wrists, nipples, anterior axillary line, umbilicus, penile shaft: fine tortuous red lines a few millimeters long (scabies ducts) and generalized eczema with scratch marks (head free, exception: scabies norvegica and infants), especially inner thighs and buttocks region. Typical are additionally inguinal and genital (penis shaft, scrotum) red-brown, itchy nodules (= scabies granulomas), which can persist for months even after successful therapy. Diagnostically difficult: "well-groomed" scabies with severe pruritus but hardly detectable mites. In case of severe immunodeficiency special form: scabies crustosa (norvegica): marker disease of HIV infection. Over months, large eczematous foci develop with an asbestos-like shimmering or bark-like scaling and head involvement (caution: confusion with psoriasis). These foci may be asymptomatic but are highly infectious (up to 10,000 mites/g of skin scales). Indicative: cases of ordinary scabies in the area. Complications: secondary impetiginization, post-scabies eczema, protozoan mania. Diagnosis: dermoscopic detection of mites, eggs, or mite feces (skybala) from mite duct by careful opening with a cannula or lancet on a microscope slide under a magnifying glass. Treatment: topical – 5% permethrin cream (Infectoscab®, day 1 + day 8 if necessary); other alternatives are benzoyl benzoate, pyrethrum extract, or allethrin/piperonyl butoxide. If necessary, keratolysis as well as antiseptic and antieczematous treatment. In case of scabies crustosa scale detachment, treat locally for several days and then anti-scabies for at least 3–4 days (permethrin 5% cream, including capillitium and under distal edges of fingernails). Systemic: if skin involvement exceeds 50%, scabies crustosa, repeated unmanageable outbreaks in community settings, polymorbid, immobile patients, or multiple recurrences: a combination of local keratolytic/antiscabiotherapy plus systemic ivermectin, e.g., 200 µg/kg bw Scarbioral® (Alberici 2000). Since ivermectin is not ovocidal: repeat administration after 1–2 weeks. Antipruritic adjunctive therapy, e.g., with antihistamines (desloratadine, clemastine) at night (*caveat:* interactions with ART). In addition, change of clothing and bedding (wash at 90° Celsius or place in an airtight plastic bag for 3–5 days); sanitation of the environment; examination and co-treatment of contacts. Aftercare: topical gluco-

corticoid-containing externals; antiseptic local treatment. Hygienic measures and simultaneous treatment of all contacts are essential. Even after successful therapy, the eczema must still be treated with local glucocorticoids, depending on the clinic (Paasch 2001, AWMF Skabies 2016).

Seborrheic dermatitis: Incidence in untreated PLWH is between 30 and 83%, depending on immune status (Chatzikokkinou 2008). The lipophilic yeast *Malassezia furfur* is thought to have pathogenetic relevance, although subtype rather than density of colonization appears to be important. Seborrheic dermatitis may be a marker of progression of HIV infection and often improves with ART. Clinical: sebaceous follicle-rich areas (eyebrows, nasolabial folds, forehead, capillitium, external auditory canal, anterior sweat groove, genitals); greasy yellow fine- to coarse-lamellar scaling on usually sharply demarcated erythema. Treatment with topical antifungal agents, such as ketoconazole, ciclopirox, or terbinafine cream, alternatively selenium disulfide, metronidazole, low-dose dithranol, or lithium succinate- and zinc sulfate-containing cream, or calcineurin inhibitors (Rigopoulos 2004). For treatment of the hairy head, antifungal shampoos are appropriate. In severe cases, systemic itraconazole 1 x 100 mg/d or terbinafine 250 mg/d (Gupta 2004, Kose 2005).

Warts: Human papillomaviruses (HPV) cause verrucae vulgares, verrucae plantares (plantar warts), verrucae planae juveniles, epidermodysplasia verruciformis, condylomata acuminata (genital warts), condylomata gigantea (Buschke-Löwenstein), bowenoid papulosis and mucinous papillomas (Heck's disease), *in situ* carcinomas, squamous cell carcinomas (see *STD)*. More than 150 types have been identified, divided into "low risk" and "high risk" according to their oncogenic potential. HPV exclusively infects epithelial cells of the skin and mucous membranes mostly via micro-injuries. Infection from person to person, but also via vectors. Symptomatic HPV infection leads after an undetermined latency period to a reactive, tumor-like, keratinizing, mostly skin-colored epithelial hyperplasia with black stipples often visible in reflected light microscopy (thrombosed vessels in papillomatosis). As a result of a cellular immune response with lasting immunity to the respective subtype, spontaneous remissions are observed in about 60%. Viral persistence is considered the leading cause for the generally high recurrence rates after therapeutic interventions and can lead to malignant transformation in high-risk HPV types. In addition to other predisposing factors (atopy, UV light exposure, smoking), immune status is a major contributor to further progression. In PLWH, HPV infections persist more frequently, become symptomatic more often, tend to recur, and spread over large areas due to autoinoculation, develop into carcinomas more quickly, and prove to be particularly refractory to treatment.
There are a plethora of treatment options: topically, patients can use keratolysis with, for example, salicylic acid-containing topicals or cyto- or virostatically active agents such as acetic saltpeter lactic acid, trichloroacetic acid, podophyllin, and 5-fluorouracil or immunomodulators such as imiquimod (Esser 2015). Dry extract of green tea leaves is available as another effective local therapy. Surgical options include scissor beating and excision, cryo-therapeutic, laser surgical, or electrocaustic ablation. Malignancy and invasive growth should be excluded histologically if clinical findings are abnormal. Often, the repeated combined use of different procedures is necessary. In individual cases, systemic therapy with interferon-alpha can be helpful, although health insurance does not usually cover this.

Xeroderma/dry skin: a frequent accompanying symptom of immunodeficiency. About one-third of all HIV patients complain of excessively dry, itchy, scaly skin and hypersensitivity to exogenous stimuli. Skin-care emulsions (containing lactic acid, urea), dexpanthenol, and oil baths. In highly inflammatory forms, 3–5 days of external corticosteroids (class 3–4) can help (Rudikoff 2002).

Literature

Alberici F, Pagani L, Ratti G, Viale P. Ivermectin alone or in combination with benzyl benzoate in treating human immunodeficiency virus-associated scabies. Br J Dermatol 2000; 142:969-72.

Ameen M. Cutaneous markers of HIV infection and progression. Curr HIV Res 2010, 8:450-5.

Avallone G, Trunfio M, Giura MT, et al. Dupilumab in HIV-positive patients with atopic dermatitis: a long-term follow-up patient and a literature review. Dermatol Online J 2021, 27(8).

Bachmeyer C, Landgraf N, Cordier F, et al. Acinetobacter baumanii folliculitis in a patient with AIDS. Clin Exp Dermatol 2005; 30: 256-8.

Beatty GW. Immune reconstitution inflammatory syndrome. Emerg Med Clin North Am 2010, 28:393-407.

Bharat A, Xie F, Baddley JW, Beukelman T, et al. Incidence and risk factors for progressive multifocal leukoencephalopathy among patients with selected rheumatic diseases. Arthritis Care Res (Hoboken) 2012; 64:612-5

Budavari JM, Grayson W. Papular follicular eruptions in human immunodeficiency virus-positive patients in South Africa. Int J Dermatol 2007;46:706-10.

Burgi A, Brodine S, Wegner S, et al. Incidence and risk factors for the occurrence of non-AIDS-defining cancers among human immunodeficiency virus-infected individuals. Cancer 2005; 104: 1505-11.

Burkey MD, Wilson LE, Moore RD, et al. The incidence of and the risk factors for MRSA bacteraemia in an HIV-infected cohort in the HAART era. HIV Med 2008, 9:858-62.

Ceccarelli M, Venanzi Rullo E, Vaccaro M, et al. HIV-associated psoriasis: Epidemiology, pathogenesis, and management. Derm Ther 2019, 32: e12806

Chatzikokkinou P, Sotiropoulos K, Katoulis A, et al. Seborrheic dermatitis – an early and common skin manifestation in HIV patients. Acta Dermatovenerol Croat 2008,16:226-30.

Clay PG. The abacavir hypersensitivity reaction: a review. Clin Ther 2002; 24:1502-14.

Clifford GM, Georges D, Shiels MS, et al. A meta-analysis of anal cancer incidence by risk group: Toward a unified anal cancer risk scale. Int J Cancer 2021, 148:38-47.

Coates SJ, Leslie KS. What's new in HIV dermatology? F1000Res. 2019 Jun 28;8. pii: F1000 Faculty Rev-980.

Ellis E, Scheinfeld N. Eosinophilic pustular folliculitis: a comprehensive review of treatment options. Am J Clin Dermatol 2004; 5:189-97.

Esser S, Helbig D, Hillen U, Dissemond J, Grabbe S. Side effects of HIV therapy. J Dtsch Dermatol Ges 2007, 5:745-54.

Esser S, Kreuter A, Oette M, et al. German-Austrian guidelines on anal dysplasia and anal cancer in HIV-positive individuals: prevention, diagnosis, and treatment. J Dtsch Dermatol Ges 2015; 13:1302-19.

Esser S, Reimann G, Brockmeyer NH. HIV-assoziierte Tumoren. MMW 1998, 1: 687-693.

Esser S, Sammet S. HIV medicine for dermatologists and venereologists. J Dtsch Dermatol Ges 2021, 19:82-97.

Facciolà A, Venanzi Rullo E, Ceccarelli M, et al. Malignant melanoma in HIV: Epidemiology, pathogenesis, and management. Dermatol Ther 2020 33:e13180.

Friedman-Kien AE. Disseminated Kaposi's sarcoma syndrome in young homosexual men. J Am Acad Dermatol 1981; 5:468-71.

Gottlieb MS, Schroff R, Schanker HM, et al. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men. N Engl J Med 1981; 305:1425-1431.

Granel F, Truchetet F, Grandidier M. Diffuse pigmentation (nail, mouth and skin) associated with HIV infection. Ann Dermatol Ven 1997; 124: 460-462.

Greenberg RG, Berger TG. Nail and mucocutaneous hyperpigmentation with azidothymidine therapy. J Am Acad Dermatol 1990; 22: 327-330.

Gupta AK, Batra R, Bluhm R, Boekhout T, Dawson TL Jr. Skin diseases associated with Malassezia species. J Am Acad Dermatol 2004; 51: 785-98.

Gupta AK, Nicol KA. Seborrheic dermatitis of the scalp: etiology and treatment. J Drugs Dermatol 2004; 3:155-8.

Hartmann M, Brust J, Schuster D, et al. Rashes in HIV-infected patients undergoing therapy with nevirapine or efavirenz. Hautarzt 2005, 56:847-53.

Hartmann M. [Dermatological signs of HIV-infection]. MMW Fortschr Med 2019, 161(Suppl 2):20-25.

Hayes BB, Hille RC, Goldberg LJ. Eosinophilic folliculitis in 2 HIV-positive women. Arch Dermatol 2004; 140: 463-5.

Hernandez-Salazar A, Rosales SP, et al. Epidemiology of adverse cutaneous drug reactions. Arch Med Res 2006; 37: 899-902.

Imaz A, Pujol M, et al. Community associated methicillin-resistant Staphylococcus aureus in HIV-infected patients. AIDS Rev 2010, 12:153-63.

Itin PH, Battegay M. Mucocutaneous infections in immunosuppression. Internist (Berl). 2008 Dec 21.

Kanaki T, Hadaschik E, Esser S, Sammet S. Eosinophilic pustular folliculitis (EPF) in a patient with HIV infection. Infection. 2021 Aug;49(4):799-801.

Kose O, Erbil H, Gur AR. Oral itraconazole for the treatment of seborrhoeic dermatitis. J Eur Acad Derm Ven 2005; 19: 172-5.

Kumar B, Saraswat A, Kaur I. Rediscovering hydrxyurea: its role in recalcitrant psoriasis. Int J Dermatol 2001; 40: 530-4.

Kumar D, Bouldin TW, Berger RG. A case of PML in a patient treated with infliximab. Arthritis Rheum 2010 62:3191–5.

Landovitz RJ1, Kofron R, McCauley M. The promise and pitfalls of long-acting injectable agents for HIV prevention. Curr Opin HIV AIDS 2016, 11:122-8

Launay O, Roudiere L, Boukli N, et al. Assessment of cetirizine, an antihistamine, to prevent cutaneous reactions to nevirapine therapy: results of the viramune-zyrtec double-blind, placebo-controlled trial. Clin Infect Dis 2004; 38:66-72.

Liautaud B, Pape JW, DeHovitz JA, et al. Pruritic skin lesions. A common initial presentation of AIDS. Arch Dermatol 1989, 125:629-32.

Liota E, Smith KJ, Buckley R, Menon P, Skelton H. Imiquimod therapy for molluscum contagiosum. J Cutan Med Surg 2000; 4:76-82.

Littera R, Carcassi C, Masala A, et al. HLA-dependent hypersensitivity to nevirapine in Sardinian HIV patients. AIDS 2006; 20: 1621-6.

Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008, 358:568-79.

Matthews SN, Cockerell CJ. Prurigo nodularis in HIV-infected individuals. Int J Dermatol 1998, 37:401-9.

Montaner JS, Cahn P, Zala C, et al. Randomized, controlled study of the effects of a short course of prednisone on the incidence of rash associated with nevirapine in patients infected with HIV-1. J Acquir Immune Defic Syndr 2003; 33: 41-46.

Nakamura M, Abrouk M, Farahnik B, et al. Psoriasis treatment in HIV positive patients: a systematic review of systemic immunosuppressive therapies. Cutis 2018, 101: 38–42

Nelson M, Schiavone M. Emtricitabine (FTC) for the treatment of HIV infection. Int J Clin Pract 2004; 58: 504-510.

Omland SH, Ahlström MG, Gerstoft J, et al. Risk of skin cancer in patients with HIV: A Danish nationwide cohort study. J Am Acad Dermatol 2018; 79: 689–95.

Osborne GE, Taylor C, Fuller LC. The management of HIV-related skin disease. Part I: infections. Int J STD AIDS. 2003; 14:78-86. Part II: Neoplasms and inflammatory disorders. Int J STD AIDS 2003; 14: 235-40

Paasch U, Haustein UF. Behandlung der endemischen Skabies mit Allethrin, Permethrin und Ivermectin. Evaluation eines Behandlungskonzeptes. Hautarzt 2001; 52:31-7.

Palefsky J, Lee J, Darragh T, et al. Treatment of anal high-grade.squamous intraepithelial lesions to prevent anal cancer. CROI 2022 #106

Philipp S, Kokolakis G, Hund M, et al. Immunological changes in psoriasis patients under long-term treatment with fumaric acid esters: risk of Kaposi sarcoma occurrence? Eur J Dermatol. 2013, 23:339-43.

Pirmohamed M, Park BK. HIV and drug allergy. Curr Opin Allergy Clin Immunol 2001; 1: 311-316.

Popivanova NI, Chudomirova KN, Baltadzhiev IG, Abadjieva TI. HIV/AIDS-associated Kaposi's sarcoma with multiple skin-mucosal disseminations following ultraviolet (puva) photochemotherapy. Folia Med (Plovdiv). 2010, 52:56-61.

Potthoff A, Brockmeyer NH, Gelbrich G, et al. For the Competence Center Cardiac Insufficiency and the Competence Network HIV/AIDS. Lipodystrophy – a sign for metabolic syndrome in patients of the HIV-HEART study. J Dtsch Dermatol Ges 2010; 8:92-8.

Psoriasis-Leitlinien. https://www.awmf.org/uploads/tx_szleitlinien/013-001l_S3_Therapie-Psoriasis-vulgaris_2021-07.pdf

Ramos H, Pagliari C, Takakura CF, Sotto MN, Duarte MI. Pruritic papular eruption associated with HIV-etiopathogenesis evaluated by clinical, immunohistochemical, and ultrastructural analysis. J Dermatol 2005; 32: 549-56.

Revollo B, Videla S, Llibre JM, et al. Routine screening of anal cytology in HIV-infected subjects and the impact on invasive anal cancer. A prospective cohort study. Clin Infect Dis 2020, 71:390-399.

Rotunda A, Hirsch RJ, Scheinfeld N, et al. Severe cutaneous reactions associated with the use of HIV medications. Acta Derm Venereol 2003; 83:1-9.

Rudikoff D. The relationship between HIV infection and atopic dermatitis. Curr Allergy Asthma Rep 2002; 2:275-81.

Schöfer H. Frühsymptome der HIV-Erkrankung an Haut und Schleimhäuten. AIDS-Forschung (AIFO) 1991; 6: 633-8.

Schoppelrey HP, Breit R. UV-Therapie bei HIV-Patienten. Hautarzt 1999; 50: 643-648

Shear NH, Milpied B, Bruynzeel DP, Phillips EJ. A review of drug patch testing and implications for HIV clinicians. AIDS 2008, 22:999-1007.

Siegel SAR, Winthrop KL. In the Real World: Infections Associated with Biologic and Small Molecule Therapies in Psoriatic Arthritis and Psoriasis. Curr Rheumatol Rep 2019, 21:36.

Silverberg MJ, Leyden W, Warton EM, et al. HIV infection status, immunodeficiency, and the incidence of nonmelanoma skin cancer. J Natl Cancer Inst 2013; 105:350–60.

Singh F, Rudikoff D. HIV-associated pruritus: etiology and management. Am J Clin Dermatol 2003; 4:177-88.

Skabies Leitlinien. http://www.awmf.org/uploads/tx_szleitlinien/013-052k_S1_Skabies-Diagnostik-Therapie_2016-12_01.pdf

Sullivan AK, Raben D, Reekie J, et al. Feasibility and Effectiveness of Indicator Condition Guided Testing for HIV: Results from HIDES I (HIV Indicator Diseases across Europe Study). PLoS One 2013, 8: e52845.

Tan J, Pina A, Borges-Costa J. Skin Diseases in the Era of Highly Active Antiretroviral Therapy: A Retrospective Study of 534 Patients. J Int Assoc Provid AIDS Care 2018; 17: 1-5.

Tarikci N, Kocatürk E, Güngör , et al. Pruritus in Systemic Diseases: A Review of Etiological Factors and New Treatment Modalities. Sci World J 2015: 803752.

Toutous-Trellu L, Abraham S, Pechere M, et al. Topical tacrolimus for effective treatment of eosinophilic folliculitis associated with human immunodeficiency virus infection. Arch Dermatol 2005; 141: 1203-8.

Van der Wouden JC, Menke J, Gajadin S, et al. Interventions for cutaneous molluscum contagiosum. Cochrane Database Syst Rev 2006; CD004767.

Van Leth F, Andrews S, Grinsztejn B, et al. The effect of baseline CD4 cell count and HIV-1 viral load on the efficacy and safety of nevirapine or efavirenz-based first-line HAART. AIDS 2005, 19:463-71.

Van Zander J, Orlow SJ. Efficacy and safety of oral retinoids in psoriasis. Expert Opin Drug Saf 2005; 4: 129-38.

Ward HA, Russo GG, Shrum J. Cutaneous manifestations of antiretroviral therapy. J Am Acad Dermatol 2002; 46:284-93.

Wieland U, Kreuter A. Merkel cell polyomavirus infection and Merkel cell carcinoma in HIV-positive individuals. Curr Opin Oncol 2011, 23: 488–93.

Witkowski JA, Parish LC. Dermatologic manifestations of complementary therapy. Skinmed 2003; 2:175-80.

Wyen C, Esser S, Owen A, et al. Cytochrome P450 2B6 (CYP2B6) and constitutive androstane receptor (CAR) polymorphisms are associated with early discontinuation of efavirenz-containing regimens. J Antimicrob Chemother 2011, 66:2092-8.

Yarchoan R, Uldrick TS. HIV-Associated Cancers and Related Diseases. N Engl J Med 2018, 378:1029-1041.

27. HIV-1-associated neurocognitive disorder (HAND) and HIV-associated myelopathy

CHRISTIAN EGGERS AND THORSTEN ROSENKRANZ

HAND

HIV-1-associated neurocognitive disorder (HAND) is caused by infection of cerebral macrophages and microglial cells with HIV. Neurons are not infected, but functional and structural disturbance of these cells occurs via immunopathological mechanisms. The CNS is a partially independent compartment from the hematolymphatic system concerning viral replication and quasispecies (Eggers 2003). On autopsy, PLWH with advanced HIV infection show aspects of AD pathology, nonspecific histologic changes, and "classic" histopathology (Everall 2009). The HAND classification (Antinori 2007) distinguishes the stages or severities of "asymptomatic neurocognitive impairment (impairment)" (ANI), "mild neurocognitive disorder (disorder)" (MND), and "HIV-associated dementia" (HAD).

Table 1: The categories of HAND ("Frascati criteria", Antinori 2007).

HIV-1-associated asymptomatic neurocognitive impairment (ANI)	Cognitive-psychological testing (age- and education-normed assessment) with deterioration by ≥ 1 standard deviation (SD) in ≥ 2 functional domains (language, attention/working memory, abstraction/executive, verbal memory, processing speed, perceptual/motor) Disorder is not relevant to daily living (e.g., cognitive accuracy, lower work effectiveness, household management, social activities)
HIV-1-associated mild neurocognitive disorder (MND)	Cognitive-psychological testing like ANI At least minor disturbance of activities of daily living, according to self-report or external history
HIV-1-associated dementia (HAD)	Cognitive-psychological testing as ANI, but deterioration by 2 standard deviations. Pronounced disturbance of activities of daily living

With ART, the prevalence of severe cases has decreased significantly, but that of mild cases has increased (Heaton 2010). Worldwide, the prevalence of impaired neurocognition in PLWH was 39%, although this includes asymptomatic cases and is subject to the method to ascertain cognitive impairment (Keng 2023). The prevalence is higher in comorbid and elderly PLWH (Goodkin 2017). After the age of 50, even with suppressed plasma viral load, there is a higher risk of dementia overall, not just HIV-associated forms (Lam 2021). The CDC stage A now carries a higher incidence of mild to moderate neurocognitive impairment. However, the "Frascati"-classification, particularly its concept of "ANI" has received criticism. Due to methodological issues with normative values, it may assign people to pathological states, not often reflective of daily experience (Gisslen 2011, Nightingale 2023). HAND is associated with shortened survival and poorer treatment adherence (Albert 1999, Vivithanaporn 2010). People with stage ANI are at greater risk for conversion to symptomatic HAND (Grant 2014).

In untreated individuals, ART improves cognitive performance and functional connectivity (Zhuang 2017). In treatment-experienced patients, the effect is less clear or debatable. Despite suppressed plasma viremia, chronic progressive and sometimes

fluctuating cognitive impairment is possible (Brew 2004, Antinori 2007, Simioni 2010, Grant 2014). Early initiation of therapy mitigates the incidence of HAND (Crum-Cianflone 2013). Over the years, improvements have become as common as deteriorations or stability in cognitive performance (Sacktor 2016). Neurocognitive impairment relevant to employment also occurs despite good viral suppression and good immune status (Dore 2003).

In untreated infection, CSF and plasma viral load are significant predictors of the development of HAND. However, this is less true when the viral load is suppressed more successfully. Rather, recent cross-sectional and longitudinal studies identified the following risk factors for cognitive impairment: low CD4 T-cell nadir, preexisting severe immunosuppression or AIDS, longer duration of HIV infection, lower educational attainment, older age, obesity, diabetes, and elevated plasma concentrations of TNF-alpha and MCP-1 (Sevigny 2004, Robertson 2007, Tozzi 2007, Bhaskaran 2008, Heaton 2010, Ellis 2011, Mind Exchange Working 2013, Grant 2014, Goodkin 2017, Rubin 2019a). The development and persistence of HAND despite ART may be explainable by chronic immune activation in the CNS (Eden 2007, Lackner 2010, Vera 2016), suggesting a "disconnection" of the brain from the systemic compartment. Intact and replication-competent proviral DNA in the brain parenchyma can still be detected after more than two years of plasma viral suppression in SIV-infected mice and PLWH (Tang 2023). A few months before death, some patients diagnosed with HAND showed no active viral replication in the brain parenchyma postmortem, but strong signs of immune activation and neurodegeneration (Desplats 2013, Gelman 2013). Whether concomitant HCV infection *per se* induces neurocognitive impairment is unclear (Clifford 2015).

A so-called CSF viral escape occurs in about 10% of individuals with well-controlled plasma viral load (Mastrangelo 2019, Pérez-Valero 2019). This is defined by a higher viral load in CSF than in plasma; the plasma virus is often below the detection limit. Clinically, there is usually headache and cognitive or focal neurological signs, but some cases are asymptomatic (Chan 2021). In symptomatic cases MRI most times shows white matter hyperintensities. The CSF is usually moderately inflammatory; the CSF virus may show resistance discordant to plasma.

More recently, a new type of encephalitis with prominent brain infiltration of CD8+ T-lymphocytes was described in PLWH with mostly apparently well-working ART (Lucas 2022). This disease manifests as a sometimes severe and life-threatening disorder with encephalopathic signs up to cerebral coma which can be explained by marked cerebral inflammation and swelling. Pathogenetically, it has been implicated with alterations in the virus-immune system interplay such as ART interruption, immune reconstitution inflammatory syndrome (IRIS) after starting ART, and CSF viral escape. On MRI prominent findings are bilateral, confluent, and symmetrical high signal intensities, localized throughout the white matter. Treatment with corticosteroids has resulted in improvement.

Clinical manifestation

HAND is classified as a subcortical dementia. With the widespread use of ART, the clinical picture has shifted to more cortical signs such as mnestic disturbances (Heaton 2011). Motor and autonomic phenomena have become less common, occurring only at advanced stages.

HAND develops over weeks and months. If it develops more quickly, other causes should be considered. If the affected person is in a reduced general or conscious state due to fever, fatigue, sedation, or an acute illness, the diagnosis may only be made after a repeat examination under improved conditions.

The fact that people complain about cognitive impairment does not mean that they are objectively cognitively impaired. The correlation between subjective complaints and neuropsychologically objectifiable disorders is low (Simioni 2010). In the case of actual disturbances, patients tend to estimate the extent as low, whereas in the case of existing depression, they tend to overestimate their degree of cognitive disturbance (Thames 2011). Symptoms are sometimes more likely to be noticed by relatives than by the affected persons themselves (external history!). Typical complaints include slowing, disturbance of memory and concentration, loss of drive, mild depressive symptoms, and affective flattening. For symptoms and findings, see Tables 2 and 3.

Table 2:. Symptoms of HAND (self-reported and external history).

Cognition	Concentration and memory disorders, slowing down of all mental performances (perception, processing)
Emotional	Loss of energy and initiative, social withdrawal, loss of social competence (dealing with money, contact with authorities), depressiveness, and reduced emotional vibrancy
Motor skills	Slowing down and disturbance of fine motor skills (e.g., typing on a computer keyboard, closing buttons), gait disturbance
Vegetative	Micturition dysfunction (urge incontinence), decreased libido, erectile impotence

Table 3: Findings for HAND.

Psychopathological findings	In early stages, decreased emotional vibrancy, personality flattening, aspontaneity, and distractibility In the advanced stage, additional time grid disturbance, and finally, disorientation to time, place, and situation. In the final stage mutism
Neuropsychological findings	Decrease in memorization (remembering named items, digit span) and mental flexibility (spelling backwards), impaired executive functions (trail-making test), psychomotor slowing (e.g., reciting months backwards)
Neurological findings	Early stage (ANI) is often unremarkable. Middle and late stages (MND, HAD): gait unsteadiness, slowing of rapid alternating movements, hypomimia, sometimes small-stepped gait, and tremor Later increase in muscle reflexes with positive Babinski, slowing of gaze saccades, positive palmomental, grasping, glabellar reflexes, and sphincter disturbance. Occasional accompanying polyneuropathy In the final stage spastic tetraplegia and incontinence

Definite attention disorder, focal or lateralizing signs (e.g., hemiparesis, aphasia), or neck stiffness are not part of the picture, nor are psychotic symptoms without accompanying cognitive-motor disturbance. The coincidence of HAND and psychosis is low. Focal and generalized epileptic seizures are also rare.

Diagnostics

The diagnosis of HAND is based on a synopsis of clinical, neuropsychological, and technical findings and always requires the exclusion of other diseases (Table 3). No technical finding alone proves the diagnosis of HAND.

Clinically, the cognitive disturbance is in the foreground. Psychopathological and, even more so, motor disturbances may be absent or discrete initially but are virtually always present in full-blown dementia (stage HAD) (Table 2). Simple screening tests for cognitive impairment include the HIV Dementia Scale (Morgan 2008, Zipursky 2013) and the somewhat more comprehensive MOCA test, which also works well in Alzheimer's disease (AD) (Overton 2013).

Table 4: Differential diagnoses of (more pronounced) HAND and diagnostic measures.

Disease	Appropriate diagnostic measure (comment)
Primary and degenerative dementias: microangiopathic leukoencephalopathy (cerebral small vessel disease), Alzheimer's disease, Lewy body dementia, frontotemporal dementia, normal pressure hydrocephalus, Parkinson's disease	Medical history (disturbance patterns typical for the disease, family history, arterial hypertension with end organ damage) detailed neurological findings neuropsychological-cognitive profile MRI, PET, etc., with typical findings CSF pressure measurement and probatory drainage of CSF, if necessary CSF with "dementia markers" such as Aß42, tau, phospho-tau, neurofilament light chain
Creutzfeldt-Jakob disease	14-3-3 protein and tau in CSF, EEG, MRI
Depression with pseudodementia	psychiatric examination
Intoxication	Drug level/drug screening
Progressive multifocal leukoencephalopathy (PML), classic form	MRI with single or multiple white sub-stance lesions (without KM enhancement, edema, or space-occupying lesions) CSF: No signs of inflammation, but positive PCR for JC virus (JCV)
PML in the setting of immune reconstitution syndrome (IRIS).	MRI with KM enhancement, edema, and possibly space-occupying lesion. CSF: If necessary, signs of inflammation, PCR detection of JCV DNA
Metabolic encephalopathy and poor general condition	Laboratory (electrolyte, kidney, liver, thyroid, and cortisol if necessary, blood count) Vit B12 deficiency (methylmalonic acid and homocysteine in serum) Hypoxemia? (Blood gas analysis) severe AZ reduction? (bedriddenness in cachexia, fever).
Neurosyphilis	Antibody diagnostics and CSF analysis (pleocytosis ≥ 15/µl) (Typical antibody findings as in florid syphilis may be absent).
Primary CNS lymphoma	CT/MRI/PET or SPECT (uni- or multifocal, mainly ventricular lesions; decreased diffusion in DWI). CSF cytology (immunocytology if necessary) EBV PCR (PCNSL are almost always EBV-induced).
Toxoplasmosis	CT/MRI (uni- or multifocal contrast-enhancing lesions; in DWI, increased diffusion in the abscess core) Antibodies in serum and CSF (seronegativity rare in toxoplasmosis)
CMV encephalitis	CSF with CMV PCR and pp65 antigen in EDTA blood; CMV serology; MRI (subependymal contrast enhancement); ophthalmologist
Cryptococcosis	CSF (opening pressure often elevated, cell count and protein sometimes normal), ink stain, fungal culture, cryptococcus antigen
VZV encephalitis	CSF with VZV PCR and serology in blood

The gold standard, however, is comprehensive neuropsychological testing of at least five cognitive domains (language, attention/working memory, abstraction/executive function, learning/recall, information processing speed, and fine motor skills). As the HIV population ages, the differential diagnosis to age-related forms of dementia, such as Alzheimer's disease, vascular dementia, Lewy body disease, or depressive pseudodementia, becomes increasingly important.

The task of **additional diagnostics** is to exclude differential diagnoses. In stages ANI and MND, routine MRI may show diffuse and relatively symmetric white matter hyperintensities (WML) with ill-defined margins. Still, these do not necessarily correlate with neurocognitive dysfunction (Mina 2021). In the stage of dementia (HAD), these abnormalities are more frequent and more pronounced and are often accompanied by global brain atrophy. These findings may also indicate microangiopathic leukoencephalopathy (small vessel disease, SAE) in elderly and additionally hypertensive individuals (Mina 2021). In contrast to PML, the so-called U-fibers are usually not involved, i.e., the subcortical changes do not extend to the cortical band. Findings of marked asymmetric hyperintensities, multiple infarcts, edema, space-occupying lesions, and contrast enhancement should raise suspicion of conditions other than HAND.

In fully developed HIV dementia (HAD) and stage AIDS (without active CNS disease such as cryptococcosis), the CSF cell count is usually normal to rather low. It may be normal or slightly elevated in stages CDC A and B. In immune reconstitution syndrome or only partially effective ART, it may also be moderately elevated, suggesting an inflammatory character of HAND. Total protein and albumin quotient may be slightly elevated (disturbance of blood-brain-barrier, BBB). Oligoclonal bands and an elevated CSF-to-plasma IgG ratio as an expression of autochthonous IgG production in the CNS are found early after infection in almost all PLWH and are thus not specific for HAND.

In untreated HAND patients, viral load in CSF is elevated compared with non-demented individuals, but this is not true for patients on ART (McArthur 2004). However, using an ultrasensitive assay (detection limit 1 copy/mL), there was a correlation between viral load in CSF and cognitive impairment (Anderson 2021).

In differentiating Alzheimer's dementia and Creutzfeldt-Jacob disease, determining the proteins Aß42, τ (tau), phosphorylated-τ and protein 14-3-3 in the CSF may be useful. Isolated changes in Aß42 (pathologic if levels are *decreased*) have also been found in HAND (Fields 2020).

The electroencephalogram (EEG) is normal, or there is a slight general slowing of the basic rhythm in the sense of a slight general change. Moderate or severe general slowing or clear and continuously occurring focal findings point to other diseases.

In common depressive pseudodementia (Pence 2012), the high level of complaints of cognitive impairment contrasts with objectively nonpathological performance on neuropsychological testing (Thames 2011).

Screening and therapy

Screening for HAND is recommended for all PLWH regardless of immune and treatment status (Mind Exchange Working 2013, www.eacsociety.org/guide-lines). This should be done before ART initiation so that baseline data are available. Depending on risk, screening should be done every 6 to 24 months. Appropriate screening instruments include the HIV Dementia Scale, the MoCA test, and the "NEU screen" instrument (Morgan 2008, Munoz-Moreno 2013, Brouillette 2015). With abnormal results,

the patients should be comprehensively examined neurologically and cognitively. The aim of a causal therapy of HAND is the suppression of viral replication in the CNS. Even though the CNS is an independent compartment of viral replication, ART usually leads to a rapid decrease of viral load in the CSF (Eggers 1999+2003) with clinical improvement within the first 3–9 months (Price 1999, Cysique 2009, Zhuang 2017). However, the clinical effect is highly variable, ranging from massive improvement in therapy-naïve, severely demented individuals to small or equivocal effects, especially in therapy-experienced individuals with minor disturbance. Leukoencephalopathy on MRI may be progressive initially but is usually regressive after one to two years. Certification of permanent inability to work based on mild HAND or suspicion may be premature.

Treatment: In general, the choice of antiviral substances should follow the principles laid out by, e.g., the European AIDS Clinical Society (EACS) (*https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf*; accessed August 2023). With regard to the specific treatment of HAND, it remains unclear which antiretroviral agents are most suitable and in which combination. Reports of inadequate suppression of CSF viral load with monotherapy with a moderately CNS-penetrating PI (Gutmann 2010) provide evidence that penetration into the CSF or parenchyma plays a role. Letendre and colleagues introduced a "CNS penetration score" (CPE), which has since been modified several times, with the fourth category (the highest, and thus best for CSF penetration) including the following agents: AZT, nevirapine, indinavir/r, dolutegravir. In category 3 are: Abacavir, FTC, etravirine, efavirenz, darunavir/r, fosamprenavir/r, lopinavir/r, maraviroc, and raltegravir (Letendre 2011). Most studies showed a better effect of ART with higher CPE scores on suppression of CSF viral load (Letendre 2008, Cysique 2011, Cusini 2013). Regarding neurocognition, some found improvement; fewer found no effect (Letendre 2023). These inconsistent results are likely due to methodological differences. Human CSF penetration, for instance, was exclusively examined using lumbar CSF. Ventricular CSF, however, is much different from lumbar CSF and harbors much higher concentrations of some antivirals, as shown for AZT and 3TC (Eggers 2020).

The importance of viral suppression in the CNS is supported by the phenomenon of CSF viral escape, which occurs in roughly one-tenth of PLWH with well-suppressed plasma virus (see above). Risk factors identified so far are longer ART duration, lower nadir CD4 T-cell count, PI-containing ART (particularly atazanavir), and a combination of the CPE score with resistance mutations (Mukerji 2018, Trunfio 2023). Most cases improved clinically and virologically after switching to resistance-adapted ART with a higher CPE score (Mastrangelo 2019).

One paper suggested a preventive effect of early ART initiation (Ellis 2011). In several cross-sectional studies, virologically stable and completely suppressed PLWH performed worse than comparable HIV-negative individuals regarding cognition and brain volume (Sanford 2018). In contrast, longitudinal studies with observation over a few years yielded inconsistent results. Some found more rapid cognitive decline despite viral load suppression (Gott 2017), whereas others found the same trajectory of cognitive performance as in HIV-negative controls (Sanford 2018). One explanation could be that fresh or early untreated HIV infection sets irreversible structural damage that effectively sets the individual back functionally, the so-called legacy effect.

In a recent prospective study, 191 PLWH with cognitive impairment despite suppressed plasma viral load were randomized to add dolutegravir, dolutegravir plus maraviroc, or placebo to their ART. Cognitive performance and depression scores improved in all three arms without significant difference, thus not supporting the idea of intensified ART in viral suppression without evidence of "CSF viral escape"

(Letendre 2022). A small randomized trial of the antidepressant paroxetine found evidence for improved cognition (Sacktor 2018). Other (non-antiviral) therapies targeting the modulation of cerebral inflammation, neurotransmission, and structural neuronal integrity have been without clinically relevant effects (Sacktor 2011, Simioni 2013).

As in general neurology, complaints of cognitive deficits are not infrequently an expression of depression ("pseudodementia"), which is why this should always be considered in the differential diagnosis. On the other hand, depression can also be associated with a genuine and objectified cognitive disorder, especially in women (Rubin 2019b). Therefore, the diagnosis of depression does not absolve the physician from the need for HAND diagnostics.

Not to be neglected is the treatment of concomitant diseases such as hepatitis and drug abuse, vascular risk factors, and adherence improvement (Mind Exchange Working 2013). Neurotoxicity of antiretroviral agents must also be considered in the presence of neurological, cognitive, and psychiatric complaints, and this is best documented for efavirenz (Hakkers 2019). There have been reports of toxic effects of otherwise suppressive ART, although some have questioned this (Munoz-Moreno 2010, Grund 2013). In suspected cases, modification of ART can be considered. Therapy interruptions are not recommended (Mind Exchange Working 2013).

HIV myelopathy

Epidemiology and pathology

HIV myelopathy (HIVM) is very rare with ART. Because it can occur without the neuropsychological disturbances of HAD, it is considered a separate clinical entity. The histomorphologic correlate is the spinal cord's vacuolization with the lateral cords' accentuation and lipid-laden macrophages' appearance (Petito 1985). The histopathology resembles that seen in funicular myelosis associated with vitamin B12 deficiency. Because the detection of viral products in the lesions is not always successful, the relevance of HIV infection of the spinal cord to HIVM is not certain. Pathogenetically, a disturbance of cobalamin-dependent transmethylation is discussed. HIVM occurs in the late stages of HIV. Only some of the affected patients with autoptic findings of HIVM have a corresponding clinical symptomatology (Dal Pan 1994).

Clinic and diagnostics

The diagnosis is based on the clinical evidence of spastic syndrome most pronounced in the legs with spastic-ataxic gait, hyperreflexia, and positive Babinski, disturbance of sphincter control, potential erectile dysfunction, as well as minor glove- and sock-shaped sensory disturbances. An independent HIVM can only be diagnosed if a possible concurrent dementia disorder is secondary to the myelopathic one. Exclusion of differential diagnoses is crucial (Table 5).

Therapy

HIVM can improve significantly even with ART (Oksenhendler 1990). A controlled study on L-methionine showed an electrophysiological but no clinical improvement.

Table 5: Differential diagnoses of HIV myelopathy and diagnostic measures.

Disease	Appropriate diagnostic measure (comment)
Mechanical myelon compression (cervical myelopathy, disc prolapse)	Degenerative cervical spine changes MRI evidence of depleted CSF space and hyperintensities in the medulla
Neurosyphilis	Antibody and CSF diagnostics (pleocytosis) – typical antibody findings, as in florid syphilis, may be lacking
CMV myelopathy	CSF (inflammatory signs), PCR for CMV in CSF Antibodies in serum and CSF (possibly elevated IgG, antibody index)
Toxoplasmosis	Contrast-enhancing focus on MRI
VZV myelitis	CSF (clear signs of inflammation) Antibodies in serum and CSF, PCR for VZV in CSF Usually preceding or accompanying cutaneous zoster manifestations and concomitant radiculitis.
HSV-1 myelitis	CSF (inflammation may be absent), PCR for HSV
HTLV-1 (Tropical Spastic Paraparesis)	Travel history (Caribbean, West Africa, and East Asia), mostly chronic evolution, sphincter disturbance, inflammatory CSF, antibodies against HTLV-1
Funicular myelosis	Vitamin B12 level, macrocytosis
Hereditary diseases (familial spastic spinal paralysis, adrenoleukodystrophy, Friedreich's ataxia, etc.)	Appropriate examinations of general neurology

Literature

Albert S, Weber C, Todak G, et al. An Observed Performance Test of Medication Management Ability in HIV: Relation to Neuropsychological Status and Medication Adherence Outcomes. AIDS and Behavior 1999;3:121-128.

Anderson AM, Tang B, Vaida F, et al. Low-Level HIV RNA in Cerebrospinal Fluid and Neurocognitive Performance: A Longitudinal Cohort Study. J Acquir Immune Defic Syndr 2021; 87:1196.

Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology 2007;69:1789-1799.

Bhaskaran K, Mussini C, Antinori A, et al. Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy. Annals of Neurology 2008; 63:213-221.

Brew B. Evidence for a change in AIDS dementia complex in the era of highly active antiretroviral therapy and the possibility of new forms of AIDS dementia complex. AIDS 2004;18 Suppl 1:S75-78.

Brouillette MJ, Mayo N, Fellows LK, et al. A better screening tool for HIV-associated neurocognitive disorders: Is it what clinicians need? AIDS 2015; 29:895-902.

Chan TYH, De Zan V, Gregg A et al. The symptomatology of cerebrospinal fluid HIV RNA escape: a large case-series. AIDS 2021;35:2341.

Clifford DB, Vaida F, Kao YT, et al. Absence of neurocognitive effect of hepatitis C infection in HIV-coinfected people. Neurology 2015; 84:241-250.

Crum-Cianflone NF, Moore DJ, Letendre S, et al. Low prevalence of neurocognitive impairment in early diagnosed and managed HIV-infected persons. Neurology 2013;80:371-379.

Cusini A, Vernazza PL, Yerly S, et al. Higher CNS penetration-effectiveness of long-term combination antiretroviral therapy is associated with better HIV-1 viral suppression in cerebrospinal fluid. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 2013;62:28-35.

Cysique LA, Bain MP, Brew BJ, et al. The burden of HIV-associated neurocognitive impairment in Australia and its estimates for the future. Sexual Health 2011;8:541-550.

Cysique LA, Vaida F, Letendre S, et al. Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy. Neurology 2009;73:342-348.

Dal Pan GJ, Glass JD, McArthur JC. Clinicopathologic correlations of HIV-1-associated vacuolar myelopathy: an autopsy-based case-control study. Neurology 1994; 44:2159-2164.

Desplats P, Dumaop W, Smith D, et al. Molecular and pathologic insights from latent HIV-1 infection in the human brain. Neurology 2013;80:1415-1423.

Dore GJ, McDonald A, Li Y, et al. Marked improvement in survival following AIDS dementia complex in the era of HAART. AIDS 2003;17:1539-1545.

Eden A, Price RW, Spudich S, et al. Immune activation of the central nervous system is still present after >4 years of effective highly active antiretroviral therapy. J Infect Dis 2007, 196:1779-1783.

Eggers C, Hertogs K, Stuerenburg HJ, et al. Delayed CNS virus suppression during HAART is associated with HIV encephalopathy, but not with viral drug resistance or poor CNS drug penetration. AIDS 2003, 17:1897-1906.

Eggers C, van Lunzen J, Buhk T, et al. HIV infection of the central nervous system is characterized by rapid turnover of viral RNA in cerebrospinal fluid. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 1999, 20:259-264.

Eggers C, Hoetelmans R and Läer S. Zidovudine and lamivudine reach higher concentrations in ventricular than in lumbar human cerebrospinal fluid. AIDS 2020:34:1883.

Ellis RJ, Badiee J, Vaida F, et al. CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. AIDS 2011, 25:1747-1751.

Everall I, Vaida F, Khanlou N, et al. Cliniconeuropathologic correlates of human immunodeficiency virus in the era of antiretroviral therapy. J Neurovirol 2009, 15:360-370.

Fields JA, Swintona MK, Soontornniyomkij B, et al. Beta amyloid levels in cerebrospinal fluid of HIV-infected people vary by exposure to antiretroviral therapy. AIDS 2020;34:1001.

Gelman BB, Lisinicchia JG, Morgello S, et al. Neurovirological correlation with HIV-associated neurocognitive disorders and encephalitis in a HAART-era cohort. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 2013, 62:487-495.

Gisslén M, Price RW, Nilsson S, et al. The definition of HIV-associated neurocognitive disorders: Are we overestimating the real prevalence? BMC Infect Dis 2011;11:356.

Goodkin K, Miller EN, Cox C, et al. Effect of ageing on neurocognitive function by stage of HIV infection: evidence from the Multicenter AIDS Cohort Study. Lancet HIV 2017, 4:e411-22.

Gott C, Gates T, Dermody N, et al. Cognitive change trajectories in virally suppressed HIV-infected individuals indicate high prevalence of disease activity. PLoS One 2017; 12.

Grant I, Franklin DR, Deutsch R, et al. Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. Neurology 2014, 82:2055-62.

Grund B, Wright EJ, Brew BJ, et al. Improved neurocognitive test performance in both arms of the SMART study: impact of practice effect. J Neurovirol 2013, 19:383-392.

Gutmann C, Cusini A, Günthard HF, et al. Randomized controlled study demonstrating failure of LPV/r monotherapy in HIV: the role of compartment and CD4-nadir. AIDS 2010, 24:2347.

Hakkers CS, Arends JE, van den Berk GE, et al. Objective and subjective Improvement of Cognition after discontinuing Efavirenz in asymptomatic patients – a randomized controlled trial. JAIDS 2019, 80:e14.

Heaton RK, Clifford DB, Franklin DR Jr, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 2010, 75:2087-2096.

Heaton RK, Franklin DR, Ellis RJ, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. Journal of Neurovirology 2011, 17:3-16.

Heaton RK, Franklin DR Jr, Deutsch R, et al. Neurocognitive change in the era of HIV combination antiretroviral therapy: the longitudinal CHARTER study. Clin Infect Dis 2015, 60:473-480.

Keng L, Winston A and Sabin CA. The global burden of cognitive impairment in people with HIV. AIDS 2023, 37:61.

Lackner P, Kuenz B, Reindl M, et al. Antibodies to myelin oligodendrocyte glycoprotein in HIV-1 associated neurocognitive disorder: a cross-sectional cohort study. Journal of Neuroinflammation 2010, 7:79.

Lam JO, Hou CE, Hojilla JC, et al. Comparison of dementia risk after age 50 between individuals with and without HIV infection. AIDS 2021, 35:821.

Letendre S. Central nervous system complications in HIV disease: HIV-associated neurocognitive disorder. Top Antivir Med 2011, 19:137-142.

Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-effectiveness rank for quantifying antiretroviral penetration into the CNS. Archives of Neurology 2008, 65:65-70.

Letendre SL, Roa J, Chen H, et al. ACTG A5324: A Randomized Trial of ART Intensification for Cognitive Impairment in PWH. Abstract 133, CROI 2022.

Lucas S, Wong KT, Nightingale S et al. HIV-Associated CD8 Encephalitis: A UK Case Series and Review of Histopathologically Confirmed Cases. Front Neurol 2021;12:628296.

Mastrangelo A, Turrini F, de Zan V, et al. Symptomatic cerebrospinal fluid escape. AIDS 2019;33 (Suppl 2):159.

Mc Arthur JC, Mc Dermott MP, Mc Clernon D, et al. Attenuated CNS Infection in Advanced HIV/AIDS With Combination Antiretroviral Therapy. Archives of Neurology 2004, 61:1687-1696.

Mina Y, Wu TX, Hsieh HC, et al. Association of White Matter Hyperintensities With HIV Status and Vascular Risk Factors. Neurology 2021;96:e1823 PMID 33637630.

Mind Exchange Working G, A, Arendt G, Grant I, et al. Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. Clin Infect Dis 2013, 56:1004-1017.

Morgan EE, Woods SP, Scott JC, et al. Predictive Validity of Demographically Adjusted Normative Standards for the HIV Dementia Scale. J Clin Exp Neuropsychol 2008, 30:83-90.

Mukerji SS, Misra V, Lorenz DR et al. Impact of Antiretroviral Regimens on CSF Viral Escape in a Prospective Multicohort Study of Antiretroviral Therapy-Experienced HIV-1–Infected Adults in the US. Clinical Infectious Diseases 2018;67:1182.

Munoz-Moreno JA, Fumaz CR, Prats A, et al. Interruptions of Antiretroviral Therapy in HIV-Infection: Are they Detrimental to Neurocognitive Functioning? Journal of Neurovirology 2010; 16:208-218.

Munoz-Moreno JA, Prats A, Perez-Alvarez N, et al. A brief and feasible paper-based method to screen for neurocognitive impairment in HIV-infected patients: the NEU screen. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 2013, 63:585-592.

Nightingale S, Ances B, Cinque P, et al. Cognitive impairment in people living with HIV: consensus recommendations for a new approach. Nature Reviews Neurology 2023.

Oksenhendler E, Ferchal F, Cadranel J, et al. Zidovudine for HIV-related myelopathy [letter]. American Journal of Medicine 1990, 88:65N-66N.

Overton ET, Azad TD, Parker N, et al. The Alzheimer's disease-8 and Montreal Cognitive Assessment as screening tools for neurocognitive impairment in HIV-infected persons. J Neurovirol 2013, 19:109-116.

Pence BW, O'Donnell JK, Gaynes BN. Falling through the cracks: the gaps between depression prevalence, diagnosis, treatment, and response in HIV care. AIDS 2012, 26:656-658.

Pérez-Valero I, Ellis R, Heaton R, et al. CSF viral escape in aviremic HIV-infected patients receiving ART. AIDS 2019; 33 475

Petito CK, Navia BA, Cho ES, et al. Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome. New England Journal of Medicine 1985, 312:874-849.

Price RW, Yiannoutsos CT, Clifford DB, et al. Neurological outcomes in late HIV infection: adverse impact of neurological impairment on survival and protective effect of antiviral therapy. AIDS Clinical Trial Group and Neurological AIDS Research Consortium study team. AIDS 1999, 13:1677-1685.

Robertson KR, Smurzynski M, Parsons TD, et al. The prevalence and incidence of neurocognitive impairment in the HAART era. AIDS 2007, 21:1915-1921.

Rubin LH, Gustafson D, Hawkins KL, et al. Midlife adiposity predicts cognitive decline in the prospective Multicenter AIDS Cohort Study. Neurology 2019;93:e261

Rubin LH, Springer G, Martin EM, et al. Elevated Depressive Symptoms are a Stronger Predictor of Executive Dysfunction in HIV-Infected Women than in Men. JAIDS 2019, 81:274.

Sacktor N, Miyahara S, Deng L, et al. Minocycline Treatment for HIV-associated Cognitive Impairment: Results from a Randomized Trial. Neurology 2011, 77:1135-1142.

Sacktor N, Skolasky RL, Seaberg E, et al. Prevalence of HIV-associated neurocognitive disorders in the Multicenter AIDS Cohort Study. Neurology 2016, 86:334-340.

Sacktor N, Skolasky RL, Moxley R, et al. Paroxetine and fluconazole therapy for HIV-associated neurocognitive impairment: results from a double-blind, placebo-controlled trial. J Neurovirol 2018;24:16.

Sanford R, Fellows LK, Ances BM, et al. Association of Brain Structure Changes and Cognitive Function with cART in HIV-Positive Individuals. JAMA Neurology 2018; 75:72-79.

Sevigny JJ, Albert SM, McDermott MP, et al. Evaluation of HIV RNA and markers of immune activation as predictors of HIV-associated dementia. Neurology 2004, 63:2084-2090.

Simioni S, Cavassini M, Annoni JM, et al. Rivastigmine for HIV-associated neurocognitive disorders: a randomized crossover pilot study. Neurology 2013;80:553-560.

Simioni S, Cavassini M, Annoni JM, et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. AIDS 2010;24:1243-1250.

Tang Y, Chaillon A, Gianella S et al. Brain microglia serve as a persistent HIV reservoir despite durable antiretroviral therapy. J Clin Invest 2023;133(12):e167417.

Thames AD, Becker BW, Marcotte TD, et al. Depression, cognition, and self-appraisal of functional abilities in HIV: an examination of subjective appraisal versus objective performance. Clin Neuropsychol 2011;25:224-243.

Tozzi V, Balestra P, Bellagamba R, et al. Persistence of neuropsychologic deficits despite long-term highly active antiretroviral therapy in patients with HIV-related neurocognitive impairment: prevalence and risk factors. J AIDS and Human Retrovirology 2007, 45:174-182.

Trunfio M, Pinnetti C, Stefania A et al. The presence of resistance associated mutations in reverse transcriptase gene is associated with CSF HIV 1 escape: A multicentric retrospective analysis. J Med Virol. 2023;95:e28704.

Vera JH, Guo Q, Cole JH, et al. Neuroinflammation in treated HIV-positive individuals: A TSPO PET study. Neurology 2016, 86:1425-1432.

Vivithanaporn P, Heo G, Gamble J, et al. Neurologic disease burden in treated HIV/AIDS predicts survival: a population-based study. Neurology 2010, 75:1150-1158.

Zhuang Y, Qiu X, Wang L, et al. Combination antiretroviral therapy improves cognitive performance and functional connectivity in treatment-naive HIV-infected individuals. J Neurovirol 2017, 23:704-712.

Zipursky AR, Gogolishvili D, Rueda S, et al. Evaluation of brief screening tools for neurocognitive impairment in HIV/AIDS: a systematic review of the literature. AIDS 2013, 27:2385-2401.

28. Neuromuscular diseases

THORSTEN ROSENKRANZ AND CHRISTIAN EGGERS

Polyneuropathies and polyradiculitis

Peripheral nerve disorders are the most common neurological complication of HIV infection. They affect approximately 30–50% of patients in the era of modern antiretroviral therapies (Kaku 2014). At the same time, primary HIV-associated neuropathies have taken a back seat to drug-toxicity-related neuropathies (Gonzalez-Duarte 2008).

Clinic

Acute inflammatory demyelinating polyneuroradiculitis (AIDP, acute Guillain-Barré syndrome, acute GBS)

AIDP characteristically occurs during seroconversion and early stages of HIV infection, rarely in the context of an immune reconstitution syndrome. Within days to a maximum of four weeks, symmetric paresis of the legs and arms typically develops, often ascending distally, and may lead to respiratory insufficiency and dysphagia if the trunk muscles and cranial nerves are affected. Sensory disturbances often present initially as irritant symptoms in the form of pain and paresthesias; sensory deficits are usually not clinically leading. When autonomic fibers are involved, life-threatening cardiac arrhythmias or blood pressure derangements are possible. Muscle reflexes are extinguished.

The CSF examination typically reveals a disturbance of the blood CSF barrier with markedly elevated total protein and, at most, mild pleocytosis of a maximum of 50 cells/µl. With and without treatment, the disease enters a plateau phase lasting several weeks, followed by a gradual remission. This can last a few weeks to two years, and disability remains in about 30% of cases.

Chronic inflammatory demyelinating polyneuroradiculitis (CIDP, chronic Guillain-Barré syndrome)

In contrast to AIDP, CIDP is a chronic progressive or relapsing disease. Paresis and sensory disturbances often develop over many months. Areflexia also usually occurs. In addition to steadily progressive courses, there are also those characterized by relapses, partial remissions, and stable phases of varying length. In contrast to HIV-negative persons, the protein elevation in the CSF is not always accompanied by a normocytosis but often by a moderate pleocytosis of up to 50 cells/µl. CIDP occurs preferentially in the early stages of infection.

Neuropathy in vasculitis

Rarely, necrotizing vasculitis occurs in the course of HIV infection. In the course, involvement of other organs such as kidneys, heart, or skeletal muscles is possible, determining the prognosis. Sometimes, there is an association of vasculitis with cryoglobulinemia and hepatitis C.

Neuropathy in diffuse infiltrative lymphocytosis syndrome (DILS)

In DILS, a rare clinical picture similar to Sjögren's syndrome, a mostly distal-symmetric PNP may occur in addition to a sicca syndrome (Ghrenassia 2015). In addition to the sicca syndrome, a pronounced infiltration by CD8 T-cells also leads to pneumonitis, lymphadenitis, gastritis, nephritis, or splenomegaly (see *Rheumatic Diseases*).

Table 1: Forms of polyneuropathy and polyradiculitis in HIV infection.

Form	HIV infection	Clinic	Special findings
Primary HIV-associated polyneuropathies			
Acute inflammatory demyelinating polyneuroradiculitis (acute Guillain-Barré syndrome, GBS).	Seroconversion, asymptomatic, without or with incipient immunodeficiency.	Symmetrical paresis > sensory disturbances, mostly areflexia	Demyelination in ENG, marked disruption of the blood-liquor barrier, and moderate CSF pleocytosis (up to 50 cells/µl)
Chronic inflammatory demyelinating polyneuroradiculitis (CIDP, chronic GBS)	Asymptomatic, possibly with incipient immunodeficiency, rarely AIDS	Distal and proximal paresis > Sensory disturbances, often areflexia in progression	Demyelination in ENG, marked disruption of the blood-liquor barrier, and moderate CSF pleocytosis (up to 50 cells/µl)
Neuropathy in vasculitis	Asymptomatic with or without incipient immunodeficiency, rarely AIDS	Mostly multiple, asymmetric deficits of single nerves, rarely distal symmetric sensorimotor deficits	Elevation of ANA, circulating immune complexes, cryoglobulinemia, often concomitant hepatitis C infection; vasculitis in nerve biopsy, also in muscle, kidney, and other organs
Neuropathy in diffuse infiltrative lymphocytosis syndrome (DILS)	Incipient immunodeficiency	Mostly distal-symmetric, rarely multifocal sensorimotor deficits	Sjögren's syndrome-like clinical picture, CD8 lymphocytes > 1200/µl.
Distal symmetric, predominantly sensory, axonal polyneuropathy	Usually prolonged infection, high viral load	Distal symmetrical, predominantly sensory disorders of the legs, often painful	Axonal changes of preferentially sensitive leg nerves in electroneurography
Secondary polyneuropathies			
Drug toxic polyneuropathy	Incipient or advanced immunodeficiency	Distal symmetrical, predominantly sensory disorders of the legs, often painful	Under therapy with d4T, ddI, ddC, dapsone, vincristine
Acute neuromuscular weakness syndrome	Incipient or advanced immunodeficiency	Rapidly progressive tetraparesis, usually only minor sensory disturbances.	Lactic acidosis usually occurs with NRTI therapy, mostly axonal lesions, possibly additional myopathy
Mononeuritis multiplex with CMV infection or lymphoma	AIDS	Asymmetric sensorimotor deficits	CMV infection of other organs, CMV DNA in plasma, history of lymphoma
Polyradiculitis in infection with CMV, *M. tuberculosis,* or in meningeosis lymphomatosa	AIDS	Flaccid paraparesis of the legs, sensibility and bladder disorders	CMV infection of other organs (CMV DNA!), acid-fast rods or lymphoma cells in CSF

Distal symmetric sensory polyneuropathy (DSSP)

DSSP is by far the most common form of HIV-associated neuropathy. Predictors include low CD4 nadir and persistent HIV replication (Octaviana 2018). For the clinic, see Table 2. Other HIV-independent risk factors include older age, drug use, HTLV-1 coinfection, diabetes mellitus, statin use, and hypertriglyceridemia (Banerjee 2011, Robinson-Papp 2012, Silva 2012).

Table 2: Clinical features of HIV-associated distal symmetric sensory polyneuropathy.

Numbness, pain, dys- and paraesthesia in the feet and lower legs
Decreased or absent Achilles' tendon reflex
Decreased or absent vibratory senses of the toes and ankles
No or only minor motor dysfunction
No or only minimal involvement of hands and arms
Slowly progressive course
In EMG/ENG, signs of axonal damage to predominantly sensory leg nerves
Vegetative disorders: orthostatic dysregulation, erectile dysfunction, trophic disorders of the skin

Drug toxic polyneuropathy

The nucleoside analogs ddI and d4T (formerly also ddC) cause distal symmetric, sensory, and axonal polyneuropathy in 10–30% of cases, which cannot be distinguished from HIV-associated DSSP either clinically or electroneurographically. Since these agents have been discontinued, the incidence of drug-induced polyneuropathies in people with HIV has decreased significantly. PNP is a possible side effect in the labeling information for many new antiretroviral drugs because it occurred more frequently in the verum groups of pivotal trials than in the control groups. Based on clinical experience, the risk of PNP from therapy with NNRTIs, PIs, or integrase inhibitors appears to be very low. Isolated cases of demyelinating neuropathy have been described with darunavir, although the causal relationship has remained questionable (Lorber 2013). A recent African study described the occurrence of sensitive PNP in 11% of 120 ART-naïve patients without neuropathy six months after starting tenofovir-containing treatment (Pillay 2019).

Table 3: Major neurotoxic drugs in HIV medicine.

Virustatics	ddI, d4T, ddC (now off the market)
Antibiotics	Dapsone, metronidazole, isoniazid
Cytostatics	Vincristine, etoposide, vincristine

Acute neuromuscular weakness syndrome associated with lactic acidosis

In the context of lactic acidosis, usually induced by NRTI, a rapidly progressive life-threatening tetraparesis can occur, which mimics the picture of AIDP. In most cases, axonal nerve damage is the underlying cause, although demyelinating changes have also been detected in isolated cases. In a small proportion of cases, a muscle biopsy also revealed findings of myositis or mitochondrial myopathy (Simpson 2004).

Amyotrophic lateral sclerosis

Motor neuron disease occurs with an incidence of 3.5/100,000 in PLWH, compared to 1–2/100,000 in the general population (Bogoch 2015). The disease is similar to that in HIV-negative patients, but the age of onset is younger, and the course is even more rapid. In individual cases, ART has been described to halt and improve the disease (Bowen 2016).

Polyneuropathies and -radiculitis in other diseases

PNP of the mononeuritis multiplex type, as occurs in the context of vasculitis (see above), may rarely also be caused by CMV infection or by non-Hodgkin's lymphoma. Acute or sub-acute polyradiculitis predominantly of the cauda equina with rapidly progressive flaccid proximal and distal paresis of the legs and bladder-, defecation- and sensory disturbances may occur with opportunistic infections (CMV, tuberculosis) or in the setting of meningeosis lymphomatosa. Other causes include alcohol abuse, diabetes mellitus, malnutrition in prolonged gastrointestinal disorders, consumptive diseases, or cachexia.

Diagnostics

In most cases, disease history and clinical findings allow the assignment to one of the above-listed PNP forms. The additional diagnostic procedures primarily serve to confirm the presence of a PNP and to differentiate it from a myelopathy, for example. Only if the stage of HIV infection does not match the recognized form of polyneuropathy – e.g., painful DSSP with good immune status, low viral load, and without neurotoxic medication – are invasive measures indicated, up to and including nerve biopsy. For practical purposes, the procedures described in Table 4 have proven useful.

Table 4: Diagnostics of polyneuropathies and polyradiculitis.

Investigation	Findings	Suspected diagnosis
Generally recommended examinations for suspected polyneuropathy		
Medical history	Medication	Drug toxic PNP
	Opportunistic diseases	Neuropathy or radiculitis in CMV, lymphoma, etc.
	Alcohol consumption	Ethyltoxic polyneuropathy
Neurological examination	Detection of PNP syndrome	e.g., no myo- or myelopathy
Electromyography	Neuropathy safeguarding	e.g., no myo- or myelopathy
Electroneurography	Demyelination	AIDP, CIDP
	Axonal neuropathy	DSSP, multiplex neuropathy, DILS
Blood tests	HbA1c, glucose profile	Diabetic polyneuropathy
	Vit B12, B1, B6, iron, ferritin	Neuropathy in malnutrition, malassimilation
	ANA, cryoglobulins, HCV serology, circulating immune complexes, ANCA	Neuropathy in vasculitides
	Treponema serology	Neurosyphilis
	CD8 T-cells > 1,200/µl	Neuropathy in diffuse infiltrative lymphocytosis
	Lactate	NRTI neuropathy
	CMV DNA (only if CD4 cells < 100/µl)	Multiplex neuropathy, radiculitis in CMV infection

Table 4: Continuation

Investigation	Findings	Suspected diagnosis
Necessary additional examinations only for specific suspected clinical diagnoses		
CSF	Blood Liquor Barrier Disorder	AIDP, CIDP
	Granulocytic pleocytosis, CMV DNA	CMV polyradiculitis
	Malignant cells, EBV DNA	Meningeosis lymphomatosa
	Mixed-cell pleocytosis, acid-fast rods, mycobacterial DNA	Tuberculous polyradiculitis
Vegetative function tests (e.g., Schellong, sympathetic skin response, heart rate variance)	Involvement of sympathetic and/or parasympathetic nerves in neuropathy	Concomitant autonomic neuropathy with, e.g., orthostatic dysregulation, erectile dysfunction
MRI of the lumbar spine	Spatial growth in the cauda equina	Spinal lymphoma Spinal toxoplasmosis
Nerve and muscle biopsy	Necrotizing vasculitis	Neuropathy in vasculitis
	Perivascular infiltration of CD8+ lymphocytes without vascular necrosis	Neuropathy in diffuse infiltrative lymphocytosis

Occasionally, affected persons complain of considerable pain and paresthesia, suggesting polyneuropathy without clinically pathological findings. In these cases, there is usually isolated damage to the small, unmyelinated nerve fibers (small fiber neuropathy). This small fiber neuropathy cannot be detected in normal electroneurographic examinations. The diagnosis is usually made with a skin biopsy demonstrating the reduction of intradermal nerve fibers. Additionally, measuring the pain-related evoked potentials can be useful (Obermann 2007).

Treatment

For therapy, see Table 5. CIDP responds significantly better to corticosteroids in PLWH than in HIV-negative patients. In DSSP, no causal treatment is known; in some cases, neuropathic symptoms improve with effective ART. Treatment is usually limited to symptomatic measures such as pain therapy. The approach is similar to painful polyneuropathies in patients without HIV (Finnerup 2015). The drugs listed in Table 6 have a low interaction potential with ART. Lamotrigine is effective in a larger controlled trial in DSSP on continued neurotoxic ART (Simpson 2003). Dosing up slowly and reducing or discontinuing early if skin reactions occur is crucial.

The tricyclic antidepressants amitriptyline and nortriptyline have marked anticholinergic effects. Therefore, the higher dose necessary for a sufficient analgesic effect is often not reached. Lower doses are ineffective in DSSP (Dinat 2015). Because of its severe interferences with other drugs, including ART, carbamazepine, widely used in neuropathy pain management, must be avoided.

Local treatment with a highly concentrated (8%) capsaicin patch is also effective for DSSP in PLWH; it is approved for this group (Thomas 2020). Smoking cannabis was effective for neurotoxic PNP symptoms in two controlled trials, but only for a short period (Abrams 2007, Ellis 2009). Following the release of cannabis flowers for

medical use, they are increasingly prescribed to PLWH with painful neuropathies as an extract from flowers or via a vaporizer. However, there is insufficient data to evaluate the benefits and risks of long-term, regular use.

Table 5: Causal treatment of polyneuropathies and polyradiculitis.

Polyneuropathy diagnosis	**Treatment (bw = body weight)**
AIDP (acute Guillain-Barré syndrome)	Immunoglobulins IV 0.4 g/kg bw daily for 5 days *Alternative:* Plasmapheresis (5 x in 7–10 days)
CIDP (chronic Guillain-Barré syndrome)	Immunoglobulins IV 0,4 g/kg bw daily for 5 days Plasmapheresis (5 x in 7–10 days) Prednisone 1–1.5 mg/kg bw daily for 3–4 weeks orally or IV, then decreasing doses over 12–16 weeks until below Cushing's threshold All three methods are equivalent in terms of effectiveness.
Neuropathy in vasculitis	Prednisone 1–1.5 mg/kg bw daily for 3–4 weeks orally or IV, then decreasing the dose over 12–16 weeks until below Cushing's threshold
Neuropathy in diffuse infiltrative lymphocytosis syndrome (DILS)	Start or optimize ART plus prednisone 1–1.5 mg/kg bw daily for 3–4 weeks, then decrease doses over 12–16 weeks until below Cushing's threshold
Distal symmetric, predominantly sensory, axonal polyneuropathy	No causal therapy is known; improvement with ART in some cases For symptomatic therapy, *see Table 6*
Drug toxic polyneuropathy	If possible, discontinue or change the use of neurotoxic drugs Recovery is somewhat delayed
Mononeuritis multiplex or polyradiculitis in CMV infection	Foscarnet IV 2 x 90 mg/kg bw daily in **combination with** ganciclovir IV 2 x 5 mg/kg bw daily
Polyradiculitis in meningeosis lymphomatosa	Initiation or optimization of ART **plus** methotrexate intraventricularly via meningeosis lymphomatosa or lumbar intrathecally 12–15 mg 2x/week until CSF is sanitized, then 1x/week for 4 weeks, then 1x/month **plus** 15 mg each of folinic acid orally with each injection **plus** systemic therapy for lymphoma (see chapter *Malignant Lymphoma*)
Polyradiculitis in infection with *M. tuberculosis*	4-fold tuberculostatic therapy *(see Opportunistic Infections/Tuberculosis Treatments)*

Table 6: Symptomatic therapy of painful polyneuropathies.

	Therapy	Side effect
1st stage:	Physical therapy (alternating baths, etc.), general measures (wide shoes), Lidocaine gel 5% or patch	Rarely allergy
2nd stage:	Trial with 3–4 x 1,000 mg paracetamol or 2–3 x 50 mg diclofenac or 4 x 40 trp. Novaminsulfone limited over 10–14 days	Nausea, vomiting, allergy (rare)
	or 8% capsaicin patch	Temporary skin redness or irritation
3rd stage:	Gabapentin 300 mg at night, increase by 300 mg every 3 days to a maximum of 3 x 1200 mg	Sleepiness, fatigue, nausea, dizziness, rarely pancreatitis
	or	
	Pregabalin 2 x 75 mg, increase to 2 x 150 mg after 1 week, further increase to 2 x 300 mg possible after another week	Nausea, vomiting, diarrhea, allergic exanthema
	or	
	Lamotrigine 25 mg in the evening, increase by 25 mg every 14 days to a maximum of 2 x 200–300 mg daily	Allergic exanthema, cephalgia, nausea
	or	
	Amitriptyline 25 mg at night, increase by 10–25 mg every 2–3 days until 3 x 50 mg	Fatigue, sleepiness, hypotension, constipation, dizziness, dry mouth, arrhythmia, urinary retention, cave: glaucoma
	or	
	Nortriptyline 25 mg in the morning, increase by 25 mg every 2–3 days until 2–3 x 50 mg	Hypotension, constipation, dizziness, dry mouth, dysrhythmia, urinary retention, cave: glaucoma
	or	
	Duloxetine 1 x 60 mg in the morning	Nausea, diarrhea, restlessness
4th stage:	Opioids or	Sedation, constipation, nausea
	Gradually increase sustained-release morphine 2 x 10 mg to a maximum of 2 x 100 mg.	Sedation, nausea, constipation
General	Change to the next stage in each case if the complaints persist. Combinations of stage 3 or stage 3 and 4 preparations are useful. If a rapid effect is desired, start with level 4 and slowly add a substance from level 3. The slower the up-dosing, often the greater the achievable dose and the greater the chance of effect. Close contact with patients is crucial for compliance and finding the best individual treatment.	

Myopathies

The incidence of myopathies, which can occur at any stage of infection, is 1–2%. Cytotoxic T-cell-mediated HIV-associated polymyositis is the most common primary HIV-associated myopathy. Even with low-dosage NRTIs, there are occasional exercise-induced myalgias. On muscle biopsy, patients show isolated evidence of mitochondrial dysfunction (Landon-Cardinal 2019).

Table 7: Overview of the most important myopathies. Except for polymyositis of drug-induced disorders, these are very rare diseases.

Primarily HIV-associated	Secondary
Polymyositis	Drug-induced mitochondrial dysfunction
Nemaline myopathy	Myopathy in vasculitis
Vacuolar myopathy	Infiltration by non-Hodgkin's lymphoma
Inclusion body myositis	Pathogen-induced myositis
Acute rhabdomyolysis (with seroconversion).	Drug toxic rhabdomyolysis

During seroconversion, rapidly progressive rhabdomyolysis with acute renal failure may occur as part of a mononucleosis-like clinical picture (Ranabhat 2021). Also, some drugs (ddI, cotrimoxazole, pentamidine, sulfadiazine, lipid-lowering agents) and the integrase inhibitors raltegravir and dolutegravir (Zembower 2008, Saad 2018) can rarely cause acute rhabdomyolysis with tetraparesis and massive increase in serum CK activity. Note that serum concentrations of many statins are increased with PIs, increasing the risk of rhabdomyolysis (Hare 2002). Raltegravir may also cause less acute proximal myopathies with muscle pain without increased serum creatine kinase activity (Lee 2012). Serum CK activity is often increased with tenofovir, especially with HBV or HCV coinfection. This is not due to muscular dysfunction but to type II macro-CK and is not correlated with any disease. In these cases, the clearance of this liver-derived CK-isoenzyme appears to be reduced by tenofovir (Schmid 2006).

Clinic

Regardless of etiology and entity, myopathy often begins with muscle soreness-like myalgias induced by physical stress, primarily affecting proximal muscle groups. Over weeks to months, muscle atrophy and paresis develop. Limb-girdle muscles are usually affected, but involvement of trunk, neck, pharyngeal, facial, or distal limb muscles is also possible.

Diagnostics

Myalgias and increased serum CK activity are common in HIV infection. Many antiretroviral drugs, especially NRTIs, NNRTIs, maraviroc, and integrase inhibitors, can trigger myalgias. The careful documentation of drug history is critical, and the improvement of myalgias after stopping the drug supports the causal relationship. However, myopathy diagnosis requires the presence of muscle atrophy, paresis, or evidence of myopathic findings on electromyogram. In these cases, muscle biopsy is indicated (Table 7).

Treatment

Mild myalgias can be treated symptomatically with non-steroidal anti-inflammatory drugs. Prednisolone (100 mg daily for 3–4 weeks, then slowly tapering off) or intravenous immunoglobulin (0.4 g/kg over 5 days) were effective as therapy for polymyositis in small studies (Johnson 2003, Viard 1992).

Literature

Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007, 68:515-21.

Banerjee S, McCutchan JA, ANces BA, et al. Hypertriglyreidemia in combination antiretroviral-treated HIV-positive individuals: potential impact on HIV sensory polyneuropathy. AIDS 2011, 25: F1-F6.

Bogoch II, Wilson MR, Chad DA, Venna N. Acute lower motor neuron syndrome and spinal cord gray matter hyperintensities in HIV infection. Neurol Neuroimmunol Neuroinflamm 2015, 2:e113.

Bowen LN, Tyagi R, Li W, et al. HIV-associated motor neuron disease: HERV-K activation and response to antiretroviral therapy. Neurology 2016 87:1756–1762.

Dinat N, Marinda N, Moch S, et al. Randomized, double-blind, crossover trial aminotriptylene for analgesia in painful HIV-associated sensory neuropathy. Plos One 2015, 10:e0126297.

Ellis RJ, Marquie-Beck J, Delaney P, et al. Human immunodeficiency virus protease inhibitors and risk for peripheral neuropathy. Ann Neurol 2008 64: 566-72.

Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009, 34: 672-80.

Finnerup NB, Attal N, Haroutounians S, et al. Pharmacotherapy for neuropathic pain in adults: a systemic review and meta-analysis. Lancet Neurol 2015 14:162-73.

Ghrenassia E, Martis N, Boyer J, et al. The diffuse infiltrative lymphocytosis syndrome (DILS). A comprehensive review. J Autoimmunol 2015. 59:19-25.

Gonzalez-Duarte A, Robinson-Papp J, Simpson DM. Diagnosis and management of HIV-associated neuropathy. Neurol Clin 2008. 26: 821-32.

Hare CB, Vu MP, Grunfeld C, Lampiris HW. Simvastatin-nelfinavir interaction implicated in rhabdomyolysis and death. Clin Infect Dis 2002; 35: e111-2.

Johnson RW, Williams FM, Kazi S, et al. Human immunodeficiency virus-associated polymyositis: a longitudinal study of outcome. Arthritis Rheum 2003; 49: 172-178.

Kaku M, Simpson DM. HIV neuropathy. Curr Opin HIV AIDS 2014. 9: 521-26.

Lee FJ, Amin J, Bloch M, et al. Skeletal muscle toxicity associated with raltegravir-based combination anti-retroviral therapy in HIV-infected adults. J Acquir Immun Defic Syndr 2013, 62:525-33.

Lorber M. A case of possible darunavir/ritonavir-induced peripheral neuropathy: case description and review of the literature. J Int Assoc Provid AIDS Care 2013, 12: 162-5.

Moodley K, Bill PLA, Patel PB, et al. A comparative study of CIDP in a cohort of HIV-infected and HIV-uninfected patients. Neurol. Neuroimmunol. Neuroinflamm 2016, 4:315-319.

Octaviana F, Safri AY, Setiawan DD, et al. Detectable plasma HIV RNA is associated with sensory neuropathy in patients with HIV treated without stavudine. J Acquir Immune Defic Syndr 2018, 4:e108-110.

Pettersen JA, Jones G, Worthington C, et al. Sensory neuropathy in HIV/AIDS patients: protease inhibitor-mediated neurotoxicity. Ann Neurol 2006, 59: 816-824.

Pillay P, Wadley AL, Cherry CL, et al. Clinical sensory neuropathy in HIV patients treated with tenofovir: a 6-month follow-up study. J Peripher Nerv Syst. 2019, 24:304-313.

Ranabhat K, Deliwala S, Hussain MS, et al. Human Immunodeficiency Virus masquerading as myopathy and rhabdomyolysis. Cureus 2021; 13: e14559.

Robinson-Papp J, Gelman BB, Grant I, et al. Substance abuse increases the risk of neuropathy in an HIB-infected cohort. Muscle Nerve 2012, 45 471-6.

Robinson-Papp J, Sharma S, Simpson DM, et al. Autonomic dysfunction is common in HIV and associated with distal symmetric polyneuropathy. J Neurovirol 2013; 172-80.

Rosenstock J, Tuchman M, LaMoreaux, et al. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain 2004;110: 628-638.

Saad M, Casado-Castillo F, Kelly P. Case report of Triumeq (abacavir/dolutegravir/lamivudine) associated rhabdomyolysis in a human immunodeficiency virus (HIV) infected patient. Medicine (Baltimore) 2019, 98:e15149.

Schmid H, Mühlbayer D, Röling D, et al. Macroenzyme creatine kinase (CK) type 2 in HIV-infected patients is significantly associated with TDF and consists of ubiquitous mitochondrial CK. Antivir Ther 2006, 11:1071-80.

Silva MTT, Neves ES, Grinzstejn B et al. Neurological manifestations of coinfections with HIV and human T-lymphotropic virus type 1. AIDS 2012; 26: 521-6.

Simpson DM, McArthur JC, Olney MD, et al. Lamotrigine for HIV-associated painful sensory neuropathies. Neurology 2003; 60: 1508-14.

Simpson DM, Estanislao L, Evans, et al. HIV-associated neuromuscular weakness syndrome. AIDS 2004; 18: 1403-12.

Thomas SE and Laycock H. The use of high dose topical capsaicin in the management of peripheral neuropathy: narrative review and local experience. Brit J Pain 2020; 14:133-140.

Viard JP, Vittecoq D, Lacroix C, et al. Response of HIV-1 associated polymyositis to intravenous immunoglobulin. Am J Med 1992; 92: 580-1.

Zembower TR, Gerzenshtein L, Coleman K, et al. Severe rhabdomyolysis associated with raltegravir use. AIDS 2008: 22: 1382-4.

29. HIV and psychiatric diseases

CHRISTIAN PERRO

Depression and anxiety disorders are the most common psychiatric disorders among people living with HIV (Capaldini 2000, Gallego 2011, Lopes 2011, Mascolini 2016). With HIV infection, the risk of mental illness is twice as high. Conversely, mental illness increases the risk of becoming infected with HIV and is also considered a negative predictor of the further course of infection (Nel 2011). Mental illnesses can express reactive disorders, be primarily related to HIV infection or its treatment, or occur independently of HIV (pre-existing). They affect quality of life and are often characterized by profound disruption of social and occupational participation. Rarely do they impair the capacity for insight and consent to such an extent that there are legal consequences, such as the initiation of legal guardianship.

Although treatment is generally no different from HIV-negative individuals, some unique features should be considered. Symptoms should be treated consistently, psychotherapeutically, and/or medicinally. Constantly, current ART should also be reviewed. For example, neuropsychiatric side effects have been repeatedly described in recent years for antiretroviral agents such as efavirenz and second-generation INSTIs (Hoffmann 2016+2019). Sometimes, it may then make sense to switch ART. From experience, individuals are often reluctant to report psychological symptoms. Therefore, patients should always be asked about psychological problems in everyday life.

Depression and other affective disorders

Depression – with or without anxiety/panic disorder – is still considered the most common affective disorder (Eshun-Wilson 2018). Depending on the stage of infection, lifetime prevalence is sometimes significantly higher than in the general population, which is thought to be 16–20% (Tegger 2008, Mascolini 2016, Eshun-Wilson 2018). Depression can be a one-time occurrence or recurrent. Depression is underdiagnosed. Even when it is diagnosed, only a fraction of patients receive adequate treatment (Mascolini 2016).

In clinical practice, the question often arises: Is the patient "just sad and in a bad mood" or are the criteria of a depressive episode already met? The diagnosis of HIV infection alone is usually not the cause of depression. The diagnosis leads to psychological distress and psychopathological symptoms, but these often do not fulfill the criteria of a diagnosis of depression according to ICD-10/11. A recommendable depression screening is PRIME-MD PHQ2 with two quick-to-answer questions (Kroenke 2003). Treatment of depression is essential in PLWH because it can improve virologic response to ART and adherence (Pence 2007, Gonzalez 2011, Ngum 2017). Psychiatric screening with targeted questions is recommended at least every 1–2 years. The exact cause of depression remains unknown, but a genetic predisposition has been established. Currently, the vulnerability-stress model applies, and neurotransmitter imbalances are assumed. Depression is characterized by main symptoms such as depressed, depressive mood, loss of interest and joylessness and/or lack of energy, and increased fatigue. Moreover, there may be additional symptoms such as feelings of guilt and worthlessness, sleep and appetite disturbances, concentration disorders, suicidal thoughts, and others.

These features should be present for at least two weeks and not describe a general personality trait. The severity depends on the number of symptoms present. Not all features need to be present at the same time. Between single and recurrent episodes,

longer-lasting depressive symptomatology (over two years = dysthymia), adjustment disorder, and mixed anxiety and depression disorders.
In addition to the psychiatric interview, the diagnostic workup should include cerebral imaging (ideally a cranial MRI) if possible, and a cerebrospinal fluid (CSF) puncture if necessary to rule out opportunistic CNS disease or incipient HIV-associated dementia (HAND) and its precursors. Third-party or self-assessment scales (HAM-D or BDI) are recommended and are often easy to perform. Immunologic and virologic values should be available. Careful medication history is also essential to identify affective disorders as possible side effects (e.g., efavirenz and some INSTIs) or interactions between psychiatric medication and ART.
After depression, the second most common disorder is anxiety and panic disorder; the less common affective disorders include the very rare primary mania, the more common bipolar affective disorder, and cyclothymia (frequent mild depressive and hypomanic swings around a balanced mood). Bipolar disorder and manias, in particular, should be treated only by psychiatrists or neurologists. In this case, a preexisting disposition should be assumed. Every depressive should, therefore, also be asked about day-long phases with an unusually low need for sleep, high energy, and an extraordinarily good mood since these episodes are often not reported spontaneously, and bipolar disorder entails other therapeutic consequences.

Treatment

Treatment need not differ from HIV-negative people. A multimodal treatment concept consisting of psychoeducation, mindfulness training, psychotherapy, and medication is favored. The latter is indicated if the affected person desires, but especially in severe and/or prolonged courses. It depends on previous experience, physical illnesses, comedication, potential side effects, previous adherence, individual preference, and ultimately the costs or availability.
No antidepressant class is better (efficacy, onset of action) than any other. There are, of course, differences in the side effect profile, interactions, and the possibility of overdose. Treatment usually consists of the so-called serotonin reuptake inhibitors (SSRI or SSNRI). Tricyclic antidepressants play a lesser role because they potentially cause more interactions and autonomic side effects such as dry mouth, urinary retention, or cardiac arrhythmias (Watkins 2011). Table 1 shows dosages and interactions of common antidepressants (*www.hiv-druginteractions.org*). The only approved herbal antidepressant, St. John's wort, should be used cautiously because of possible interactions with ART. Newly added in recent years are studies on rapid-acting antidepressants (RAADs); ketamine and esketamine were approved last year. However, both are so far only available under inpatient conditions. The principle of "start low and go slow" applies to the start of pharmacological treatment.
Regarding symptoms, all depressed people should be asked about suicidal thoughts. This is usually perceived as relieving rather than embarrassing. In the case of manifest suicidal thoughts, they should be asked about plans or previous suicide attempts. If true, the individual should be moved to an emergency psychiatric presentation. Recognized risk factors for suicidality are a known mental illness (> 90% of all suicide victims), suicide attempts in self and/or family history, male gender, and high age (prevalence increases at retirement age).
While mild and reactive depressive syndromes can undoubtedly be treated by general practitioners, treatment-resistant and recurrent depressive disorders should always be managed by specialists, as highly effective alternatives exist, for example, with awake and light therapy, irreversible MAO inhibitors, electroconvulsive therapy (ECT), or, more recently, ketamine (Berger 2012, Westring 2022).

Table 1: Commonly used antidepressants in PLWH.

Drug	Metabolism, Interactions (IA)	Dosage
Sertraline (SSRI)	CYP2B6, CYP2C9, CYP2C19, CYP2D6; no relevant IA with cytochromes known	50–100 mg QD, starting with 25 mg, always in the morning.
Escitalopram (SSRI)	Mainly CYP2C19; no relevant IA with cytochromes known	10–20 mg QD, start with 5–10 mg, always in the morning, QTc prolongation dose-dependent
Mirtazapine (NaSSA)	CYP3A4, CYP1A2, CYP2D6; no relevant IA with cytochromes known	15–45 (60) mg QD, always at night, good sleep induction, not in diabetes
Bupropion (NDRI)	CYP2B6; in vitro inhibitor of CYP2D6 (metabolite)	150–300 mg QD; start with 150 mg for at least four weeks, a very good increase in energy
Duloxetine (SNRI)	CYP1A2, CYP2D6; inhibitor of CYP2D6	30–60 (120) mg QD, start with 30 mg, always in the morning, good for chronic pain
Venlafaxine (SNRI)	CYP2D6, CYP3A4, CYP2C19, CYP2C9; no relevant IA with cytochromes known	75–375 mg QD, start with 37.5 mg, always in the morning, a good increase in energy usually with higher doses
Amitriptyline (Tricyclic)	CYP2C19, CYP2C8, CYP2C9, CYP3A4, CYP2D6; no relevant IA with cytochromes known	25–(150) mg, multiple daily dosing, moderate sedation, and level monitoring are useful.
Trimipramine (Tricyclic)	CYP2C19, CYP2D6, CYP2C9; no relevant IA with cytochromes known	25–150 mg, evening, dose-dependent strong sedation
Trazodone (dual serotonergic)	CYP3A4, CYP2D6; no relevant IA with cytochromes known	25–100 mg at night for resistant sleep disorders, high interaction potential, and vegetative side effects
MILNA (SSNRI)		25–100 mg, similar to other SSNRIs.

Trazodone is recommended for resistant sleep disorders, not in primary antidepressant therapy. SSRI: serotonin reuptake inhibitor, NaSSA: noradrenergic-specific serotonergic antidepressant, NDRI: noradrenergic-dopaminergic reuptake inhibitor, SNRI: serotonergic-noradrenergic reuptake inhibitor, MAOH: monoamine oxidase inhibitor. QD: once daily, BID: twice daily.

Psychotherapy is generally recommended as an alternative to medication for mild depressive disorders and coping with the illness. In particular, cognitive behavioral therapy (CBT) and short-term psychodynamic methods achieve high recommendation levels in the guidelines.

Psychotic disorders

In HIV infection, psychotic symptoms are usually independent of HIV, except for delirium and intoxication or in the context of depression. The best-known psychotic disorder is schizophrenia. Its features usually exist before infection (Cournos 2005). Whether schizophrenia increases the likelihood of HIV infection is not known with certainty. Primary diagnoses after age 40 are a rarity and require intensive diagnostic testing. The hallmarks of schizophrenia are hearing voices, delusions, or a sense of being made ("the world has been changed because of me; everything has meaning to me"). In addition, there are often other symptoms such as body hallucinations ("animals crawling under my skin", "implanted chip in my head"), observational

experience, disturbances of affect, disturbance of thought structure (incoherence, disjointedness), and posture (stereotypies, catatonia). All symptoms should be present for over a month and not related to intoxicants.
It is essential to know that a psychotic person usually does not question his perceptions. For the affected person, these are inherently logical and true; correction is not possible. Counterarguments should be made only cautiously, if at all. They have no therapeutic benefit and serve as diagnostic reassurance.

Therapy

Rapid drug therapy is essential and, for the time being, independent of the etiological classification since the increasing duration of untreated psychosis is infectiously and psychiatrically unfavorable in terms of prognosis (Nurutdinova 2012). In the acute situation, benzodiazepines are appropriate. However, if possible, treating psychotic disorders should be reserved for specialists. So-called atypical antipsychotics (AAP, formerly atypical neuroleptics) are most suitable, as they have a less severe antidopaminergic effect. HIV-infected patients are more likely to have extrapyramidal motor movement disorders when taking conventional antipsychotics (AP); the cause is still unclear. The dose should always be chosen carefully. The classic atypical antipsychotic clozapine should be used cautiously and only by a specialist in HIV infection because of the increased risk of neutropenia.
Psychotic illnesses that manifest themselves only after HIV diagnosis should always give cause for intensive diagnostics. Often, they are the first signs of opportunistic infections or the preliminary stages of HIV-associated dementia; they should then be classified as organic psychotic disorders. In addition to the underlying disease, these disorders should be treated symptomatically with antipsychotics. Injectables (now up to 3 months) seem to have advantages with regard to compliance and maintenance of remission but should be reserved for specialists.

Table 2: Antipsychotics frequently used in Germany.

Drug	Metabolism	Dose range
Aripiprazole (AAP)	CYP3A4 (CYP2D6)	5–15 mg, QD
Amisulpride (AAP)	Renal elimination	50–800 mg, BID
Risperidone (AAP)	CYP2D6, CYP3A4	1–3 mg, QD
Quetiapine (AAP)	CYP3A4	25–800 mg, QD (sustained-release tablets if necessary)
Olanzapine (AAP)	CYP1A2, CYP2D6, hepatic conjugation	5–20 mg, QD
Haloperidol (AP)	CYP3A4, CYP2D6	0.5–10 mg QD (emergency drug!)
Flupentixol (AP)	CYP2D6	Frequently as depot 20–40 mg/14 days IM
Cariprazine	CYP3A4	1.5–6 mg

Note: Depot preparations of haloperidol, risperidone, aripiprazole, olanzapine, and flupentixol are available. QD: once daily, BID: twice daily. AAP atypical antipsychotics (formerly atypical neuroleptics), AP conventional antipsychotics

Psychotherapeutic approaches play only a minor role in psychotic disorders, although they have proven effective. Psychotic disorders lead in about 85% to only incomplete recovery and thus usually to considerable, permanent participation restrictions. In severe psychotic crises, however, there are often few alternatives to psychiatric hospitalization (Berger 2012).

Addictive disorders

Addictions are common in the general population and at least as common in PLWH; it is assumed that 80–90% practice "inconspicuous" use, and only 10–20% develop long-term problems (addiction). It often takes 5–8 years before help systems are contacted. In general, the awareness of problems regarding the use of harmful substances or even a possible addiction is relatively low. In particular, ChemSex, i.e., sex in connection with new psychoactive substances (NSP) and resulting complications, is a highly topical issue. At least half of MSM report substance use during sex (ASTRA study 2014). These are primarily young users; the use goals are defined differently, and identification runs through sex, not the drug itself (see *Sexual Dysfunction*). Intravenous drug use remains a significant risk factor for HIV and hepatitis C co-infection (Lucas 2011).

Addiction is also a significant cause of social, occupational, and health decline in PLWH -particularly alcohol dependence (Gruber 2010, Lopes 2011, Watkins 2011); ethanol-triggered neurodegeneration is thought to be synergistic with neurodegeneration triggered by HIV itself (Hahn 2010). Dependent alcohol use is also a factor that significantly increases mortality in HIV (Obel 2011). The CAGE questions were developed for evaluation in practice:

- Have you ever thought about drinking less? (Cut down drinking)
- Have you ever been annoyed because someone criticized your drinking behavior? (Annoyed)
- Have you ever felt guilty about drinking? (Guilt)
- Have you ever had to consume alcohol in the morning to get through the day or get rid of a hangover? (Eye-opener)

If more than two questions are answered positively, there is an urgent suspicion of alcohol dependence.

Benzodiazepines are likely to exacerbate cognitive deficits in prolonged use. Still, they invariably disrupt memory functions and sleep architecture, making them useless for prolonged therapy despite their excellent short-term effects. HIV treatment providers are often a great confidante. Suspected or known addictions should be addressed, and various outpatient, in-patient, and rehabilitative services should be offered. In a French HIV cohort, persistent benzodiazepine use was present in up to 29% (Roux 2011). However, whether this influences the course of the disease is not precisely known. In general, benzodiazepines with a short half-life (e.g., triazolam, midazolam) should be avoided during concurrent ART, as respiratory depression, among other effects, has been observed.

Less well known and often insufficiently considered are addictions in the field of non-substance-related addictions (e.g., internet addiction, chat, and gaming addiction) or addictions to substances of synthetic or herbal origin, so-called "legal highs" (e.g., "bath salts"). More traditional addictive substances such as khat or cannabis are not well known in connection with HIV infection in terms of infection risk and course. Adequate care structures are mostly lacking, as these issues are significantly behind alcohol and opiate addiction care in psychiatric addiction care. Overall, awareness of these addictions does not seem to be high among the general population, physicians, and other therapeutic disciplines.

Since ongoing addictive drug use can lead to changes in metabolism, and ART can affect substitution treatments for opiate addicts, drug interactions should be particularly monitored in this group (see *ART*).

Treatment

Addiction-related conversations should follow the principles of "motivational interviewing" (Miller and Rollnick 1991). A non-confrontational approach and an empathic basic attitude are crucial. Often, there is little awareness of the problem and a high degree of defense mechanisms (rationalization). The first step is to create awareness and to approach the topic in a non-judgmental way. Often, it is necessary to clarify the contradiction, "Actually, I don't want to, but..." (desire vs. functional). Confrontational interviewing techniques have proven ineffective because they usually only encourage shame and associated repressive behavior. Unlike alcohol or benzodiazepine dependence, attention to HIV infection plays a vital role in opiate addiction therapies. Addicts should urgently be referred to specialized counseling and therapy services. Drug therapy, on the other hand, plays only a minor role, apart from substitution therapy. Alcohol addicts are temporarily treated with the glutamatergic modulator acamprosate and the opiate antagonist naltrexone. A novel therapeutic option exists with the opiate antagonist nalmefene. Nalmefene is indicated for treating alcohol-addicted individuals for whom complete abstinence is not an option; it is intended to reduce excessive drinking, which should reduce the somatic and social late effects of alcohol dependence. Aversive therapy with disulfiram should be reserved for specialized centers because of its potential risk. Opiate addicts can also be treated with naltrexone at their request to ensure abstinence.

Personality disorders

The best-known personality disorder is narcissism; the most common is emotionally unstable or borderline personality disorder. As a rule, a personality disorder can be explained by the fact that the person concerned repeatedly exhibits/applies behavioral patterns even though they are fraught with negative consequences. One study (Newville 2012) has shown that antisocial ("dissocial"), depressive, and borderline personality disorders, in particular, increase HIV risk and continued risk behaviors. The latter appears to lead to an increased risk of HIV infection, particularly in conjunction with addictive disorders (Chen 2007). A borderline personality disorder is manifested by feelings of emptiness and a severe fear of abandonment; most notable, however, are frequent self-injury of all kinds, severe, unpredictable mood swings, and the expression of frequent suicidal ideation. Dissocial personalities are conspicuous by a severe disregard for social norms and persistent denial of one's guilt with generally high emotional coldness. This should be considered in HIV therapy since a person with such accentuated personality traits will not change his behavior. Should such personality disorders become apparent in everyday practice, a psychiatric and/or psychotherapeutic presentation is advisable. Positive effects are most likely achieved through psychotherapy (Berger 2012).

Legal aspects and psychiatric emergencies

During HIV diagnostics and therapy, there may be doubts about the person's capacity to consent and/or act. There may also be actions with a high potential of endangering oneself or others, especially in the case of neurocognitive diseases or in advanced stages of HIV. In case of doubt, the capacity to consent should be assessed by a psychiatrist. According to psychiatric doctrine, a person is capable of giving consent if his or her ability to absorb and understand information for a specific personal decision-making situation is not significantly limited by a current mental state. The capacity to consent also exists only in cases where decisions can be made without

coercion. Incapacity is different; it only includes permanent conditions. Should it be necessary, legal guardianship can be appointed for individual areas of responsibility. Any person can apply for such guardianship to the competent guardianship courts, and a psychiatric report is only mandatory if the person concerned does not agree to it. In the case of acute danger to oneself or others, people can be accommodated based on state laws; the procedures are always somewhat different according to the jurisdiction, but what they all have in common is that ultimately, a judge must decide, based on personal conviction, whether the person concerned should remain in a psychiatric hospital (Berger 2012).

Primarily, psychiatric emergencies are delirium, characterized by a disturbance of orientation and consciousness, psychotic/manic exacerbation with agitation, severe intoxication, and acute suicidal crisis.

Literature

Arendt G, Nolting T. Neurological complications of HIV infection. Nervenarzt 2008, 79:1449-62; 1463.

Berger, M. Psychische Erkrankungen, Klinik und Therapie. 4. Auflage. Urban und Fischer, München. 2012.

Chen EY, Brown MZ, Lo TT, Linehan MM. Sexually transmitted disease rates and high-risk sexual behaviors in borderline personality disorder versus borderline personality disorder with substance use disorder. J Nerv Ment Dis 2007, 195:125-9.

Cournos F, McKinnon K, Sullivan G. Schizophrenia and comorbid human immunodeficiency virus or hepatitis C virus. J Clin Psychiatry 2005, 66 Suppl 6:27-33.

Eshun-Wilson I, Siegfried N, Akena DH, Obuku EA, Joska JA. Antidepressants for depression in adults with HIV infection (Review). Cochrane Database of Systematic Reviews 2018. Issue 1 Art. No.:CD008525.

Gallego L, Barreiro P, López-Ibor JJ. Diagnosis and clinical features of major neuropsychiatric disorders in HIV infection. AIDS Rev 2011, 13:171-9.

Gruber VA, McCance-Katz EF. Methadone, buprenorphine, and street drug interactions with antiretroviral medications. Curr HIV/AIDS Rep 2010, 7:152-60.

Gonzalez JS, Batchelder AW, Psaros C, et al. Depression and HIV/AIDS treatment nonadherence: a review and meta-analysis. J AIDS 2011, 58:181-7.

Hahn JA, Samet JH. Alcohol and HIV disease progression: weighing the evidence. Curr HIV/AIDS Rep 2010, 7:226-33.

Hoffmann C, Welz T, Sabranski M, et al. High Rates of neuropsychiatric events leading to dolutegravir discontinuation in women and older patients. HIV Medicine 2017, 18:56-63.

Hoffmann C, Llibre JM. Neuropsychiatric Adverse Events with Dolutegravir and Other Integrase Strand Transfer Inhibitors. AIDS Rev 2019;21:4-10.

Lopes M, Olfson M, Rabkin J, et al. Gender, HIV status, and psychiatric disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2012, 73:384-91.

Lucas GM. Substance abuse, adherence with antiretroviral therapy, and clinical outcomes among HIV-infected individuals. Life Sci 2011, 88:948-52.

Mascolini M. High Depression Rates With HIV – and its Scathing Clinical Impact. CFA The Center for AIDS Information & Advocacy 2016.

Nel A, Kagee A. Common mental health problems and antiretroviral therapy adherence. AIDS Care 2011, 23:1360-5.

Newville H, Haller DL. Relationship of axis II pathology to sex- and drug-related risk behaviors among patients in HIV primary care. AIDS Care 2012, 24:763-8.

Ngum P, Fon P, Ngu R, Verla V, Luma H. Depression Among HIV/AIDS Patients on Highly Active Antiretroviral Therapy in the Southwest Regional Hospitals of Cameroon: A Cross-Sectional study. Neurol Ther 2017, 6: 103-114.

Nurutdinova D, Chrusciel T, Zeringue A, et al. Mental health disorders and the risk of AIDS-defining illness and death in HIV-infected veterans. AIDS 2012, 26:229-34.

Obel N, Omland LH, Kronborg G, et al. Impact of non-HIV and HIV risk factors on survival in HIV-infected patients on HAART: a population-based nationwide cohort study. PLoS One 2011, 6:e22698.

Pence BW, Miller WC, Gaynes BN, et al. Psychiatric illness and virologic response in patients initiating highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2007, 44:159-66.

Persidsky Y, Ho W, Ramirez SH, et al. HIV-1 infection and alcohol abuse: neurocognitive impairment, mechanisms of neurodegeneration and therapeutic interventions. Brain Behav Immun 2011; 25 Suppl 1:S61-70.

RKI Robert-Koch-Institut Berlin; Epidemiologische Kurzinformation des Robert-Koch-Instituts, 2021.

Roux P, Fugon L, Michel L, et al. Determinants of benzodiazepine use in a representative population of HIV-infected individuals: the role of HIV status disclosure (ANRS-EN12-VESPA study). AIDS Care 2011, 23:1163-70.

Tegger MK, Crane HM, Tapia KA, et al. The effect of mental illness, substance use, and treatment for depression on the initiation of highly active antiretroviral therapy among HIV-infected individuals. AIDS Patient Care STDS 2008, 22:233-43.

Watkins CC, Pieper AA, Treisman GJ. Safety considerations in drug treatment of depression in HIV-positive patients: an updated review. Drug Saf 2011, 34:623-39.

30. HIV and rheumatology

GUIDO SCHÄFER

Rheumatologic diseases are common both in the general population and among PLWH. They encompass various clinical manifestations within the spectrum of autoimmune and autoinflammatory conditions. Among the frequently encountered conditions are rheumatoid arthritis and multiple types of spondyloarthritides. Other examples of rarer diseases are subgroups of collagenoses and vasculitides. Given the extensive nature of these diseases, it is impractical to delve into each of them in great detail within this context. Moreover, the available data concerning PLWH is often limited. Consequently, this chapter aims to present conceptual frameworks and assistive measures for managing PLWH with co-morbid rheumatologic diseases.

Prevalence

A cohort analysis conducted in France (Lebrun, 2017) examined the prevalence of (auto-) immunological diseases among more than 33,000 PLWH, revealing a prevalence rate of approximately 4%. This finding was substantiated in a separate analysis (Schäfer, 2019). Interestingly, two conditions, namely psoriasis and inflammatory bowel disease, exhibited the highest prevalence rates despite not being primarily diagnosed or treated by rheumatologists. However, there is a significant overlap, particularly with psoriatic arthritis, which is likely underdiagnosed, and associations with spondyloarthritides in inflammatory bowel disease. Furthermore, some of the same immunomodulatory therapies are employed for these conditions. The research also demonstrated associations between HIV infection and chronic viral hepatitides (hepatitis B and C), which, in turn, contribute to the development of autoimmunological phenomena (Lebrun, 2017). In laboratory diagnostics, it is essential to consider that HIV infection, like other viral infections, can trigger autoimmune responses. Consequently, various autoantibodies are often detected in clusters among PLWH, although they frequently lack clinical significance (Iordache, 2017). Notably, these include antinuclear antibodies (ANA), rheumatoid factor (RF), cyclic citrullinated antibodies (CCP-AK), and antiphospholipid antibodies. Several rheumatologic diseases are strongly associated with the T cell-associated immune system, as demonstrated in studies focusing on rheumatoid arthritis, sarcoidosis, and systemic lupus erythematosus (Virot, 2017). Importantly, when CD4 T-cell count increases due to successful antiretroviral therapy (ART), there is a risk of immune reconstitution syndrome (IRIS), which may trigger disease relapse or initial manifestation of these rheumatologic conditions, which must be distinguished from treatment failure.

Special features

In most rheumatological studies, PLWH are excluded, resulting in a lack of systematic data on the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs) in PLWH. As a result, case reports, or case series are often relied upon in these situations. However, caution is warranted when interpreting such reports due to potential selection or publication biases. Likely, cases with positive outcomes and successful therapeutic responses without complications are more frequently reported. A commonly shared opinion suggests that because of a greater experience with conventional therapies (csDMARDs), such as methotrexate, these should be prioritized in PLWH. However, conventional and “more modern” DMARD options lack systematic randomized controlled trials for PLWH. Consequently, it does not

appear rational to withhold the latter options from PLWH and deprive them of treatment that aligns with established guidelines.

- Most DMARDs are associated with frequent, generally harmless bacterial infections (such as bronchitis, skin infections, and cystitis) and viral infections (especially gastroenteritis, nasopharyngitis, and bronchitis). These infections can typically be managed on an outpatient basis. However, caution is advised in individuals with a poor immune status.
- The evaluation of (latent) tuberculosis status should always be conducted. Generally, this assessment is done during the initial HIV diagnosis. However, when a rheumatological disease is diagnosed, and before the initiation of immunosuppression, treatment for latent tuberculosis should be considered (using standard regimens), preferably in consultation with rheumatologists (see *Tuberculosis*).
- The selection of rheumatologic therapy should also consider the presence of chronic active or previous hepatitis B (see *Co-infection*). For instance, rituximab significantly increases the risk of hepatitis B reactivation, necessitating appropriate prophylaxis.
- Vaccination status should be carefully considered (see *Vaccinations*). Some immunomodulatory therapies heighten the risk of herpes zoster outbreaks or hepatitis B reactivation. Additionally, immune responses to vaccines are often diminished, and live vaccines may be contraindicated under specific immunosuppressive therapies. Ideally, vaccines should be administered before initiating immunosuppression. Still, this may be challenging in practice due to disease relapse or high disease activity and the initiation of treatments such as high-dose prednisolone. As a rule of thumb, a stable phase of the rheumatic disease is the optimal time for vaccination.
- Interactions between medications must be considered. While antibody therapies (biologics) generally have few issues in this regard (as the liver or kidneys do not metabolize them), Janus kinase inhibitors (a relatively new class of drugs) and specific cortisone preparations can pose significant problems when used concomitantly with specific antiretroviral substances. Even with intra-articular triamcinolone administration, systemic interactions with drugs like ritonavir or cobicistat can occur.
- In individuals with a compromised immune status or inadequate viral suppression, challenges may arise in managing concurrent rheumatologic diseases and immunomodulatory therapy. Atypical opportunistic infections and oncological diseases, which can be exacerbated by DMARD therapy, are potential concerns. Therefore, prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) should be considered, especially in combined or prolonged immunosuppression (Salzer, 2018).

Selected features of important rheumatologic therapies

Corticosteroids: Steroids play a vital role in acute therapy due to their rapid efficacy and controllable dosing. Other DMARDs require weeks to months to achieve full immunomodulatory effects (though side effects may occur early). Systemic cortisone treatment (usually prednisolone) leads to immunosuppression that depends on the dosage and duration of therapy. Vaccinations should be postponed during higher doses (> 20 mg/d). Interactions with other medications should also be kept in mind.

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs): Many csDMARDs have been used for decades.

Methotrexate (MTX) remains the standard treatment for rheumatoid arthritis and other conditions. It is administered weekly subcutaneously or orally, with folic acid taken the following day. Severe side effects are rare unless there is accidental misuse

(e.g., daily instead of weekly intake). Nausea, which often occurs, may necessitate discontinuation. MTX pneumonitis is less common than previously believed, while pneumologic involvement of the underlying rheumatologic disease is more frequent.

Hydroxychloroquine (HCQ), a standard therapy in systemic lupus erythematosus, has minimal immunosuppressive effects and allows for the administration of live vaccines. Regular eye examinations are necessary to detect rare retinopathy.

Other agents in this group (including azathioprine, leflunomide, and sulfasalazine) are used much less frequently or in special indications.

Biological DMARDs (bDMARDs):

TNF-alpha Inhibitors: TNF-alpha inhibitors (adalimumab, infliximab, certolizumab-pegol, etanercept, golimumab) are the biologics with the most extended experience in rheumatology. Numerous case reports exist regarding their use in PLWH (Kaur 2007, Cepeda 2008, Gaylis 2012, Liang 2017, Marco 2019, Rafael 2019). Latent tuberculosis should be excluded and treated before initiating therapy if necessary, as TNF-alpha inhibitors carry the highest risk of tuberculosis reactivation among DMARDs. These inhibitors are primarily used in rheumatoid arthritis, various forms of spondylarthritis, inflammatory bowel disease (IBD), and psoriasis.

Anti-B-cell-directed therapies: The CD20 antibody **rituximab** is approved for use in rheumatology, particularly in ANCA-associated vasculitides and rheumatoid arthritis. It causes immunoglobulin deficiency lasting approximately six months. Vaccinations should be completed before starting rituximab therapy or timed for optimal efficacy in the interval between doses. Reactivation of hepatitis B is a potential risk. **Belimumab**, an antibody against soluble human B lymphocyte stimulator protein (BLyS), is approved for systemic lupus erythematosus, but there is not much experience in PLWH.

T-Lymphocyte Co-stimulation Inhibitor: **Abatacept** is approved for rheumatoid arthritis but lacks published literature regarding its use in PLWH. Particular caution should be exercised due to its impact on T-cell interaction in patients with low CD4 counts.

Interleukin-1 Inhibitors: **Anakinra** and **canakinumab** are primarily used in various autoinflammatory syndromes ("fever syndromes"). Despite being expensive, Canakinumab offers the advantage of less frequent dosing compared to daily doses of anakinra.

Interleukin-6 Inhibitors: **Tocilizumab** and **sarilumab** are used in large vessel vasculitis/giant cell arteritis (tocilizumab) and rheumatoid arthritis. A relevant feature is the almost obligatory 'negative' CRP (caveat: masked infections, e.g., cases of unrecognized diverticulitis with intestinal perforation).

Interleukin-12/23 Inhibitors: **Ustekinumab** (inhibiting IL12/23) and **guselkumab** (inhibiting IL23) are used for psoriasis (-arthritis) and have shown positive case reports in PLWH (Paparizos 2011, Bartos 2018, Wang 2019).

Interleukin-17A Inhibitors: **Secukinumab** and **ixekizumab** are approved for psoriasis (-arthritis) and spondylarthritides. Thrush is a common side effect during therapy (Di Lernia 2019). **Bimekizumab** is a newer antibody that uniquely neutralizes both *IL-17A* and *IL-17F, but there is no experience in PLWH.*

Targeted synthetic DMARDs (tsDMARDs):

Janus kinase inhibitors (JAKi): This class of drugs with several approved agents shows a short half-life with daily oral intake as a characteristic. This ensures good controllability in the event of side effects. Noteworthy is a significantly increased risk of herpes zoster, so a zoster vaccination – even in those < 50 years – before using

JAKi seems particularly useful. Indications and the number of agents (e.g., tofacitinib, baricitinib, upadacitinib, and filgotinib) are increasing. Some papers report the effects of JAKi on the viral reservoir (e.g., Gavegnano 2017). However, the relevance for practice remains unclear. Related to the Janus kinase inhibitors are the tyrosine kinase inhibitors, which may play an increasing role in the future (assuming successful further developments). JAK inhibitors should be used with caution in patients aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or who did so for a long time in the past, those at increased risk of cancer and those with risk factors for blood clots in the lungs and in deep veins (EMA 2023).

Conclusions

Rheumatological diseases and their therapy in the context of HIV infection form one of the most interesting clinical and scientific interfaces between rheumatology and infectious diseases. In decisive points, there are parallels:

- Review vaccination status and immunizations, if applicable.
- Evaluation (and treatment) of cardiovascular risk profile and relevant aspects of lifestyle (obesity, blood lipids, hypertension, etc.).
- Consideration of increased risk of oncologic disease (regular screenings should be performed).
- Knowledge of opportunistic infections is essential with the use of immunosuppressants.

By acknowledging and addressing these factors, healthcare professionals can effectively navigate the complexities of managing rheumatological diseases in PLWH, ultimately providing optimal care within this unique clinical and scientific interface.

Literature

Bartos G, Cline A, Beroukhim K, et al. Current biological therapies for use in HIV-positive patients with psoriasis: case report of guselkumab used and review. Dermatology 2018, 24:13030/qt3db748cg.

Cepeda EJ, Williams FM, Ishimori ML.The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. Ann Rheum Dis 2008;67:710–712

Di Lernia V, Casanova DM, Garlassi E. Secukinumab in an HIV-positive patient with psoriasis. J Dtsch Dermatol Ges. 2019 Jun;17(6):646-648.

EMA (European Medicines Agency 2023): https://www.ema.europa.eu/en/medicines/human/referrals/janus-kinase-inhibitors-jaki#overview-section (accessed 11 July 2023).

Gavegnano C, Brehm JH, Dupuy FP, et al. Novel mechanisms to inhibit HIV reservoir seeding using Jak inhibitors. PLoS Pathog 2017, 13:e1006740.

Gaylis NB. Long-term follow-up of an HIV-infected patient with reactive arthritis treated with infliximab. J Clin Rheumatol 2012, 18:153-4.

Iordache L, Bengoufa D, Taulera O, et al. Nonorgan-specific autoantibodies in HIV-infected patients in the HAART era. Medicine (Baltimore). 2017, 96:e6230.

Kaur PP, Chan VC, Berney SN. Successful etanercept use in an HIV-positive patient with rheumatoid arthritis. J Clin Rheumatol 2007, 13:79-80.

Lebrun D, Hentzien M, Cuzin L, et al. Epidemiology of autoimmune and inflammatory diseases in a French nationwide HIV cohort. AIDS 2017, 31:2159-66.

Liang SJ, Zheng QY, Yang YL, Yang Y, Liu CY. Use of etanercept to treat rheumatoid arthritis in an HIV-positive patient: a case-based review. Rheumatol Int 2017, 37:1207-1212.

Marco J, Bays A. Anti-TNF Therapy in Patients with HIV Infection [abstract]. Arthritis Rheumatol 2019; 71 (suppl 10). https://acrabstracts.org/abstract/anti-tnf-therapy-in-patients-with-hivinfection/.

Nakamura M, Abrouk M, Farahnik B, et al. Psoriasis Treatment in HIV-Positive Patients: A Systematic Review of Systemic Immunosuppressive Therapies. Cutis 2018, 101, 38-42

Paparizos V, Rallis E, Kirsten L, Kyriakis K. Ustekinumab for treating HIV psoriasis. J Dermatolog Treat 2012, 23:398-9.

Peluso MJ, Chen J, Munter S, et al. Outcomes of immunomodulatory and biologic therapy in people living with HIV. AIDS 2020, 34:1171-1179.

Rafael MA, Lourenço LC, Oliveira AM, et al. Successful treatment of severe perianal Crohn's disease with infliximab in an HIV-positive patient. Clin J Gastroenterol 2019, 12:583-587.

Salzer HJF, Schäfer G, Hoenigl M, et al. Clinical, Diagnostic, and Treatment Disparities between HIV-Infected and Non-HIV-Infected Immunocompromised Patients with Pneumocystis jirovecii Pneumonia. Respiration 2018, 96:52-65.

Schäfer G, et al. HIV-positive Menschen mit rheumatologischen Systemerkrankungen – eine Kohortenanalyse zu einem kooperativen deutschen Pilotprojekt. PW 140, DÖAK 2019.

Virot E, Duclos A, Adelaide L, et al. Autoimmune diseases and HIV infection: A cross-sectional study. Medicine (Baltimore) 2017, 96:e5769.

Wang DM, Fernandez AP, Calabrese CM, Calabrese LH. Treatment of psoriasis with ustekinumab in a patient with HIV-related Kaposi sarcoma. Clin Exp Dermatol 2019, 44:113-115.

31. Sexuality
Male sexual dysfunction

SEBASTIAN NOE
(earlier versions edited by Christoph Mayr)

Male sexual dysfunction (SD) usually refers to changes that disrupt "normal" sexual function. These are essentially
- Erectile Dysfunction (ED)
- Decrease or loss of libido
- Disorders of ejaculation

Sexual dysfunction in male PLWH is common: between 30% and 50% appear to be affected (Collazos 2007, De Ryck 2012, Tindall 1994, Goggin 1998). In a recent observational study of 501 male PLWH, the prevalence of ED was 58.5% (Fumaz 2017). Of the men surveyed, 19% reported regular use of PDE5 inhibitors.
Data from the German 50/2010 study of men aged 50 years and older showed that among participants with HIV infection, 7.7% suffered from hypogonadism, compared to 3.5% of men without HIV. Interestingly, the frequency of pure testosterone deficiency in the two groups did not differ significantly; the differences were due to a higher burden of symptoms of SD in men living with HIV (Postel 2021).

Etiology

Both psychological and somatic factors can play a role in developing sexual dysfunction, whereby an organic (co-)cause can be identified in up to 80% of all affected persons (NIH 1993).

Age is the most critical biological influencing factor (Feldman 1994). The reason lies in multiple age-related and degenerative changes of the organs and structures involved, including endocrine, neuronal, micro- and macrovascular changes. However, accumulating risk factors and co-morbidities will likely play a role (see below). In Germany, the prevalence of erectile dysfunction in men between 30 and 80 years of age is estimated at 19% (Braun 2000). In the 50/2010 study, 50% of participating men aged 50 years and older reported moderate to significant loss of sexual function. HIV was the only significantly associated parameter (Mueck 2010).

Risk factors/co-morbidity: In men living with HIV, common risk factors of ED are excessive alcohol or drug use or smoking. Metabolic disorders (hyperlipidemia, diabetes mellitus, obesity) and cardiovascular disease (especially arterial hypertension) are significant promoters. Pathophysiologically, ED is based on neuronal (neuropathy) and vascular (micro- and macroangiopathy) changes. Therefore, it can be an early sign of a general (poly-)neuropathy and/or angiopathy (e.g., coronary heart disease). Hormonal disorders, neurological diseases (e.g., herniated discs), and infectious diseases are also considered risk factors. A common cause in younger men is chronic kidney and liver dysfunction (hepatitis, cirrhosis). Psychosocial problems, relationship conflicts, and psychiatric disorders often accompany sexual dysfunction. Sleep apnea may also be a cause – mask breathing at night significantly improves ED (Taskin 2009). Cycling over three hours/week is also considered an independent risk factor for moderate to severe ED. Special bicycle saddles can prevent this (Huang 2005, Schrader 2008).

Medications: Many medications negatively affect libido and erectile function (Table 1). In the MACS cohort, these were mainly antidepressants and antihypertensives (Hart 2012). Decreased spontaneous erections and libido have been described with 5-alpha reductase inhibitors for treating LUTS (lower urinary tract symptoms) (Corona 2012).

Table 1: Substances/substance classes that can cause erectile dysfunction.

Alcohol	Nicotine
Antihypertensives	Antidepressants
Diuretics	Antirheumatic drugs (NSAIDs)
Lipid-lowering agents	H2 antagonists, proton pump inhibitors
Antiepileptic drugs	Tranquilizer
Opiates	Progestins/estrogens
Chemotherapeutics, ART	Amphetamines, hallucinogens

An association with sexual dysfunction has been described with the use of older antiretroviral agents (e.g., Cove 2004). In contrast, few consistent results are available on today's drugs.

Diagnosis

In addition to clinical examination, basic diagnostics include sexual, social, and family history and a complete history of medication and drug use. The testicular function cannot be reliably assessed by total testosterone in men living with HIV because of increased sex hormone binding globulin (SHBG); therefore, free testosterone should be measured or estimated (Bhasin 2018). To also detect pre-clinical changes or further classify the genesis of a testosterone deficit, LH (Luteinizing Hormone) should also be determined; determination of FSH (follicle-stimulating hormone) is dispensable outside of fertility diagnostics. Due to circadian rhythms, only early-morning measurements are usable (ideally by 8 a.m.), and results should always be confirmed by repeated measurements (at least twice). If characteristic symptoms of testosterone deficiency are present, repeated low-normal free testosterone concentrations are also sufficient for the diagnosis.

In a large cross-sectional study of 1,317 men living with HIV (often with lipodystrophy), 16% had testosterone deficiency; visceral fat and high BMI were predictive (Rochira 2011). De Ryck (2013) found signs of erectile dysfunction in 62%. In total, 37% of men living with HIV and sexual dysfunction also had a testosterone deficit. The critical question is that of nocturnal, morning, and spontaneous erections. A low invasive diagnostic tool is the nocturne penile tumescence (NPT) measurement; 3–6 erections/night of at least 10 minutes duration and at least 70% rigidity are considered average values.

Depending on the suspected genesis of a testosterone deficit, sonography of the testes (in the case of a suspected primary component of hypogonadism) or MRI of the skull, including fine-slice MRI of the pituitary gland (in the case of a suspected secondary component of hypogonadism) may be necessary additional examinations. Vascular diagnostics (Doppler sonography of the penis, pharmacocavernosography) and neurophysiological procedures (e.g., sphincter and pudendal nerve EMG) are reserved for urological specialists.

Table 2: Laboratory diagnostics for erectile dysfunction.

Special hormone diagnostics	**Environmental diagnostics**
Free testosterone	Blood count
LH	Glucose, HbA1c
(FSH)	Cholesterol (incl. HDL, LDL)
Prolactin	Triglycerides
TSH	Urine status

Treatment of sexual dysfunction

Knowing the risk factors and changing lifestyle habits is a priority. Studies show the positive effect of physical training, weight reduction, and abstinence from nicotine on erectile function (Hannan 2009, Reis 2009). In addition, attention must be paid to medication selection when treating co-morbidities. For example, nebivolol appears to have an advantage over metoprolol in preventing ED (Brixius 2007, Cordero 2010). Phosphodiesterase-5 inhibitors (PDE-5 inhibitors) have significantly improved erectile dysfunction therapy. They are easy to take, effective, and well-tolerated (Waldkirch 2005, Nehra 2009, Alwaal 2011). Intracavernosal corpus cavernosum auto-injection or intraurethral application of vasoactive prostaglandins (alprostadil) plays a role today only for a few men who do not respond adequately to PDE-5 inhibitors. A complete andrologic diagnosis should always precede their use, and men should be trained. The vacuum erection device (VED) is a good non-drug alternative with 80–95% response rates.

It is essential to be aware of possible interactions of PDE-5 inhibitors. Their active levels are significantly increased via inhibition of the cytochrome P450 enzyme system. Especially with boosted PIs, start with a low dose! Specifically, we recommend a small test dose (e.g., a 1/4 tablet of sildenafil 50 mg). This is usually sufficient and can be increased if there are no side effects. If effects do not occur (long-lasting HIV infection, multimorbidity, psychological overlay), the approved maximum dose should not be exceeded. Simultaneous use of nitrate- or nitrite-containing substances (molsidomine; "poppers") is contraindicated, as therapy-resistant hypotension may result. In case of doubt, it is advisable to exclude severe cardiovascular diseases.

In case of psychosocial problems, relationship conflicts, or depressive development, psychotherapeutic or sexual medical counseling is advised. A review of psychosocial interventions showed that group therapy – with and without sildenafil – significantly and long-lasting improved the signs of ED (Melnik 2007).

PDE-5 inhibitors

Sildenafil (Viagra®) was the first PDE-5 inhibitor approved; generic versions have been available since 2013. It is sold in dosages of 25, 50 and 100 mg. The effect occurs after 12–40 minutes, but can be delayed by a high-fat meal or alcohol consumption. The maximum concentration is reached after about one hour, and the duration of action is about 8–12 hours. The response rate depends on the etiology of the ED and varies from 43% to 83%. Cephalgia (11%), facial flushing (11%), dyspepsia (3%), dizziness (3%), rhinitis (2%), and color vision disturbances (1%) are common. Previous studies showed no increased risk of myocardial infarction or death.

Vardenafil (Levitra®) was approved in 2003 and inhibits phosphodiesterase-5 or hydrolysis of cGMP tenfold more than sildenafil, but bioavailability is low at 15%. The effect with 10 and 20 mg occurs after 15–30 minutes and can last up to 12 hours; the maximum plasma concentration is 60 min. Vardenafil is also effective and tolerable with concomitant antihypertensive therapy. Side effects, as with sildenafil, include cephalgia (10–21%), skin redness (5–13%), dyspepsia (1–6%), and rhinitis (9–17%). A double-blind, placebo-controlled study showed slight superiority to sildenafil (Rubio-Aurioles 2007) with reasonable safety.

Tadalafil (Cialis®) was also approved in 2003. There are doses of 5, 10 and 20 mg. The maximum plasma concentration is 2 hours; the effect occurs after 15–20 minutes. Since the plasma half-life is approximately 17.5 hours, response times of up to 36 hours are possible. This fact, in particular, promotes the popularity of tadalafil ("weekend pill"). The most common side effects include cephalgia (7–21%),

dyspepsia and heartburn (1–17%), myalgias (3–7%), back pain (4–9%), rhinitis (5%), and facial flushing (1–5%). Clinical effects on the cardiovascular system were not observed, and the incidence of myocardial infarction was not increased in any study. Since the end of 2017, significantly cheaper generics have been available.

Avanafil (Spedra®) is a fast-onset and selective PDE-5 inhibitor (onset of action after 30–40 minutes, half-life approximately 75 minutes). It has been approved in Europe since 2014 (50, 100, 200 mg) and has also shown satisfactory response in people with diabetes. Potential side effects are similar to those of the other PDE-5 inhibitors.

Recently, studies in MSM point to the correlation between drug use and PDE-5 inhibitors and risky sexual behavior (Purcell 2005, Swearingen 2005, Spindler 2006, Dirks 2012).

Due to a relative NO deficiency, the success of PDE5 inhibitors is limited in some diseases, such as diabetes mellitus or CHD. Alternative therapeutic concepts with sGC stimulators, Rho kinase inhibitors, and new NO donors are emerging (Lasker 2010). Topical therapy with alprostadil (1%-containing gel) is being investigated, as is gene transfer therapy to be applied locally (Alwaal 2011).

Testosterone

In case of confirmed testosterone deficiency and clinical symptoms, intramuscular injections (testosterone enanthate 250 mg IM every 14 to 21 days or testosterone undecanoate 1000 mg every three months after saturation dose after six weeks) or application of gel as a transdermal system (e.g., Testogel 25 mg/50 mg daily) can be considered. Peroral substitution is obsolete and associated with an increased risk of liver toxicity. Relevant side effects are hair loss, skin irritation (with gel!), liver value and lipid elevations in serum, polyglobulia, and water retention in the tissue.

Therapy of ejaculatio praecox

Various options are available for prolonging the time until ejaculation; for example, learning techniques for delaying orgasm and psychotherapeutic support can be helpful. Prolongation can be achieved with SSRIs, although only dapoxetine (Prilegy®) is approved for this indication.

Chemsex

MARTIN VIEHWEGER

In the last decade, a new phenomenon – predominantly among men who have sex with men (MSM) – has become established: chemsex. The term, used in English-speaking countries since around 2004 (in Germany since 2009), describes the use of certain chemical psychoactive substances to reduce inhibitions and to amplify one's own sexual experience. This happened through online networks and dating forums (Stuart 2016). Chemsex is the result of a change in the use of technology (dating apps, media), easier availability of sex on the one hand and substances on the other. Since chemsex primarily refers to a phenomenon of sexual culture between men* in the strictest sense (according to David Stuart), masculine pronouns will be used here. Chemsex practices are not solely due to gender or identity but take place independently of them. For this purpose, the term "sexualized substance use" is introduced to clarify specific vulnerabilities, needs, and, if necessary, therapeutic consequences.

Most of the available data come from the US and the UK. The experience of German NGOs, especially AIDS help centers, confirms a comparably frequent use of drugs during sex here. Depending on the effect, the substances are called "uppers" (activating intoxication) or "downers" (relaxing intoxication). Joint consumption takes place at sex parties in clubs but mostly at private (after-)parties at homes, with substances often being consumed together over the entire weekend and in different combinations as well as applications. The most common substance classes are 3- or 4-methyl methcathinone (mephedrone, metaphedrone), gamma-Butyrolactones (precursor of gamma-hydroxybutyrates; GBL, GHB), ketamines, methamphetamines (crystal meth, "T") and cocaine (see glossary at the end of the chapter). They are often combined with poppers (amyl nitrite) as well as PDE5 inhibitors (sildenafil, tadalafil, and others) (Bracchi 2015, Stuart 2016). Substance use occurs inhalational (smoking), intranasally (sniffing), intravenously (slamming), orally (swallowing "gobs"), and rectally (suppositories). "Slamming", often injecting unknown quantities of unknown mixtures of many drugs mentioned above, plays a unique role. Half of the users have used substances within the last three months, and a quarter of them have at least three different ones in combination. HIV-positive men are more likely to use other substances simultaneously and more frequently (Bracchi 2015, Hegazi 2017).

Substance use is most common among MSM (Deimel 2016) and most likely to occur in major cities with higher tourist traffic (Hockenhull 2017): London (13%), Amsterdam (11%), Barcelona (8%), Zurich (7%), Berlin (5%). A survey conducted at STD clinics in London between January 2015 and June 2016 revealed high levels of prevalence, with 655 of 818 clients using substances during sex. 30% of respondents described themselves as open to various substances, of whom more than half (57%) were open to the above-mentioned chemsex substances. 13.5% had already injected drugs at least once.

Many users avoid interviews out of fear or shame and to protect the "chemsex community" (Stuart 2016). A high number of unreported cases may, therefore, be assumed. Validated surveys are scarce. Many MSM have already had experience with at least one of the substances mentioned above at parties; new users are also confronted with the substances through sexual partners.

Substance use carries an enormously increased risk of infection with classic sexually transmitted infections (syphilis, gonorrhea, chlamydia), viral hepatitis (A–C), and HIV. Chemsex mainly occurs with changing sex partners, during group sex, and in the context of high-risk sexual practices (fisting, urethral sounding). Shared use of

sex toys, shared needles, and, most importantly, unprotected (raw) sexual intercourse (barebacking) are additional significant risk factors. Chemsex users are more likely to use post-exposure prophylaxis or to be HIV-positive (Bracchi 2015, Deimel 2016). Substance use also weakens adherence to ART, with the risk of possible development of resistance. In addition, the interactions between antiretroviral substances and the substances used in chemsex are underestimated (Bracchi 2015). The interactions between the so-called "boosters" (ritonavir or cobicistat) and the chemsex substances GHB/GBL, alcohol, or amyl nitrite (poppers) should be highlighted. Hazards include overdoses and dose level reductions (Pebody 2015) (see www.hiv-druginteractions.org). Fatal accidents after consumption with GHB or GBL are no longer rare. GHB/ GBL are discredited for being used as so-called "knockout drops" (Hockenhull 2017), where someone can be stealthily put to sleep. Many substances are not well-known to the public, experience in dosage and in combination(s) is low, and access to information is difficult. There is a rapid risk of psychological dependence and associated substance abuse. Mephedrone or methamphetamine should be emphasized here. Under the influence of drugs, interpersonal communication regarding consensual sexual practices is more complex (Bourne 2015).

Substance use is primarily intended to reduce the sexual inhibition threshold of the "user", increase the sensation of pleasure, and prolong the sexual act. Euphoria (intense excitement or happiness) often contrasts with pseudo-intimacy: intimate acts are accepted under the influence of drugs that would otherwise not be permitted. Reasons for using sexually stimulating substances may include testing limits, escapism, defense against social pressure to perform and optimize life experiences, competition, compensation for social or personal conflicts, and defense toward deadening monotony or everyday normativity. Substance use before sex reduces the sense of shame, lowers the threshold of contact (entactogenic), increases sexual appetite (sex drive), and prolongs pleasure (Stuart 2016). It empowers specific sexual practices (kinks). These effects may be desirable in the context of coming out or sexual identity exploration. In discussion groups, there were also indications of internalized homophobia, supposed pressure of subcultural affiliation in case of negative self-image, and guilty experience of otherness. MSM can quickly become vulnerable to health risks (Deimel 2016, Villarreal 2017).

In another group discussion, illicit substances are perceived as particularly harmful. At the same time, the physical and health-economic damage – viewed in terms of society as a whole – still mainly occurs in the abuse of alcohol and cigarettes (Bourne 2014). Lack of access to information, prejudice, and stigma pose additional risks (Villarreal 2017). Most users may go through a phase in their lives with substance use without incident, but many experience severe physical and psychological trauma, some of which can be life-threatening (Hudson 2017). Stuart (2017) concludes, "... chemsex will be a lifelong phenomenon that defines an important period in the history of homosexuals."

Therapeutic concepts

The fundamental question is when use becomes overuse/abuse. Currently, opportunities for education and counseling for "users" exist primarily in low-threshold services offered by the gay community or self-help. These services are particularly valuable in conjunction with access to free STD testing and anonymous substance checks. In the case of indications of substance use, a complete medical history, including sexual and drug history, as well as an initiating counseling interview are required from a medical perspective: appreciative, unprejudiced communication with an evaluation of restricted or limited interests, social deprivation, focusing of leisure activities on the next chemsex session, financial restrictions due to substance

procurement, changing patterns of drug use and forms of application, more frequent sick leave, depression, and concentration issues.

Overall, out-patient and/or in-patient somatic withdrawal is very complex. Specialized outpatient facilities and withdrawal clinics for long-term withdrawal and rehabilitation are rare. Especially in the withdrawal of GBL (inpatient possible, e.g., with Xyrem®), there is little experience: internal medicine clinics are overburdened with the alternating between hyper- and hypokinetic delirium during withdrawal. In contrast, psychiatric clinics often have no possibilities for somatic monitoring of circulatory functions (necessary in the withdrawal of GBL). Medical and psychotherapeutic staff are rarely sensitized and not adequately trained. With few exceptions, no well-established, adapted aftercare (post-withdrawal) concepts exist. High relapse rates have been the rule up to now.

For the needs of chemsex users, new integrative, therapeutic concepts are needed: bodywork – letting people experience closeness and intimacy anew, reoccupying sexual fantasies, finding, fostering, and practicing social skills: practicing occupational therapy-guided craft exercises and transforming them into practical skills suitable for everyday life. Create alternative opportunities, e.g., invitations to game nights, readings on topics such as, among many others, masculinity, drag workshops, or open mics. Enduring shame – not taking "no" as a devaluation, listening and understanding each other in the age of anonymous dating apps. Education and training in sexuality and intimacy for those affected, and training for medical staff and psychotherapists to give clients adequate conversation and therapy options during withdrawal. Offer workshops for saunas/bars/clubs on safer clubbing and partying for professional staff.

To identify and understand these needs, the ChemSexNetwork Berlin met for the first time in 2018 and proposed relevant services to interested individuals working in the field. The network tries to promote synergies, create a common understanding of different sexual cultures, improve social/sexual skills, develop treatment pathways and guidelines, and represent common political interests. It sees itself as a skills-building forum. The support of controlled consumption by a network of NGOs and self-help, sports, and leisure groups is being discussed. There are promising approaches in "mindfulness-based" complementary psychosocial interventions (Gonzales-Baeza 2017).

To evaluate existing services and create new ones, BISS, the Federal Initiative on Sexualized Substance Use, was constituted in 2022. BISS deals with the topic of sexualized substance use, including chemsex and the interplay between sexuality and patterns of use, such as substance use, media use, and the effects associated with them.

Skin and soft tissue infections

Skin and soft tissue infections (SSTI) are common in injecting substance use. They usually heal without medical intervention or are treated with simple incision and drainage (Review: Bamberger, year?). Rare complications can result in sepsis, necrotic fasciitis, endocarditis, septic embolism, amputation, and death. Injecting with a needle that has been used previously and the length of time injected increases the likelihood of developing an SSTI. Some drugs, such as amphetamines or cocaine, are lipophobic and are not readily absorbed intramuscularly or subcutaneously. These substances immediately induce a burning sensation and initiate an inflammatory response caused by the immediate chemical reaction itself, and usually resolve without treatment in a few days. Symptoms include redness, heat, pain, and functio laesa. An abscess filled with pus usually develops three to ten days after injection and slowly increases in size and discomfort the following week. The traditional single

incision is recommended for small abscesses (less than 4 cm in diameter). Despite the lack of proven efficacy of antibiotics, it is recommended to use Staphylococcus-covering antibiotics (e.g., cephalexin or dicloxacillin – narrow-spectrum Beta-lactam antibiotic of the penicillin class) after successful incision. The so-called cellulitic abscesses (areas of erythema extending beyond the borders of the abscess itself) must be closely monitored and treated with antibiotics to prevent rapid progression and cellulitis. Here, ceftriaxone (1 gram given every 24 hours until erythema resolves, followed by oral antibiotics as above) may be effective. Patients who experience erythema that increases daily beyond the limits of an abscess often require hospitalization. Affected patients with a pus-filled wound who refuse incision should not be offered antibiotics. There would be a risk of selecting antibiotic-resistant bacteria because antibiotics do not adequately penetrate pus-filled spaces.

Glossary of common substances in chemsex

Mephedrone (Meow Meow, MCAT, plant food): Tablets or powder (intravascular, intranasal, or rectal administration).
Effects: euphoria, more intense music experience, improved mood, decreased hostility, improved mental function, and sexual stimulation.
Side effects: anxiety and paranoia, overstimulation of the heart, circulation, and nervous system, and risk of epileptic seizures.

GHB/GBL (G, Gina, liquid ecstasy): liquid or powder added to an alcohol-free beverage, occasionally intravascular.
Effects: euphoria, decreased inhibitions, increased sex drive. Enhancement of the effects of other drugs. Relaxant effects may make receptive anal intercourse easier or more pleasurable.
Side effects: memory lapses, clumsiness, drowsiness, tremors, agitation. Very risky in combination with alcohol and/or amphetamines. Overdose may cause "G-sleep" – unconsciousness requiring medical intervention.

Crystal methamphetamine (Crystal, tina, meth, ice, T): Inhalation (glass tube); intranasal; intravascular; rectal.
Effects: euphoria, increased energy during sex or dancing, increased self-confidence, feelings of invincibility and impulsivity, decreased experience of pain, intense sexual stimulation, and decreased inhibitions.
Side effects: sleep disturbances, loss of appetite, tremors or convulsions, irregular heartbeat, depression, fatigue, and paranoia.

Ketamine (K, special K, vitamin K): tablets; as intranasal or intravascular administration powder.
Effects: In subanesthetic doses, ketamine produces a dissociative state characterized by detachment from one's physical body and the external world. A so-called "K-hole" can occur at sufficiently high doses, a form of extreme dissociation with visual and auditory hallucinations.
Side effects: confusion, agitation, panic attacks, impaired short-term and long-term memory, and depression (with long-term use). Hardening of the bladder walls and problems with urination (ketamine bladder).

Cocaine (coke, Charlie, snow, blow): powder for intranasal or inhalation use ("crack cocaine").
Effects: increased energy, confidence, and exhilaration. People who use cocaine often describe more sociable and physically stronger behavior.
Side effects: increased body temperature and heart rate; risk of heart attack. Long-term damage to the cartilage of the nose.

Literature

Alwaal A, Al-Mannie R, Carrier S. Future prospects in the treatment of erectile dysfunction: focus on avanafil. Drug Des Devel Ther 2011;5:435-443.

Asboe D, Catalan J, Mandalia S, et al. Sexual dysfunction in HIV-positive men is multi-factorial: a study of prevalence and associated factors. AIDS Care 2007;19:955-65.

Bamberger J. The Care and Treatment of Skin and Soft Tissue Infections among Injection Drug Users in the Community Setting. https://de.scribd.com/document/90871022/

Banks E, Joshy G, Abhayaratna WP, et al. Erectile dysfunction severity as a risk marker for cardiovascular disease hospitalization and all-cause mortality: a prospective cohort study. PLoS Med 2013, 10:e1001372

Bhasin S, Brito JP, Cunningham GR, et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2018, 103:1715-1744.

Bracchi M, Stuart D, Castles R, Khoo S, Back D, Boffito M. Increasing use of 'party drugs' in people living with HIV on antiretrovirals: a concern for patient safety. AIDS 2015, 29:1585-92.

Bourne A, Weatherburn P. "Chemsex" and harm reduction need among gay men. International Journal of Drug Policy. December 2015, 26:1171-1176.

Braun M, Wassmer G, Klotz T, et al. Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. Int J Impotence Res 2000; 12: 305-11.

Bourne et al. The Chemsex Study. Sigma Research, London School of Hygiene & Tropical Medicine, 2014.

Brixius K, Middeke M, Lichtenthal A, et al. Nitric oxide, erectile dysfunction and beta-blocker treatment (MR NOED study): benefit of nebivolol versus metoprolol in hypertensive men. Clin Exp Pharmacol Physiol 2007, 34:327-31.

chelwest.nhs.uk; 80% drop in new HIV diagnoses at 56 Dean Street since 2015. Available from:http://www.chelwest.nhs.uk/about-us/news/80-drop-in-new-hiv-diagnoses-at-56-dean-street- since-2015

Collazos J, Martinez E, Mayo J, et al. Sexual Dysfunction in HIV-infected patients treated with HAART. JAIDS 2002; 31:322-26

Collazos J. Sexual dysfunction in the highly active antiretroviral therapy era. AIDS Rev 2007;9:237-45.

Colson AE, Keller MJ, Sax PE, et al. Male sexual dysfunction associated with antiretroviral therapy. J AIDS 2002; 30:27-32.

Cordero A, Bertorneu-Martinez V, Mazon P, et al. Erectile dysfunction in high-risk hypertensive patients treated with beta-blockade agents. Cardiovasc Ther 2010:28:15-22.

Corona G, Rastrelli G, Maseroli E, et al. Inhibitors of 5a-reductase-related side effects in patients seeking medical care for sexual dysfunction. J Endocrinol Invest 2012, 35:915-20

Cove J, Petrak J. Factors associated with sexual problems in HIV-positive gay men. Int J STD AIDS 2004; 15: 732-6.

Crum NF, Furtek KJ, Olson PE, et al. A review of hypogonadism and erectile dysfunction among HIV-infected men during the pre- and post-HAART eras: Diagnosis, pathogenesis, and management. AIDS Patient Care STDS 2005; 19:655-71.

Deimel D, Stöver H, Hößelbarth S, et al. Drug use and health behaviour among German men who have sex with men: Results of a qualitative, multi-centre study. Harm Reduction Journal 2016, 13:36

De Ryck I, Van Laeken D, Nöstlinger C, et al. Sexual satisfaction among men living with HIV in Europe. AIDS Behav 2012, 16:225-30.

De Ryck I, Van Laeken D, Apers L, et al. Erectile Dysfunction, Testosterone Deficiency, and Risk of Coronary Heart Disease in a Cohort of Men Living with HIV in Belgium. J Sex Med 2013, 10:1816-22.

De Tubino Scanavino M. Sexual Dysfunctions of HIV-Positive Men: Associated Factors, Pathophysiology Issues, and Clinical Management. Adv Urol 2011:854792.

Deutsche Gesellschaft für Urologie. Leitlinien: Diagnostik und Therapie von Libido- und Erektionsstörungen 2001. http://www.uni-duesseldorf.de/WWW/AWMF/ll/043-031.htm

Ding H, Du W, Wang H, et al. Efficacy and Safety of Udenafil for Erectile Dysfunction: A Meta-analysis of Randomized Controlled Trials. Urology 2012 Apr 11.

Dirks H, Esser S, Borgmann R, et al. Substance use and sexual risk behaviour among HIV-positive men who have sex with men in specialized out-patient clinics. HIV Med 2012, 13:533-40

Feldman HA, Goldstein I, Hatzichritou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994; 151: 54-61.

Fumaz CR, Ayestaran A, Perez-Alvarez N, et al. Clinical and Emotional Factors Related to Erectile Dysfunction in HIV-Infected Men. Am J Mens Health 2017, 11:647-653.

Goggin K, Engelson ES, Rabkin JG, et al. The relationship of mood, endocrine, and sexual disorders in HIV+ women: an exploratory study. Psychosom Med 1998; 60:11-6.

González-Baeza A, et al. Effectiveness of a mindfulness-based intervention, 2017. IdiPAZ EACS, Poster.

Grinspoon S, Corcoran C, Askari H, et al. Effects of androgen administration in men with the AIDS wasting syndrome. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998; 129:18-26.

Guaraldi G, Luzi K, Murri R, et al. Sexual dysfunction in HIV-infected men: role of antiretroviral therapy, hypogonadism and lipodystrophy. Antivir Ther 2007;12:1059-65.

Hannan JL, Maio MT, Komolova M, et al. Beneficial impact of exercise and obesity interventions on erectile function and its risk factors. J Sex Med. 2009; 6 Suppl 3:254-61.

Hart TA, Moskowitz D, Cox C, et al. The cumulative effects of medication use, drug use, and smoking on erectile dysfunction among men who have sex with men. J Sex Med 2012, 9:1106-13.

Hegazi A, Lee MJ, Whittaker W, et al. Chemsex and the city: sexualised substance use in gay bisexual and other men who have sex with men attending sexual health clinics. Int J STD AIDS 2017, 28:362-366.

Hockenhull J, Murphy KG, Paterson S. An observed rise in g-hydroxybutyrate-associated deaths in London: Evidence to suggest a possible link with concomitant rise in chemsex. Forensic Science International. 2017, 93–97.

Huang JS, Wilkie SJ, Sullivan MP, et al. Reduced bone density in androgen-deficient women with acquired immune deficiency syndrome wasting. J Clin Endocrinol Metab 2001; 86:3533-9.

Huang V, Munarriz R, Goldstein I. Bicycle riding and erectile dysfunction: an increase in interest (and concern). J Sex Med 2005, 2:594-5.

Hudson D. It's time we had a grown-up talk about gay men, drugs and sex. Gaystarnews, Article September 2017

Lallemand F, Salhi Y, Linard F, et al. Sexual dysfunction in 156 ambulatory HIV-infected men receiving highly active antiretroviral therapy combinations with and without protease inhibitors. JAIDS 2002; 30: 187-90.

Lamba H, Goldmeier D, Mackie NE, et al. Antiretroviral therapy is associated with sexual dysfunction and with increased serum oestradiol levels in men. Int J STD AIDS 2004; 15:234-7.

Lasker GF, Maley JH, Kadowitz PJ. A Review of the Pathophysiology and Novel Treatments for Erectile Dysfunction. Adv Pharmacol Sci 2010:730861

Melnik T, Soares BG, Nasselo AG. Psychosocial interventions for erectile dysfunction. Cochrane Database Syst Rev 2007, 18:CD004825.

Mueck B, Koegl C, Wolf E, et al. Sexual dysfunction in an aging HIV positive population compared to HIV negative control groups. Results from the German 50/2010 cohort study. Oral Presentation 10, 1st International Workshop on HIV & Aging, Baltimore, MD, USA,10/2010.

Nehra A. Erectile dysfunction and cardiovascular disease: efficacy and safety of phosphodiesterase type 5 inhibitors in men with these conditions. Mayo Clin Proc 2009, 84:139-48.

NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. JAMA 1993;270:83-90.

Pebody R. Substance use and social problems predict HIV infection in American gay men. NAM Publications, Jan 2015. 24

Postel N, Wolf E, Balogh A, et al. Functional Hypogonadism and Testosterone Deficiency in Aging Males With and Without HIV-infection. Exp Clin Endocrinol Diabetes 2021, 129:798-802

Purcell DW, Wolitski RJ, Hoff CC, et al. Predictors of the use of Viagra, testosterone, and antidepressants among HIV-seropositive gay and bisexual men. AIDS 2005, 19 Suppl 1: S57-66.

Reis LO, Favaro WJ, Barreiro GC, et al. Erectile dysfunction and hormonal imbalance in morbidly male is reversed after gastric bypass surgery: a prospective randomized controlled trial. Int J Androl 2010, 33:736-44.

Rochira V, Zirilli L, Orlando G, et al. Premature decline of serum total testosterone in HIV-infected men in the HAART-era. PLoS One 2011, 6:e28512.

Rubio-Aurioles E, Porst H, Eardley I, et al. Comparing vardenafil and sildenafil in the treatment of men with erectile dysfunction and risk factors for cardiovascular disease: a randomized, doubleblind, pooled crossover study. J Sex Med 2006, 3:1037-49.

Schrader SM, Breitenstein MJ, Lowe BD. Cutting off the nose to save the penis. J Sex.Med 2008, 5:1932-40.

Schrooten W, Colebunders R, Youle M, et al. Sexual dysfunction associated with protease inhibitor containing highly active antiretroviral treatment. AIDS 2004; 15:1019-23.

Shabsigh R, et al. Erectile dysfunction as a predictor for metabolic syndrome. Abstract 1236, 100. Ann Meeting of the AUA 2005, San Antonio.

Spindler H, et al. Use of Viagra and crystal methamphetamine and high-risk sexual behaviour. XVI IAC, Toronto 2006, #MOPE0342

Stuart D. A chemsex crucible: the context and the controversy. J Fam Plann Reprod Health Care 2016, 42:295-296.

Swearingen SG, Klausner JD. Sildenafil use, sexual risk behavior, and risk for sexually transmitted diseases, including HIV infection. Am J Med 2005; 118:569-70.

Taskin U, Yigit O, Acioglu E, et al. Erectile dysfunction in severe sleep apnea patients and response to CPAP. Int J Impot Res. 2009.

Tikkanen MJ, Jackson G, Tammela T, et al. Erectile dysfunction as a risk factor for coronary heart disease: Implications for prevention. Int J Clin Pract. 2007, 61:265-268.

Tindall B, Forde S, Goldstein D, et al. Sexual dysfunction in advanced HIV disease. Aids Care 1994; 6:105-7.

Villarreal D. Meth: Alcohol and Other Drugs Harm More People. Hornet, Article April 15, 2017. 2

Waldkirch E, Schultheiss D, Ückert S, et al. Therapie der erektilen Dysfunktion. In: Truß MC, Stief CG, Machtens S et al. (Hrsg.): Pharmakotherapie in der Urologie. Berlin – Heidelberg: Springer Verlag 2005: 342-52

Wang Q, Young J, Bernasconi E, et al. The prevalence of erectile dysfunction and its association with antiretroviral therapy in HIV-infected men: the Swiss HIV Cohort Study. Antivir Ther 2013, 18:337-44.

Weatherburn B "Chemsex" and harm reduction need among gay men. Int J Drug Policy 2015, 26: 1171-76.

Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med. 2013 Apr 18;11:108.

Trans*Medicine

MARTIN VIEHWEGER

Transmedicine is the general healthcare profile for people who do not identify with the gender they were assigned at birth. Transition describes the process of social, legal, and/or medical alignment with an individual's gender identity, such as through coming out, name change, hormone treatment, and/or surgery. The self-knowledge of being trans* is not freely chosen, and the feelings associated with it cannot simply be turned off or discarded.

The number of consultations on transition processes is increasing (Kost 2022). The extent to which this is a phenomenon of raising awareness or whether the incidence of people in transition is growing cannot yet be ascertained. People in transition who do not have access to medical facilities use the offers of the illegal market in self-experimentation (Viehweger 2022). Although these people gather an astonishing amount of information in their research, uncertainties often remain due to different, sometimes one-sided, and even adversarial views from the community. Medical education, accompaniment, and empowerment can lead to risk reduction, psychological stabilization, and happiness in an otherwise dysphoric setting among a vulnerable, often traumatized group.

Epidemiology

Sexual orientation can be divided into several dimensions:

- gender identity ("how do I feel?", e.g., female, male, other),
- sexual identity/desire or attraction ("sexually attracted to" for example, heterosexual, homosexual, or bisexual),
- gender expression ("how do I present myself to the outside world?", e.g., feminine, masculine, other),
- sex assigned at birth (male/female).

The dimensions do not have to correspond and can change (Cerwenka 2018). Some transgender persons apply to change their civil status and first name. Between 2008 and 2016, these applications increased from 903 to 1,868 per year (Bundesamt für Justiz 2017). The frequency of transgendering is 4.6 per 100,000 people in an international meta-analysis (Arcelus 2015). Regarding intersexuality, about 150 children with "variants/disorders of sex development (DSD)" are born each year in Germany (Bundesärztekammer 2015). According to the German Ethics Council estimate, 80,000 intersex people live in Germany (Höhne 2008).

The heteronormative orientation of society can be a health risk for LGBTI+ persons. Heteronormativity describes the notion that there are exclusively two biologically and socially overlapping genders (women and men) related to each other in their sexual orientation (Wagenknecht 2007). This manifests in normative social expectations that intersex, transsex, and non-heterosexual people do not conform to. Heteronormativity can manifest socially in the non-recognition of innate variations in gender characteristics, gender identity, gender self-representation, or sexual orientation. This lack of recognition can range from prejudice and discrimination to physical and sexual assault (Beigang 2017). It also includes legal regulations that exclude LGBTI+ persons from certain rights. Such experiences can affect physical and mental health and negatively influence health behaviors (Meyer 2003, Hatzenbuehler 2009). For example, the sometimes-pejorative labels of "gay" or "lesbian" can lead to negative internalized attitudes toward homosexuality (Berg 2015), which can foster lower self-acceptance, self-deprecation, or a sense of loneliness

in lesbian, gay, and bisexual people and have a negative impact on mental health (Krell 2015). An essential resource in coping with discriminatory experiences and forming a positive self-image is provided by LGBTI communities and their civil society organizations, which provide important contact, networking, and counseling services. Contact with people with similar life experiences and interests, as well as joint activities, can positively influence psychological well-being (Ceatha 2019).
The lifeworld experience of the trans* persons concerned always has priority. It is about improving the subjective quality of life to feeling comfortable in one's body and the environment. The medical art lies not only in the prescription of hormones but also in the accompaniment. The responsibility is not to take away from the clients – they decide which changes and steps they want to take.
The prevalence of HIV is likely to be significantly higher in transgender people. According to a survey of transgender people in the US, 1.4% lived with HIV, compared to 0.3% in the general population (James 2016). In addition, 46% did not know their HIV status. A review of 88 studies (Becasen 2018) estimated HIV prevalence among transgender women in the United States at 14.1% (95% confidence interval 8.7–22.2) and among transgender men at 3.2% (1.4–7.1). Another review (Baral 2013) was as high as 19.1% (17.4–20.7) globally for transgender women. HIV thus remains a significant health issue for transgender people.

Medical Aspects

In summary, the somatic medical aspect of "trans medicine" is based on a thorough anamnesis, information about effects and side effects of hormonal support, but also about irreversible operations, the prescription, and adjustment of appropriate hormones, laboratory-chemical and somatic course controls, care of pre- and post-operative interventions, as well as being accompanied in the transition process. Finalizing the transition process is unnecessary, but it is very welcome to arrive.
The medical history should include questions about pronouns and first names (both should be marked in the file so they can be used directly to address the patient in the future). The transition history should include experiences (DIY use of hormones so far?), social outing, peer group membership, psychotherapies, and counseling sessions. The joint reflection of visions/exact ideas of what hormones should achieve is elementary (avoid vague terms such as "more masculine/feminine" and record concrete wishes such as "breast growth", "cessation of menstruation", and "beard growth"). Which physical elements need to be transferred from dysphoria to happiness? Can hormones sufficiently fulfill the desired vision (i.e., physical changes will be more or less achievable depending on when the hormonal transition is initiated)?
The decisive factor is the person's individual situation to be accompanied in their process. There is a difference between the continuation of hormone substitution established for years and the new setting of a previously hormone-naïve person. People who present themselves with the wish for an initial prescription of hormones can be adolescents or already in an advanced stage of life. Depending on this, ideas and needs appear with different (side) effects, collateral changes, and risks.

Being supportive

Physical changes require time and patience. In addition, what part of life (when) hormones are started needs to be understood and explored. Physical changes last between 3–24 months, depending on body characteristics (Radix 2014). In the beginning, deciding on a starting dosage is worthwhile, which is also constantly maintained over the first 3–4 months. Especially at the beginning, there are often all kinds of (side) effects, which subside after the first few weeks. After 2–3 months, it is worthwhile to re-evaluate the changes consciously. Accordingly, dose adjustments can be made.

Doctors, psychotherapists, psychiatrists, medical professionals, social workers, nurses, medical assistants, and laboratory assistants should accompany and educate during the transition without blocking the decisions of the transitioning person. This is often not easy for the professionals either: on the one hand, most are socialized within the binary system, making it challenging to act medically outside of a binary mindset. On the other hand, there is always a desire for reassurance (for legal reasons). With the current medical guidelines, this problem has been significantly minimized. It is essential to accompany and support the transitioning person to enable them to make informed decisions.

Hormone substitution

Binary

In the binary model, there is a possibility of alignment from the gender that a person was assigned at birth and likely socialized to the other gender (i.e., male to female or *vice versa*). Many trans* patients are not satisfied until they are recognized in their desired gender. "Passing" as male or female often plays an important role. More diverse approaches, ways of looking at things, and "role models" also lead through the transition process.

The rules of a binary-normed society are usually very narrowly defined. Often, a cis man-born male is accused of effemination, for example, because he wears long hair or nail polish, without defining himself as trans*. Trans* people are repeatedly misread by societies that define them too narrowly. There is no "passing", and the desired attributes are perceived as insufficiently pronounced. A binary-thinking, heteronormative society often has difficulties with re-assignment. This results in problems for the trans* person. However, this assignment is essential for most trans* people, giving support, security, clarity, and structure.

Non-binary

To acquire a sexual identity for oneself, to not have to place oneself in the binary, requires a fundamental process of emancipation. But from what? It takes place on several levels: educational gender (physiognomic gender plus education) – identity formation referential to peer group – gender identity – sexual preference – to name a few. This is not a complete mapping of the process of emancipation and coming out; it is merely an attempt at conceptualization and is not static. This form of emancipation can be perceived as both a potential and a burden. The resources the person has in the process, what environment they grew up in, and how much social or medical support they receive are decisive influencing factors. Last but not least, it depends on how much resistance to the norm the person can muster of their own accord and how much positive resonance and acceptance they receive to deal with stressful situations and to become stronger.

MtF (male to female)

Estrogens: are available on the German pharmacy market as valerate or hemihydrate in oral and transdermal form. Injections are not approved (due to frequent cardiovascular events). It is recommended that the pill form be taken sublingually – this is the most common starting application (convenience). After dose correction, transdermal applications are often prescribed: gel, spray, or patches are applied in this case to areas with little hairy skin, sweating should be avoided at least 1 hour before and after application, and intimate contact should not be made in the corresponding areas for at least 2 hours. The starting dose for a binary transitioning individual is 2 mg estrogen sublingually/day and can reach up to 6–8 mg sublingually, depending on progression. Appropriate conversion tables will help calculate dosage when switching from sublingual to transdermal. The starting dose for non-binary people may vary by half- or quarter-dose per day.

Testosterone blockers: are necessary according to need, sexual culture, and dysphoria. In the Anglo-American and Helvetic area, aldosterone is preferred: it has less neurocognitive effects, less frequent liver disorders, and more polyuria and breast growth (the latter is mainly desired). In the German area (an anti-androgen), cyproterone is often prescribed. Clarifications about possible liver disorders, mental side effects, and unclear effects on dysplasias/neoplasias must be made, but the result is much stronger. People in binary transition receive 100 mg of aldosterone in the morning or, equivalently, 5 mg of cyproterone acetate. People in non-binary transition mostly forgo testosterone receptor (androgen) blockade.

Progesterone: Additional progesterone (rectal, oral, or transdermal) can be given about six months after starting estrogen, depending on individual need. Breast growth and increase in libido, often lost, are possible. However, progesterone always has mental side effects that can be well-integrated or destabilizing, depending on individual resilience. It can be taken cyclically and is more popular in the binary transition context.

FtM (female to male)

Testosterone: is available as a topical gel, 4-week or 3-month injections. The gel has the advantage of daily self-applications, creating less fluctuation, which aligns with circadian rhythms. If there is an aversion to daily confrontation with transition, or if stronger initiating processes (e.g., voice change or suppression of menstruation) are desired, injections are used every four weeks or every three months as a depot. The "hormone gap" (high values shortly after application and low values a few days before the next application) should always be explained. Testosterone as a gel in binary transition is mainly done with two strokes (approx. 20–40 mg) of gel as a start and is mainly kept that way and only rarely increased. In the non-binary spectrum, ½ stroke or a knife tip is sufficient, depending on vision and physical dysphoria. Testosterone as a monthly injection can be given intramuscularly every four weeks and, with the advantage of self-application, offers more independence and less gap between depot doses. Testosterone as a quarterly injection is not possible as a self-administration. Still, it is sometimes done within the community with so-called T-buddies (primarily medically trained people offering peer-to-peer support). Significant gaps between depot doses are sometimes difficult to endure. They often occur at the beginning with a surge of acne, mood swings, an increase in libido, and usually the wait before the subsequent injections with a down or low feeling, lack of concentration, and fatigue. Since low doses with injections are impossible (or wasteful), no options are available for non-binary transitions.

Emancipation and empowerment

Part of the emancipation process may well be "empowering": reclaiming terms that are socially used negatively, as part of the individual non-conforming identity discovery process, as a resource. Many transgender people feel invisible in the binary model because they identify with their male and female parts. Dissolving this missing visibility is difficult because one handles the terms masculinity and femininity without questioning them or finding a definition for oneself. In addition, how then is the leap to leave behind the binary model to define oneself anew, differently, in-between, outside, or beyond?

Glossary, terms, labels

Especially during the time of questioning, coming out, and/or at the beginning of a transition, it is essential for many trans* people to be addressed with the correct name. This provides security and a sense of belonging. Therefore, it is essential to respect labels. Important terms:

Asterisk: Symbol (*), which is used as a placeholder. Trans* thus stands for all terms beginning with the prefix trans-, among others. The use of the asterisk is criticized in the US.

Binary gender system: According to the heteronormative worldview, gender roles are assigned, and identities other than male or female are negated.

I-flat: Inward majuscule to avoid the generic masculine and to address persons of both genders (e.g., I-flat: students).

Cisperson (cis – Latin prefix for "this side"): Is a person whose gender identity matches the sex assigned to them at birth.

Cross-dressers (also transvestites): Wear clothes of the opposite sex for various reasons but usually identify with the sex assigned to them at birth.

Gender gap: This includes people who have a non-binary gender identity (e.g., students).

Gender: The "social sex", describing the socially constructed genders. In English, gender and sex (physical sex) are not equated, unlike in German.

Gender fluid: Attempts to describe a gender identity alternating between two or more genders.

The ***(gender star)** denotes men, women, and all other gender identities simultaneously.

Gender reassignment: Also Gender adjustment, formerly sex reassignment. The medical process intended to align the body or primary and/or secondary sex characteristics with gender identity.

Gender identity or identity gender: Discribes inner consciousness of a person, which gender they have. Possible gender identities include agender (no gender identity), androgynous (both female and male), bigender (alternating between the two), demigender (only partial identification with one gender), gender fluid (alternating between two or more), non-binary (an umbrella term for all gender identities that are neither male nor female), pangender (presence of all gender identities).

Inter* or intersexuality: Describes people whose bodies do not correspond to what is considered physically female or male in society due to primary and secondary sex characteristics and/or chromosome set but who combine characteristics physically constructed as both male and female.

Non-binary: Does not fit into the two-part gender system, i.e., man and woman. Instead, there would have to be another gender description or none at all for it.

TGNS (https://www.tgns.ch): The Transgender Network Switzerland works with various organizations, advises media, and supports trans* people in everything concerning transition and legal advice.

Transwoman: A woman who was classified as a boy at birth because of her body. Acronyms: AMAB (assigned/designated male at birth), MtF (male-to-female).

Transgender (previously, transsexual): Feeling that one does not belong, or only partially belongs, to the sex assigned at birth. Trans* people are transgender. The alternative is the gender variant.

Transition: The process of social, legal, and/or medical alignment with gender identity.

Transman: Male, classified as a girl at birth because of his body. Acronyms: AFAB (assigned/designated female at birth), FtM (female-to-male).

Transperson: A person who does not identify or only partially identifies with the sex assigned at birth.

Transsexual: Outdated term for transgender (see above). Medically correct, but criticized because of the wrong connotation of sexual orientation.

Literature

Arcelus J, Bouman WP, Van Den Noortgate W, et al. Systematic review and meta-analysis of prevalence studies in transsexualism. Eur Psychiatry 2015, 30:807–815

Baral SD, Poteat T, Strömdahl S et al. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. Lancet Infect Dis 2013, 13:214–222

Becasen JS, Denard CL, Mullins MM, et al. Estimating the Prevalence of HIV and Sexual Behaviors Among the US Transgender Population: A Systematic Review and Meta-Analysis, 2006 – 2017. Am J Public Health 2018:e1–e8

Beigang S, Fetz K, Kalkum D, et al. Diskriminierungserfahrungen in Deutschland. Ergebnisse einer Repräsentativ- und einer Betroffenenbefragung. Nomos Verlag, Baden-Baden, 2017.

Berg RC, Weatherburn P, Ross MW, et al. The Relationship of Internalized Homonegativity to Sexual Health and Well-Being Among Men in 38 European Countries Who Have Sex With Men. J Gay Lesbian Ment Health 2016, 19:285–302.

Bundesamt fur Justiz. Zusammenstellung der Geschäftsubersichten der Amtsgerichte fur die Jahre 1995 bis 2016. https://www.bundesjustizamt.de/DE/SharedDocs/Publikationen/Justizstatistik/Geschaeftsentwicklung_Amtsgerichte.pdf;jsessionid=03AA13E646A5B84608D39B33A774A33E.2_cid377?__blob=publicationFile&v=12 (Stand: 10.02.2020)

Bundesärztekammer. Stellungnahme „Versorgung von Kindern, Jugendlichen und Erwachsenen mit Varianten/Störungen der Geschlechtsentwicklung (Disorders of Sex Development, DSD)“ des wissenschaftlichen Beirats. Dtsch Arztebl 2915, 112: A-598/B-510/C-498

Callen-Lorde protocols for the provision of hormone therapy, Asa Radix, MD, MPH 2014

Ceatha N, Mayock P, Campbell J, et al. The Power of Recognition: A Qualitative Study of Social Connectedness and Wellbeing through LGBT Sporting, Creative and Social Groups in Ireland. Int J Environ Res Public Health 2019, 16:3636

Cerwenka S, Brunner F. Sexuelle Identität, sexuelle Attraktion und sexuelles Verhalten – Dimensionen sexueller Orientierungen in der Survey-Forschung. Z Sex-Forsch 2918, 31:277–294.

Hatzenbuehler ML. How does sexual minority stigma “get under the skin”? A psychological mediation framework. Psychol Bull 2009, 135:707–730

Höhne SO, Finke R. Intersexualität bei Kindern. Uni-Med Verlag Ag, 2008 Bremen, London, Boston.

James SE, Herman JL, Rankin S, et al. The Report of the 2015 US Transgender Survey. National Center for Transgender Equality, Washington, DC

Kost C. Geschlechter- und Altersverteilung bei Transsexualität 2021. 23.02.2022 https://www.cornelia-mertens.de/?p=17644

Krell C, Oldemeier K, Muller S. Coming-out – und dann…?! Ein DJI-Forschungsprojekt zur Lebenssituation von lesbischen, schwulen, bisexuellen und trans* Jugendlichen und jungen Erwachsenen. Deutsches Jugendinstitut, Munchen, 2015

Meyer IH. Prejudice, Social Stress, and Mental Health in Lesbian, Gay, and Bisexual Populations: Conceptual Issues and Research Evidence. Psychol Bull 2003, 129:674–697.

Viehweger M. Beobachtung der Schwerpunktpraxis (Infektiologie und Transmedizin) ViRo zwischen 10/2020 – 10/2022

Wagenknecht P. Was ist Heteronormativität? Zu Geschichte und Gehalt des Begriffs. In: Hartmann J, Klesse C, Wagenknecht P et al. (Hrsg) Heteronormativität. Empirische Studien zu Geschlecht, Sexualität und Macht. VS Verlag fur Sozialwissenschaften, 2007. Wiesbaden, S. 17–34

SECTION 7

Prevention

32. Prevention of HIV infection

CHRISTOPH D. SPINNER, CHRISTIAN HOFFMANN

Even more than four decades after AIDS was first described, no effective prophylactic vaccine is available. Several potentially promising vaccine candidates are currently being tested (see *Vaccines*), although none has yet demonstrated sufficient efficacy. Preventive measures will remain indispensable for the time being to avoid HIV infections and to stop this pandemic. Those strategies focusing solely on ABC rules (abstinence, being faithful, condom use) are known to have limitations and have largely been put to one side: in 2020, according to UNAIDS, there were 1.5 million new infections worldwide or about 4,000 per day. Treatment as Prevention (TasP) alone will not be enough either. The "U=U" (undetectable equals untransmittable) campaign, founded in 2016, is now supported by more than 400 organizations in 60 countries. Still, successful ART for all remains an unrealistic goal. The 90-90-90 target issued by UNAIDS in 2015 (90% of all HIV infections are detected, treated, & below detection) was not achieved by the end of 2020, with actual levels at 81-87-91 (UNAIDS 2021), according to the Global AIDS Report.

In many Western countries, it is mainly the first 90 hurdle that causes problems: Of the 91.400 infections in Germany, only about 90% were diagnosed in 2020. Even if 97% of these were treated and of these again, 96% had an undetectable viral load, it can thus still be assumed that there are almost 15,000 viremic people in the country – enough to keep an epidemic alive. In addition, phylogenetic studies revealed that about 30% of new infections are caused by highly viremic recent seroconverters (Chibo 2012).

Additional prevention strategies remain indispensable. With pre-exposure prophylaxis (PrEP), taking antiretroviral agents *before* a risk contact, another effective and safe individual prevention has become available. PrEP is very successful – for example, in England's most prominent HIV clinic, "56 Dean Street", they reduced new diagnoses to a fraction of earlier years within a few months (Nwokolo 2017). About 845,000 people in at least 54 countries were using PrEP to protect against HIV infection in 2020. While this was 43% more than in 2019, it was nowhere near the targeted 3 million worldwide. Most users were in the US, Europe, and a few African countries such as Kenya and South Africa – significant coverage gaps remain in other regions of the world (UNAIDS 2021).

This chapter will describe TasP, PrEP, and other medical prevention strategies such as circumcision. Vaccines and post-exposure prophylaxis (PEP) will be discussed separately.

Treatment as Prevention (TasP)

Rarely has a study attracted so much attention in the medical community. The journal SCIENCE declared the data the "breakthrough of 2011," and "The Economist" even wrote of the "end of AIDS." What had happened? In HTPN052, 1763 HIV-discordant (predominantly heterosexual) couples in the US, India, Brazil, Thailand, and 5 African countries were followed (Cohen 2011). The partners living with HIV had to be antiretrovirally untreated and have CD4 T-cells between 350 and 550/µl. They were subsequently randomized to start ART immediately or only when the CD4 T-cells fell below 250/µl or if AIDS appeared. All couples received intensive education and training on condom use. The primary endpoint was new infections occurring in the negative partners, especially those attributable to the infected partners ("linked infections"). After 1,7 years, 28 infections were identified as "linked". The only infec-

tion in the immediately treated group occurred either before or immediately after ART initiation. Even when this case was counted as linked, the overall effect of ART was 96% protection, unprecedented compared to all prevention interventions ever studied (Karim 2011). Even with more extended observation, there was not a single linked infection when the viral load was below the detection limit in the HIV-positive partner (Cohen 2016).

However, it has long been known that antiretroviral therapies contribute to prevention. Here are a few studies on HIV-discordant couples:

- Among 415 couples in Uganda diagnosed with 90 new infections within 30 months, there was not a single infection when the viral load was below 1,500 copies/mL in the infected partner. With each log level rise, the risk increased by a factor of 2.45 (Quinn 2000).
- In a study of 493 couples from Thailand, the factor was 1.81, and no infection below 1,094 copies/mL was observed (Tovanabutra 2002).
- A study in Spain of 393 heterosexual couples showed a transmission rate of 8.6% from 1991 to 2003. Not a single infection was observed if the infected partners were on ART (Castilla 2005).
- Among 534 MSM in San Francisco, the probability of transmission per partnership decreased by 60% between 1994 and 1998 (Porco 2004). HIV incidence decreased despite a higher number of partners and risk contacts.
- In a Spanish study, 76 pregnancies occurred naturally in 62 couples (22 positive women, and 40 positive men, all on ART). Not a single new HIV infection was observed (Barreiro 2006).

These studies clearly show that the lower the viral load in plasma, the lower the infectivity. In a meta-analysis of 11 cohorts with 5,021 heterosexual couples (and 461 HIV transmissions), not a single transmission was seen below 400 copies/mL (Attia 2009). Antiretroviral therapy has thus become the mainstay of prevention. In 2008, the Federal Commission on AIDS Issues (EKAF) was the first institution in the world to respond publicly to these findings. "HIV-infected people without other STDs are not sexually infectious under effective antiretroviral therapy" was the title of the provocative EKAF paper; it can still be found at https://saez.ch/article/doi/saez.2008.13252 EKAF stated that a person with HIV does not transmit the virus if the following conditions are met:

1. The patient adheres to ART and is monitored regularly by physicians or medical practitioners
2. The viral load has been below the detection limit for at least six months
3. There are no sexually transmitted infections

The EKAF paper initially caused a stir. Critics feared that, despite all the differentiations, it would be misunderstood as an "all-clear" and that people would expose themselves or others to the risk of HIV infection. In the end, these fears did not prove true. Our Swiss colleagues were right. U=U was established.

ART and viral load in other body fluids

Viral load in other body fluids usually parallels that in plasma. Regardless of the chosen ART regimen, decline and rebound occur during treatment interruptions (Palich 2019). In a study of 205 women with plasma viremia below 400, 400–9999, and above 10,000 copies/mL, rates of detectable HIV RNA in the genital tract were 3, 17, and 48%, respectively (Cu-Uvin 2000).

In a few people, HIV RNA remains detectable in bodily fluids despite a plasma viral load of below 50 copies/mL. However, it is unclear whether these are intact, infectious viruses. In ejaculate samples from 304 MSM, HIV RNA was detectable in 20 (6.6%) (Lambert-Niclot 2012) and about 8% in 195 heterosexual African men

(Mujugira 2016). In anal mucosa, HIV RNA was still found in 2% of 143 Thai MSM on ART (Phanuphak 2018), and in cervical swabs from 1,114 African women, it was 5.8%, with a decreasing trend with increasing ART duration (King 2017). In another study in pregnant women, the rate was 2.5%; none of the 7 patients were detectable (although low?) HIV transmitted the infection to the child (Frenkel 2022).

The PARTNER study

But how high is the residual risk when the viral load is below the detection limit? A European study aimed to test the EKAF statement and answer this question. PARTNER-1 enrolled 1,166 HIV-discordant couples (both heterosexual and MSM) in which the infected partners were on ART < 200 copies/mL and who occasionally had condomless sex. HIV-negative partners were tested every six months, and couples also received a detailed questionnaire about their sex lives. After an observation period of 1.3 years and approximately 58,000 condomless sexual contacts, an initial evaluation showed that not a single linked HIV infection had occurred (Rodger 2016). The PARTNER study thus impressively underscored the protective value of ART. A follow-up study of exclusively MSM couples (PARTNER-2) also showed not a single HIV infection transmitted by the positive partner, even when sexually transmitted infections were present. The number of condomless sexual contacts was 76,000, of which the number of contacts involving ejaculation was 20,500 (Rodger 2019).

Meanwhile, the Opposites Attract study is another large study in which not a single infection from the infected partner was observed in 358 MSM couples during nearly 17,000 un-safer sex contacts (Bavinton 2018). Even if the criticism of the PARTNER study remains that only couples were recruited in which transmission had not occurred before the start of the study despite unprotected sex (selection bias?), the transmission risk through condomless sex was quantified as "effectively zero" (Rodger 2019).

A systematic review of 8 studies comprising 7,762 serodiscordant couples across 25 countries recently concluded that there is "almost zero risk of sexual transmission of HIV" with viral loads of less than 1,000 copies per mL (Broyles 2023). Among all studies, two cases of transmission occurred when the index patient's most recent viral load was less than 1,000 copies per mL. However, the interpretation of both cases was complicated by long intervals (i.e., 50 days and 53 days) between the transmission date and the most recent index viral load result.

Counseling HIV discordant couples in times of TasP

So many studies have shown it clearly: effective HIV therapy leads to a negligible risk of HIV transmission. In most cases, the viral load in bodily fluids and plasma drops in parallel. Regarding occasional viruses detected in the ejaculate while on ART, it remains unclear whether they are complete, infectious viruses (Nunnari 2002). Although genital inflammation and the menstrual cycle may influence genital viremia (Curlin 2013), the PARTNER study has shown that HIV transmission is very unlikely even with concurrent STI.

This information can be a significant relief for patients. Nevertheless, there will still be people who want more "security". Clinicians should provide differentiated and individual advice on this issue. No one can guarantee an absolute zero risk. Individual cases are theoretically possible. Much also depends on the decision of the uninfected partner. Pressure should not be exerted under any circumstances. People who continue to use or want a condom sometimes feel discriminated against. Sex should be fun; fear is not a good companion. Clear communication always helps.

One question often helps at this point: Why does this minimal residual risk of becoming infected with HIV remain such a big issue? Some very rational people are some-

times not impressed even by robust data. Transmission risk of probably significantly less than 1:100,000 is still perceived as threatening – at the same time, other risks are consciously taken and calculated. People drive cars or ski, use drugs, smoke, drink, box, dive – all things that probably involve at least similar or much higher health risks. It is not uncommon for AIDS phobia to come to light in such conversations. An irrational fear of HIV can also indicate unresolved conflicts, and the causes of the phobic thoughts often lie deeper. In such cases, (HIV-experienced) psychological counseling can be helpful.

Pre-exposure Prophylaxis (PrEP)

PrEP is the prophylactic use of antiretroviral drugs by people who are not HIV-infected. Unlike PEP, the drugs are taken *before* and not *after* exposure. Continuous PrEP must be distinguished from PrEP on demand. PrEP only makes sense if relevant risks are taken – sex with PLWH whose viral load is below the detection limit is not one of them.

Continuous PrEP with TDF/FTC: This is still the standard and the only approved PrEP in Europe. Table 1 summarizes the data from randomized studies. The first breakthrough study was published at the end of 2010: In iPrEx, 2499 MSM from six countries received either TDF/FTC or placebo. After 1.2 years, 36 versus 64 infections had occurred, corresponding to a 44% reduction in risk of infection (Grant 2010). Only in 3/34 patients with a new infection during the study, tenofovir or FTC was found in the plasma. Other studies also found a similar protective effect (Thigpen 2011, Baeten 2012). However, setbacks were also seen. The FEM-PrEP trial was stopped in April 2011 due to ineffectiveness, and the three-arm VOICE trial in African women also showed no benefit (Marrazzo 2015).

Table 1: Randomized trials (selection) of continuous PrEP with TDF and FTC.

Name, reference	n	Risk group, location: Type of PrEP	Protective effect
Bangkok Tenofovir Study Choopanyia 2013	2,415	IDU in Thailand: TDF	49% with TDF
PARTNERS PrEP Baeten 2012	4,758	Heterosexual couples in Africa: TDF, TDF+FTC	67% with TDF, 75% with TDF+FTC
iPREX Grant 2011	2,499	MSM worldwide: TDF+FTC	44% with TDF+FTC
CAPRISA 004 Abdool 2010	889	Women in South Africa: Vaginal TDF Gel	39% with TDF gel
TDF 2 Thigpen 2012	1,219	Young women and men in Botswana: TDF+FTC	62% with TDF+FTC
FEM-PrEP van Damme 2012	2,064	Women in Kenya, South Africa, and Tanzania: TDF+FTC	None (study stopped)
VOICE Marrazzo 2015	5,029	Women in South Africa, Uganda, and Zimbabwe: TDF+FTC, TDF, vaginal TDF gel	None, neither with TDF or TDF+FTC orally nor with the TDF gel.
PROUD McCormack 2016	544	MSM in the UK: TDF+FTC	86% with TDF+FTC
DISCOVER Ogbuagu 2021	5,387	MSM in Europe and North America: TDF+FTC versus TAF+FTC	IRR for TAF+FTC 0.54 (95% CI: 0.23–1.26)

In some cases, it remained unclear why some studies were successful, and others were not. The most important factor, however, is hardly surprising – adherence: If you don't take PrEP, you won't be protected! In some trials, notably FEM-PrEP and VOICE, adherence was poor for several reasons: the daily tablet or gel applications may have been inconvenient for women, or there may have been insurmountable social barriers. Protection was highest in trials when at least 70% of tablets were taken (Fonner 2016).
However, success also depends on other factors, including HIV prevalence of potential and viral load of infected sexual partners, concurrent STDs, and various biological factors. Sexual behavior and the risks of the situation (condom use, sexual preferences, ChemSex) may also play a role. Finally, it depends on the setting. The higher the risk, the higher the protection: in PROUD, an English study of a total of 544 MSM at increased risk for HIV (unprotected anal sex in the past three months), the effect of TDF/FTC was so impressive (HIV incidence 1.2 versus 9.0/100 person-years) that the study was stopped early (McCormack 2016).
According to a new meta-analysis, unanswered questions remain, especially about efficacy in heterosexual contacts (Murchu 2022).

Frequently asked questions (and answers) about PrEP

- Who is eligible? → People at increased risk of HIV infection: MSM with inconsistent condom use, changing or untreated HIV-infected partners, and people with intravenous drug use.
- How should these groups be identified? → For example, consider PrEP in all patients with an STD or post-exposure prophylaxis in the past.
- How should PrEP be taken? → Approval is for continuous administration (1 x 1 tablet TDF/FTC daily).
- What about PrEP on demand? It is debatable for men with corresponding risk constellation: 2 tablets 2–24 hours before, one each 24 and 48 hours later ("off label" use!). *Of note, this is not an option for women!*
- Are there other options? A large number of on-demand regimens are circulating that are based only on pharmacodynamic considerations but have not been validated and are therefore unsafe
- Who can prescribe PrEP? → Ideally, those experienced in HIV medicine and other specialist groups (pediatrics, gynecology, urology, dermatology) after training.
- How high is the risk of resistance with PrEP in undetected HIV infection? → According to previous experience and mathematical models, the risk is relatively low.
- Who will pay for PrEP? → It depends on the country; see below.
- How to monitor PrEP? → See below.

PrEP on demand with TDF/FTC: Does it have to be daily, continuous use? Not necessarily. In the IPERGAY trial, 400 negative MSM in France and Canada were instructed to take two TDF/FTC or placebo tablets each before (2–24 hours) and one tablet each 24 and 48 hours after high-risk sexual contacts. After nine months, only 2 HIV infections had occurred in the active arm, compared to 14 on placebo (0.9 versus 6.6/100 person-years) – an 86% reduction (Molina 2015). There were more gastrointestinal (14% vs. 5%, p=0.002) and renal adverse events (18% vs. 10%, p=0.03) on TDF/FTC. In a more extended observation, the protective effect increased even more, rising to 97% (Molina 2017). Although adherence was also far from perfect in IPERGAY, protection was thus at least as high as in studies with continuous PrEP. In women, on the other hand, occasion-based PrEP does not appear to be

as effective (Bekker 2017). Compared with colorectal tissue, levels of TDF/FTC rise more slowly in the female genital tract and fall more rapidly (Cottrell 2016). Thus, on-demand PrEP with TDF/FTC is unsuitable for women and cannot be recommended.

PrEP failure, risks, problems

Reports of true PrEP failures have been relatively rare to date. If they do occur, they mainly occur with PrEP on demand, in those cases when PrEP was not taken or not taken correctly. Meanwhile, some cases have been described in which infection with multidrug-resistant strains of HIV occurred despite correctly taking PrEP (Knox 2017, Markowitz 2017, Colby 2018). It does not have to be multidrug resistance – even the combination of M184V and K65R is likely sufficient to nullify the effect of PrEP (Koole 2022). In contrast, transmission of non-resistant viruses despite good PrEP adherence has been a rarity to date (Cohen 2018).

The emergence of resistance through PrEP also appears to be a relatively rare phenomenon. In a systematic review of 13 randomized trials in which 622 transmissions occurred on PrEP or placebo, resistance to TDF or FTC was found in 19 (3%) (Gibas 2019). According to a recent review, the risk was also relatively low; resistance was observed mainly in acute HIV infection at study inclusion and mostly involved FTC (Murchu 2022). In London, the rate of primary FTC resistance was 30% if PrEP was used before infection, compared with 1% not having taken PrEP (Girometti 2022). In contrast, in the IPERGAY trial, no resistance was found among the 31 patients who became infected despite PrEP use (Delaugerre 2018).

In any case, the low risk of resistance is no argument against it: it is estimated that for every case of FTC resistance caused by PrEP, between 5–40 new infections can be prevented. It should be noted that with PrEP, if infection does occur, antibody formation is delayed. It may therefore make sense to determine viral load immediately in case of doubt. The viral load is often low on PrEP (Marzinke 2021).

Overall, PrEP is safe: in a systematic analysis, no more adverse events occurred with TDF/FTC than with placebo (Fonner 2016). However, long-term observations over more than three or five years are lacking. Experience with TDF/FTC from antiretroviral therapy may not always translate to PrEP. PrEP places exceptionally high demands on physician education as a treatment for healthy individuals. Potential risks such as bone density reduction or nephrotoxicity, but also a possible increased STD risk, must be weighed against the individual HIV risk. However, the risk of renal events seems very low, at least in young people with healthy kidneys. According to a recent meta-analysis, it can be considered to limit renal monitoring to the elderly, individuals with creatinine clearance less than 90 mL/min, and those with pre-existing renal disease (Schaefer 2022).

A significant problem is adherence. A review of 59 studies with nearly 44,000 participants found a 41% dropout rate within six months (Zhang 2022). In a recent study from Washington, 27% of all MSM with newly diagnosed HIV infection had prior PrEP experience, and more than 50% had discontinued PrEP less than six months earlier (Cannon 2022).

PrEP in practice

TDF/FTC has been licensed as continuous PrEP since 2016, but there is still a great deal of variation among countries in terms of the scale of implementation. In around 20 European countries such as France, Belgium, Spain or Germany, PrEP is provided or reimbursed. In others, generic PrEP is available in healthcare settings but is not fully reimbursed or is only available through pilot, research, or demonstration projects. There is no formal implementation of PrEP in numerous other countries in

central Europe, the Baltic states, the Balkans, and Central Asia, in Russia or Turkey. According to the European Centre for Disease Prevention and Control, 17 European countries (five in the EU) had not formally implemented PrEP in their healthcare systems. Specific key populations, such as people who inject drugs, prisoners, and undocumented immigrants, remain ineligible for PrEP in many European countries (ECDC 2023). However, the situation regarding PrEP implementation and availability in Europe is fast-moving and evolving.

In some countries, PrEP care also includes the necessary laboratory tests, particularly for HIV and syphilis. Individualized counseling with careful risk evaluation of potential PrEP users remains essential to check the actual indication (repeatedly!) and avert possible failure due to improper use. Checklists have proven helpful in this context. Around 30 National PrEP guidelines were published very soon after approval in Europe and are valuable tools (Spinner 2019).

Practical PrEP checklist (short version)

- Patients are tested at baseline with the 4th generation p24/HIV antibody test and informed about indication, risks, costs, and controls.
- There is no replicative hepatitis B (check vaccination indication!) and no evidence of acute retroviral syndrome.
- Four weeks after starting PrEP, repeat 4th generation p24 antigen/HIV antibody test to exclude HIV infection in the diagnostic window.
- TDF/FTC is safe only if creatinine clearance or GFR > 80 mL/min, to be carefully weighed at 60–80 mL/min, and is contraindicated if below 60 mL/min.
- Follow-up visits every three months (HIV, syphilis, renal function); if eGFR > 80 mL/min and absence of other renal risk factors, creatinine monitoring can be extended to 6–12 months.
- Three-month intervals apply for HIV and syphilis testing, even later, and also for on-demand PrEP – HIV infections should not be overlooked!
- Risk-adapted testing for STIs such as gonococci, syphilis, chlamydia (swabs can also be taken by patients if needed), and hepatitis C.

Future PrEP

Two approaches, in particular, can potentially replace TDF/FTC in the future. These are TAF/FTC and the long-acting INSTI cabotegravir.

TAF/FTC: In DISCOVER, the largest PrEP study involving just over 5,000 MSM and transgender women, continuous administration of TAF/FTC was non-inferior to TDF/FTC in a double-blinded randomized comparison (Mayer 2020). The risk of infection was nearly halved after 96 weeks (Ogbuagu 2021). In the US, PrEP with TAF/FTC was approved for MSM and transgender women in August 2019. This does not apply to Europe: in 2021, Gilead announced it would not pursue a marketing authorization for PrEP in the European Union.

Due to the significantly higher costs of TAF/FTC (Descovy®) of > 500 euros per month and the current lack of reimbursement for PrEP, this option continues to play little role in most countries. However, TAF/FTC "on private prescription" may be an option for nephroprotection – especially in older people with pre-existing renal disease. The pharmacokinetic profile is comparatively favorable – protective levels can be achieved faster and longer with TAF (Mayer 2020). It should be emphasized, however, that no clinical studies have been conducted to date on TAF/FTC as PrEP on-demand.

Cabotegravir (Apretude®) is the first long-acting injectable PrEP, which is developed by ViiV Healthcare. Apretude® does not contain tenofovir or FTC but the second-

generation INSTI cabotegravir. In two large studies, long-acting cabotegravir 600 mg (CAB-LA, injected intramuscularly every eight weeks) was tested against TDF+FTC, including a global trial in 4,500 MSM (HPTN 083) and one in 3,200 women (HTPN 084). In HPTN 083, CAB-LA was superior, with an incidence of 0.41 versus 1.22 per 100 person-years (Landovitz 2021); the trial was terminated early. As a caveat, however, the difference occurred primarily because many participants randomized to TDF/FTC had not been taking their PrEP regularly. In addition, four unexplained infections were observed with CAB-LA, surprisingly, *despite* timely injections and adequate drug levels. Very similar results were also observed in HTPN 084 (Delany-Moretlwe 2022). In this study, the protective effect of cabotegravir was also more significant, primarily because adherence was poor in the TDF/FTC arm. Levels suggesting daily use of TDF/FTC were found in only 42% of women.

Besides the acceptability of regular intramuscular injections, the critical question is how to deal with the long "PK tail" – cabotegravir levels decline slowly over months after administration. In one PrEP study, 23% of men and 63% of women still had detectable levels 60 weeks after their last injection, and some still had detectable levels two or even three years later (Landovitz 2018). These suboptimal levels could mean a significantly increased risk of resistance, as shown in the monkey model (Radzio-Basu 2019).

The so-called "Long-acting Early Viral Inhibition" (LEVI) Syndrome was first described in early 2023. This means getting an HIV infection while on CAB-LA PrEP. Due to the cabotegravir plasma levels, viral replication is much lower; often, people have minimal or very few symptoms, if any. On an ultrasensitive RNA test, viremia is usually low or still undetectable, leading to delayed antibody production. Unfortunately, the development of resistance in LEVI cases is the rule rather than the exception. Further research is needed to evaluate the use of HIV RNA screening in this setting and if the LEVI syndrome occurs with other potent, long-acting PrEP agents.

However, in December 2021, the FDA approved Apretude® for use in at-risk adults and adolescents weighing at least 35 kilos for PrEP to reduce the risk of sexually acquired HIV. Approval in Europe is expected by mid-2023. We will see whether the availability of long-acting injectable PrEP will increase PrEP uptake and adherence in these groups.

Taken together, CAB-LA PrEP represents a tremendous advance in HIV prevention options. A potential "cost" of rolling out this prevention intervention may be the risk of INSTI resistance among persons who acquire HIV while using CAB-LA (review of pros and cons: Parikh 2022).

Other approaches: Of interest is the nucleoside reverse transcriptase translocation inhibitor islatravir. It persists for a long time in PBMCs, with a half-life of over 100 hours. An initial study proved potential protective protection over 12 months with a subdermal implant (Matthews 2021). Two significant Phase III trials, Impower-022 and -024, evaluated monthly doses of islatravir against TDF/FTC. However, after lymphopenias were observed, enrollment was initially halted in December 2021 (see *New Drugs*). Likely, the islatravir as a PrEP option will not be pursued further. However, besides TAF, cabotegravir, and islatravir, various other compounds are in clinical testing, including lenacapavir and monoclonal antibodies (review: Cambou 2021).

Medical prevention, in addition to TasP and PrEP

The risk of sexual transmission of HIV is significantly lower than generally assumed. According to a meta-analysis, it is estimated at 1.4% for receptive anal intercourse per contact and markedly lower for vaginal intercourse (Patel 2014). It is reduced by

99.2% by condoms and ART. Viral load, genital lesions, and STDs, as well as acute HIV infection, can significantly increase the risk of transmission. And yet, HIV transmission is a – relatively – rare event. Therefore, to test the effectiveness of a prevention strategy, huge populations are often needed, which have to be observed over a long period. It is all the more admirable how many excellent studies have been conducted in recent years on PrEP, such as microbicides and circumcision.

Circumcision

Circumcision of the male foreskin reduces the risk of infection by various pathogens during condomless sexual intercourse. This also applies to HIV. Large randomized trials involving more than 10,000 heterosexual men in Uganda, Kenya, and South Africa saw a 50–60% reduction in HIV transmission risk. A meta-analysis of 49 studies found a relative risk of 0.58 for circumcision (Sharma 2018). This protection is explained by the presence of CD4-positive Langerhans cells, the primary target cells of HIV, in the male foreskin. However, in MSM, the protective effect of circumcision is likely lower at 23% (Yuan 2019). WHO therefore recommends circumcision as a preventive measure only for heterosexual men.

The procedure is not without problems. Surgical complications (infections, postoperative bleeding) occur in about 3–4%. Sexual behavior after circumcision, and ethical and logistical problems are only some issues (Lie 2006). It should be noted that while the risk is reduced for circumcised heterosexual men, it is not reduced for their female partners. In a randomized trial in Uganda, the wives of circumcised men tended to become infected more often (Wawer 2009). The main reason was probably that couples had sex earlier than recommended after the procedure. Maintaining a waiting period of several weeks after the procedure is essential.

Preventive treatment of HSV and other pathogens

Genital infections significantly increase the risk of contracting HIV. Bacterial vaginosis, for example, increases the transmission from women to men by threefold (Cohen 2012). Human herpesvirus 2 (HSV-2) is particularly relevant for prevention, especially since this virus can be readily quantified and measured. Interestingly, HIV viral load increases in plasma and vaginal fluid when HSV infection occurs (LeGoff 2007). According to a meta-analysis, HIV risk increases by 2.7 for men and 3.1 for women when HSV-2 seropositivity is present – when antibodies to HSV-2 are detectable in the blood (Freeman 2006).

Prevalent HSV-2 infection (HSV-2 seropositivity) is associated with a three-fold increased risk of HIV acquisition among both men (relative risk 2,7) and women (3.1) in the general population (Freemann 2006). Thus, a substantial proportion of new HIV infections is attributable to concomitant HSV infection, with estimates of 38–69% for women and 8–49% for men. For this reason, several studies have investigated the protective value of herpes treatment in HIV-negative and HIV-positive individuals.

People without HIV: Can HSV-2 suppression with acyclovir reduce the risk of HIV-1 acquisition? HPTN 039, a Phase III study, addressed this question (Celum 2008). A total of 1871 homosexual men from the US and Peru and 1380 women from Zimbabwe, Zambia, and South Africa received 400 mg of oral acyclovir or placebo twice daily. All participants were HIV-negative and HSV-2 positive at baseline. Although fewer HSV ulcers were observed in the active arm, HIV incidence was not reduced in the acyclovir arm (3.9/100 person-years) compared with placebo (3.3/100). The disappointing results were confirmed by the Mwanza trial, which also found no reduction in 821 women in Tanzania (Watson-Jones 2008). The reason for this is unclear – resistance to acyclovir is probably not the reason. It is likely that

genital HSV reactivation cannot be prevented by acyclovir (Johnston 2012). The approach of using acyclovir to prevent HIV in HIV-negative individuals is invalid. Azithromycin prophylaxis, which can at least prevent bacterial STIs, also had no protective effect (Kaul 2004).

People with HIV: Can transmission rates be reduced if partners with HIV, rather than those who are HIV-negative, are treated with acyclovir? A large study of 3,408 discordant African couples had no effect despite a significantly reduced rate of genital HSV ulcers (Celum 2010). However, this and other studies showed a weak but still measurable effect of acyclovir on HIV viral load as an interesting side effect. According to a meta-analysis, it is as high as 0.33 log levels with acyclovir or valaciclovir (Ludema 2011). This even led to a certain reduction in the risk of HIV progression in untreated PLWH (Lingappa 2010, Reynolds 2012). Fortunately, standard dose acyclovir or valacyclovir does not appear to select for HIV resistance (Baeten 2011). There is also evidence of an antiretroviral effect in pregnant women (Roxby 2012) or in breast milk (Drake 2012), which can be increased by higher doses of valacyclovir (Perti 2013). The hope for new, potent acyclovir derivatives (Van de Perre 2008, Vanpouille 2010) has not yet been realized.

Microbicides, lubricating creams, diaphragm

Microbicides are chemical agents, usually applied topically as vaginal gels, that kill or immobilize HIV and other pathogens. Heterogeneous mechanisms are currently being investigated. These include inactivating substances that destroy viral structures and agents that inhibit docking to the target cell or antiretroviral drugs. The perfect microbicides would not only be cheap, easy to use, and non-toxic but preferably also active against other STIs, as these increase the risk for HIV transmission, as described above.

Inactivating microbicides: No product has demonstrated a convincing protective effect to date. In large randomized studies, the risk of HIV transmission even increased in some cases, as under nonoxynol-9 or cellulose sulfate (van Damme 2008). PRO 2000 was also ineffective (McCormack 2010), as was the use of diaphragms and/or lubricating creams (Padian 2007).

Antiretroviral microbicides: In September 2010, the results of the CAPRISA trial gained much attention. In this study, a 1% tenofovir gel was studied double-blinded in 889 HIV-negative women in South Africa (Abdool Karim 2010). HIV incidence was reduced from 9.1 to 5.6/100 years by the gel versus placebo. There was as much as a 54% reduction in transmission risk in women who used the gel regularly. The safety and tolerability of tenofovir gel was excellent. Despite minimal use, hundreds of thousands of infections could be prevented in countries like South Africa (Williams 2011). Following this initial success ("proof of concept"), microbicide research has focused on antiretroviral agents, including, for example, the experimental NNRTI dapivirine. Two large Phase III trials (ASPIRE and IPM 037) of dapivirine-containing vaginal rings applied monthly showed 27% and 31% protection, respectively (Baeten 2016, Nel 2016). Nevertheless, many unanswered questions/problems remain, including acceptance and adherence, bioavailability, and, most importantly, the relatively moderate efficacy to date (Review: Traore 2018). No microbicide has yet made it to the market.

Doxy-PEP

Is Doxy-PEP a new option to reduce the STD burden in the MSM community? A large open-label, randomized study involving 501 PLWH or MSM and transgender women who were taking PrEP were randomly assigned to take 200 mg of

doxycycline within 72 hours ***after*** condomless sex (doxycycline post-exposure prophylaxis, doxy-PEP) or receive standard care (PrEP) without doxycycline (Luetkemeyer 2023). All participants had at least one STD in the past year. In the intervention arm, the incidences of the three STIs evaluated were markedly lower (combined by two-thirds), namely gonorrhea, chlamydia, and syphilis. Of the participants with gonorrhea culture available, tetracycline-resistant gonorrhea occurred in 5 of 13 in the doxycycline group and 2 of 16 in the standard care group. The authors concluded that their findings "support its use among MSM with recent bacterial STIs". Doxy-PEP after condomless sex has also been beneficial against syphilis and chlamydia, although not gonorrhea, in a study in France (Molina 2018).

By early 2023, it seems too early to recommend this strategy, as the long-term consequences are unknown, especially the risk of selection and dissemination of syphilis and chlamydia strains with doxycycline resistance. Another problem could be the still unknown effects on the human microbiome. Finally, the decision for doxy-PEP (other than HIV PrEP) is not private; one must consider that widespread implementation of doxy-PEP could generate antimicrobial resistance in non-target pathogens and commensals. However, while leading to reductions in population-level transmission of STDs, doxy-PEP could reduce population-level consumption of antibiotics used to treat STDs, which might offset some of the increase in the use of doxycycline for doxy-PEP. While markedly reducing STDs, this could also have beneficial effects on HIV transmission. Clear guidelines for the community and clinicians on doxy-PEP's utility and potential risks are urgently needed.

Literature

Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for preventing HIV infection in women. Science 2010, 329:1168-74.

Attia S, Egger M, Müller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS. 2009, 23:1397-404.

Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med 2012, 367:399-410.

Baeten JM, Lingappa J, Beck I, et al. Herpes simplex virus type 2 suppressive therapy with acyclovir or valacyclovir does not select for specific HIV-1 resistance in HIV-1/HSV-2 dually infected persons. J Infect Dis 2011, 203:117-21.

Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women. N Engl J Med. 2016 Feb 22. [Epub ahead of print].

Barreiro P, del Romero J, Leal M, et al. Natural pregnancies in HIV-serodiscordant couples receiving successful antiretroviral therapy. J AIDS 2006;43:324-6.

Bavinton BR, Pinto AN, Phanuphak N, et al. Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study. Lancet HIV 2018, 5:e438-e447.

Bekker LG, Roux S, Sebastien E, et al. Daily and non-daily pre-exposure prophylaxis in African women (HPTN 067/ADAPT Cape Town Trial): a randomised, open-label, phase 2 trial. Lancet HIV 2017 Oct 3.

Broyles LN, Luo R, Boeras D, Vojnov L. The risk of sexual transmission of HIV in individuals with low-level HIV viraemia: a systematic review. Lancet 2023, S0140-6736(23)00877-2.

Cambou MC, Landovitz RJ. Challenges and Opportunities for Preexposure Prophylaxis. Top Antivir Med 2021;29:399-406.

Cannon CA, Ramchandani MS, Buskin S, Dombrowski J, Golden MR. Previous Pre-Exposure Prophylaxis Use Among Men Who Have Sex with Men Newly Diagnosed with HIV Infection in King County, Washington. J AIDS 2022 Apr 29.

Castilla J, Del Romero J, Hernando V, et al. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. J AIDS 2005, 40:96-101.

Celum C, Wald A, Hughes J, et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomized, double-blind, placebo-controlled trial. Lancet 2008, 371:2109-19.

Celum C, Wald A, Lingappa JR, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. NEJM 2010, 362:427-39.

Chibo D, Kaye M, Birch C. HIV transmissions during seroconversion contribute significantly to new infections in men who have sex with men in Australia. AIDS Res Hum Retroviruses 2012, 28:460-4.

Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2013, 381:2083-90.

Coelho LE, Torres TS, Veloso VG, et al. Pre-exposure prophylaxis 2.0: new drugs and technologies in the pipeline. Lancet HIV 2019, 6:e788-e799.

Cohen CR, Lingappa JR, Baeten JM, et al. Bacterial vaginosis associated with increased risk of female-to-male HIV-1 transmission: a prospective cohort analysis among African couples. PLoS Med 2012, 9:e1001251.

Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. N Engl J Med 2016, 375:830-9.

Cohen MS, Ying QC, McCauley M, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. N Engl J Med 2011; 365:493-505

Cohen SE, Sachdev D, Lee SA, et al. Acquisition of tenofovir-susceptible, emtricitabine-resistant HIV despite high adherence to daily pre-exposure prophylaxis: a case report. Lancet HIV. 2018 Nov 29.

Colby DJ, Kroon E, Sacdalan C, et al. Acquisition of Multidrug-Resistant Human Immunodeficiency Virus Type 1 Infection in a Patient Taking Preexposure Prophylaxis. Clin Infect Dis 2018, 67:962-964

Cottrell ML, Yang KH, Prince HM, et al. A Translational Pharmacology Approach to Predicting Outcomes of Preexposure Prophylaxis Against HIV in Men and Women Using Tenofovir Disoproxil Fumarate With or Without Emtricitabine. J Infect Dis 2016, 214:55-64.

Curlin ME, Leelawiwat W, Dunne EF, et al. Cyclic changes in HIV shedding from the female genital tract during the menstrual cycle. J Infect Dis 2013, 207:1616-20.

Cu-Uvin S, Caliendo AM, Reinert S, et al. Effect of HAART on cervicovaginal HIV-1 RNA. AIDS 2000, 14: 415-21.

Delany-Moretlwe S, Hughes JP, Bock P, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. Lancet 2022, 399:1779-1789.

Delaugerre C, Rodriguez C, Capitant C, et al. Drug resistance among patients who acquired HIV infection in a preexposure prophylaxis trial. AIDS. 2018 Oct 23;32(16):2353-2361.

Drake AL, Roxby AC, Ongecha-Owuor F, et al. Valacyclovir suppressive therapy reduces plasma and breast milk HIV-1 RNA levels during pregnancy and postpartum: a randomized trial. J Infect Dis 2012, 205:366-75.

ECDC EVIDENCE BRIEF. Pre-exposure prophylaxis for HIV prevention in Europe and Central Asia 2022 progress report, February 2023. Available at https://www.ecdc.europa.eu/sites/default/files/documents/hiv-infection-prevention-pre-exposure-prophylaxis-dublin-declaration-feb-2023.pdf.

Eshleman SH, Fogel JM, Piwowar-Manning E, et al. The LEVI syndrome: characteristics of early HIV infection with cabotegravir for PrEP. Abstract #160, CROI 2023, Seattle.

Fonner VA, Dalglish SL, Kennedy CE, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. AIDS 2016, 30:1973-83.

Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. AIDS 2006;20:73-83.

Frenkel LM, Morrison RL, Fuller TL, et al. Brief Report: Vaginal Viral Shedding With Undetectable Plasma HIV Viral Load in Pregnant Women Receiving 2 Different Antiretroviral Regimens: A Randomized Clinical Trial. J Acquir Immune Defic Syndr. 2021 Dec 1;88(4):361-365.

Gibas KM, van den Berg P, Powell VE, Krakower DS. Drug Resistance During HIV Pre-Exposure Prophylaxis. Drugs 2019, 79:609-619.

Girometti N, McCormack S, Tittle V; 56 Dean Street Collaborative Group. Rising rates of recent preexposure prophylaxis exposure among men having sex with men newly diagnosed with HIV: antiviral resistance patterns and treatment outcomes. AIDS 2022, 36:561-566.

Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010, 363:2587-99.

Johnston C, Saracino M, Kuntz S, et al. Standard-dose and high-dose daily antiviral therapy for short episodes of genital HSV-2 reactivation: three randomised, open-label, cross-over trials. Lancet. 2012, 379:641-7.

Karim SS, Karim QA. Antiretroviral prophylaxis: a defining moment in HIV control. Lancet 2011, 378:e23-5.

Kaul R, Kimani J, Nagelkerke NJ, et al. Monthly antibiotic chemoprophylaxis and incidence of sexually transmitted infections and HIV-1 infection in Kenyan sex workers: a randomized controlled trial. JAMA 2004;291:2555-62.

King CC, Ellington SR, Davis NL, et al. Prevalence, Magnitude, and Correlates of HIV-1 Genital Shedding in Women on Antiretroviral Therapy. J Infect Dis 2017, 216:1534-1540

Knox DC, Anderson PL, Harrigan PR, Tan DH. Multidrug-Resistant HIV-1 Infection despite Preexposure Prophylaxis. N Engl J Med 2017, 376:501-502.

Lambert-Niclot S, Tubiana R, Beaudoux C, et al. Detection of HIV-1 RNA in seminal plasma samples from treated patients with undetectable HIV-1 RNA in blood plasma on a 2002-2011 survey. AIDS 2012, 26:971-5.

Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. N Engl J Med 2021, 385:595-608. 34379922.

Landovitz RJ, Li S, Eron JJ Jr, et al. Tail-phase safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in HIV-uninfected adults: a secondary analysis of the HPTN 077 trial. Lancet HIV 2020;7:e472-e481.

LeGoff J, Weiss HA, Gresenguet G, et al. Cervicovaginal HIV-1 and herpes simplex virus type 2 shedding during genital ulcer disease episodes. AIDS 2007;21:1569-78.

Lie RK, Emanuel EJ, Grady C. Circumcision and HIV prevention research: an ethical analysis. Lancet 2006; 368: 522-5.

Lingappa JR, Baeten JM, Wald A, et al. Daily aciclovir for HIV-1 disease progression in people dually infected with HIV-1 and herpes simplex virus type 2: a randomised placebo-controlled trial. Lancet 2010, 375:824-33.

Ludema C, Cole SR, Poole C, Chu H, Eron JJ. Meta-analysis of randomized trials on the association of prophylactic acyclovir and HIV-1 viral load in individuals coinfected with herpes simplex virus-2. AIDS 2011, 25:1265-9.

Luetkemeyer AF, Donnell D, Dombrowski JC, et al. Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections. N Engl J Med 2023, 388:1296-1306.

Markowitz M, Grossman H, Anderson PL, et al. Newly Acquired Infection With Multidrug-Resistant HIV-1 in a Patient Adherent to Preexposure Prophylaxis. J AIDS 2017, 76:e104-e106.

Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. N Engl J Med 2015, 372:509-18.

Marzinke MA, Grinsztejn B, Fogel JM, et al. Characterization of Human Immunodeficiency Virus (HIV) Infection in Cisgender Men and Transgender Women Who Have Sex With Men Receiving Injectable Cabotegravir for HIV Prevention: HPTN 083. J Infect Dis. 2021 Nov 16;224(9):1581-1592.

Matthews RP, Patel M, Barrett SE, et al. Safety and pharmacokinetics of islatravir subdermal implant for HIV-1 pre-exposure prophylaxis: a randomized, placebo-controlled phase 1 trial. Nat Med. 2021 Oct;27(10):1712-1717.

Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet 2020, 396:239-254. 32711800.

McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 2016, 387:53-60.

McCormack S, Ramjee G, Kamali A, et al. PRO2000 vaginal gel for prevention of HIV-1 infection (Microbicides Development Programme 301): a phase 3, randomised, double-blind, parallel-group trial. Lancet 2010, 376:1329-37.

Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. N Engl J Med 2015, 373:2237-46.

Molina JM, Charreau I, Spire B, ANRS IPERGAY Study Group. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV 2017, 4:e402-e410.

Molina JM, Charreau I, Chidiac C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. Lancet Infect Dis 2018; 18:308-317.

Mujugira A, Coombs RW, Heffron R, et al. Seminal HIV-1 RNA Detection in Heterosexual African Men Initiating Antiretroviral Therapy. J Infect Dis 2016, 214:212-5.

Murchu EO, Marshall L, Teljeur C, et al. Oral pre-exposure prophylaxis (PrEP) to prevent HIV: a systematic review and meta-analysis of clinical effectiveness, safety, adherence and risk compensation in all populations. BMJ Open 2022, 12(5):e048478. 35545381.

Nel A, van Niekerk N, Kapiga S,et al. Safety and Efficacy of Dapivirine Vaginal Ring for HIV-1 Prevention in African Women. NEJM 2016, 375:2133-43.

Nunnari G, Otero M, Dornadula G, et al. Residual HIV-1 disease in seminal cells of HIV-1-infected men on suppressive HAART: latency without on-going cellular infections. AIDS 2002;16:39-45.

Nwokolo N, Hill A, McOwan A, Pozniak A. Rapidly declining HIV infection in MSM in central London. Lancet HIV 2017, 4:e482-e483.

Ogbuagu O, Ruane PJ, Podzamczer D, et al. Long-term safety and efficacy of emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV-1 pre-exposure prophylaxis: week 96 results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet HIV 2021, 8:e397-e407. 34197772.

Padian NS, van der Straten A, Ramjee G, et al. Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomised controlled trial. Lancet 2007;370:251-61.

Palich R, Ghosn J, Chaillon A et al. Viral rebound in semen after antiretroviral treatment interruption in an HIV therapeutic vaccine double-blind trial. AIDS 2019, 33:279-284.

Parikh UM, Koss CA, Mellors JW. Long-Acting Injectable Cabotegravir for HIV Prevention: What Do We Know and Need to Know about the Risks and Consequences of Cabotegravir Resistance? Curr HIV/AIDS Rep 2022; 19:384-393.

Patel P, Borkowf CB, Brooks JT, et al. Estimating per-act HIV transmission risk: a systematic review. AIDS 2014, 28:1509-19.

Perti T, Saracino M, Baeten JM, et al. High-dose Valacyclovir Decreases Plasma HIV-1 RNA More Than Standard-dose Acyclovir in HIV-1, HSV-2 Positive Persons: a Randomized, Crossover Trial. J Acquir Immune Defic Syndr. 2013 Mar 28. [Epub ahead of print].

Phanuphak N, Pattanachaiwit S, Pankam T, et al. Sexually transmitted infections and HIV RNA levels in blood and anogenital compartments among Thai men who have sex with men before and after antiretroviral therapy: implication for Treatment as Prevention programme. J Int AIDS Soc 2018, 21:e25186.

Porco TC, Martin JN, Page-Shafer KA, et al. Decline in HIV infectivity following the introduction of HAART. AIDS 2004, 18:81-8.

Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of HIV type 1. N Engl J Med 2000, 342:9219.

Radzio-Basu J, Council O, Cong ME, et al. Drug resistance emergence in macaques administered cabotegravir long-acting for pre-exposure prophylaxis during acute SHIV infection. Nat Commun 2019, 10:2005.

Reynolds SJ, Makumbi F, Newell K, et al. Effect of daily aciclovir on HIV disease progression in individuals in Rakai, Uganda, co-infected with HIV-1 and herpes simplex virus type 2: a randomised, double-blind placebo-controlled trial. Lancet Infect Dis 2012, 12:441-8.

RKI. HIV in Deutschland 2020. Epidemiologisches Bulletin 25.11.2021. https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2021/47/Art_01.html

Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. Lancet 2019, 393:2428-38.

Rodger AJ, Cambiano V, Bruun T, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. JAMA 2016; 316:171-181.

Roxby AC, Drake AL, Ongecha-Owuor F, et al. Effects of valacyclovir on markers of disease progression in postpartum women co-infected with HIV-1 and herpes simplex virus-2. PLoS One 2012, 7:e38622.

Schaefer R, Amparo da Costa Leite PH, Silva R, et al. Kidney function in tenofovir disoproxil fumarate-based oral pre-exposure prophylaxis users: a systematic review and meta-analysis of published literature and a multi-country meta-analysis of individual participant data. Lancet HIV 2022, 9:e242-e253. 35271825.

Sharma SC, Raison N, Khan S, et al. Male circumcision for the prevention of human immunodeficiency virus (HIV) acquisition: a meta-analysis. BJU Int 2018, 121:515-526.

Spinner CD, Lang GF, Boesecke C, et al. Summary of German-Austrian HIV PrEP guideline. HIV Med 2019, 20:368-376.

Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012, 367:423-34.

Tovanabutra S, Robison V, Wongtrakul J, et al. Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. J Acquir Immune Defic Syndr. 2002. 29:275-83.

Traore YL, Chen Y, Ho EA. Current State of Microbicide Development. Clin Pharmacol Ther 2018, 104:1074-1081.

UNAIDS 2021. www.unaids.org/en/resources/documents/2021/2021_unaids_data.

Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med 2012, 367:411-22.

Van Damme L, Govinden R, Mirembe FM, et al. Lack of effectiveness of cellulose sulfate gel for the prevention of vaginal HIV transmission. N Engl J Med 2008, 359:463-72.

Van de Perre P, Segondy M, Foulongne V, et al. Herpes simplex virus and HIV-1: deciphering viral synergy. Lancet Infect Dis 2008, 8:490-7.

van de Vijver DAMC, Richter AK, Boucher CAB, et al. Cost-effectiveness and budget effect of pre-exposure prophylaxis for HIV-1 prevention in Germany from 2018 to 2058. Euro Surveill 2019, 24.

Vanpouille C, Lisco A, Derudas M, et al. A new class of dual-targeted antivirals: monophosphorylated acyclovir prodrug derivatives suppress both human immunodeficiency virus type 1 and herpes simplex virus type 2. J Infect Dis 2010, 201:635-43.

Vernazza P, Hirschel B, Bernasconi E, et al. HIV-infizierte Menschen ohne andere STD sind unter wirksamer antiretroviraler Therapie sexuell nicht infektiös. Schweizerische Ärztezeitung 2008;89: 5.

Watson-Jones D, Weiss HA, Rusizoka M, et al. Effect of herpes simplex suppression on incidence of HIV among women in tanzania. N Engl J Med 2008, 358:1560-71.

Wawer MJ, Makumbi F, Kigozi G, et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. Lancet 2009, 374:229-37.

Williams BG, Abdool Karim SS, Karim QA, Gouws E. Epidemiological impact of tenofovir gel on the HIV epidemic in South Africa. J AIDS 2011, 58:207-10.

Wilson DP, Law MG, Grulich AE, et al. Relation between HIV viral load and infectiousness: a model-based analysis. Lancet 2008, 372:314-20.

Yuan T, Fitzpatrick T, Ko NY, et al. Circumcision to prevent HIV and other sexually transmitted infections in men who have sex with men: a systematic review and meta-analysis of global data. Lancet Glob Health 2019, 7:e436-e447.

Zhang J, Li C, Xu J, et al. Discontinuation, suboptimal adherence, and reinitiation of oral HIV pre-exposure prophylaxis: a global systematic review and meta-analysis. Lancet HIV 2022, 9:e254-e268. 35364026.

33. Preventive HIV-1 vaccination: current status

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The HIV-1 pandemic will only be brought under control by effective vaccination. This chapter provides an overview of the current status of vaccine development.

Induction of HIV-1-specific antibodies

Analogous to other effective vaccines, initial attempts were made to develop vaccines that could induce neutralizing antibodies against the envelope protein of HIV-1. These vaccines used gp120, gp160, parts of gp160, or peptides from gp160 of different HIV-1 variants. Antibodies were stimulated that could neutralize laboratory viruses in vitro but poorly neutralize viruses from patients (Mascola 1996).

In two phase III studies (VAX003, VAX004), two different gp120 molecules (Pitisuttithum 2006, Flynn 2005) failed to reduce new infection rates despite the induction of antibodies to gp120. The envelope molecule gp160 can be poorly neutralized by antibodies because prior to binding of gp120 to the CD4 receptor, epitopes essential for biological function are hidden in indentations of the gp120 molecule. These epitopes are additionally masked by variable sequence loops and glycan shields (Kwong 2002). As a result, antibodies can block the gp160 binding site for the CD4 molecule only to a limited extent. Only after binding of a gp160 trimer to CD4 does a conformational change of the V3 loop expose the binding domain for the coreceptors CCR5 or CXCR4. Antibodies against the V3 loop can neutralize, but these activated binding sites are only detectable by antibodies for a short time. They are spatially shielded, so high antibody concentrations are necessary for neutralization (Labrijn 2003).

Infected individuals form neutralizing antibodies, mostly directed against variable sequence segments of gp120 in which the viruses can rapidly develop mutations. Therefore, the antibodies of most individuals neutralize only their own HI viruses, but only insufficiently HI viruses from others. Only 10–30% of infected patients develop cross-reactive neutralizing antibodies within 2 to 3 years of infection, but most are directed against variable sequences in gp120. Only 1 to 2% of infected individuals generate very broadly neutralizing antibodies (bNAbs) that can neutralize 70–90% of HIV-1 variants. Target structures of these antibodies are conserved CD4 binding sites in gp120, the base of the V3 loop with glycan structures, glycopeptide epitopes in the V1 and V2 loops, or a domain in gp41 essential for fusion.

It is still unclear why only a few people can produce these broadly neutralizing antibodies. Some very effective antibodies show unusual properties such as long CDR3 regions, a high level of affinity maturation with many somatic mutations, or cross-reactivity to human antigens. The breadth of recognition depends on contact with viral variants, and long virus exposure is required for intense affinity maturation, making it difficult to induce such antibodies with a vaccine.

Meanwhile, initial trials with broadly neutralizing antibodies derived from infected individuals have demonstrated a strong antiviral effect in HIV-1-infected patients (Lynch 2015, Caskey 2015+2017). In this context, the antibody 3BNC117 led to a significant reduction in plasma viremia and a broader humoral immune response against HIV-1 (Schoofs 2017). Since resistance mutations occurred with monotherapies using bNAbs (Scheid 2016, Bar 2016), combinations are now being investigated (Mendoza 2018). Modifications of antibodies isolated from infected individuals have significantly increased potency (Rudicell 2014). A newly developed tri-specific antibody (SAR441236) that has binding sites of the three neutralizing antibodies vRC01,

PGDM1400, and 10E8v4 is currently being tested in clinical trials after showing very potent activity in the SHIV monkey model (Xu 2017).
Two large studies (HVTN 704/HPTN 085, MSM/transgender in the Americas and Europe; HVTN 703/HPTN 081, women in Africa) tested whether infusions of the bnAb VRC01, given every eight weeks, could reduce HIV-1 infection rates over 22 months compared with placebo. VRC01 showed no significant protective effect overall. Only viruses with high sensitivity to VRC01 (IC80 <1µg/mL) showed protection. This indicates that for effective protection by passive antibody administration, high concentrations of even more potent antibodies and combinations of antibodies are needed to avoid resistance (Corey 2021).
Data from animal models and clinical studies suggest that non-neutralizing antibodies may also have a role in controlling HIV-1 via Fc receptor-mediated immune responses such as ADCC (antibody-dependent cellular cytotoxicity) (Horwitz 2017, Rerks-Ngarm 2009). Although the protective effect of non-neutralizing antibodies appears comparatively weak, attempts are being made to integrate the induction of such antibodies into vaccination strategies (Costa 2016).
Another approach is passive genetic immunization by transferring genes of neutralizing antibodies. In rhesus monkeys, transfer of antibody genes into muscle cells using an adeno-associated virus (AAV) vector induced the production of SIV-ENV neutralizing antibody constructs that protected the monkeys against SIV infection (Johnson 2009). Protection against HIV-1 infection was also achieved in the humanized mouse model by transferring genes for neutralizing antibodies using an AAV vector (scAAV) (Balazs 2012).

Induction of HIV-1-specific T-cells

Difficulties in inducing neutralizing antibodies have focused interest on vaccines that stimulate HIV-1-specific T-cells. Cytotoxic T-cells (CTL) play an important role in controlling HIV-1 infection (Koup 1994, Harrer 1996a). However, CTL can only recognize cells that are already infected, so unlike neutralizing antibodies, they do not confer sterilizing immunity. However, the observation of HIV-1-specific CTLs in HIV-1 exposed but uninfected subjects raised the hope that CTL could prevent an ongoing HIV-1 infection by eradicating small foci of viral infection (Herr 1998, Rowland-Jones 1998). Even if a T-cell-based vaccine could not prevent infection, there is the chance that it could influence the course of infection by reducing the viremia after infection, as seen in the SIV monkey models (Letvin 2006). HIV-1 can evade detection by CTL by the development of mutations. Our observations in long-term survivors demonstrated the importance of the quality of the CTL response with the targeting of conserved CTL epitopes (Harrer 1996b). Therefore, it is crucial for the effectiveness of a vaccine that sufficient highly conserved CTL epitopes are present in the vaccine for the r individual HLA alleles.
Vaccination techniques capable of loading viral peptides onto HLA class I molecules on the surface of dendritic cells, are needed to induce CTL. Attenuated live vaccines are not considered for safety reasons. DNA vaccines are not very immunogenic on their own, but in a prime-boost strategy can significantly increase the immunogenicity of subsequent vaccinations with viral vectors. Lipopeptides and the combination of peptides with cytokines such as GM-CSF allow induction of CTL but may present relatively few epitopes.

Recombinant viral vectors

These vectors can induce CTL without relevant risks. Currently, adenovirus vectors, Canary Pox virus (canary pox virus), MVA (Harrer 2005), NYVAC (Gomez 2007), adeno-associated virus (AAV), and Sendai virus vectors (Nyombayire 2017) are being evaluated.

A great disappointment was the termination of two placebo-controlled Phase IIb trials, the HVTN 502 study (STEP trial) (Buchbinder 2008) and the HVTN 503 study (Phambili Study) (Gray 2011). Both studies used a mixture of three Merck recombinant non-replicative adenovirus type 5 vectors (MRKAd5 V520) expressing the HIV-1 proteins Gag, Pol, and Nef. The vaccine was immunogenic (McElrath 2008), but the trial was stopped because of a lack of efficacy. There was even a trend for a higher infection rate in the verum arm in the STEP trial in individuals with high titers of preexisting antibodies to the adenovirus 5 vector. Since it could not be ruled out that in the case of a strong immune response against adenovirus 5, this vaccine could promote HIV-1 infection, the Phambili study was also discontinued, which by then had also failed to show any protective effect of the MRKAd5 vaccine (Gray 2011).

A combination of priming with DNA vaccines and subsequent booster vaccinations with recombinant adenoviruses can enhance the vaccination response (Jaoko 2010). In the HVTN-505 study (Hammer 2013), circumcised men who lacked neutralizing antibodies to adenovirus 5 were first vaccinated with a DNA vaccine (6 plasmids: HIV-1 clade B Gag, Pol, Nef, and ENVs of clades A, B, and C) three times (weeks 0, 4, 8). This was followed by vaccination with four recombinant adenovirus 5 vectors (Gag-Pol fusion protein and three ENVs of clades A, B, and C) at week 24. Despite the induction of HIV-1-specific T-cells and antibodies, vaccination did not affect the infection rate or the level of viremia in infected subjects. The vaccine did not induce neutralizing antibodies and only modestly induced antibodies against the V1/V2 loop, which were associated with protection in the RV144 trial. However, subsequent data analysis showed that the induction of a strong, polyfunctional CD8 T-cell response against the envelope reduced the risk of infection (Janes 2017).

Because the increased risk of infection correlated with the antibody titer to the AD5 vector in the STEP study, new vectors derived from less common adenovirus serotypes were developed. In addition, to cover viral variants, mosaic vaccines optimized for the expression of epitopes of different HIV-1 subtypes were developed. An HIV mosaic vaccine in an AD26 vector showed good immunogenicity and tolerability in monkey experiments and in a phase 1/2 study in volunteers (Barouch 2018). In the Phase 2b study (HPX2008/HVTN 705/Imbokodo study) in African women initiated in 2018, the tetravalent Ad26.Mos4.HIV vaccine containing four different mosaic constructs (Ad26.Mos1.Gag-Pol, Ad26.Mos2.Gag-Pol, Ad26.Mos1.Env, Ad26.Mos2S.Env) was combined with a Clade C gp140 envelope trimer in a heterologous "double prime, double boost" vaccination regimen. Still, this vaccination also did not confer significant protection.

A Phase III trial (HPX3002/HVTN 706/Mosaico) in men and transgender individuals in the Americas and Europe, combining vaccination with the tetravalent Ad26.Mos4.HIV vaccine with administration of two envelope trimers (Clade C gp140 and Mosaic gp140 HIV) started in 2019 but was discontinued in 2023 because of lack of efficacy.

The RV144 trial (Rerks-Ngarm 2009) in Thailand was the first HIV vaccination trial to reduce new HIV-1 infections by approximately 31% significantly. In this trial, subjects received four vaccinations with a Sanofi-Pasteur canarypox vector (ALVAC-HIV vCP1521) expressing the HIV-1 subtype B Gag and protease proteins and the HIV-1 subtype E envelope protein and two booster vaccinations with the AIDSVAX B/E

gp120 glycoproteins. Among the 8198 individuals in the placebo arm, 74 new HIV-1 infections occurred within the three-year observation period, whereas only 51 new HIV-1 infections were observed among the 8197 vaccinated individuals. The effectiveness of the vaccination correlated with the risk of infection and was 42.4% at low risk and only 3.7% at high risk after 42 months.
Vaccination did not affect viremia in the subjects infected in the study. Vaccination induced only a weak T-cell response, whereas almost all vaccinated individuals developed high titers of envelope-specific antibodies, which had only a weak to moderate ability to neutralize different HIV-1 variants. Moreover, their detection did not correlate with a lower infection rate. Interestingly, induction of high IgG titers against the V1/V2 loop was associated with protection, whereas high IgA antibody titers against gp120 were associated with increased infection rates (Haynes 2012).
Given these positive results, this vaccination approach using the ALVAC HIV vector (vCP2438 as in RV144 but replacing the CRF01_AE gp120 gene with a subtype C gp120 gene) was tested in the HVTN 702 phase III study (Uhambo study) in South Africa. In this study, booster vaccinations were given with two monomeric subtype C gp120 molecules (TV1.C and 1086.C) and with a different adjuvant (MF59) instead of subtype B/E gp120 molecules. Unlike RV144, there was no effect on the infection rate or the level of viral load at infection (Gray 2021). The reason for this discrepancy with RV144 is thought to be a comparatively higher risk of infection in the Uhambo study. The results were not influenced by the medical pre- and post-exposure prophylaxis offered, which was used by only 3% of participants.

Combinations of vaccines with PREP

The success of drug-based pre-exposure prophylaxis (PrEP) has implications for vaccine trial design. Therefore, the ongoing three-arm PREPVacc trial of 1,668 participants in Africa is testing not only two experimental vaccination strategies (DNA-HIV-PT123 + AIDSVAX B/E gp120 at weeks 0, 4, 24, 48) and DNA-HIV-PT123 + CN54gp140 trimer (week 0, 4) + MVA/CN54gp140 (week 24, 48) against placebo. In addition, all participants will be randomized to receive PrEP with TDF/FTC or TAF/FTC for 26 weeks (https://clinicaltrials.gov/ct2/show/NCT04066881).

New approaches to vaccination

Despite intensive efforts in recent decades, no effective HIV-1 vaccine has yet been developed. The main reasons for this are the biological properties of HIV-1, which also means that almost all infected people without therapy ultimately die from the infection. Only a few people are able to generate the very broadly neutralizing antibodies necessary for vaccine protection, and conventional vaccination techniques have not achieved induction of these broadly neutralizing antibodies. In addition, HIV-1 can significantly limit the efficacy of cytotoxic T-cells (CTL) by causing the viral protein Nef to downregulate HLA-A and HLA-B molecules from the surface of infected cells, thereby inhibiting the recognition and destruction of infected cells. In addition, certain variants of the viral protein Vpu can also block HLA-C-restricted CTL by downregulating HLA-C molecules. As a result, although HIV vaccines can induce HIV-1-specific CTL, they generally have only limited efficacy and thus cannot prevent infection.
At least, important lessons could be learned from the failures of the large vaccination trials that will contribute to the development of new vaccination strategies:
In 2013, a study of rhesus monkeys immunized with a rhesus monkey CMV vector (RhCMV68-1/SIV) attracted great interest (Hansen 2013a). Although vaccination

with this SIV protein-expressing vector did not prevent SIV infection, approximately half of the animals could eliminate SIV infection. The reason for this success was the induction of unusual, "non-canonical" CD8 killer cells (Hansen 2013b). These recognized their peptides not on HLA class I molecules, as is usual for CD8 T-cells, but on HLA class II molecules or HLA E molecules (Hansen 2016), which are not downregulated by the viral Nef molecule. Meanwhile, HLA-II-restricted HIV-1-specific CD8 CTL have also been described in a small subset of HIV-1-infected humans (Ranasinghe 2016), although such cells' role in effectively controlling HIV-1 in humans remains to be defined. Induction of non-canonical CD8+ killer cells is not a general property of rhesus monkey CMV. Still, it depends on certain properties of the RhCMV68 vector used, which has restricted cell tropism for fibroblasts due to the inactivation of eight genes. Restoration of these inactive genes in the rhesus monkey CMV vector resulted in loss of induction of HLA-E-restricted CTL and loss of protective effect against SIV. Since the RhCMV68-1/SIV vector does not infect humans, human chimeric CMV vectors were developed, but in a human clinical trial, they could only generate classical CTL and not non-canonical CTL (Murray 2017). Meanwhile, further studies led to a better understanding of the induction mechanisms of HLA-E-restricted CTL (Verweij 2021), raising the hope that methods can be developed to induce HLA-E-restricted HIV-specific T-cells.

The native gp160 trimer, in contrast to the gp120/gp160 monomers, contains conformational epitopes to which neutralizing antibodies can bind. Therefore, modified envelope trimers (gp140 SOSIPs) were developed to allow better presentation of antibody epitopes important for neutralization. The IAVIW001 trial, which began in 2019, is currently testing whether an envelope trimer vaccine (BG505 SOSIP.664 gp140 in combination with adjuvant $AS01_B$) can induce neutralizing antibodies.

Due to somatic mutations, the genes encoding broadly neutralizing antibodies in B-cells differ significantly from the original germline genes. The original germline genes encoding these antibodies are present in most individuals, but the antibodies encoded by the germline genes do not bind adequately to the envelope of HIV-1. Specific vaccines must stimulate B-cells expressing germline-encoded antibodies to induce broadly neutralizing antibodies. Sequential inoculations with additional modified vaccines are then used to induce affinity maturation of B-cells with somatic mutations to simulate the natural development of broadly neutralizing antibodies. For this purpose, vaccines (e.g., eOD-GT8 engineered Outer Domain Germline-Targeting Version 8) have been developed that were able to stimulate and expand germline-encoded B-cell receptors in mice (Lee 2022). According to a press release from IAVI, in the IAVI G001 study, 97% of 48 subjects developed B-cells producing VRC01 class IgG after two vaccinations with the eOD-GT8 60mer. Further studies will attempt to induce broadly neutralizing antibodies by sequentially stimulating these B-cells with modified vaccines.

Vaccination with mRNA

The development of mRNA technology represents a major advance in the development of HIV-1 vaccines. The production and modification of complex large molecules such as gp140 SOSIPs or eOD-GT8 is very time-consuming. In contrast, modifications of proteins can be obtained very fast by changes in the coding mRNA sequence. This considerably shortens development times. In addition, large amounts of mRNA can be produced more easily and quickly than complex proteins, so necessary adaptations of the vaccines to new virus variants can also be carried out quickly and efficiently. Because mRNA vaccines induce viral protein production in the cell, they can

induce CTL very potently, unlike protein vaccines. Since mRNA can activate Toll-like receptors that recognize viral nucleic acids, no further adjuvants are needed, unlike protein vaccines. A disadvantage is the instability of the mRNA, which requires storage at low temperatures in freezers, making it difficult to use in countries without sufficient infrastructure.

The great success of SARS-CoV-2 specific mRNA vaccines has stimulated the use of mRNA vaccines in HIV-1 vaccine development. For example, several Phase 1 studies are currently testing the immunogenicity of mRNA vaccines encoding different HIV-1 envelope trimers. In addition, IAVI-led studies are testing whether sequential immunization with mRNA-encoded vaccines can stimulate and affinity-mature B-cells with germline receptors for neutralizing antibodies.

Outlook

Due to the sophisticated immune evasive properties of HIV, effective preventive HIV vaccines could not be developed using vaccination methods effective in other infections. Therefore, new strategies to circumvent immune evasion of HIV-1 are needed. Intensive basic research has now enabled the development of new technologies such as vaccination with mRNA, production of envelope-trimers, sequential vaccination for targeted affinity maturation of B-cells, and induction of non-canonical CTL. However, it is currently unclear if and when new vaccination approaches will ultimately lead to a universally applicable, effective preventive HIV-1 vaccine; there is reasonable hope to make substantial progress through innovative research in the coming years.

Literature

Balazs AB, Chen J, Hong CM, et al. Antibody-based protection against HIV infection by vectored immunoprophylaxis. Nature 2012; 481:81–84.

Bar KJ, Sneller MC, Harrison LJ, et al. Effect of HIV Antibody VRC01 on Viral Rebound after Treatment Interruption. N Engl J Med 2016; 375:2037-50.

Barouch DH, Tomaka FL, Wegmann F, et al. Evaluation of a mosaic HIV-1 vaccine in a multicentre, randomised, double-blind, placebo-controlled, phase 1/2a clinical trial (APPROACH) and in rhesus monkeys (NHP 13-19). Lancet 2018; 392:232-243.

E SP, Mehrotra DV, Duerr A, et al. Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. Lancet 2008; 372: 1881-1893.

Caskey M, Klein F, Lorenzi JC, et al. Viraemia suppressed in HIV-1-infected humans by broadly neutralizing antibody 3BNC117. Nature 2015; 522:487-91.

Caskey M, Schoofs T, Gruell H, et al. Antibody 10-1074 suppresses viremia in HIV-1-infected individuals. Nat Med 2017; 23:185-191.

Corey L, Gilbert PB, Juraska M, et al. HVTN 704/HPTN 085 and HVTN 703/HPTN 081 Study Teams. Two Randomized Trials of Neutralizing Antibodies to Prevent HIV-1 Acquisition. N Engl J Med. 2021 384:1003-1014.

Costa MR, Pollara J, Edwards RW, et al. Fc Receptor-Mediated Activities of Env-Specific Human Monoclonal Antibodies Generated from Volunteers Receiving the DNA Prime-Protein Boost HIV Vaccine DP6-001. J Virol 2016, 90:10362-10378.

Flynn NM, Forthal DN, Harro CD, Judson FN, Mayer KH, Para MF. Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection. J Infect Dis 2005; 191:654-65.

Gomez CE, Najera JL, Jimenez EP, et al. Head-to-head comparison on the immunogenicity of two HIV/AIDS vaccine candidates based on the attenuated poxvirus strains MVA and NYVAC co-expressing in a single locus, the HIV-1BX08 gp120 and HIV-1(IIIB) Gag-Pol-Nef proteins of clade B. Vaccine 2007; 25:2863-85.

Gray GE, Allen M, Moodie Z, et al. Safety and efficacy of the HVTN 503/Phambili study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomised, placebo-controlled test-of-concept phase 2b study. Lancet Infect Dis 2011; 11:507-15.

Gray GE, Bekker LG, Laher F, et al. HVTN 702 Study Team. Vaccine Efficacy of ALVAC-HIV and Bivalent Subtype C gp120-MF59 in Adults. N Engl J Med. 2021; 384:1089-1100.

Gray GE, Mngadi K, Lavreys L, et al. Phase IIB Efficacy trial of mosaic HIV-1 vaccine regimen in African women: Imbokodo. Conference on retroviruses and opportunistic infections, February 12-16 2022. Oral Abstract 121.

Hammer SM, Sobieszczyk, ME, Janes H, et al. Efficacy Trial of a DNA/rAd5 HIV-1 Preventive Vaccine. NEJM 2013; 369 :2083-2092.

Hansen SG, Platak M Jr, Ventura AB, et al. Immune clearance of highly pathogenic SIV infection. Nature 2013a; 502:100-104.

Hansen SG, Sacha JB, Hughes CM, et al. Cytomegalovirus vectors violate CD8+ T cell epitope recognition paradigms. Science 2013b; 340:1237874.

Hansen SG, Wu HL, Burwitz BJ, et al. Broadly targeted CD8 T cell responses restricted by major histocompatibility complex E. Science 2016; 351:714-20.

Harrer T, Harrer E, Kalams SA, et al. Strong cytotoxic T cell and weak neutralizing antibody responses in a subset of persons with stable nonprogressing HIV type 1 infection. AIDS Res Hum Retroviruses 1996a; 12:585-92.

Harrer T, Harrer E, Kalams SA, et al. Cytotoxic T lymphocytes in asymptomatic long-term nonprogressing HIV-1 infection. Breadth and specificity of the response and relation to in vivo viral quasispecies in a person with prolonged infection and low viral load. J Immunol 1996b; 156:2616-23.

Harrer E, Bauerle M, Ferstl B, et al. Therapeutic vaccination of HIV-1-infected patients on HAART with a recombinant HIV-1 nef-expressing MVA: safety, immunogenicity and influence on viral load during treatment interruption. Antivir Ther 2005; 10:285-300

Haynes, BF, Gilbert PB, McElrath MJ. Immune-Correlates Analysis of an HIV-1 Vaccine Efficacy Trial. N Engl J Med 2012;366:1275-86.

Herr W, Protzer U, Lohse AW, et al. Quantification of CD8+ T lymphocytes responsive to human immunodeficiency virus (HIV) peptide antigens in HIV-infected patients and seronegative persons at high risk for recent HIV exposure. JID 1998; 178:260-265.

Horwitz JA, Bar-On Y, Lu CL, et al. Non-neutralizing Antibodies Alter the Course of HIV-1 Infection In Vivo. Cell 2017;170(4):637-648.

Janes HE, Cohen KW, Frahm N, et al. Higher T-Cell Responses Induced by DNA/rAd5 HIV-1 Preventive Vaccine Are Associated With Lower HIV-1 Infection Risk in an Efficacy Trial. J Infect Dis 2017, 215:1376-1385.

Jaoko W, Karita E, Kayitenkore K, et al. Safety and immunogenicity study of Multiclade HIV-1 adenoviral vector vaccine alone or as boost following a multiclade HIV-1 DNA vaccine in Africa. PLoS One. 2010; 5(9):e12873.

Johnson PR, Schnepp BC, Zhang J, et al. Vector-mediated gene transfer engenders long-lived neutralizing activity and protection against SIV infection in monkeys. Nat Med 2009, 15: 901-906.

Koup RA, Safrit JT, Cao Y, et al. Temporal association of cellular immune responses with the initial control of viremia in primary human immunodeficiency virus type 1 syndrome. J Virol 1994; 68:4650-4655.

Kwong PD, Doyle ML, Casper DJ, et al. HIV-1 evades antibody-mediated neutralization through conformational masking of receptor-binding sites. Nature 2002; 420:678-82.

Labrijn AF, Poignard P, Raja A, et al. Access of antibody molecules to the conserved coreceptor binding site on glycoprotein gp120 is sterically restricted on primary human immunodeficiency virus type 1. J Virol 2003; 77:10557-65.

Lee JH, Nakao C, Appel M et al. Highly mutated antibodies capable of neutralizing N276 glycan-deficient HIV after a single immunization with an Env trimer. Cell Rep 2022; 38(10):110485.

Letvin NL, Mascola JR, Sun Y, et al. Preserved CD4+ central memory T cells and survival in vaccinated SIV-challenged monkeys. Science 2006; 312:1530-3.

Lynch RM, Boritz E, Coates EE, et al. VRC 601 Study Team. Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection. Sci Transl Med 2015; 7:319ra206.

Mascola JR, Snyder SW, Weislow OS, et al. Immunization with envelope subunit vaccine products elicits neutralizing antibodies against laboratory-adapted but not primary isolates of human immunodeficiency virus type 1. J Infect Dis 1996; 173:340-8.

McElrath MJ, de Rosa SC, Moodie Z, et al. HIV-1 vaccine-induced immunity in the test-of-concept Step Study. Lancet 2008; 372: 1894-1905.

Mendoza P, Gruell H, Nogueira l, et al. Combination therapy with anti-HIV-1 antibodies maintains viral suppression. Nature 2018; 561:479-484

Murray SE, Nesterenko PA, Vanarsdall AL, et al. Fibroblast-adapted human CMV vaccines elicit predominantly conventional CD8 T cell responses in humans. J Exp Med 2017; 214:1889–1899.

Nyombayire J, Anzala O2, Gazzard B, et al. First-in-Human Evaluation of the Safety and Immunogenicity of an Intranasally Administered Replication-Competent Sendai Virus-Vectored HIV Type 1 Gag Vaccine: Induction of Potent T-Cell or Antibody Responses in Prime-Boost Regimens. J Infect Dis 2017, 215:95-104.

Pitisuttithum P, Gilbert P, Gurwith M, et al. Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand. J Infect Dis 2006; 194:1661-71.

Ranasinghe S, Lamothe PA, Soghoian DZ, et al. Antiviral CD8+ T Cells Restricted by Human Leukocyte Antigen Class II Exist during Natural HIV Infection and Exhibit Clonal Expansion. Immunity 2016, 45:917-930.

Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. NEJM 2009, 361:2209-20.

Rowland-Jones SL, Dong T, Fowke KR, et al. Cytotoxic T cell responses to multiple conserved HIV epitopes in HIV-resistant prostitutes in Nairobi. J Clin Invest 1998, 102:1758-65.

Rudicell, R. S. et al. Enhanced potency of a broadly neutralizing HIV-1 antibody in vitro improves protection against lentiviral infection in vivo. J. Virol 2014; 88: 12669–12682.

Scheid JF, Horwitz JA, Bar-On Y, et al. HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption. Nature 2016; 535:556-60.

Schoofs T, Klein F, Braunschweig M, et al. HIV-1 therapy with monoclonal antibody 3BNC117 elicits host immune responses against HIV-1. Science 2017, 352: 997-1001.

Verweij MC, Hansen SG, Iyer R, et al. Modulation of MHC-E transport by viral decoy ligands is required for RhCMV/SIV vaccine efficacy. Science. 2021;372(6541):eabe9233.

Xu L, Pegu A, Rao E, et al. Trispecific broadly neutralizing HIV antibodies mediate potent SHIV protection in macaques. Science 2017; 358:85-90.

34. Post-exposure prophylaxis (PEP)

SEBASTIAN NOE

HIV post-exposure prophylaxis (HIV PEP, hereafter simplified as PEP) is a measure to reduce the risk of HIV infection. As the name suggests, it is used when an "event" has occurred that involves a potential risk of infection for someone. It differs significantly from pre-exposure prophylaxis (PrEP), taken before such an event occurs. PEP and PrEP (therefore) also differ in the medications to be taken. PEP corresponds to a complete antiretroviral therapy and can be the same used to treat an HIV infection.

In principle, transmission of HIV is only possible if ***both*** of the following conditions are met:

Virus-containing material (e.g., blood, seminal fluid, vaginal secretions) must enter a person's body (purely superficial contacts, e.g., contact with blood on intact skin, are not sufficient in this regard)

AND

thereby have a sufficient amount of replicable virus (which is why, for example, people with a viral load < 200 copies/mL cannot transmit HIV (sexually) (Rodger 2019).

In addition to the type of secretion and the amount of virus contained, the duration of contact and the potential entry site also play a role, among other factors. Relevant exposure to HIV can essentially be assumed in the following events (DAIG 2018):

- Injury via HIV-contaminated instruments or injection equipment
- Wetting of open wounds and mucous membranes with HIV-contaminated fluid
- Condomless sexual intercourse with a PLWH
- Use of HIV-contaminated injection equipment
- Transfusion of HIV-contaminated blood or blood products

Apart from occupational events, in practice, it is primarily sexual contacts that lead to medical consultation and the question of the need for PEP. HIV transmission rates may markedly vary by the type of exposure. There is a broad range of transmission risks in different contact settings. Table 1 provides an overview of HIV transmission per contact.

Table 1: Probability of infection during unprotected sexual contact (German-Austrian recommendations on PEP 2018).

Type of (unprotected) contact	Probability of infection per contact
Receptive anal intercourse with a **known** HIV-positive partner	0.24–2.76%
With ejaculation	0.48–2.85%
Without ejaculation	0.15–1.53%
Receptive anal intercourse with a partner of unknown HIV serostatus	0.06–0.49%
Insertive anal intercourse with a partner of unknown HIV serostatus	0.02–0.19%
Receptive vaginal intercourse	0.05–0.15%
Insertive vaginal intercourse	0.03–5.6%
Oral sex	Case Reports

Effectiveness and limits of PEP

At least 24 to 36 hours usually elapse before systemic disease is established after tissue infiltration of HIV; this is the rationale for using antiretroviral drugs as PEP. The understanding of "early therapy" also has legal relevance. In the absence of placebo-controlled randomized trials – which would no longer be justifiable from an ethical perspective – none of the antiretroviral combination therapies has been officially approved as chemoprophylaxis.

PEP does not provide 100% protection against HIV infection, and transmission despite PEP has been reported. Possible reasons could be transmitted resistance, lack of adherence, misunderstandings regarding the intake, or starting PEP too late.

In general, it is recommended that a physician makes the indication with experience in HIV. However, (suspected) exposure to HIV often occurs when specialists cannot be consulted (e.g., in the evening/at night or on weekends). Here, it is crucial to initiate PEP in case of doubt. It can always be terminated prematurely later, after a specialized medical consultation.

Central questions regarding the indication are the serostatus of the "index person" and the exact course of the event. With this information, the risk of infection can usually be estimated. The often unknown serostatus of the index person can also be clarified if necessary. However, this can only be done if the index person is known, can be contacted, and consents to an HIV test. Table 2 provides an overview of the indication according to various events.

Immediate measures and initiation of PEP

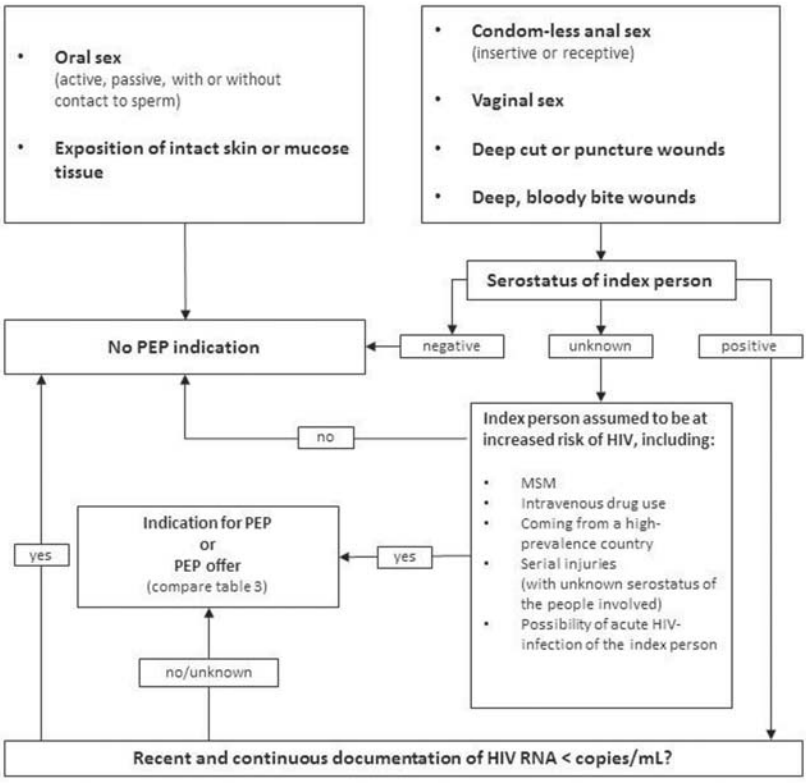
After puncture wounds or cuts with contaminated needles or instruments, blood flow and thus natural flushing of the wound should first be allowed; "ligation" is obsolete. This should be followed by irrigation with an antiseptic or even soap and water. In the case of contact with damaged or inflamed skin, water and soap and, if necessary, generous application of a skin antiseptic will suffice. Contaminated eyes should be rinsed immediately with copious amounts of water, and the same applies to the oral cavity, which should preferably be rinsed several times for 15 seconds each time. After exposure during penetrative anal or genital intercourse, the glans and foreskin should be washed gently with soap under running water. Vaginal or bowel rinses are not recommended due to the potential risk of injury.

Although this section deals with the prevention of HIV infection, it should not be unmentioned that transmission of other infectious diseases is also possible. Above all, with regard to the prevention of HBV infection, it must be determined whether immune protection exists or whether active and passive immunization must be performed in a timely manner. Serological tests for HIV should be accompanied by serologies for hepatitis B and C and syphilis.

Introduction of PEP

Once the indication for PEP has been established, starting as soon as possible is essential. Ideally, PEP should be started within the first two hours after exposure. A timely start can also be considered up to 24 hours post-event. If the exposure occurred more than 72 hours ago, PEP is probably no longer useful.

Although the German-Austrian guidelines in the 2018 revised version recommend a combination of TDF/FTC with raltegravir or dolutegravir, it should be noted that adherence to PEP seems to be a significant problem (Fernandez 2020). In addition to tolerability, the mode of intake is likely to play a major role. Therefore, in the author's opinion, there is much to be said for an integrase inhibitor-based single-tablet regimen (see Table 3) used in HIV therapy.



Possible resistance must be considered if the index person is HIV-infected and viremic. In these cases, an individual PEP regimen is useful, which should be compiled by physicians experienced in HIV. In any case, possible interactions and contraindications of antiretroviral drugs must be considered. For example, regimens containing TDF should not be used in cases of impaired renal function or osteoporosis, and dolutegravir should be avoided if metformin is taken continuously at a dose of > 1,700 mg daily. Caution should be exercised with boosted regimens (i.e., cobicistat- or ritonavir-containing combinations), particularly in those with co-medication, as interactions are likely.

The alternative to TDF+FTC previously recommended by the guidelines, namely AZT/3TC, must be considered obsolete. It can be replaced by TAF+FTC in the author's opinion. The role of dual antiretroviral therapies in the context of PEP is unclear. Promptly after initiation of PEP, testing for pre-existing HIV infection (as well as hepatitis B and C) should be performed, but should not delay initiation of PEP.

Monitoring after initiation of PEP

Medical monitoring is not completed with the initiation of PEP. It is crucial to remain in contact with the exposed person to identify and respond to possible intolerances and/or side effects. Depending on the regimen used, this may also include monitoring of transaminases and renal function.

PEP can usually be terminated after 28 (-30) days. Serological control tests for HIV and, if applicable, HBV and HCV should be performed again six and twelve weeks after completion of PEP.

Table 2: German-Austrian recommendations (2018) for the use of PEP.

Occupational circumstances (source secured HIV-positive)	
Massive percutaneous inoculation (> 1 mL) of blood or body fluid with high virus concentration	Recommended, regardless of viral load
Deep, bleeding injury (cut or puncture) with a hollow needle or contaminated instrument (e.g., scalpel)	Recommended if VL > 50 copies/mL Offer when VL < 50 copies/mL
Superficial injury (e.g., with a surgical needle) without bleeding	Offer when VL > 50 copies/mL
Contact of mucous membrane or injured/damaged skin with fluids with high virus concentration	Not recommended if VL < 50 copies/mL
Percutaneous contact with body fluids other than blood (such as urine or saliva)	Not recommended
Contact of intact skin with blood (even with high virus concentration)	Not recommended
Skin or mucous membrane contact with urine and saliva	Not recommended
Non-occupational circumstances **Exposure with confirmed HIV-positive source**	
Transfusion of blood products containing HIV or receipt of blood products that are highly likely to contain HIV	Recommended
Use of HIV-contaminated injection equipment by several drug addicts together or in succession	Recommended
Unprotected vaginal or anal sexual intercourse (broken condom) with a person infected with HIV	Recommend if VL > 1,000 copies/mL Offer when VL 50–1,000 copies/mL No indication if VL < 50 copies/mL
Exposure with unknown status of the index person/source	
Unprotected homosexual anal intercourse especially in typical situations	Offer
Unprotected heterosexual vaginal or anal intercourse with a partner from a risk group (active IVDU, bisexual, high prevalence area)	Offer
Unprotected heterosexual vaginal or anal intercourse with a partner without special risk (prostitution!)	Not recommended
Oral sex with ingestion of semen into the mouth (HIV positive or negative)	Not recommended
Kissing, other sexual practices without semen/blood/mucous-skin contact, and S/M practices without blood-to-blood contact	
Injury to used syringe equipment used to inject drugs, medications, or insulin	Not recommended

Monitoring in case of a decision against PEP

Even if one decides against PEP, serological controls should be performed at the time of presumed exposure and six and twelve weeks thereafter. If symptoms of acute HIV infection occur in the interim, HIV PCR is also warranted.
Do not forget to evaluate general HIV exposure risk and discuss PrEP options, if appropriate.

Table 3: Antiretroviral combinations are recommended in the German-Austrian Guidelines for HIV post-exposure prophylaxis. STR = single-tablet regimen.

NRTIs		INSTI or PIs
TAF/FTC 25/200 mg	plus	Bictegravir (as STR Biktarvy® 1 x 50/200/25mg)
TDF + FTC (Truvada® or generic) 1 x 1 tbl. of 245/200 mg	plus either	Dolutegravir (Tivicay®) 1 x 1 tbl. of 50 mg or Raltegravir (Isentress®) 2 x 1 tbl. of 400 mg or 1 x 2 tbl. of 600 mg
If not available:		
TAF/FTC 10/200 mg	plus either	Darunavir 800 mg and cobicistat 150 mg (as STR Symtuza® 1 x 800/150/200/10 mg) or Elvitegravir 150 mg and cobicistat 150 mg (as STR Genvoya® 1 x 150/150/200/10 mg)
TDF/FTC (Truvada® or generic) 1 x 1 tbl. of 245/200 mg	plus	Darunavir 800 mg and ritonavir 100 mg (each once daily, to be taken together)

Literature

Deutsche AIDS-Gesellschaft e.V. und Österreichische AIDS Gesellschaft. (2018). Deutsch-Österreichische Leitlinie zur Postexpositionellen Prophylaxe der HIV-Infektion (update 2018). AWMF online.

Fernandez I, deLazzari E, Inciarte A, et al. Network meta-analysis of post-exposure prophylaxis randomized clinical trials. HIV Med 2021, 22:218-224.

Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. Lancet 2019, 393:2428-2438.

(Earlier versions of this chapter were created by Thore Lorenzen)

SECTION 8

Drugs

35. Drug Profiles

CHRISTIAN HOFFMANN

The following chapter gives a brief overview of the most important (as of early 2023) antiretroviral agents and some selected preparations that play a role in the treatment of opportunistic infections, Kaposi's sarcoma or hepatitis C. Please always refer to the product information.

3TC (lamivudine)

Original manufacturer: ViiV Healthcare. Generics are available for some preparations.

Approval and indication: As part of combination therapy for untreated or pretreated PLWH. The lower dosage of 100 mg in Zeffix® (generics) approved for HBV should be avoided in PLWH!

- Epivir® film-coated tablets: 150 or 300 mg 3TC (generic)
- Epivir® solution: 10 mg 3TC per mL (240 mL)

Combination preparations (all film-coated tablets) with 3TC:
- Combivir®: 150 mg 3TC + 300 mg AZT (generic)
- Delstrigo®: 300 mg 3TC + 300 mg TDF + 100 mg doravirine
- Dovato®: 300 mg 3TC + 50 mg dolutegravir
- Kivexa®: 300 mg 3TC + 600 mg abacavir (generics)
- Triumeq®: 300 mg 3TC + 600 mg abacavir + 50 mg dolutegravir
- Trizivir®: 150 mg 3TC + 300 mg AZT + 300 mg abacavir (only until 2024)

Dose: 1 x 300 mg or 2 x 150 mg daily. Children receive 4 mg/kg. Reduction in renal insufficiency, below a GFR of 30 mL/min use the solution:

Creatinine clearance (mL/min)	First dose	Maintenance dose
>50, 30–49	150 mg (15 mL)	1 x 150 mg (15 mL)
15–29	150 mg (15 mL)	1 x 100 mg (10 mL)
5–14	150 mg (15 mL)	1 x 50 mg (5 mL)
<5	50 mg (5 mL)	1 x 25 mg (2.5 mL)

Adverse events: Rare with the single agent. Complaints such as fatigue, nausea, or headache are primarily due to AZT and abacavir.

Comment: Well tolerated and still much-prescribed cytidine analog. Available in diverse combinations and dosages. Rapid resistance, but reduces viral fitness. Also effective against HBV (caveat: also immediate resistance, also the risk of HBV rebounds).

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Abacavir

Manufacturer: ViiV Healthcare. Generics are available for some preparations.

Approval and Indication: As part of combination therapy in both untreated and pretreated PLWH. Abacavir is a component of:

- Ziagen® film tablets: 300 mg abacavir (generic)
- Ziagen® solution: 20 mg abacavir per mL (240 mL)

Combination preparations with abacavir (all film-coated tablets)
- Kivexa®: 600 mg abacavir + 300 mg 3TC (generic)
- Triumeq®: 600 mg abacavir + 300 mg 3TC + 50 mg dolutegravir
- Trizivir®: 300 mg abacavir + 150 mg 3TC + 300 mg AZT (only until 2024)

Dose: 2 x 300 mg or 1 x 600 mg daily, with or without food. Although hepatically metabolized, avoid in severe renal impairment (GFR <20 mL).

Adverse events: In 2–8% hypersensitivity reactions (HSR), usually in the first six weeks, slowly increasing. Itching and rash may be absent, sometimes only fever and feeling of illness. Also, gastrointestinal symptoms, rarely elevated transaminases, dizziness, sore throat, or cough. In addition to HSR, an increased risk of myocardial infarction should be noted, probably due to the thrombogenic effects of abacavir on platelets (activation).

Warnings: Negative HLA-B*5701 genetic testing (written informed consent!) is mandatory; it significantly but does not ultimately reduce the risk of HSR. Abacavir is contraindicated after therapy interruption if HSR cannot be retrospectively ruled out. HSR is potentially life-threatening if re-exposed!

Comment: NRTI with good CNS penetration. HSR (HLA testing mandatory!). It is less used than in the past because of cardiovascular risk. Some generics are available.

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Acyclovir

Manufacturer: Various. Trade names e.g. Aciclobeta®, Aciclovir®, Zovirax®.

Approval and indication: herpes zoster. Additionally, for the prevention of severe herpes simplex infections in severely immunosuppressed adults.

Dose: In monosegmental herpes zoster, 5 x 800 mg orally daily for one week. In multisegmental or complicated herpes zoster, 3 x 10 mg/kg i.v is better. In renal insufficiency, the dose is lower: if creatinine clearance is 25–10 mL/min, 3 x 800 mg; if <10 mL/min, 2 x 800 mg.

For genital HSV infection: 5 x 400 mg daily. In severe cases (ulcerating genital herpes), intravenous treatment with daily 3 x 5–10 mg/kg i.v. For HSV encephalitis or esophagitis, 3 x 10 mg/kg i.v.

Adverse events: Rare. Headache, nausea, and creatinine elevations occur. With intravenous administration, phlebitis.

Comment: Well-tolerated HZV/HSV drug. Cheap generics are available! Start therapy for HSV within the first 24 hours of the onset of symptoms if possible (4 days for VZV). Ensure adequate fluid intake.

Agenerase® see Amprenavir (withdrawn from the market)

Amphotericin B

Manufacturers: Bristol-Myers Squibb (Amphotericin B®), Gilead Sciences (Ambisome®), Dermapharm (Ampho-Moronal®). In some countries, generics are available.

Approval and indication: Amphotericin B for organ and generalized mycoses, especially candidiasis, aspergillosis, cryptococcosis, and histoplasmosis. The liposomal-modified AmBisome® (significantly more expensive) is also approved for secondary therapy in visceral leishmaniasis, whereas suspension and tablets are approved only for oral thrush. Amphotericin is a component of the following preparations:

- Amphotericin B® 50 mg powder vials
- AmBisome® vials with 50 mg dry substance
- Ampho-Moronal® suspension containing 100 mg/mL
- Ampho-Moronal® 10 mg lozenges

Dose: For amphotericin B®, always test the dose first (see below). For aspergillosis, 1.0–1.5 mg/kg; for the other mycoses, 0.5–1 mg/kg is usually sufficient. No more than 1.5 mg/kg, as overdose may cause fatal respiratory and cardiac arrest! For AmBisome®, the initial daily dose of 1 mg/kg can be gradually increased to 3 mg/kg.

Adverse events: Nephrotoxicity! Hypokalemia! Gastrointestinal complaints. Frequent fever, chills, and circulatory problems 10–20 min after the start of infusion. Thrombophlebitis (CVC!). With Ambisome®, side effects are less pronounced.

Warnings: Daily electrolytes (always ZVK because of hypokalemia! Keep sodium high normal), creatinine, urea, GPT, blood count. Do not combine with nephrotoxic substances. Always pre-water with 1000 mL NaCl 0.9%. At first administration, test dose 5 mg in 250 mL glucose 5% over 30–60 min, measure blood pressure, and pulse. Half of the planned dose after tolerating the test dose on the same day. In case of fever/ chills (can be impressive!): Pethidine (e.g., Dolantin®) half an ampoule i.v. (50 mg) plus one ampoule clemastine (e.g., Tavegil®), repeat after 30 min if necessary, additional prednisolone 1 mg/kg only if persistent. In case of severe side effects, switch to Ambisome®, which is probably not more effective but less nephrotoxic than amphotericin B (no test dose, no prewashing, no CVC required). Never mix infusions; always darken. The slower (>3 hrs) infused, the better it is tolerated! Always use glucose 5% as a solution!

Amprenavir (Agenerase®) – PI discontinued in 2008, replaced by fosamprenavir

Apretude® – see cabotegravir

Atazanavir

Original manufacturer: BMS. Meanwhile, only generics are available in many countries.

Approval and Indication: In HIV-positive adults and children 6 years of age and older as part of a combination. Atazanavir is a component of the following preparations:

- Atazanavir (generic) hard capsules 200 mg, 300 mg
- Reyataz® powder with 50 mg in each 1.5 g
- Evotaz® 300 mg with 150 mg cobicistat (EU approval, not marketed in many EU countries).

Dose: Daily 1 x 300 mg combined with 100 mg ritonavir or 150 mg cobicistat, unchewed, with a meal. If unboosted, use 1 x 400 mg (consider limitations: No tenofovir, no prior virologic failure, no PPIs). With efavirenz and probably nevirapine, the atazanavir dose should be increased to 400 mg even when boosted. In children by weight: 15–20 kg: 150 mg, 20–40 kg: 200 mg, at least 40 kg: 300 mg, each plus 100 mg ritonavir.

Adverse events: Very frequently, bilirubin increase (up to 50%!) also with icterus, rarely transaminase increase. Relatively rarely gastrointestinal complaints, headache. In contrast to other PIs, there are probably fewer dyslipidemias.

Interactions: Caution in liver cirrhosis (Child B, C). Cave PPI, antacids (see interactions)! Do not combine with midazolam, simvastatin, lovastatin, ergotamine, rifampicin, calcium antagonists. Life-threatening interactions are possible with amiodarone, lidocaine (systemic administration), tricyclic antidepressants, and quinidine (level determination!). Clarithromycin: no combination with boosted atazanavir. Dose reduction of rifabutin by 75% (instead of 300 mg/day only 150 mg every other day or three times per week).

Comment: Formerly much prescribed PI, which, among other things, due to its side effects (hyperbilirubinemia, icterus!) hardly plays a role anymore, the original preparation was taken off the market. Relevant interactions have to be considered, especially with PPIs, but also with tenofovir.

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Atovaquone

Manufacturer: GlaxoSmithKline.

Approval and indication: acute treatment of moderately severe PCP in cases of intolerance to cotrimoxazole. Combined with proguanil, it is also for treating and preventing malaria. Off Label: PCP prophylaxis (as a reserve), acute treatment of cerebral toxoplasmosis. Atovaquone is a component of the following preparations:

- Wellvone® suspension containing 750 mg atovaquone/5 mL (210 mL).
- Malarone® film-coated tablets containing 250 mg atovaquone and 100 mg proguanil

Dose: As PCP (or toxo) therapy daily 2 x 750–1,500 mg (2 x 1–2 scoops to 5 mL) for 21 days. For prophylaxis, 2 x 750 mg (2 x 1 scoopful at 5 mL) or 1 x 1,500 mg daily. For malaria therapy, see FA. Take with a meal, the bioavailability increases 2–3 times.

Adverse events: Frequently gastrointestinal, skin exanthema. Less commonly, headache insomnia. Increased liver enzymes and amylase. Anemia, leukopenia (rare).

Interactions: Take with a high-fat meal as this improves absorption. Rifampicin, possibly also rifabutin, reduces plasma levels of atovaquone by about 50%. Fluconazole is likely to increase levels.

Comment: Only rarely used now. Considerably more expensive than other drugs for PCP prophylaxis!

Atripla®

Manufacturer: The Gilead/BMS/MSD co-production was withdrawn from the market in 2021; only generics are now available.

Approval and Indication: Adult PLWH who have had a viral load below 50 copies/mL on current ART for over three months and have no prior virologic failure or resistance.

- Efavirenz/emtricitabine/tenofovir disoproxil (formerly Atripla®) with 600 mg efavirenz, 200 mg FTC, 300 mg TDF

Dose: One tablet daily in the evening, unchewed, on an empty stomach.

Notes: Note the above indication restriction and side effects; see especially Efavirenz (CNS) and TDF (kidney). Numerous generics are available but much more expensive than single substances.

Comment: Atripla® was the first single-tablet regimen, now off the market. The generics are rarely used; efavirenz is no longer recommended.

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Azithromycin

Manufacturer: Various. Trade names, e.g., Azithromycin®, Zithromax®, Ultreon®.

Approval and indication: treatment and prevention of MAC infection. Upper and lower respiratory tract infections, otitis media. Uncomplicated gonorrhea, uncomplicated genital infections due to Chlamydia trachomatis, ulcus molle. Azithromycin is a component of the following preparations (selection):

- Ultreon® film-coated tablets 600 mg
- Zithromax® 250 mg and 500 mg, film-coated tablets
- Zithromax® powder for oral suspension (containing 200 mg per 5 mL)

Dose: Primary prevention of MAC infection: Weekly 1,200 mg (1 x 2 tablets Ultreon® 600 mg per week). MAC therapy: Daily 1 x 1 tablet Ultreon® 600 mg, only in combination with ethambutol and rifabutin.

Respiratory infections: Total dose 1500 mg, distributed over three days (1 x 500 mg each).

Gonorrhea (with ceftriaxone!), Chlamydia (not LGV!): 1500 mg as a single dose.

Adverse events: Gastrointestinal with stomach cramps, nausea, vomiting, diarrhea! Rarely increased transaminases and cholestasis. Reversible ototoxicity at high doses. Rarely taste irritation or discoloration of the tongue. Allergies.

Comment: Macrolide antibiotic with a long half-life and good tissue penetration. A single dose is sufficient for many STDs and 3–5 days for respiratory infections. Formerly commonly used for MAC infections, it is also used as continuous therapy.

AZT (zidovudine)

Manufacturer of the original preparations: ViiV Healthcare. Also generics!

Approval and Indication: As part of combination therapy for both untreated and pretreated patients. AZT is a component of the following preparations:

- Retrovir® hard capsules: 100 mg AZT and 250 mg AZT
- Retrovir® film-coated tablets: 300 mg AZT
- Retrovir® solution: 100 mg AZT per 10 mL (200 mL)
- Retrovir® concentrate: 10 mg AZT per mL (5 vials of 200 mg each).
- Combivir® film tablets: 300 mg AZT + 150 mg 3TC
- Trizivir® film tablets: 300 mg AZT+150 mg 3TC+300 mg abacavir

Dose: 2 x 250 mg daily. In Combivir® and Trizivir® 2 x 300 mg daily. Severe renal insufficiency (creatinine clearance less than 20 mL/min, hemodialysis): 300 mg daily. Hepatic insufficiency: 3 x 100 mg daily.

Adverse events: Nausea, vomiting, bloating, headache, muscle pain. Macrocytic anemia (MCV almost always elevated), rarely neutropenia. Also, LDH, CK elevations, and elevated transaminases. Rarely lactic acidosis.

Interactions: Increased myelotoxicity with ganciclovir, cotrimoxazole, dapsone, pyrimethamine, sulfadiazine, and various chemotherapeutic agents, among others. In particular, avoid combination with ribavirin. Initially, monthly checks of blood count, transaminases, CK, and bilirubin. Gastrointestinal symptoms usually subside after a few weeks. Anemia may take months to develop.

Comment: The first NRTI (thymidine analog, approval 1987!) is rarely used due to side effects and twice-daily administration.

Detailed discussion in this book: page 49

Bictegravir

Manufacturer: Gilead Sciences.

Approval and indication: Adult PLWH (pretreated or naive) without known resistance to single agents.

- Biktarvy® film-coated tablets containing 50 mg bictegravir, 200 mg FTC, 25 mg TAF

Dose: 1 x 1 tablet daily, regardless of food intake. There is no dose adjustment in renal insufficiency (up to a GFR of 30 mL/min) or moderate hepatic impairment.

Adverse events: Overall well tolerated, mainly tested against dolutegravir in pivotal studies; so far, hardly any differences in tolerability, also about possible sleep disturbances and other CNS side effects (relatively rare). In some cases, significant weight gain, causes and mechanisms are unclear.

Interactions: Fewer interactions are expected due to the lack of a booster than with, for example, Genvoya®. However, levels decrease in combination with rifampicin (contraindicated). Rifabutin is also not recommended, nor is carbamazepine, St. John's wort. Relatively small tablets. A safety interval of 2 hrs is recommended with antacids. There is a high resistance barrier, which is also effective against many pre-existing resistances, but approval restrictions (see above).

Comment: Approved in 2018, a much-used fixed combination of TAF+FTC plus an unboosted INSTI with a high resistance barrier. Has largely replaced Genvoya®. There are no plans to introduce the single agent bictegravir.

Detailed discussion in this book: page 74, 174

Cabenuva® – see cabotegravir

Cabotegravir

Manufacturer: ViiV Healthcare.

Approval and indication: In combination with rilpivirine injection (Rekambys®) in adults virologically suppressed on stable ART without resistance or failure to NNRTIs or INSTIs. Both drugs are packaged in the US, with the single trade name Cabenuva®.

- Vocabria® vials of 400 mg (2 mL) or 600 mg (3 mL)
- Vocabria® 30 mg film-coated tablets (lead-in and oral bridging only).
- Apretude® vials of 600 mg (3 mL) for PrEP (every 8 weeks)
- Apretude® 30 mg film-coated tablets (for PrEP lead-in and oral bridging only)

Dose: As "lead-in" (may be omitted), one tablet daily for 28 days, the initial dose of 600 mg i.m. on the last day, another 600 mg dose after one month, 600 mg every two months after that (400 mg if given monthly), up to 7 days before/after the target date. Oral bridging is possible for up to two months. See detailed package info if doses are missed. Start classic ART if discontinued within one month. No dose adjustment in renal or hepatic insufficiency.

Adverse events: Overall, well tolerated. Pain at injection sites (approx. 80%, swelling, redness) is usually mild and rarely leads to discontinuation. Headache, depression (neuropsychiatric adverse events).

Warnings, interactions: Shake vials vigorously for 10 seconds. Use longer needles in obese patients. Use with caution in HIV subtype A and BMI >30. Strictly gluteal, always the same buttock. Do not use with rifabutin, carbamazepine, phenytoin.

Comment: In 2020, the first approved long-acting therapy. Use only with rilpivirine and not with other antiretroviral agents. Note indication restrictions.

Detailed discussion in this book: page 75

Caelyx® see Doxorubicin, liposomal

Cidofovir

Original manufacturer: Gilead Sciences. Originator (Vistide®) was discontinued in 2014; generics are still available.

Approval and indication: CMV retinitis in PLWH without renal dysfunction when other therapies are unsuitable (resistance or contraindications to ganciclovir or foscarnet).

- Cidofovir vials containing 375 mg in 5 mL (= 75 mg/mL)

Dose: Weekly 5 mg/kg i.v. as induction, from day 21 maintenance with 5 mg/kg i.v. Every two weeks. Plan (comedication, hydration, see below) required!

Adverse events: Renal insufficiency, possible even after a single dose. Rarely neutropenia, dyspnea, alopecia, decreased intraocular pressure, iritis, and uveitis. Fever, shivering, headache, rash, nausea/vomiting are more likely due to probenecid, usually resolved within 12 hours, and are relieved by food intake, antipyretics, and antiemetics.

Warnings, interactions: Beware of nephrotoxicity! Before each administration, check renal function (serum creatinine, electrolytes, proteinuria). If serum creatinine increases by more than 0.3 mg/dl, reduce the dose to 3 mg/kg (discontinue at

0.5 mg/dl increase)! Cidofovir is contraindicated if serum creatinine >1.5 mg/dl, creatinine clearance <55 mL/min, or proteinuria >100 mg/dl. Always ensure adequate hydration!

In case of normal renal function, the following regimen is recommended (protocol!):

Std –3	2 g probenecid (4 tbl. of 500 mg), possibly 20 tr. Novamin sulfone plus 50 mg prednisolone beforehand
Std –3 to –1	1000–2000 mL NaCl 0.9%
Std 0 to +2	Cidofovir in 500 mL NaCl 0.9% over 1–2 h Parallel 1,000 mL NaCl 0.9
Std +4	1 g probenecid (2 tbl. of 500 mg), possibly 20 tr. novamine sulfone beforehand
Std +10	1 g probenecid (2 tbl. of 500 mg), possibly 20 tr. novamine sulfone beforehand

Discontinue nephrotoxic drugs such as amphotericin B, foscarnet, or vancomycin (7 days prior). Probenecid is necessary to reduce nephrotoxicity – cave interactions with paracetamol, acyclovir, ACE inhibitors, ASA, benzodiazepines, clofibrate, methotrexate, furosemide, and theophylline.

Comment: Reserve drug for CMV disease, now very rarely used due to nephrotoxicity. The effect in PML is questionable.

Clarithromycin

Manufacturers: Various. Trade names, e.g., Clarithromycin-CT®, Klacid®, Mavid®.

Approval and indication: prevention and treatment of MAC infection. Infections of the respiratory tract, ENT area, and skin. Clarithromycin is a component of the following preparations (selection):

- Mavid® 500 mg film-coated tablets
- Klacid® 250 mg film-coated tablets

Dose: MAC 2 x 500 mg daily, in primary and secondary prophylaxis. From creatinine clearance <30 mL/min, dose reduction by 50%. For respiratory infections, a dose of 2 x 250 mg is sufficient.

Adverse events: Mainly gastrointestinal complaints. Allergic reactions, headache, elevation of liver enzymes.

Interactions: Numerous interactions. Do not co-administer rifampicin, carbamazepine, cisapride, terfenadine, pimozide, or other macrolides. Lopinavir and ritonavir increase clarithromycin levels.

Comment: Macrolide antibiotic with a shorter half-life than azithromycin. The daily dose should not exceed 2 x 500 mg. Hardly used anymore.

Clindamycin

Manufacturer: Various. Trade names e.g. Clindabeta®, Sobelin®.

Approval and indication: In HIV, especially in cerebral toxoplasmosis. Otherwise, it is also for severe infections by anaerobes or staphylococci (due to good penetration into tissue and bone, also frequently used in dentistry).

Dose: Daily 4 x 1 Amp. à 600 mg i.v. or 4 x 1 Tbl. à 600 mg (always plus Daraprim® and Leukovorin®). As maintenance therapy (oral) with half the dose. In renal insufficiency, reduction to one-quarter to one-third of the usual dose.

Adverse events: Diarrhea in 10–30%. Allergies are also common and often require discontinuation. In Clostridium difficile infection, pseudomembranous colitis: the spectrum ranges from mild to severe, mucous-bloody diarrhea that can lead to peritonitis, shock, and toxic megacolon.

Interactions, warnings: Clindamycin is contraindicated in inflammatory bowel disease and antibiotic-induced -colitis. Caution in impaired liver -or kidney function, asthma. Cave concurrent administration of antiperistaltics! In case of diarrhea under clindamycin, discontinue clindamycin and start treatment with metronidazole, possibly vancomycin.

Comment: It is still partly indispensable for toxoplasmosis but should be used cautiously because of the risk of colitis.

Cobicistat

Manufacturer: Gilead Sciences, partly co-productions

Approval and indication: as a pharmacoenhancer for elvitegravir, atazanavir, and darunavir. Cobicistat is a component of the following preparations:

- Tybost® 150 mg film-coated tablets

Fixed combinations of 150 mg each of cobicistat:

- Evotaz®: plus 300 mg atazanavir (approved in the EU but not marketed in many countries).
- Genvoya®: plus 150 mg elvitegravir + 200 mg FTC + 10 mg TAF
- Rezolsta®: plus 800 mg darunavir (approved in the EU but not marketed in many countries).
- Stribild®: plus 150 mg elvitegravir + 200 mg FTC + 300 mg TDF
- Symtuza®: plus 800 mg darunavir + 200 mg FTC + 10 mg TAF

Dose: Once daily, with a meal. No dose adjustment is required for renal impairment. Creatinine increases (usually <0.4 mg/dl) due to inhibition of creatinine secretion do not indicate renal function deterioration.

Adverse events: more hyperbilirubinemia with atazanavir than with ritonavir.

Interactions: As booster (potent CYP3A inhibitor and substrate), numerous interactions! Do not combine with efavirenz, nevirapine, etravirine, and PIs other than atazanavir or darunavir. No dose adjustment with rilpivirine. For maraviroc, 2 x 150 mg is sufficient. Contraindicated drugs include carbamazepine, rifampicin, ergotamine, amiodarone, simvastatin, lovastatin, St. John's wort. Also, avoid sildenafil. The list of contraindications is long!

Comment: The first pharmacoenhancer was developed only for boosting. Approval for Elvitegravir, Darunavir (and Atazanavir). The single substance is hardly ever used – as a rule, it makes no sense to take fixed combinations apart, and atazanavir is no longer needed.

Combivir®

Original manufacturer: ViiV Healthcare. Various generics are available.

Approval and indication: In HIV infection as part of combination therapy in both untreated and pretreated patients.

• Combivir® film tablets: 300 mg AZT + 150 mg 3TC (generic)

Dose: 2 x 1 tablet daily, regardless of meals. In case of impaired renal function (creatinine clearance below 50 mL/min) or anemia, the single substances should be given in reduced doses instead of Combivir®. For side effects, see especially AZT.

Comment: In 1998, the first combination drug, now an alternative only in rare resistance situations. The twice-daily administration and the potential side effects of AZT are significant drawbacks.

Cotrimoxazole

Manufacturer: Diverse, hence numerous trade names such as Cotrimstada® and Eusaprim®.

Approval and indication: Prevention and therapy of Pneumocystis pneumonia. Prophylaxis and treatment reserve in cerebral toxoplasmosis. Also, for other infections, for example urinary tract infections.

• Cotrim forte® tablets containing 160/800 mg trimethoprim/sulfamethoxazole
• Cotrim 480® tablets with 80/400 mg trimethoprim/sulfamethoxazole
• Eusaprim® oral suspension for adults (= 16/80 mg/mL), children (8/40 mg/mL)
• Cotrim ampoules® with 80/400 mg

Dose: As PCP **prophylaxis**, 80/400 mg daily or 160/800 mg trimethoprim/sulfamethoxazole three times a week. As PCP **therapy**, 5 mg/kg (based on trimethoprim) orally or i.v. every 8 hours for 21 days, so usually 3 x 5 to 6 amp. of 80/400 mg. Toxoplasmosis prophylaxis: 160/800 mg daily. Halve dose at a creatinine clearance of 15–50 mL/min, below which cotrimoxazole is contraindicated.

Adverse events: Allergies. In high doses, myelotoxicity (anemia, neutropenia!), nausea, vomiting, headache, transaminase elevations. In the case of mild allergies, treatment can often be continued.

Comment: Caution in case of sulfonamide allergy! Oral suspension can be used to desensitize from 12.5, 25, 37.5, 50, and 75 to 100% of the dose of the 480 mg tablet within six days. Cotrimoxazole may increase the effect of anticoagulants and reduce that of oral contraceptives.

Crixivan® – first-generation PI, withdrawn from the market in 2019

Cymeven® see Ganciclovir

Daclatasvir, Daklinza® – rarely used HCV NS5A inhibitor

D4T, stavudine – toxic NRTI, was withdrawn from the market in 2019

Dapsone

Manufacturer: Fatol.

Approval and indication: Prophylaxis of PCP and toxoplasmosis. It is rarely used in dermatology (bullous pemphigoid), rheumatology, and leprosy.

• Dapsone-Fatol® 50 mg tablets

Dose: 100 mg daily after a meal. Alternative: 1 x 1 tbl. à 50 mg **plus** pyrimethamine 1 x 2 tbl. à 25 mg/wk **plus** folinic acid 1 x 2 tbl. à 15 mg/wk.

Adverse events: Allergies (itching, rash), fever. Frequently also hemolytic anemia (LDH elevation almost obligatory!), hepatitis.

Comment: Reserve drug, contraindicated in severe anemia and G6PD deficiency. LDH below dapsone is not diagnostically useful. Rifabutin and rifampicin decrease dapsone levels.

Daraprim® see pyrimethamine

Darunavir

Original manufacturer: Janssen-Cilag. Generics for the single substance

Approval and indication: Untreated and pretreated adults (as single agent) and children with HIV infection.

• Prezista® film-coated tablets of 400, 600, and 800 mg
• Prezista® 75 and 150 mg film-coated tablets, suspension (100 mg/mL) for children
• Rezolsta®: 800 mg plus 150 mg cobicistat (EU approval, not marketed in many countries)
• Symtuza®: 800 mg plus 150 mg cobicistat, 200 mg FTC, 10 mg TAF

Dose: Daily 1 x 800 mg plus 1 x 100 mg ritonavir (or 1 x 150 mg cobicistat) each with meal. In case of PI resistance mutations better 2 x 600 mg + 2 x 100 mg ritonavir. Children: dose according to body weight. 20–30 kg 375 mg/50 mg RTV BID, 30–40 kg 450/60 mg, >40 kg 600 mg/100 mg BID.

Adverse events: Moderate gastrointestinal symptoms, especially diarrhea. Dyslipidemia may not be as pronounced as with other PIs. Skin rash in up to 7% in first two weeks, usually mild (therapy can be continued in most cases).

Interactions: Caution with sulfonamide allergy; do not start concurrently with NNRTI (DD of allergic exanthema difficult). Various interactions – do not combine with other PIs, St. John's wort, simvastatin, terfenadine, midazolam, ergotamine, rifampicin, phenobarbital, phenytoin, carbamazepine. Caution with anticoagulants, no ticagrelor. Dose adjustment also with efavirenz (due to low darunavir levels 2 x 600/100 mg), rifabutin (reduce to 150 mg every other day), calcium antagonists (increased levels), methadone (decreased). Interactions with contraceptive pills. Use low doses of PDE5 inhibitors! Start atorvastatin and rosuvastatin at the lowest dose.

Comment: Well-tolerated, universally applicable PI with high resistance barrier and activity also against PI-resistant viruses. Also available as STR since 2017. There are numerous interactions to consider. The single agent is generic.

Detailed discussion in this book: page 69

Dasabuvir (Exviera®) – HCV NS5A inhibitor that is hardly ever used anymore

Daunorubicin (liposomal)

Manufacturer: Gilead Sciences, Fresenius.

Approval and indication: AIDS-associated Kaposi's sarcoma with less than 200 CD4 T-cells/µl and extensive mucocutaneous or visceral involvement.

• DaunoXome® vials of 50 mg each (25 mL)

Dose: 40 mg/m² in 250 mL 5% glucose solution (no other solutions!), intravenously over 30–60 min, repeated every 2–3 weeks.

Adverse events: During infusion, back pain, flushing (flushing, up to 14%), dyspnea, usually in the first few minutes, rapidly remitting with infusion stopped. Fatigue, headache, myelosuppression, cardiomyopathy. Extravasation.

Warnings: Contraindicated in severe cardiomyopathy. Cardiac monitoring (ECG, echo) before and during therapy is essential. Myelosuppression (neutrophils <1,000/µl, platelets <50,000/µl).

Comment: In KS, an alternative to pegylated liposomal doxorubicin probably slightly lower remission rates.

DDC (zalcitabine, HIVID®) – sales were discontinued in 2006

DDI (didanosine, Videx®) – sales were discontinued in 2020

Delavirdine (Rescriptor®) – NNRTI was never approved in Europe

Delstrigo®

Manufacturer: MSD.

Approval and indication: For adults and children 12 years of age and older (at least 35 kg) whose viruses do not show resistance to the individual substances.

• Delstrigo® film-coated tablets: 200 mg FTC + 300 mg TDF + 100 mg doravirine

Dose: 1 x 1 tablet daily, regardless of a meal. Do not use in renal dysfunction with GFR less than 50 mL/min.

Adverse events: Rather rarely, sleep disturbances, abnormal dreams (less common than with efavirenz), headache, and occasionally rash (see doravirine). Occasional nausea. For renal dysfunction and osteoporosis, see tenofovir.

Interactions: Do not combine with rifabutin, rifampicin, various anticonvulsants (including carbamazepine), and St. John's wort (doravirine levels decrease). Caution in severe hepatic insufficiency (Child C). No dose adjustment is necessary when combined with PPIs. Effective in some typical NNRTI resistance despite indication restriction (see above).

Comment: This fixed combination licensed in late 2018 has shed some of the drawbacks of NNRTIs (higher resistance barrier, PPIs possible, no food restrictions). Because of TDF, renal function must be considered.

Detailed discussion in this book: page 171

Descovy®

Manufacturer: Gilead Sciences.

Approval and indication: HIV infection. Adults and adolescents (12 years and older, weight at least 35 kg).

• Descovy® film-coated tablets: 10 mg or 25 mg TAF + 200 mg FTC

Dose: One tablet daily, meal-independent, unchewed. Two doses, depending on concomitant therapy! With boosted PIs (atazanavir, darunavir, lopinavir) and some other substances (itraconazole!), 10 mg TAF (gray tablet!) is sufficient; otherwise, 25 mg (blue!). Advise patients of the two doses to avoid mistakes.

Adverse events: Well tolerated, less nephrotoxic than Truvada®, and can be used up to moderate renal impairment (GFR 30–60 mL/min). Less unfavorable effects on bone density than TDF. Instead, there are no lipid-lowering effects, possibly slightly more headache and probably also weight gain, especially in INSTI combinations (mechanisms unclear).

Interactions: The 10 mg TAF should also be used with concomitant administration of ketoconazole itraconazole. The concomitant administration of carbamazepine, St. John's wort, tipranavir, rifampicin, and rifabutin is not recommended (TAF levels decrease!).

Comment: Approval in May 2016. TAF is less nephrotoxic than TDF (see Tenofovir) but probably causes more weight gain. However, Descovy® has a cost problem since the price drop of Truvada® generics; without a well-founded application to the health insurance company, considerable co-payments loom! Note two dosages, frequent source of error. Also HBV-effective.

Detailed discussion in this book: page 55

Dolutegravir

Manufacturer: ViiV Healthcare.

Approval and indication: PLWH, including adolescents over 6 years of age (at least 40 kg, dose-adapted), in combination with other agents. Dolutegravir is a component of the following preparations in the dose of 50 mg:

• Dovato® Tablets 50 mg plus 300 mg 3TC
• Tivicay® tablets 50 mg (for children also 10 mg, 25 mg – only until 2024, also 5 mg dispersible tablets for preparation of a suspension)
• Triumeq® tablets50 mg plus 300 mg 3TC + 600 mg abacavir
• Juluca® tablets 50 mg plus 25 mg rilpivirine

Dose: 1 x 1 tablet of 50 mg daily, with or without a meal (Juluca® with a meal, because of rilpivirine!). To overcome resistance or with certain comedications (see below), increase the dose to 50 mg twice daily. No dose adjustment is necessary for renal insufficiency. The pediatric dose is based on body weight.

Adverse events: CNS symptoms, including sleep disturbances, dizziness, and paresthesias lead to discontinuation in approximately 5% (more common than among other INSTIs). Occasional headache, nausea, increase in transaminases and CK. Weight gain (mechanism unclear).

Interactions: In combination with efavirenz, nevirapine, fosamprenavir, tipranavir and rifampicin, 2 x 50 mg dolutegravir should be given. Avoid these combinations if the dolutegravir dose must be increased anyway due to resistance! Combination

with etravirine only in the presence of boosted PIs. Do not combine with St. John's wort, antiepileptic drugs. Antacids only to be taken with a significant time delay. Reduce metformin dose if necessary (metformin levels rise!).

Comment: In 2014, it was the first integrase inhibitor that does not require a booster and can still be given once daily. Universal and flexible use in various fixed combinations or dual therapies, mostly well tolerated, with few interactions and a high resistance barrier.

Detailed discussion in this book: page 76

Doravirine

Manufacturer: MSD.

Approval and indication: Adult PLWH and children 12 years and older (at least 35 kg) without resistance to NNRTIs.

- Pifeltro® 100 mg film-coated tablets
- Delstrigo® film-coated tablets: 100 mg doravirine + 300 mg TDF + 300 mg 3TC

Dose: 1 x 100 mg daily, regardless of meals.

Adverse events: Relatively well tolerated, fewer CNS symptoms (dizziness, sleep disturbances) than with efavirenz. Headache, gastrointestinal complaints, and exanthema/rash are all relatively rare. For the fixed combination, see also tenofovir.

Interactions: Strong enzyme inducers such as carbamazepine, rifampicin, rifabutin, and St. John's wort are contraindicated. Combination with PPIs, however, is possible. There is no data for pregnancy. Doravirine can be combined with all antiretroviral drugs without dose adjustment. The combination tablets are relatively large.

Comment: New NNRTI that has overcome some weaknesses of this substance group. Relatively high resistance barrier, no food restrictions, combination with other antiretroviral agents and PPIs possible.

Detailed discussion in this book: page 60

Dovato®

Manufacturer: ViiV Healthcare.

Approval and indication: HIV infection, adults and adolescents over 12 years of age (at least 40 kg), without resistance to INSTIs and 3TC.

- Dovato® film-coated tablets: 300 mg 3TC + 50 mg dolutegravir

Dose: One tablet daily, regardless of meals. Avoid a creatinine clearance of less than 30 mL/min; here, use the single substances and dose individually.

Adverse events: Overall, well tolerated; see single agents for details. Occasional sleep disturbances are possible with dolutegravir.

Interactions, warnings: In case of INSTI resistance and in salvage regimens with efavirenz, etravirine, nevirapine, and tipranavir, rather avoid (dolutegravir would have to be doubled to BID here). This also applies to rifampicin, carbamazepine, or St. John's wort. It is not recommended for moderate to severe hepatic impairment. Caution with metformin (reduce dose if necessary). In first-line therapy, only in people without hepatitis B, with less than 500,000 copies/mL and more than 200 CD4 T-cells/µl.

Comment: This was the first dual regimen for treatment-naïve patients in 2019. Equivalent to triple combinations even in pretreated, high resistance barrier. Caution in active hepatitis B (3TC alone is not sufficient).

Detailed discussion in this book: page 177, 201

Doxorubicin (liposomal)

Manufacturer: Janssen-Cilag.

Approval and indication: including AIDS-associated Kaposi's sarcoma with <200 CD4 T-cells/µl and extensive mucocutaneous or visceral involvement.

• Caelyx® 10 mL (20 mg) and 25 mL (50 mg) vials

Dose: 20 mg/m² i.v. in 250 mL 5% glucose over 30 min, every 2–3 weeks.

Adverse events: Cardiomyopathy. Myelosuppression and stomatitis (rarely severe), palmar-plantar erythrodysesthesia (PPED, hand-foot syndrome), therapy: cooling of affected areas. Cave extravasation (never s.c./i.m./bolus administration!).

Interactions, warnings: Contraindicated in severe bone marrow depression (neutrophils <1,000/µl, platelets <50,000/µl), cardiomyopathy, prior therapy with anthracycline doses above the cumulative dose. ECG and cardiac echo (EF?) before and during treatment, cumulative dose of 450 mg/m² and above before each cycle. PPED is promoted by sweating – avoid tight gloves, sun, sauna, and long showers with hot water. Detailed instructions for dose modification for PPED in the package insert. The substance is expensive.

Dutrebis® see raltegravir

Edurant® see rilpivirine

Efavirenz

Manufacturers: BMS (Sustiva®); MSD (Stocrin®); Gilead/BMS/MSD (Atripla®). Generic drugs are also available.

Approval and indication: HIV infection.

• Sustiva® 600 mg film-coated tablets (Generic)
• Sustiva® 50 mg, 100 mg, 200 mg hard capsules
• Sustiva® Oral solution (30 mg/mL, 180 mL = 5.4 g)
• Atripla® film-coated tablets 600 mg plus 200 mg FTC + 300 mg tenofovir DF

Dose: 600 mg daily just before bedtime, on an empty stomach. See the Pediatrics chapter for dose adjustment in children/adolescents under 40 kg.

Adverse events: CNS symptoms common in the first few weeks: nightmares, confusion, dizziness, lightheadedness, depression, difficulty concentrating, insomnia, and feelings of depersonalization. Also, exanthema (15%) within the first weeks, usually mild, usually further treatment possible. Increase in liver and bile levels (yGT). Dyslipidemia, occasionally painful gynecomastia.

Interactions, warnings: Caution in women of childbearing age. Do not take with high-fat meals (possibly higher absorption and side effects). No concomitant administration with ergotamines, astemizole, cisapride, midazolam, terfenadine and triazolam. If combined with rifampicin, increase efavirenz to 800 mg; if combined with rifabutin, increase the rifabutin dose by 50%. If combined, dose increases of darunavir

(2 x 600 mg BID) and maraviroc (2 x 600 mg if not given boosted PI). Combination with atazanavir is not recommended.

Comment: This NNRTI has been prescribed for a long time but is rarely used due to CNS adverse events. It is to be considered in first-line therapy only with concurrent TB therapy. Inexpensive generics available.

Detailed discussion in this book: page 61

Elbasvir see Zepatier®

Elvitegravir

Manufacturer: Gilead Sciences.

Approval and indication: Adult PLWH without integrase resistance. Elvitegravir is a component of the following film-coated tablets:

- Vitekta® with 85 or 150 mg elvitegravir (not marketed in many countries)
- Stribild® with 150 mg elvitegravir, 150 mg cobicistat, 200 mg FTC, 300 mg TDF
- Genvoya® with 150 mg elvitegravir, 150 mg cobicistat, 200 mg FTC, 10 mg TAF

Dose: With each meal, unchewed. The single agent elvitegravir (EU approval, but not marketed in most countries) must be dosed differently: Either 85 mg (for atazanavir/r, lopinavir/r) or 150 mg (darunavir/r 600/100 BID, fosamprenavir/r). Once daily, with the first dose of the day for PIs.

Adverse events: Well tolerated, most likely nausea, diarrhea, headache. Nephrotoxicity is to be noted, especially with Stribild® and Genvoya® (see there). Probably also weight gain.

Interactions: Elvitegravir is metabolized by CYP3A and others. Do not combine with rifampicin, carbamazepine, phenytoin, St. John's wort. Caution also with efavirenz and nevirapine! Plasma concentration is strongly increased by atazanavir and darunavir, therefore, dose reduction (see above).

Comment: Integrase inhibitor that needs to be boosted. Broad cross-resistance with raltegravir. Single-agent is irrelevant; FDCs Stribild® and Genvoya® are rarely initiated due to interaction issues.

Detailed discussion in this book: page 77

Emtricitabine (FTC)

Manufacturer: Gilead Sciences (collaborations with Janssen, among others), generics.

Approval and indication: HIV infection.

Emtriva® hard capsules: 200 mg FTC, solution: 10 mg FTC per mL

With 200 mg of each component of the following combination preparations (film-coated tablets)

- Descovy®: plus 10 or 25 mg TAF
- Truvada®: plus 300 mg tenofovir DF (TDF), generic!

Each containing 200 mg of the following STRs/fixed combinations (film-coated tablets)

- Atripla®: plus 300 mg TDF + 600 mg efavirenz (generic).
- Biktarvy®: plus 25 mg TAF + 50 mg bictegravir
- Eviplera®: plus 300 mg TDF + 25 mg rilpivirine
- Genvoya®: plus 10 mg TAF + 150 mg elvitegravir + 150 mg cobicistat
- Odefsey®: plus 25 mg TAF + 25 mg rilpivirine
- Stribild®: plus 300 mg TDF + 150 mg elvitegravir + 150 mg cobicistat
- Symtuza®: plus 10 mg TAF + 800 mg darunavir + 150 mg cobicistat

Dose: 1 x 200 mg daily. In case of decreased creatinine clearance, use single preparation, dose as follows: 200 mg every two days for GFR 30–49 mL/min, 15–20 mL/min every three days, below 14 mL/min, or dialysis every four days.

Adverse events: Rare, most likely headache, nausea, diarrhea, rash. Possibly also hyperpigmentation.

Comment: Well-tolerated cytidine analog, biochemically and in the resistance spectrum similar to 3TC, but with a longer half-life. Component of various combination preparations, the single preparation has no significance. Generics are available for some preparations.

Detailed discussion in this book: page 51

Enfuvirtide see T-20

Epivir® see 3TC (at the beginning of the drug section)

Epclusa®

Manufacturer: Gilead Sciences.

Approval and indication: Chronic hepatitis C, all genotypes. Combine with ribavirin in certain situations (see chapter *Hepatitis*).

- Epclusa® film-coated tablet: 400 mg sofosbuvir and 100 mg velpatasvir

Dose: 1 x 1 tablet daily, regardless of food intake. No dose adjustment in mild/moderate renal impairment or in moderate or severe hepatic impairment.

Adverse events: Well-tolerated, nausea, headache, fatigue, hardly more frequent than with placebo.

Interactions: 12 weeks (in compensated cirrhosis and GT3 with additional ribavirin). Do not combine with efavirenz, etravirine, nevirapine (decrease velpatasvir concentration), St. John's wort. Maintain time intervals with PPIs. Combination with boosted PIs is possible.

Comment: Combination (NS5A inhibitor and polymerase inhibitor) approved in July 2016 for chronic hepatitis C. Effective against all genotypes. Similar efficacy and safety profile to Harvoni®, but equally high cost.

Ethambutol

Manufacturer: Riemser, Fatol and others.

Approval and indication: Tuberculosis and MAC infections, always in combination!

- EMB-Fatol® Film bl. containing 100 mg, 250 mg, 400 mg and 500 mg (N2:50; N3:100).
- EMB-Fatol® solution for injection with 1 g in 10 mL (N2:10)
- Myambutol® film-coated tablets 400 mg (N2:50; N3:100)
- Myambutol® Injection solution containing 400 mg/4 mL (N2:10) and 1,000 mg/10 mL (N2:5).

Dose: Daily 15 to 25 mg/kg (maximum 2 g), usually 1 x 3 tablets of 400 mg. In combination therapies only. Dose reduction if creatinine clearance is below 75 mL/min to 15 mg/kg, below 40 ml/min to 15 mg/kg every other day. Above a GFR of 30 mL/min individually, level determinations.

Adverse events: Optic neuritis with visual disturbances (decreased vision, visual field loss, and loss of red-green color vision) is reversible if ethambutol is discontinued immediately. Nausea, vomiting, abdominal pain, headache, dizziness. Pruritus, joint pain, elevated serum uric acid levels (acute gout attacks possible!), abnormal liver function tests.

Warnings: Ethambutol is contraindicated in the presence of pre-existing optic nerve damage. Ophthalmologic examination before initiation of therapy and at 4-week intervals thereafter (color vision, visual field, visual acuity). If drug-induced visual disturbances occur, discontinue the drug immediately to avoid optic atrophy. Check liver values and uric acid monthly.

Etravirine

Manufacturer: Janssen-Cilag.

Approval and Indication: Pretreated adults and children 6 years of age and older. Only in ART combinations containing a boosted PI.

- Intelence® 200 mg and 100 mg (25 mg tablets for children)

Dose: 2 x 200 mg (2 x 1 pill) after a meal.

Adverse events: Mostly mild rash in the second week, rarely nausea. In mild manifestations, treatment can usually be continued. Discontinue immediately in severe exanthema, isolated cases of TEN and DRESS syndrome.

Interactions: The tablets are dissolvable in water. Etravirine is a substrate of the CYP P450 enzyme system, but at the same time, an inducer of CYP3A4 and an inhibitor of CYP2C9 – thus, numerous interactions are expected. Do not combine with atazanavir, tipranavir, other NNRTIs. Also, avoid rifampicin, carbamazepine, phenobarbital, phenytoin, and St. John's wort.

Comment: The first second-generation NNRTI was approved in 2008 for pretreated patients. It is well tolerated and effective against NNRTI-resistant viruses (K103N!). Always combine with a boosted PI (darunavir!).

Detailed discussion in this book: page 62

Eviplera® (USA: Complera®)

Manufacturer: Gilead Sciences.

Approval and indication: Adult PLWH (if untreated, only if less than 100,000 HIV-RNA copies/mL).

• Eviplera® film-coated tablets: 200 mg FTC + 300 mg TDF + 25 mg rilpivirine

Dose: 1 x 1 tablet daily, with a meal (at least 400 calories) to achieve adequate absorption. Do not use in renal dysfunction with creatinine clearance <50 mL/min.

Adverse events: Rare, most likely rash (see rilpivirine). Occasionally nausea. It is better tolerated than efavirenz, but CNS disturbances occur (depression). For renal dysfunction, see tenofovir.

Interactions: Do not combine with rifabutin, rifampicin, various anticonvulsants (including carbamazepine), PPIs, and St. John's wort (rilpivirine levels decrease). Keep time away from H2 antagonists and antacids. Due to the increased risk of resistance, do not use it if the viral load is high.

Comment: Approved as a second single-tablet regimen in 2011. Avoid if viral load is high; always ensure adequate absorption (meal! No PPIs!). Has been replaced mainly by Odefsey® (TAF instead of TDF) since 2016.

Detailed discussion in this book: page 171

Evotaz® see atazanavir or cobicistat

Exviera® – no longer plays a role in hepatitis C

Fluconazole

Manufacturer: Pfizer and various other companies. Many trade names.

Approval and indication: Candidiasis, cryptococcosis, and some rare mycoses.

• Fluconazole capsules® with 50, 100, 150 and 200 mg
• Diflucan® 40 mg/mL and 10 mg/mL, powder for oral suspension
• Fluconazole infusion vials with 100, 200 and 400 mg

Dose: Orally 1 x 100 mg daily for oropharyngeal candidiasis, 1 x 200 mg for 7–10 days for esophagitis. Double the dose on the first day. If persistent after 10 days, try a higher dose (up to 800 mg daily).
Cryptococcal meningitis: Initially 400–800 mg daily, combined with flucytosine and amphotericin B. After acute treatment (6 weeks), 200 mg daily. Reduce dose to 50% (25%) at creatinine clearance of 10–50 mL/min (<10).

Adverse events: Rarely gastrointestinal discomfort and transaminase elevations. Reversible alopecia in about 10% at doses above 400 mg/day.

Interactions: No effect against *C. krusei*, aspergilli. Use higher doses for *C. glabrata*. Reduced fluconazole levels with rifabutin/rifampicin. Fluconazole increases levels of rifabutin, atovaquone, clarithromycin, theophylline, opiates, marcumar, benzodiazepines, cyclosporine, anticonvulsants, and AZT.

Comment: Agent of choice for candidiasis and for secondary prophylaxis of cryptococcosis (also acute therapy). The tablets are well absorbed; infusions are only useful in case of poor adherence/absorption or severe mucositis.

Fortovase® see Saquinavir

Fosamprenavir

Manufacturer: ViiV Healthcare (formerly GlaxoSmithKline).

Approval and indication: Adult PLWH and children 6 years of age and older, treatment-naïve and pre-treated.

- Telzir® 700 mg film-coated tablets (US: Lexiva®)
- Telzir® Suspension with 50 mg/mL (225 mL bottle)

Dose: 2 x 700 mg + 2 x 100 mg ritonavir (2 x 2 pills), independent of a meal. Other dosages are not approved in Europe.

Adverse events: most commonly diarrhea. Less commonly, nausea, vomiting, and rash (up to 20%). Rarely Stevens-Johnson syndrome (<1%).

Interactions: Numerous interactions! Contraindications include midazolam, ergotamine, flecainide, propafenone, rifampicin, St. John's wort, simvastatin, carbamazepine. Life-threatening interactions are possible with amiodarone, lidocaine, tricyclic antidepressants, and quinidine.

Comment: formerly much-used PI that no longer has a role due to diarrhea and twice-daily administration. Distribution is expected to be discontinued in 2024.

Foscarnet

Manufacturer: AstraZeneca.

Approval and indication: Reserve agent for induction and maintenance therapy of CMV retinitis. Severe, acyclovir-resistant herpes or varicella-zoster infections.

- Foscavir® infusion bottles of 250 mL containing 24 mg/mL

Dose: During induction therapy (2–3 weeks) of CMV retinitis, 2 x 90 mg/kg i.v. daily over at least 2 hours. Maintenance therapy: 1 x 90–120 mg/kg daily over 2 hours. HSV and VZV: 2 x 60 mg/kg i.v. for 2 weeks.

Adverse events: Nephrotoxicity! Mostly reversible after discontinuation. Electrolyte shifts (hypocalcemia, hypokalemia) are also common. Less commonly, anemia, neutropenia, fever, rash, headache, nausea, vomiting, diarrhea. Often painful penile ulcers (washing after each urination!).

Notes, rating: Hydration! At least 2.5 liters daily. To prevent hypocalcemia, infuse one ampule of 10% calcium solution in 100 mL of 5% glucose immediately before infusion. Give 500–1,000 mL of 5% glucose before or after administration. Do not mix infusions. Initially check Na, K, Ca, creatinine, and blood count 3 x/week. Do not combine with other nephrotoxic substances; adjust the dose in case of renal insufficiency.

Fostemsavir

Manufacturer: ViiV Healthcare.

Approval and Indication: In Europe, approval is "for the treatment of adults with multidrug-resistant HIV-1 infection for whom no other suppressive antiretroviral treatment regimen is available."

- Rukobia® 600 mg sustained-release tablets

Dose: One tablet twice daily, with or without meal. No dose adjustments are necessary for renal or hepatic insufficiency.

Adverse events: Well-tolerated in studies to date. Rarely headache, nausea, vomiting, diarrhea, mostly mild. CK and GPT elevations.

Interactions: No experience in pregnancy. Do not combine with potent enzyme inducers such as carbamazepine, rifampicin, phenytoin, mitotane, enzalutamide, and St. John's wort, including elbasvir/grazoprevir. The TAF dose should be 10 mg.

Comment: With its approval in 2021, it has been the first oral attachment inhibitor on the market. Important, well-tolerated option for multidrug-resistant viruses. Very limited indication.

Detailed discussion in this book: page 83, 218

Fuzeon® see T-20

Ganciclovir

Original manufacturer: Hoffmann-La Roche. Generics.

Approval and indication: CMV retinitis.

- Cymeven® Injection vials containing 500 mg

Dosage: Acute therapy with normal renal function: Daily 2 x 5 mg/kg as i.v. infusion over one hour. Duration of treatment: 14 to 21 days. Maintenance therapy: Daily 1 x 6 mg/kg i.v. 5 days a week.

Adverse events: Leukopenia, anemia, and thrombocytopenia are dose-limiting. Less frequently, nausea and vomiting. Central nervous complaints such as confusion.

Interactions: Check blood counts every two days. Discontinue if neutrophils are below 500/µl (G-CSF if necessary). Contraindication in case of neutropenia <500/µl, thrombocytopenia <25,000/µl, and concurrent chemotherapy. Caution with AZT (increased toxicity!). Teratogenic. Adjust the dose if renal function is impaired.

Comment: Often preferred to oral valganciclovir in acute virus-threatening lesions, otherwise used only in exceptional cases.

Genvoya®

Manufacturer: Gilead Sciences.

Approval and indication: Adult PLWH, including children of 12 years and older (35 kg) without resistance mutations.

- Genvoya® film-coated tablets containing 150 mg elvitegravir, 150 mg cobicistat, 200 mg FTC, 10 mg tenofovir AF

Dose: One tablet daily, with food, unchewed.

Adverse events: Overall well tolerated, most likely headache, diarrhea. Cobicistat inhibits tubular secretion of creatinine and thus may mimic mild renal dysfunction. Weight gain (mechanism unclear).

Interactions: Can be given up to a GFR of 30 mL/min (discontinue below that!); Stribild® strict renal monitoring is not required. However, cobicistat is a potent CYP3A inhibitor. Substances such as lovastatin, simvastatin, midazolam, carbamazepine, rifampicin, and St. John's wort should be avoided. No other antiretroviral agents.

Distance of 4 hours from antacids and multivitamins. Choose low doses for azoles, rifabutin, calcium antagonists, and PDE-5 inhibitors.

Comment: In January 2016, the first TAF-containing combination. Has replaced the TDF-containing (otherwise identical) Stribild®. However, it is rarely used due to the booster (interactions) and a relatively low resistance barrier. In recent years, it has been mainly replaced by Biktarvy®.

Detailed discussion in this book: page 83

Glecaprevir see Maviret®

Grazoprevir see Zepatier®

Harvoni®

Manufacturer: Gilead Sciences.

Approval and indication: a fixed-dose combination of the NS5B polymerase inhibitor sofosbuvir and the NS5A inhibitor ledipasvir, usually for 12 weeks in genotypes 1, 4, 5, 6. In therapy-naive patients with GT1 without cirrhosis and low viral load, 8 weeks are also possible.

• Harvoni® film-coated tablets containing 400 mg sofosbuvir and 90 mg ledipasvir

Dose: 1 x 1 tablet daily, regardless of meals. No dose adjustment in renal impairment up to a GFR of 30 mL/min; avoid below.

Adverse events: Headache, fatigue, nausea (usually mild).

Interactions: Life-threatening cardiac arrhythmias with amiodarone. Sofosbuvir and ledipasvir are not metabolized by the cytochrome P450 system and can be combined with most ART regimens. Tenofovir levels may increase with boosted regimens. Avoid potent intestinal P-gp inducers such as carbamazepine, St. John's wort, or rifampicin.

Comment: Well-tolerated fixed combination that is very effective, especially in genotypes 1 and 4. Few interactions with ART. Like all DAAs, it is expensive. In recent years, it has been largely displaced by pangenotypic DAAs.

HIVID® see DDC – no longer on the market

Ibalizumab

Manufacturer: TaiMed Biologics (together with Theratechnologies)

Approval and Indication: Reserve agent indicated for "adults with multidrug-resistant HIV-1 infection in whom no other suppressive antiviral regimen can be composed."

Dose: Starting dose of 2,000 mg i.v. (10 ampoules) over at least 30 min, followed by a maintenance dose of 800 mg (4 ampoules) over at least 15 min every 2 weeks, after dissolution in 250 mL NaCl each. There is no data on hepatic and renal insufficiency, but administration is probably possible.

Adverse events: Limited experience in a few hundred people. The most common are diarrhea, dizziness, nausea, and rash. Infusion Reactions: Monitor for one hour after loading dose; maintenance doses possible over 15 min if well tolerated.

Notes: Ampoules should be stored in the refrigerator (2–8 degrees). Dissolved preparation can be stored at room temperature for a maximum of 4 hours and in the refrigerator for 24 hours. Resaturation is necessary if maintenance administration is delayed by at least three days. There is no data on interactions, but these are rather unlikely.

Comment: Monoclonal antibody against CD4 that must be infused every two weeks. Narrow indication, very expensive, no longer marketed in Europe since 2022, only available as an import.

Indinavir – PI withdrawn from the market at the end of 2019

Intelence® see Etravirine

Interferon alpha 2a/2b

Manufacturers: Various, such as Roche Schering Plough.

Approval and indication: chronic hepatitis C (no longer in use), chronic hepatitis B (rarely used). It is also effective in Kaposi's sarcoma (if CD4 T-cells >250/µl), but no official approval.

- Pegasys®: prefilled syringes with 135, 180 µg interferon alpha-2b

Dose: Pegasys® 180 µg 1 x per week. Subcutaneous administration. No longer in use for HCV. HBV: 48 weeks. Treatment duration in KS depends on success.

Adverse events: Fever, muscle pain. Depression (suicidality!), fatigue, sleep, and personality disorders. Anemia, thrombocytopenia, and leukopenia. Autoimmune thyroiditis. Reversible hair loss.

Interactions, warnings: flu-like symptoms a few hours after administration are alleviated by paracetamol. Contraindications are severe cardiac, hepatic, thyroid, or renal dysfunction, bone marrow damage, and CNS disorders (e.g., seizure disorders and depression). Check blood count initially every two weeks, later monthly. TSH every three months. Interferons must be stored in the refrigerator. Has also a moderate antiretroviral effect.

Comment: Obsolete for hepatitis C, rarely used in hepatitis B. For KS and multidrug-resistant HIV infection, it is still useful in rare cases. However, use is off-label (and has many side effects).

Invirase® see Saquinavir

Isentress® see Raltegravir

Isoniazid

Manufacturer: Various. Different trade names.

Approval and indication: Combination treatment of tuberculosis. Prophylactic therapy for people with a high risk of TB (positive reaction to a skin test, close contact with persons with newly diagnosed infectious TB, etc.; recommendations may vary)

- Isozid comp® film-coated tablets containing 200, 300, 400 mg INH and 40, 60, 80 mg vitamin B6 (pyridoxine HCl)
- Also in various combination preparations (see rifampicin).

Dose: 1 x 200 to 300 mg (4 to 5 mg/kg, maximum 300 mg) orally daily, i.v. only in severe cases during the first two weeks of therapy. For prevention of peripheral neuropathies, 100 mg pyridoxine orally once daily. In children: 1 x 6 (up to 10) mg/kg daily, maximum 300 mg.

Adverse events: Toxic hepatitis is more frequent in the elderly, people with liver disease, and alcohol abuse. Cave peripheral neuropathy! INH should then be discontinued, followed by several weeks of pyridoxine and vitamin B12. Psychosis, CNS symptoms. Fever, rash, nausea/vomiting, pancytopenias.

Interactions, warnings: Contraindicated in acute hepatitis and with a history of INH-induced hepatopathy, pronounced febrile reactions, peripheral neuropathy, and macrohematuria. Always combine with vitamin B6.

Various interactions with barbiturates, cycloserine, theophylline, phenytoin, and rifampicin, the dose of which may need to be reduced due to CNS disturbances. Decreased absorption with concomitant administration of aluminum-containing antacids. Caution with alcohol.
Initially, check blood count, transaminases (TA), bilirubin, and kidney function every two weeks. Discontinue isoniazid if TA increases to more than three times baseline and symptoms occur; if it increases 5-fold, discontinue even without symptoms.

Itraconazole

Manufacturer: Various. Various trade names.

Approval and indication: Histoplasmosis, aspergillosis, resistant Candida infections (2nd choice). Also for derma/nail mycoses.

- Sempera Capsules® à 100 mg
- Sempera Liquid® 10 mg/mL suspension (150 mL)

Dose: Fluconazole-resistant candidiasis: 1–2 x 100 mg (up to 2 x 200 mg) daily, preferably as suspension. Histoplasmosis, aspergillosis daily 2 x 200 mg/day.

Adverse events: Nausea, vomiting, exanthema, dizziness. Toxic hepatitis.

Notes: To increase absorption, take capsules immediately after a full meal. Do not co-administer with H2 blockers, antacids, rifampicin, rifabutin, carbamazepine, phenytoin, simvastatin, lovastatin, and INH (decrease bioavailability of itraconazole). Itraconazole increases serum levels of cyclosporine, calcium antagonists, digoxin, lovastatin, simvastatin, and indinavir. Negative inotropic effect, do not use in heart failure.

Comment: Due to numerous interactions and uncertain plasma levels, it hardly plays a role anymore. However, compared to fluconazole, it is effective against many non-albicans strains, aspergilli, and histoplasmosis.

Juluca®

Manufacturer: ViiV Healthcare (a joint distribution with Janssen-Cilag).

Approval and Indication: Adult PLWH on stable, virologically successful ART (at least six months), without prior treatment failure or resistance to rilpivirine or dolutegravir.

- Juluca® film-coated tablets containing 50 mg dolutegravir plus 25 mg rilpivirine

Dose: 1 tablet daily, unchewed, with a meal. No dose adjustment up to a creatinine

clearance of 30 mL/min; administration is also possible in mild to moderate hepatic impairment.

Adverse events: In the SWORD trials, predominantly mild or moderate at the switch, rarely leading to discontinuation. Mainly gastrointestinal and neuropsychiatric (see also individual substances).

Interactions: No concomitant administration with PPIs (see also rilpivirine), some anticonvulsants (carbamazepine), St. John's wort, and rifampicin, among others. When combined with rifabutin, an additional 25 mg of rilpivirine is recommended. Caution with metformin (maximum dose 1,000 mg). Individuals with hepatitis B may show rebounds as Juluca® does not contain HBV active substance.

Comment: The first NRTI-free, dual "maintenance therapy" in a fixed combination was approved in 2018. Indication restrictions (only with "stable" pretreatment) and dietary restrictions must be considered.

Detailed discussion in this book: page 200

Kaletra® see Lopinavir

Kivexa® (US: Epzicom®)

Original manufacturer: ViiV Healthcare. Generics available.

Approval and indication: HIV infection.

• Kivexa® film-coated tablets containing 600 mg abacavir plus 300 mg 3TC

Dose: 1 tablet daily. In case of impaired renal function (GFR below 50 mL/min), we prefer to give single substances to adjust the 3TC dose.

Adverse events: Hypersensitivity reaction (HSR) to abacavir (see there!). Probably slightly increased risk of myocardial infarction (abacavir).

Comment: Formerly much-used combination preparation, recently used less frequently. HLA testing is obligatory, probably because of its prothrombogenic properties, and therefore, to be used with caution in cardiovascular risk. See otherwise also under 3TC and abacavir.

Detailed discussion in this book: page 55

Lamivudine see 3TC (at the beginning of the drug section)

Ledipasvir see Harvoni®

Lenacapavir

Manufacturer: Gilead.

Approval and Indication: Adults with multidrug-resistant HIV-1 infection for whom a suppressive ART regimen cannot otherwise be established.

• Sunlenca® vial (463.5 mg lenacapavir in 1.5 mL)
• Sunlenca® Tablets 300 mg

Dose: On days 1 and 2, each 600 mg as tablets; on day 8 then 300 mg as a tablet, each independent of a meal. On day 15, then 927 mg as a subcutaneous abdominal injection (2 x 1.5 mL injections). Continue 927 mg every 6 months (± 2 weeks). No dose adjustment up to a GFR of 15 mL/min.

Adverse events: Overall, well tolerated. Pain and swelling at injection sites are very common but rarely lead to discontinuation. Median duration six days. Nodules and indurations may persist for months, however. Also nausea.

Interactions: Lenacapavir is a substrate of CYP3A, P-gp, and UGT1A1. Do not co-administer rifampicin, rifabutin, carbamazepine, phenytoin, St. John's wort. Also not with efavirenz, nevirapine, etravirine, atazanavir/c, or tipranavir/r! Steroids low dose, also simvastatin.

Comment: In 2022, lenacapavir was the first-in-class capsid inhibitor, with six-month subcutaneous injections. Important new option in multidrug resistance, limited indication.

Detailed discussion in this book: page 92, 219, 274

Lopinavir

Original manufacturer: AbbVie. Generic available.

Approval and indication: HIV infection, in adults and children over 2 years of age.

- Kaletra® film-coated tablets containing 200 mg lopinavir + 50 mg ritonavir
- Kaletra® film-coated tablets containing 100 mg lopinavir + 25 mg ritonavir
- Kaletra® solution containing 80 mg lopinavir + 20 mg ritonavir per mL

Dose: 1 x 4 tablets (800 mg lopinavir/200 mg ritonavir) regardless of meals. In the case of PI resistance, it is better to use 2 x 2 tablets. The 100 mg tablets were developed for children (also as Aluvia®). In combination with efavirenz (probably also nevirapine), the dose must be increased to 2 x 500/125.

Adverse events: Primarily diarrhea, nausea, dyslipidemias. Less commonly headache, elevations of transaminases.

Notes: The solution contains ethanol and should be stored in the refrigerator. Numerous interactions! Many drugs metabolized CYP3A- or CYP2D6-mediated are contraindicated, including flecainide, propafenone, terfenadine, ergotamine, cisapride, and midazolam. Rifampicin and St. John's wort reduce efficacy. Cave simvastatin, carbamazepine, phenobarbital, or sildenafil (blood pressure drop), amiodarone, Marcumar, lidocaine, tricyclic antidepressants, cyclosporine, tacrolimus. Level determinations in case of impaired liver function.

Comment: Formerly much-used PI. Now rarely used due to common side effects (diarrhea and dyslipidemias), interactions, and pill count.

Detailed discussion in this book: page 69

Maraviroc

Manufacturer: ViiV Healthcare.

Approval and indication: Pre-treated adults with CCR5-tropic HIV (in the US also therapy-naïve). Also, children 2 years and older (at least 10 kg).

- Celsentri® 150 and 300 mg tablets (25 and 75 mg for children).
- Celsentri® solution with 20 mg/mL

Dose: 300 mg twice daily regardless of food intake (in children, the dose is based on body weight). Dose adjustments depending on concomitant ART:

Concomitant drug	Maraviroc dose
Doravirine, tenofovir, other NRTIs, dolutegravir, fostemsavir	2 x 300 mg
Efavirenz (or rifampicin **without** concomitant PI or other potent CYP3A4 inhibitors	2 x 600 mg
Strong CYP3A4 inhibitors: boosted PIs and elvitegravir/c, but also itraconazole, ketoconazole, and clarithromycin	2 x 150 mg
Efavirenz plus concurrent PI	2 x 150 mg

In the combination, the dose is based on the PI; in the combination of inhibitor and inducer, the inhibitor dominates

In impaired renal function, no dose adjustment is necessary up to a GFR of 30 mL/min; avoid below. With concomitant administration of a potent CYP3A4 inhibitor above a GFR of 80 mL/min, only 150 mg once daily.

Adverse events: Well-tolerated, rarely headache, dizziness, fatigue, nausea. In high doses, orthostatic hypotension. Isolated reports of CK elevations.

Hints: A prior tropism test (also from proviral DNA) is obligatory! Concomitant administration of maraviroc with rifampicin *plus* efavirenz is not recommended. Caution with concomitant administration of INH *plus* cotrimoxazole (hepatotoxicity). St. John's wort may decrease maraviroc levels; avoid it.

Comment: The only CCR5 antagonist in HIV therapy to date. Pretreatment only. Excellent tolerability, but complicated dose regimen depending on concomitant therapy. Prior tropism determination is mandatory.

Detailed discussion in this book: page 87

Maviret®

Manufacturer: AbbVie.

Approval and indication: Chronic hepatitis C, 12 years and older.

• Maviret® film-coated tablets containing 100 mg glecaprevir and 40 mg pibrentasvir

Dose: 1 x 3 tablets (300/120 mg) daily, together with a meal. No dose adjustment in any renal impairment up to dialysis. No adjustment in mild hepatic impairment; not recommended in cirrhosis child B/C.

Adverse events: Like all DAAs, quite well tolerated, most likely headache, diarrhea, fatigue, asthenia.

Interactions: Duration of therapy is 8 weeks; in case of compensated liver cirrhosis, 12 weeks. With pretreatment and genotype 3 also 16 weeks. Many interactions: combination with efavirenz, etravirine, nevirapine, boosted PIs, or elvitegravir/c is not recommended. Also, dabigatran, carbamazepine, rifampicin, rifabutin, St. John's wort, PPIs, some statins (atorvastatin, simvastatin), and ethinylestradiol.

Comment: This combination of PI and NS5A inhibitor was approved in 2017 for chronic hepatitis C. Effective for all genotypes. Consider interaction and costs.

Mycobutin® see Rifabutin

Nelfinavir

Manufacturer: Pfizer (US).

Approval and indication: HIV infection.

• Viracept® film-coated tablets 625 mg available as import only

Dose: Daily 2 x 1,250 mg (2 x 2 tablets) with meals.

Adverse events: Diarrhea is very common! Meteorism, nausea.

Comment: Roche withdrew approval in 2013 due to a lack of demand. In the US, the substance is still available through Pfizer. It should no longer be used.

Nevirapine

Manufacturer: Boehringer-Ingelheim. Generics, various trade names.

Approval and indication: HIV infection. Therapy-naïve individuals with good immune status (females >250, males >400 CD4 T-cells/µl) should rather avoid nevirapine due to an increased risk of hepatotoxicity (see below).

• Viramune sustained-release tablets® 400 mg, 200 mg, in pediatrics also 50, 100 mg
• Viramune suspension® with 10 mg/mL

Dose: Daily 1 x 1 sustained-release tablet of 400 mg or 2 x 1 tablet of 200 mg each, independent of meals. A two-week phase-in period (1 x 200 mg/day – starter pack!) reduces the exanthem rate. In children, the dose is according to weight.

Adverse events: Hepatotoxicity (10–15%) and drug exanthema, especially in primary therapy with good CD4 T-cells (females >250/µl, males >400/µl). Use with caution in hepatic dysfunction. With prolonged administration, the GGT is almost always elevated (levels up to 150 U/l are tolerable).

Interactions: Do not combine with rifampicin, ketoconazole, St. John's wort, and the "pill." Favorable lipid profile.

Comment: As with all NNRTIs, resistance develops rapidly. Initially burdened by allergies and hepatotoxicity (dose creep), therefore rarely prescribed. Good long-term tolerability. Generics available.

Detailed discussion in this book: page 62

Norvir® see Ritonavir

Odefsey®

Manufacturer: Gilead Sciences.

Approval and indication: HIV infection. Adults, children 12 years and older, without resistance to single agents, untreated only if below 100,000 copies/mL.

• Odefsey® film-coated tablets: 200 mg FTC + 25 mg TAF + 25 mg rilpivirine

Dose: 1 x 1 tablet daily, unchewed, with a meal! Do not use in severe renal impairment (GFR below 30 mL/min).

Adverse events: Rare, most likely rash (see rilpivirine). Occasionally, sleep problems and nausea. For renal dysfunction, see tenofovir.

Interactions: Do not combine with rifabutin, rifampicin, anticonvulsants (including carbamazepine), PPIs, St. John's wort (rilpivirine and/or TAF levels decrease). H2 antagonists should be taken 12 hours apart, and antacids at least 2 hours before or 4 hours after. Do not use if viremia is high due to the increased risk of resistance.

Comment: Has largely replaced Eviplera® since approval in 2016, as TAF is slightly less nephrotoxic than TDF. It is often used as "maintenance" therapy in patients with good adherence (excellent long-term tolerability). Resistance risk is unacceptably high in first-line treatment, especially with high viremia.

Detailed discussion in this book: page 177

Pegasys®, PegIntron® see Interferon

Pentamidine

Manufacturer: Sanofi Aventis/GlaxoSmithKline.

Approval and indication: Treatment and secondary prophylaxis of PCP if cotrimoxazole is not possible or available. Also, for visceral leishmaniasis.

• Pentacarinate® 300 mg vials

Dose: 200–300 mg i.v. for 5 days (4 mg/kg), then half dose. In very mild cases, daily inhalations of 300 mg. In renal impairment with creatinine clearance of 50 to 10 mL/min: 4 mg/kg every 24 to 36 hours; below 10 mL/min: 4 mg/kg every two days. As prophylaxis inhalations of 300 mg 1–2 x / month.

Adverse events: Frequent with intravenous administration! Nausea, vomiting, metallic taste, nephrotoxicity (creatinine increase in the 2nd week of therapy) up to renal failure. Hypo- or hyperglycemia (possible for months after end of treatment), hypotension, cardiac arrhythmias, pancreatitis. Leukopenia, thrombocytopenia. With inhalation, occasionally cough irritation, rarely asthma attack.

Interactions, notes: *Inhalation:* Pentamidine is contraindicated as an aerosol in bronchial asthma and therapy with beta-blockers. Inhalation is ineffective in various pulmonary diseases. Before inhalation, a ß-mimetic (e.g., Berotec®) may be helpful to open airways. *Infusions*: Caution in hepatic or renal insufficiency, hyperglycemia, cytopenia. Adequate electrolyte and fluid intake. Cave nephrotoxic drugs! During and after infusion (slowly over 2 hours!), the person should lie down (blood pressure drop). Daily control of kidney/electrolytes, blood count, blood sugar, weekly bilirubin, alkaline phosphatase, and transaminases.

Pibrentasvir see Maviret®

Pifeltro® see Doravirin

Pyrimethamine

Manufacturer: GlaxoSmithKline.

Approval and indication: Prophylaxis and treatment of cerebral toxoplasmosis. Prophylaxis of Pneumocystis pneumonia.

• Daraprim® 25 mg tablets

Dose: Toxoplasmosis treatment: Daraprim® 2 x 2 tablets at 25 mg (for 3 days, then halve dose) **plus** leucovorin® 3 x 1 tablet at 15 mg/wk **plus either** sulfadiazine, clindamycin, or atovaquone (second choice).

In PCP prophylaxis with dapsone: Daraprim® 1 x 2 tablets at 25 mg/wk **plus** dapsonefatol® 1 x 1 tablet at 50 mg **plus** leucovorin® 1 x 2 tablets at 15 mg/wk.

Adverse events: Nausea, colic, vomiting, diarrhea, leukopenia, anemia, or thrombocytopenia (folinic acid!). Rarely seizures, tremors, or ataxia.

Warnings: Contraindicated in megaloblastic anemia following folic acid deficiency. Caution in seizures, renal insufficiency, bronchial asthma, or G6PD deficiency. Always substitute folinic acid (not folic acid!) to reduce bone marrow suppression. Initially, blood count weekly.

Raltegravir

Manufacturer: MSD.

Approval and indication: Pretreated and untreated adults, including children 4 weeks of age and older.

- Isentress® film-coated tablets of 600 mg, 400 mg. For children, chewable tablets of 25 mg and 100 mg, also granulated sachets (100 mg)
- Dutrebis® 400 mg plus 150 mg 3TC (approved but not marketed in many countries).

Dose: 1 x 2 tablets of 600 mg (1200 mg) or 2 x 1 tablets of 400 mg daily (800 mg), with or without meals. No dose adjustment is required for impaired renal or moderately impaired hepatic function. In children, dosage is based on body weight (see *Children's Chapter*).

Adverse events: Very well tolerated. Occasional dizziness and sleep disturbances. Transaminase elevations. Rash (mild, very rare). Case reports of CK elevations and rhabdomyolysis. Weight gain possible.

Interactions: Raltegravir is eliminated via UGT1A1-mediated glucuronidation, so relevant interactions with other antiretroviral agents are unlikely. Caution with potent inducers of UGT1A1 – rifampicin decreases plasma levels, possibly doubling the raltegravir dose. Omeprazole or other antacid medications increase plasma levels of raltegravir. Combine only if unavoidable.

Comment: Raltegravir was the first integrase inhibitor in HIV therapy; it is well tolerated and has few interactions. Single dosing is possible with the 600 mg tablet, but no STR exists. The resistance barrier seems to be lower than for dolutegravir or bictegravir.

Detailed discussion in this book: page 78, 175

Rebetol® see ribavirin

Rekambys® (US: Cabenuva®)

Manufacturer: ViiV Healthcare.

Approval and Indication: Only in combination with cabotegravir injection (Vocabria®) in adults virologically suppressed on stable ART without resistance or failure to NNRTIs or INSTIs. Both drugs, rilpivirine and cabotegravir LA, are packaged in the US with the single trade name Cabenuva®.

- Rekambys® Rilpivirine 600 mg (2 mL) or 900 mg (3 mL) vials

Dose: "Lead in" (may be omitted) with one tablet of rilpivirine 25 mg daily for 28 days each with a meal, then an initial dose of 900 mg i.m. on the last day, another 900 mg dose after one month, then 900 mg every two months (600 mg also given monthly) up to 7 days before/after the target date. Oral bridging is possible for up to 2 months. Start conventional ART within one month if doses are missed or discontinued. No dose adjustment in renal or hepatic insufficiency.

Adverse events: Overall, well tolerated. Pain at injection sites (approx. 80%, swelling, redness) is usually mild and rarely leads to discontinuation. Headache, depression.

Notes, interactions: Shake vials vigorously for 10 seconds. Use longer needles in obese patients. Caution with subtype A, caution with BMI >30. Strictly gluteal, always the same buttock. Do not use with rifabutin, carbamazepine, phenytoin, dexamethasone, St. John's wort.

Comment: In 2020, the first approved long-acting therapy only with cabotegravir, not other antiretroviral agents. Note the indication restrictions.

Detailed discussion in this book: page 216

Rescriptor® – NNRTI never approved in Europe

Retrovir® see AZT

Reyataz® – 2019, withdrawn from the market; see atazanavir

Rezolsta® see Darunavir

Ribavirin

Manufacturer: Roche and Essex. Numerous generics!

Approval and indication: Chronic hepatitis C, only in combination with interferon. The approval for HIV/HCV co-infection explicitly applies only to Copegus®.

Dose: 800 mg daily for body weight <65, 1,000 mg for 65–85, 1,200 mg for >85 kg. Capsules are divided into two daily doses and taken with food. Duration of therapy depends on genotype and therapy success.

- Copegus Film-Coated Tablets® 200 mg, 400 mg
- Rebetol hard capsules® 200 mg
- Rebetol solution® with 40 mg/mL (100 mL)

Adverse events: Hemolytic anemia is most common (Hb drop of at least 2 g/dL), along with gastrointestinal symptoms, headache, and fatigue. In combination with NRTIs, rarely lactic acidosis, pancreatitis.

Interactions, warnings: Ribavirin is contraindicated in severe heart disease, renal insufficiency, decompensated cirrhosis, and hemoglobinopathies. Potentially teratogenic, no use during pregnancy.
If hemoglobin values <10 g/dL or drop significantly more than 2 g/dL, reduce the dose to 600–800 mg/day. Discontinue at <8.5 g/dl. Consider erythropoietin or transfusions before reduction/discontinuation: Dose reductions with ribavirin jeopardize therapeutic success.
Depression occurring with efavirenz may be exacerbated by ribavirin.
Blood checks (blood count, OT, PT, amylase, lipase) are initially every two weeks, then monthly. Determine lactate in case of unspecific symptoms!

Comment: Used only in exceptional cases in hepatitis C therapy.

Rifabutin

Manufacturer: Pfizer.

Approval and indication: Infections with Mycobacterium avium complex (MAC) in combination with other substances (mostly ethambutol and azithromycin). Possibly also in tuberculosis.

- Mycobutin® 150 mg capsules

Dose: 300 mg rifabutin (+ azithromycin + ethambutol) daily.

Renal impairment: dose reduction of 50% if creatinine clearance <30 mL/min. Dose adjustments with concomitant administration of antiretroviral drugs:

Drug	Recommendation
Atazanavir/r, Darunavir/r, Lopinavir/r, Tipranavir/r	Rifabutin: 150 mg three times per week (some guidelines recommend trying 150 mg daily)
Elvitegravir/c, Bictegravir	Avoid, plasma levels markedly reduced
Efavirenz	Rifabutin: 450 mg/day or 2–3 x 600 mg/week
Nevirapine, doravirine, etravirine, raltegravir, dolutegravir, fostemsavir	Standard dosage

Adverse events: Nausea, increase in liver enzymes. Uveitis usually occurs with a daily dose of > 300 mg and combination with clarithromycin or fluconazole. Red coloration of urine, skin, and body secretions (inform affected persons!).

Interactions, warnings: contraindicated in case of hypersensitivity to rifabutin and rifampicin; also in case of thrombocytopenia and severe liver dysfunction. Initially biweekly, later monthly checks of blood count and liver enzymes. Rifabutin may reduce the effectiveness of the following drugs, among others: Analgesics, anticoagulants, corticosteroids, cyclosporines, digitalis (except digoxin), dapsone, oral antidiabetics, oral contraceptives, narcotic analgesics, phenytoin, and quinidine. Erythromycin, ketoconazole, itraconazole, fluconazole, and clarithromycin may increase plasma levels of rifabutin. Take antacids no earlier than three hours after rifabutin.

Comment: Various interactions, should only used by experienced physicians.

Rifampicin

Manufacturer: Various. Many trade names, also in combinations (see below).

Approval and indication: Tuberculosis. Only in combination therapies!

- Rifa® tablets containing 150, 300, 450, 600 mg rifampicin
- Eremfat® syrup containing 20 mg rifampicin per mL
- Eremfat® 300 mg and 600 mg injection vials
- Rifinah® or Tebesium duo®: film-coated tablets, each containing 300 mg rifampicin and 150 mg isoniazid
- Rifater® or Tebesium trio®: coated or film-coated tablet, each containing 120 mg rifampicin, 50 mg isoniazid, 300 mg pyrazinamide

Dose: Daily 600 mg (body weight >50 kg) or 450 mg (body weight <50 kg). They are preferably taken in the morning and fasting!

Adverse events: Toxic hepatitis (up to 20%), cholestasis. Red coloration of urine and other body fluids. Soft contact lenses may turn permanently reddish. Allergies are common. Gastrointestinal complaints.

Interactions, warnings: Caution in chronic liver disease. Discontinue rifampicin in case of GPT >100 U/l (gradual re-exposure after normalization possible), furthermore in case of severe and persistent diarrhea (caution: pseudomembranous colitis!). Rifampicin should not be combined with NNRTIs (except efavirenz), PIs, or elvitegravir/c. Doses for dolutegravir and raltegravir should be doubled. Rifampicin accelerates the metabolism of many other pharmaceuticals, reducing their effectiveness. This applies to atovaquone, coumarins, barbiturates, benzodiazepines, beta-blockers, clarithromycin, contraceptives, steroids, oral antidiabetics, cyclosporine, dapsone, digitalis, doxycycline, erythromycin, haloperidol, ketoconazole, methadone, phenytoin, theophylline, trimethoprim, verapamil. Combination with ketoconazole or voriconazole is contraindicated.
Antacids, opiates, and anticholinergics reduce the bioavailability of concomitant orally administered rifampicin (time interval!). Do not use it during pregnancy. Check blood count and liver values every two weeks.

Comment: See rifabutin. Combine only with NRTIs, efavirenz, and possibly raltegravir.

Rilpivirine

Manufacturer: Janssen-Cilag.

Approval and indication: Previously untreated HIV infection, less than 100,000 copies/mL. Since 2013, it has also been licensed for pretreated patients with virological suppression and without resistance.

- Edurant® film-coated tablets with 25 mg rilpivirine

The following fixed combinations (film-coated tablets) also contain 25 mg of rilpivirine:

- Eviplera®: plus 200 mg FTC + 300 mg TDF
- Odefsey®: plus 200 mg FTC + 25 mg TAF
- Juluca®: plus 50 mg dolutegravir

Component of the depot combination (long-acting) with cabotegravir.

- Rekambys®: 600 mg (2 mL) or 900 mg (3 mL) vials of rilpivirine (in the US as Cabenuva®)

Dosage: 1 x 1 tablet daily, unchewed, necessarily with a meal.

Adverse events: Rare, most likely rash (mostly mild, less than with efavirenz!), occasionally nausea. It is better tolerated (fewer CNS side effects, more favorable lipid profile) than efavirenz. CNS disturbances and depression may occur, however. Occasionally elevated bilirubin. At high doses, QT prolongations (not increased at the approved dose).

Interactions: Do not combine with rifabutin, rifampicin, various anticonvulsants (including carbamazepine), PPIs, and St. John's wort (rilpivirine levels decrease). H2 antagonists should be taken 12 hours apart, and antacids at least 2 hours before or 4 hours after rilpivirine. Use with caution in severe hepatic impairment. Partial but not complete cross-resistance to other NNRTIs.

Comment: Was the 5th NNRTI used in November 2011, primarily as a single-tablet regimen Odefsey®. Increased resistance risk with high viral load, therefore most likely

to be used in pretreated PLWH with viral suppression. Good absorption is essential (with a meal, no PPIs).

Detailed discussion in this book: page 63

Ritonavir

Manufacturer: AbbVie. Generics available.

Approval and indication: HIV infection. It is also used as an ingredient in Kaletra® (see lopinavir), the HCV drug Viekirax®, and the SARS-CoV-2 drug Paxlovid®.

- Norvir® 100 mg tablets
- Norvir® oral solution containing 80 mg per mL

Dose: Use only as a pharmacoenhancer/booster. Daily dosages:

- Atazanavir (generics, 1 x 300 mg): 1 x 100 mg ritonavir.
- Darunavir (Prezista®, 2 x 600 mg): 2 x 100 mg ritonavir
- Darunavir (Prezista®, 1 x 800 mg): 1 x 100 mg ritonavir
- Fosamprenavir (Telzir®, 2 x 700 mg): 2 x 100 mg ritonavir
- Lopinavir (Kaletra®): Fixed combination, see lopinavir.
- Saquinavir (Invirase®, 2 x 1000 mg): 2 x 100 mg ritonavir
- Tipranavir (Aptivus®, 2 x 500 mg): 2 x 200 mg ritonavir

Adverse events: Dose-dependent frequent nausea, vomiting, diarrhea, perioral paresthesias (tingling), electrifying sensations in arms/legs. Increased liver enzymes, dyslipidemia, lipodystrophy, and rarely diabetes mellitus.

Interactions: Numerous interactions, even at the low booster doses! Contraindicated are rifampicin, amiodarone, astemizole, bepridil, terfenadine, flecainide, cisapride, triazolam, ergotamine, simvastatin, lovastatin, quinidine, St. John's wort. Sildenafil should also be avoided. Caution or, if possible, level measurement with methadone, immunosuppressants (cyclosporine, tacrolimus), macrolides (erythromycin, clarithromycin), steroids, calcium antagonists, tricyclic and other antidepressants, neuroleptics (haloperidol, risperidone,), antifungals (keto/itraconazole), carbamazepine, tolbutamide, rifabutin, theophylline, Marcumar.

Comment: One of the first PIs. Therapeutic doses should be avoided because of gastrointestinal side effects; at lower doses suitable as a "booster" for almost all other PIs. Numerous interactions.

Detailed discussion in this book: page 67

Rukobia® see Fostemsavir

Saquinavir

Manufacturer: Hoffmann-La Roche.

Approval and indication: Adult PLWH.

• Invirase 500® film-coated tablets containing 500 mg saquinavir

Dose: 2 x 1000 mg saquinavir + 2 x 100 mg ritonavir. The package insert recommends an introductory dose over 7 days with 2 x 500/100 mg for therapy-naive patients.

Adverse events: Primarily gastrointestinal, rarely increased liver enzymes, headache. As with all PIs with prolonged use, lipodystrophy, dyslipidemia, and decreased glucose tolerance. QT prolongation!

Interactions: Contraindicated for concomitant treatment with rifampicin, astemizole, terfenadine, triazolam, ergotamine, simvastatin, St. John's wort. If saquinavir is not combined with other PIs, it must be taken with meals. Cave QT prolongation. Concomitant use with drugs that prolong the QT or PR interval is contraindicated! ECG before starting therapy (QT >450 ms contraindication) and after 10 days.

Comment: The first PI on the market in 1995. No longer in use due to the number of pills and QT prolongation (ECG controls).

Sempera® see Itraconazole

Simeprevir (Olysio®) – was withdrawn from the market in 2018

Sobelin® see Clindamycin

Sofosbuvir

Manufacturer: Gilead Sciences.

Approval and Indication: As part of combination therapy for untreated or pretreated chronic hepatitis C.

• Sovaldi® film-coated tablets of 400 mg (1 bottle of 28).

Ingredient of the following combination preparations (all film-coated tablets)
• Epclusa® 400 mg plus 100 mg velpatasvir
• Harvoni® 400 mg plus 90 mg ledipasvir
• Vosevi® 400 mg plus 100 mg velpatasvir plus 100 mg voxilaprevir

Dose: 400 mg once daily, with a meal. Dose reduction is generally not recommended. The dose in severe renal impairment is unclear; no dose adjustment is necessary for liver impairment.

Adverse events: Well-tolerated, adverse events primarily due to the combination partners. No specific side effect is known so far. Most likely exhaustion, headache, nausea, and insomnia.

Notes, interactions: Like all DAA, it should be prescribed only by a physician experienced in HCV therapy. Duration of treatment and combinations depend on genotype, degree of liver fibrosis, and type of prior treatment. No dose adjustments are necessary with NRTIs, rilpivirine, efavirenz, darunavir/r, and raltegravir. However, sofosbuvir is a P-gp substrate, so do not combine with P-gp inducers such as carbamazepine, rifampicin, or St. John's wort.

Comment: Well-tolerated HCV polymerase inhibitor, now hardly plays a role as a single agent. Due to its considerable costs, like all DAAs, it should be prescribed only by experienced physicians.

Sovaldi® see Sofosbuvir

Stavudine® – toxic NRTI, withdrawn from the market in 2019

Stocrin® see Efavirenz

Stribild®

Manufacturer: Gilead Sciences.

Approval and indication: adult PLWH, either not pretreated or, if pretreated, without resistance mutations.

- Stribild® film-coated tablets containing 150 mg elvitegravir, 150 mg cobicistat, 200 mg FTC, 300 mg tenofovir DF

Dose: One tablet daily, with food, unchewed.

Adverse events: Well-tolerated. Nephrotoxicity, in particular, should be noted. Above <70 mL/min, Stribild® should be avoided; monitor renal values monthly for the first year. Cobicistat inhibits tubular secretion of creatinine and may mimic mild renal dysfunction. Discontinue if GFR <50 mL/min. Nausea (slightly more common than with other combos), diarrhea, headache, and occasional depression. See otherwise for tenofovir.

Interactions: Cobicistat is a potent CYP3A inhibitor. Substances such as atorvastatin, lovastatin, simvastatin, midazolam, carbamazepine, rifampicin, and St. John's wort should be avoided. No other antiretroviral agents. Distance of 4 hours from antacids and multivitamins. Choose low doses for azoles, rifabutin, calcium antagonists, and PDE-5 inhibitors.

Comment: In May 2013, the first complete ART with an integrase inhibitor in a single tablet per day. Care must be taken with the kidney. It has been replaced mainly by Genvoya® since 2016 (contains TAF instead of TDF).

Sulfadiazine

Manufacturer: Heyl.

Approval and indication: Treatment and prophylaxis of cerebral toxoplasmosis, only in combination with pyrimethamine.

- Sulfadiazine-Heyl® tablets containing 500 mg

Dose: As therapy daily 4 x 2–3 tablets of 500 mg (daily dose 4–6 g). As prophylaxis use half dose (4 x 1 tablet of 500 mg)! At creatinine clearance of 10–50 mL/min half dose, below one-third of the dose.

Adverse events: Very commonly allergies with pruritus, fever, and urticaria, often therapy-limiting. Rarely Stevens-Johnson syndrome. Gastrointestinal complaints. Renal problems with renal insufficiency, crystalluria, and nephrolithiasis in up to 7%. Anemia, leukopenia, thrombocytopenia, elevation of liver enzymes.

Interactions, warnings: Contraindicated in sulfonamide hypersensitivity and allergy to sulfonylurea-type antidiabetics, acetazolamide, or thiazide diuretics; also in G6PD deficiency, renal insufficiency, and severe liver damage or liver dysfunction (e.g., acute hepatitis); and during pregnancy and lactation. Sulfadiazine may increase the effect of sulfonylureas (oral antidiabetics), anticoagulants, and diphenylhydantoin. Ensure adequate fluid intake (at least 2 l per day). Initially, check blood count, GPT, creatinine, and urea at least weekly. Urine checks! In the case of crystalluria, alkalize urine.

Sunlenca® see Lenacapavir

Sustiva® see Efavirenz

Symtuza®

Manufacturer: Janssen-Cilag (with Gilead Sciences).

Approval and indication: HIV infection, adults and adolescents 12 years and older (body weight of at least 40 kg).

- Symtuza® film-coated tablets containing 800 mg darunavir + 150 mg cobicistat + FTC 200 mg plus 10 mg TAF

Dose: 1 tablet daily with a meal. In case of impaired renal function, no dose adjustment is necessary up to a creatinine clearance of 30 mL/min. Do not use in severe hepatic impairment.

Adverse events: Diarrhea, dyslipidemias, allergies (see individual substances).

Interactions, notes: Boosted PI; therefore, some interactions should be noted; see darunavir. Approval is limited to those without darunavir resistance.

Comment: Since approval in October 2017, it has been the only PI-containing single-tablet regimen. Apart from diarrhea, it is well tolerated. A very high resistance barrier. However, some interactions need to be considered.

Detailed discussion in this book: page 173

T-20 (enfuvirtide)

Manufacturer: Hoffmann-La Roche.

Approval and indication: Pre-treated PLWH with treatment failure or intolerance on ART regimens with at least PI, NRTI, or NNRTI.

- Fuzeon® 90 mg/mL powder and solvent

Dose: 2 x 90 mg subcutaneously daily.

Adverse events: Generally well tolerated. Almost obligatory skin reactions at the injection site: redness, inflammation, induration, exanthema. Possibly increased risk of bacterial pneumonia, cave risk factors (low CD4 count, high viral load, drug addicts, smokers, history of lung disease).

Interactions, notes: Interactions not known. Injection sites: upper arm, anterior hip, abdomen. Change injection sites! There may be less irritation on the back. Do not inject at sites with signs of inflammation from previous injections, in nevi, scars, or skin abrasions. T-20 is expensive.

Comment: Entry inhibitor is now only used in individual cases with intensive pretreatment. T-20 must be injected subcutaneously twice daily. Limited mainly by the mode of application and by local skin reactions.

Detailed discussion in this book: page 88

Tenofovir-DF (TDF) and Tenofovir-AF (TAF)

Manufacturer: Gilead Sciences. Generics for TDF.

Approval and indication: HIV infection. Chronic hepatitis B (TDF). To be distinguished are the two prodrugs tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF, generic; some manufacturers do not use the fumarate but other salts such as succinate or maleate).

- Viread® film-coated tablets: 300 mg TDF (generics)
- Vemlidy® film-coated tablets: 25 mg TAF (not licensed for HIV, hepatitis B only)

TDF is a component of the following combination preparations (all film-coated tablets):
- Atripla® : 300 mg TDF + 200 mg FTC + 600 mg efavirenz (generic)
- Delstrigo® : 300 mg TDF + 300 mg 3TC + 100 mg doravirine
- Eviplera® : 300 mg TDF + 200 mg FTC + 25 mg rilpivirine
- Stribild® : 300 mg TDF + 200 mg FTC + 150 mg elvitegravir + 150 mg cobicistat
- Truvada® : 300 mg TDF + 200 mg FTC (generic)

TAF is a component of the following combination preparations (all film-coated tablets):
- Biktarvy® : 25 mg TAF + 200 mg FTC + 50 mg bictegravir
- Descovy® : 10 mg or 25 mg TAF + 200 mg FTC
- Genvoya® : 10 mg TAF + 200 mg FTC + 150 mg elvitegravir + 150 mg cobicistat
- Odefsey® : 25 mg TAF + 200 mg FTC + 25 mg rilpivirine
- Symtuza® : 10 mg TAF + 200 mg FTC + 800 mg darunavir

Dose: Daily 1 x 300 mg TDF or 1 x 10–25 mg TAF, depending on concomitant medication. Reduce TDF at GFR 30–49 mL/min (only every 48 hours). No dose adjustment for TAF. Avoid both TDF and TAF below 30 mL/min.

Adverse events: Mostly well tolerated. Renal side effects are rare (renal failure, tubulopathies including Fanconi syndrome, nephrogenic diabetes insipidus), such as bone density reduction osteomalacia. Both are much less common under TAF. Typical of TDF are CK elevations (up to 48%, macro-CK, disease value unclear). Possibly more headaches, cholesterol elevations, and weight gain with TAF than with TDF.

Notes, interactions: With TDF, checks of creatinine clearance and serum phosphate (before initiation of therapy, then every four weeks in the first year of treatment, and every three months thereafter) are crucial. Checks are not that strict with TAF. Concomitant administration with drugs that are also excreted by active tubular secretion may result in increased serum concentrations of both agents: Cidofovir, acyclovir, valaciclovir, ganciclovir, valganciclovir. Atazanavir and lopinavir increase tenofovir levels. Tenofovir decreases plasma levels of atazanavir (always boost with 100 mg ritonavir).

Comment: TDF and TAF are the orally bioavailable prodrugs of tenofovir, an acyclic nucleotide analog and one of the most widely used agents in HIV therapy. The slightly less toxic (kidney, bone) TAF has partially replaced TDF. However, TDF is available generically, which is usually much cheaper than TAF.

Detailed discussion in this book: page 51, 52

Tipranavir

Manufacturer: Boehringer-Ingelheim.

Approval and indication: Adult PLWH with multiple prior treatments and resistance to various PIs.

- Aptivus® Soft Capsules 250 mg
- Aptivus® 100 mg/mL solution (95 mL)

Dose: 2 x 500 mg tipranavir plus 2 x 200 mg ritonavir with meals.

Adverse events: mainly diarrhea and nausea. Transaminase elevations, rarely clinical hepatitis to liver failure. More frequently than with other PIs, dyslipidemias (20%). Rarely skin rash (urticarial or maculopapular). Isolated reports of intracranial hemorrhage (causality unclear).

Interactions, warnings: Tipranavir is metabolized via CYP3A, and various interactions are to be expected. Do not combine with other PIs. Fluconazole and clarithromycin increase serum levels of tipranavir (TDM!), and antacids reduce them by 30%: stagger dosing. Tipranavir/r massively increases serum levels of atorvastatin (use pravastatin or fluvastatin). Dose reduction of at least 75% also for rifabutin. Numerous contraindications such as rifampicin, amiodarone, flecanide, terfenadine, etc. Contraindicated also in liver cirrhosis, caution in hepatitis B/C. Monthly checks of transaminases.

Comment: Only useful in particular resistance situations. Hepatotoxicity, must also be boosted with increased doses of ritonavir. Numerous interactions must be taken into account.

Detailed discussion in this book: page 71

Tivicay® see dolutegravir

Triumeq®

Manufacturer: ViiV Healthcare.

Approval and indication: HIV infection, in adults and adolescents over 12 years of age (at least 40 kg).

- Triumeq® film-coated tablets: 600 mg ABC + 300 mg 3TC + 50 mg dolutegravir

Dose: One tablet daily, regardless of meals. Avoid from a creatinine clearance of less than 50 mL/min; here, it is better to use the single substances and dose individually.

Adverse events: Overall well tolerated; see single agent, especially abacavir (HRS, cardiovascular events). Neuropsychiatric adverse events (sleep disturbances, insomnia, etc.) due to dolutegravir.

Notes, interactions: The warnings for abacavir must be considered; HLA typing is obligatory! In case of INSTI resistance and in salvage regimens with efavirenz, etravirine, nevirapine, and tipranavir rather avoid (dolutegravir would have to be increased to BID). This also applies to rifampicin, carbamazepine, or St. John's wort. It is not recommended for patients with moderate/severe hepatic impairment.

Comment: This was the first single-tablet regimen without tenofovir in 2014. Very effective, high resistance barrier. HLA screening for abacavir-HRS is mandatory. However, it is now often replaced by Dovato® or Biktarvy® because of abacavir. It hardly plays a role in first-line therapy anymore.

Trizivir®

Manufacturer: ViiV Healthcare (formerly GlaxoSmithKline).

Approval and indication: HIV infection.

- Trizivir film-coated tablets® containing 150 mg 3TC + 300 mg AZT + 300 mg abacavir

Dose: 2 x 1 tablet daily. In case of impaired renal function (creatinine clearance below 50 mL/min), giving the single substances (adjust dosage of 3TC and AZT) is better.

Adverse events: Mainly gastrointestinal; see also the individual substances. With regard to mitochondrial toxicity, there may be additive effects.

Comment: No longer needed, distribution will be discontinued by 2024.

Trogarzo® see Ibalizumab

Truvada®

Manufacturer: Gilead Sciences. Numerous, significantly less expensive generics.

Approval and indication: HIV infection.

- Truvada® film tablets: 300 mg tenofovir DF + 200 mg FTC

Dose: 1 x 1 tablet daily, regardless of food intake. Caution in renal dysfunction, in this case, generally avoid Truvada®. If no alternatives are possible: if creatinine clearance is 30–49 mL/min, dose reduction to 1 tablet every two days, below which do not use Truvada®.

Adverse events: Monitoring of renal values; see tenofovir.

Interactions: See tenofovir. Useful in co-infection with chronic hepatitis B, as both tenofovir and FTC have HBV activity – exacerbation of hepatitis is possible if discontinued.

Comment: One of the standard backbones, subjectively well tolerated. Moderate renal and osseous problems (see tenofovir). Numerous generics are available, some inexpensive (under 50 euros per month).

Detailed discussion in this book: page 53

Tybost® see Cobicistat

Valganciclovir

Manufacturer: Hoffmann-La Roche. Generics available.

Approval and indication: Oral induction and maintenance therapy of CMV retinitis.

- Valcyte® 450 mg tablets

Dose: As induction, 2 x 900 mg daily for 3 weeks (or until scarring of CMV lesions), then suppression therapy 1 mg daily. It should be taken with meals! In case of renal function impairment, the following dosages apply:

Crea Cl (mL/min)	Induction therapy	Maintenance therapy
≥ 60	900 mg twice a day 900 mg once a day	
40–59	450 mg twice a day	450 mg once a day
25–39	450 mg once a day	450 mg every other day
10–24	450 mg every other day	450 mg twice a week

Adverse events: frequently leukopenia, but also thrombocytopenia or anemia. Gastrointestinal complaints with nausea, vomiting, and diarrhea are more frequent than with intravenous therapy with ganciclovir.

Warnings, interactions: Check blood count at least 2–3 times/week during induction. Discontinue if neutrophils are below 500/µl (G-CSF if necessary!). Contraindication in case of neutropenia <500/µl, thrombocytopenia <25,000/µl, and concurrent chemotherapy (Kaposi's sarcoma, NHL). Valganciclovir is potentially teratogenic and carcinogenic. Generic drugs are preferred. Discontinue when immune reconstitution is sufficient (see chapter *AIDS*).

Comment: The first orally well-acting CMV drug. It has largely displaced all other CMV therapies as a prodrug of ganciclovir; a similar side effect profile is expected: neutropenia, anemia, and thrombocytopenia.

Velpatasvir see Vosevi® and Epclusa®

Videx® see DDI

Vikierax® – no longer plays a role in hepatitis C

Viracept® see Nelfinavir

Viramune® see Nevirapine

Viread® see Tenofovir

Vistide® see Cidofovir

Vitekta® see Elvitegravir

Vocabria® see Cabotegravir

Vosevi®

Manufacturer: Gilead Sciences.

Approval and indication: Chronic hepatitis C, all genotypes.

- Vosevi® film-coated tablets: 400 mg sofosbuvir, 100 mg velpatasvir, 100 mg voxilaprevir.

Dose: 1 x 1 tablet daily, unchewed, with a meal. No dose adjustment in moderate renal impairment up to a GFR of 30 mL/min. No administration in moderate hepatic impairment.

Adverse events: Fairly well tolerated, most likely nausea, headache, fatigue, myalgias, and bilirubinemia.

Notes, interactions: Duration in untreated patients is 8 weeks; in patients with DAA pre-treatment, it is 12 weeks. Many interactions: Combinations with efavirenz, etravirine, nevirapine, atazanavir, and lopinavir are not recommended. Also, amiodarone, dabigatran, edoxaban, phenytoin, carbamazepine, rifamycin, St. John's wort, rosuvastatin, and ethinylestradiol.

Comment: Triple fixed combination for chronic hepatitis C (all genotypes), licensed in summer 2017. Useful, especially in cases of prior DAA failure. High costs!

Zepatier®

Manufacturer: MSD.

Approval and indication: chronic hepatitis C, genotypes 1 and 4.

• Zepatier® film-coated tablets: 50 mg elbasvir and 100 mg grazoprevir.

Dose: 1 x 1 tablet daily, regardless of food intake. No dose adjustment, even in severe renal insufficiency, even in hemodialysis. No administration in moderate or severe hepatic impairment.

Adverse events: Fairly well tolerated, nausea, headache, fatigue.

Interactions, notes: Duration of therapy is usually 12 weeks (in case of interferon pretreatment and NS5A polymorphisms in GT1a therapy, extension to 16 weeks and addition of ribavirin recommended). In GT1a, resistance testing is essential beforehand. Combination with efavirenz, etravirine, nevirapine, elvitegravir/c and boosted PIs is not recommended due to significant interactions.

Comment: Fixed combination (of NS5A inhibitor and protease inhibitor) for chronic hepatitis C approved in summer of 2016. Effective only in GT1/4. It has a similar efficacy and safety profile to Harvoni® but is cheaper. Useful in patients with hepatitis C and renal insufficiency.

Zerit® – toxic NRTI, withdrawn from the market in 2019

Ziagen® see Abacavir

Zidovudine see Retrovir

Zovirax® see Acyclovir

36. Drug interactions

TIM UMLAND AND ANDREAS HINTZ

Interactions play a significant role in HIV therapy. This is due, on the one hand, to the more or less extensive concomitant medication of many PLWH and, on the other hand, to the fact that ART itself has a clinically relevant potential for interactions depending on the agents used. In particular, PIs and NNRTIs, like many other agents, are metabolized via the CYP3A4 isoenzyme. In this context, the inhibitory effect of boosted HIV therapy can lead to toxic drug level changes of the concomitant medication. On the other hand, the inducer effect of some NNRTIs can cause subtherapeutic drug levels of co-medication by accelerating its elimination.
The following section shows a tabular overview of the harmless (+) drug combinations and those that should be avoided (–). If changes in drug activity levels occur due to the HIV drugs, this is indicated by arrow symbols "↑" or "↓".
In individual cases, unfavorable combinations may be unavoidable due to lacking alternatives. Monitoring of possible side effects and close monitoring of drug levels is then recommended. If interactions are uncertain or not sufficiently tested, this is indicated by a question mark "?". The following overviews are not a substitute for a detailed look at the specialist information and your research but are intended to provide a supplementary, rapid, and practical decision-making aid. They are based on the current information on the University of Liverpool website (www.drug-interactions.org). For individual questions, the interaction hotline (number?) of the IFI Institute, Hamburg, is also available.

Abbreviations:

+	Combination of these drugs possible
–	Combination of these drugs should be avoided
↑↓	increased or decreased active drug level
?	interactions uncertain or not verified, a combination perhaps possible – monitoring recommended

Combinations of ART + ART

Combining two NRTIs and one NNRTI or INSTI is usually done in fixed combinations. If these are broken up, or a combination with another backbone is required, there are practically no restrictions (see also national guidelines). The combination of two NRTIs and a usually boosted PI is also problem-free. Darunavir (DRV) is assumed to be boosted with ritonavir or cobicistat (Symtuza®). If a PI/NNRTI, PI/INSTI, or NNRTI/INSTI combination is required, check the interactions in the Liverpool database (see above). This also applies if maraviroc is part of the antiretroviral therapy. For reasons of space, the tabular presentation of these combinations is omitted here.

ART + concomitant medications

Gastrointestinally active substances

	DRV	DOR	EFV	ETV	NVP	CAB/RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Antacids[4]	+	+	+	+	+	↓/↓[1]	+	↓[3]	↓[3]	↓[3]	↓[3]	+
Cimetidine	+	+	+	+	+	+/↓[1]	+	+	+	+	+	+
Famotidine	+	+	+	+	+	+/↓[1]	+	+	+	+	+	+
Loperamide	↑	+	+	+	+	+/+	+	+	?	+	+	+
MCP	+	+	+	+	+	+/+	+	+	+	+	+	+
Mesalazine	+	+	+	+	+	+/+	+	+	+	+	+	+
Ondansetrone[5]	+	+	+	+	+	+/?[2]	+	+	↑	+	+	+
Ranitidine	+	+	+	+	+	+/↓[1]	+	+	+	+	+	+
PPIs[4]	+	+	+	+	+	+/–	+	+	+	+	+	+

[1] When combining RPV with antacids/H2 antagonists, observe time interval (loss of effect).
[2] Caution due to possible QT time prolongation
[3] Due to the complex formation of INSTIs with some minerals, observe time intervals (technical info).
[4] No interactions for CAB/RPV as injection with antacids / H2 antagonists / PPI.
[5] Caution with the combination of CAB/RPV as an injection with ondansetron.

Antiarrhythmics

	DRV	DOR	EFV	ETV	NVP	CAB/RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Amiodarone	–	+	?	↓	↓	+/?	+	+	–	↑[1]	+	↑
Flecainide	–	+	+	↓	+	+/?	+	+	↑	+	+	?[2]
Lidocaine	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	+
Propafenone	–	+	↓	↓	↓	+/+	+	+	↑	+	+	+

[1] Bictegravir levels may increase with amiodarone; for the fixed combination TAF/FTC, an increase in TAF levels with amiodarone should also be considered
[2] QT prolongation possible

Antibiotics/tuberculostatics

	DRV	DOR	EFV	ETV	NVP	CAB/ RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Amikacin	+	+	+	+	+	+/+	+	+	+	+	+	+
Amoxicillin	+	+	+	+	+	+/+	+	+	+	+	+	+
Azithromycin	+	+	+	+	+	+/+	+	+	?	+	+	?[8]
Bedaquilin	↑[1]	+	↓	↓	+	+/?	+	+	↑	+	+	?[8]
Ciprofloxacin	+	+	+	+	+	+/+	+	+	+	+	+	?[8]
Clarithromycin	↑[2]	?	↓	↓	?	+/?	↑[5]	+	↑	?	+	↑
Clindamycin	↑[2]	+	↓	↓	↓	+/+	+	+	↑[2]	+	+	+
Cotrimoxazole	+	+	+	+	+	+/+	+	+	+	+	+	+
Dapsone	+	+	+	+	+	+/+	+	+	+	+	+	+
Ertapenem	+	+	+	+	+	+/+	+	+	+	+	+	+
Erythromycin	+	?	?	?	?	+/?	+	+	?	?	+	↑
Ethambutol	+	+	+	+	+	+/+	+	+	+	+	+	+
Gentamycin	+	+	+	+	+	+/+	+	+	?	+	+	+
Isoniazid	+	+	+	+	+	+/+	+	+	+	+	+	+
Levofloxacin	+	+	+	+	+	+/?[1]	+	+	+	+	+	?[6]
Linezolid	+	+	+	+	+	+/+	+	+	+	+	+	+
Meropenem	+	+	+	+	+	+/+	+	+	+	+	+	+
Metronidazole	+	+	+	+	+	+/+	+	+	+	+	+	+
Moxifloxacin	+	+	↓	↓	+	+/?[1]	+	+	+	+	+	?[8]
Ofloxacin	+	+	+	+	+	+/+	+	+	+	+	+	(↑)
Pentamidine	+	+	+	+	+	+/?[1]	+	+	+	+	+	+
Pyrazinamide	+	+	+	+	+	+/?[1]	+	+	+	+	+	+
Pyrimethamine	+	+	+	+	+	+/+	+	+	+	+	+	+
Rifabutin	↑[3]	↓[4]	↓	?	?	+/?	?	+	↑[3]	–	+	(↑)
Rifampicine	–	–	+[7]	–	–	–/–	↓[6]	↓[6]	–	–	↓[6]	–
Rifapentine	–	–	+	–	–	–/–	↓[6]	?	–	–	?	–
Streptomycin	+	+	+	+	+	+/+	+	+	+	+	+	+
Tetracyclines	+	+	+	+	+	+/+	+	+	+	+	+	+
Vancomycin	+	+	+	+	+	+/+	+	+	+	+	+	+

[1] QT prolongation possible
[2] Dose reduction should be considered (clindamycin) or may be considered (clarithromycin); caution especially in impaired renal function
[3] According to the package insert, the combination is not recommended; in case of concomitant use, dose reduction of rifabutin to 150 mg/day x three days a week
[4] Doravirine ↓, therefore increase the dose to 100 mg in the morning and 100 mg in the evening
[5] Level of the HIV drug increases
[6] Active level of the HIV drug decreases; increase the dose (see technical information)
[7] If necessary, dose increase of EFV to 800 mg/d in > 60 kg bw (see technical information)
[8] QT prolongation possible

Antidepressants

	DRV	DOR	EFV	ETV	NVP	CAB/ RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Amitriptyline	↑	+	+	+	+	+/+	+	+	↑	+	+	+
Bupropion	↓	+	↓	+	↓	+/+	+	+	+	+	+	+
Citalopram	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	?[1]
Desipramine	↑	+	+	+	+	+/+	+	+	↑	+	+	+
Doxepin	↑	+	+	+	+	+/+	+	+	↑	+	+	+
Fluoxetine	↑	+	+	+	+	+/+	+	+	↑	+	+	+
St John's Wort	–	–	–	–	–	+/–	–	–	–	–	–	–
Lithium	+	+	+	+	+	+/+	+	+	+	+	+	+
Mirtazapine	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	+
Nortriptyline	↑	+	+	+	+	+/+	+	+	↑	+	+	+
Paroxetine	?	+	+	+	+	+/+	+	+	?	+	+	+
Sertraline	?	+	↓	↓	+	+/+	+	+	+	+	+	+
Trazodone	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	+
Venlafaxine	↑	+	↓	↓	↓	+/+	?	+	↑	+	+	+

[1] QT prolongation possible

Antidiabetics (oral)

	DRV	DOR	EFV	ETV	NVP	CAB/ RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Glibenclamide	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	↑
Glimepiride	?	+	↑	↑	+	+/+	+	+	↓	+	+	↑
Metformin	?	+	+	+	+	+/+	+	↑[1]	↑[1]	↑[1]	+	+
Repaglinide	↑	–	?	↓	↓	+/+	+	+	↑	+	+	↑
Rosiglitazone	+	+	+	+	+	+/+	+	+	+	+	+	+
Sitagliptin	+	+	↓	↓	↓	+/+	+	+	+	+	+	+

[1] Please refer to the technical information, especially in case of impaired renal function

Antihelmintics

	DRV	DOR	EFV	ETV	NVP	CAB/ RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Albendazole	↓	+	↓	↓	↓	+/+	+	+	↓	+	+	+
Diethylcarbamazine	+	+	+	+	+	+/+	+	+	+	+	+	+
Ivermectin	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	+
Levamisole (ergamisole)	+	+	+	+	+	+/+	+	+	+	+	+	+
Niclosamide	+	+	+	+	+	+/+	+	+	+	+	+	+
Oxamniquine	?	+	+	+	+	+/+	+	+	↑	+	+	+
Praziquantel	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	+
Pyrantel	+	+	+	+	+	+/+	+	+	+	+	+	+
Suramin	+	+	+	+	+	+/+	+	+	+	+	+	+
Triclabendazole	↑	+	?	?	?	+/+	+	+	↑	+	+	+

Antihistamines

	DRV	DOR	EFV	ETV	NVP	CAB/RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Cetirizine	+	+	+	+	+	+/+	+	+	+	+	+	+
Fexofenadine	↑	+	+	↑	+	+/+	+	+	↑	+	+	+
Levocetirizine	+	+	+	+	+	+/+	+	+	+	+	+	+
Loratadine	↑	+	+	+	+	+/+	+	+	↑	+	+	+

Anticoagulants/antiplatelet agents

	DRV	DOR	EFV	ETV	NVP	CAB/RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Apixaban	–	+	↓	↓	↓	+/+	+	+	–	+	+	(↑)
Aspirin/ASS	+	+	+	+	+	+/+	+	+	+	+	+	+
Clopidogrel	↓[1,3]	+	↑	↓	?	+/+	+	+	↓[1,3]	+	+	+
Dabigatran	?	+	+	↑	+	+/?	+	+	↑	+	+	+
Dipyridamole	?	+	↓	↓	+	+/+	+	+	+	+	+	+
Edoxaban	↑	+	+	+	+	+/+	+	+	↑	+	+	+
Enoxaparin	+	+	+	+	+	+/+	+	+	+	+	+	+
Fondaparinux	+	+	+	+	+	+/+	+	+	+	+	+	+
Heparin	+	+	+	+	+	+/+	+	+	+	+	+	+
Phenprocoumon	?[2]	+	↓	?[2]	↓	+/+	+	+	?[2]	+	+	+
Prasugrel	+	+	+	+	+	+/+	+	+	+	+	+	+
Rivaroxaban	–	+	↓	↓	↓	+/+	+	+	–	+	+	(↑)
Ticagrelor	–	+	↓	↓	↓	+/+	+	+	–	+	+	+
Warfarin	?[2]	+	?[2]	↑	?[2]	+/+	+	+	↓	+	+	+

[1] Check the package insert
[2] Control of INR value recommended
[3] Clopidogrel ↓ due to decreased conversion to active metabolites; use alternatives

Anticonvulsants

	DRV	DOR	EFV	ETV	NVP	CAB/RPV	MVC	DTG	EVG/c	BIC	RAL	FTRL
Carbamazepine	–	–	↓	–	↓	–/–	?[1]	?[1]	–	–	?[1]	–
Gabapentine	+	+	+	+	+	+/+	+	+	+	+	+	+
Lamotrigine	?	+	↓	+	+	+/+	+	+	+	+	+	+
Levetiracetam	+	+	+	+	+	+/+	+	+	+	+	+	?[2]
Oxcarbazepine	–	–	+	?	?	–/–	?[1]	?[1]	?[1]	–	?[1]	–
Phenobarbital	–	–	–	–	–	–/–	–	–	–	–	–	–
Phenytoin	–	–	–	–	–	–/–	–	–	–	–	–	–
Pregabaline	+	+	+	+	+	+/+	+	+	+	+	+	+
Topiramat	+	+	+	+	+	+/+	+	+	+	+	+	+
Valproate	?	+	+	+	+	+/+	+	+	?	+	+	+

[1] Active level of the HIV drug decreases! Increase the dose in combination with carbamazepine; see the package insert.
[2] QT prolongation possible

Antifungals

	DRV	DOR	EFV	ETV	NVP	CAB/ RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Amphoter. B	+	+	+	+	+	+/+	+	+	+	+	+	+
Caspofungin	+	+	↓	↓	↓	+/+	+	+	+	+	+	↑
Fluconazole	+	↑[1]	+	↑[1]	↑[1]	+/↑[1]	+	+	↑[2]	+	+	↑
Flucytosin	+	+	+	+	+	+/+	+	+	?	+	+	+
Itraconazole	↑[2]	↑[1]	↓	↓	–	+/↑[1]	↑[1]	+	↑[2]	↑[1]	+	(↑)
Ketoconazole	↑[2]	↑[1]	–	↑[1]	–	+/↑[1]	↑[1]	+	↑[2]	↑[1]	+	(↑)
Nystatin	+	+	+	+	+	+/+	+	+	+	+	+	+
Posaconazole	↑[1]	↑[1]	↓	↑[1]	↑[1]	+/↑[1]	↑[1]	+	↑[2]	?	+	(↑)
Terbinafine	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	+
Voriconazole	↑[2]	↑[1]	–	?	?	+/↑[1]	↑[1]	+	?	+	+	(↑)

[1] Active level of the HIV drug increases!
[2] Both active levels increase
When using -azoles during ART, the maximum dosage should be observed according to the specialist information or checked via hiv-druginteractions.org.

Calcium antagonists (CCB)

	DRV	DOR	EFV	ETV	NVP	CAB/ RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Amlodipine	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	+
Diltiazem	↑	↑[2]	↓	↓	↓	+/↑[2]	↑[2]	+	↑	↑[2]	+	(↑)
Felodipine	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	+
Lercanidipine	–[1]	+	↓	↓	↓	+/+	+	+	-[1]	+	+	+
Nifedipine	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	+
Verapamil	↑	↑[2]	↓	↓	↓	+/↑[2]	↑[2]	+	↑	↑[2]	+	(↑)

[1] Levels of calcium antagonists may rise sharply, especially in combination with boosted ART (lercanidipine is contraindicated). Titrate cautiously, ECG monitoring if necessary.
[2] Active level of the HIV drug increases!

Immunosuppressants/cytostatics

	DRV	DOR	EFV	ETV	NVP	CAB/ RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Azathioprine	+	+	+	+	+	+/+	+	+	+	+	+	+
Carboplatin	+	+	+	+	+	+/+	+	+	+	+	+	+
Ciclosporin	↑[1]	↑[2]	↓	↓	↓	+/↑[2]	↑[2]	+	↑[1]	↑[2]	+	+
Cisplatin	↑	+	+	+	+	+/+	+	+	↑	?	+	+
Cyclophosphamide	?	+	↓	↓	↓	+/+	+	+	↓	+	+	+
Cytarabine	+	+	+	+	+	+/+	+	+	+	+	+	+
Daunorubicin	+	+	+	+	+	+/+	+	+	+	+	+	↑
Docetaxel	↑	+	↓	↓	↓	+/?	?	+	↑	+	+	↑
Doxorubicin	+	+	+	+	+	+/+	+	+	+	+	+	↑
Etoposide	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	+
Fluorouracil	+	+	+	+	+	+/+	+	+	?	?	+	(↑)
Gemcitabine	+	+	+	+	+	+/+	+	+	+	+	+	+
Irinotecan	–	+	↓	↓	↓	+/+	+	+	↑	+	+	↑
Methotrexate	+	+	+	+	+	?/+	+	+	↑	+	+	↑
Mycophenolate	↓	+	↓	+	+	+/+	+	+	↑	+	+	+
Oxaliplatin	+	+	+	+	+	+/+	+	+	+	+	+	?[4]
Paclitaxel	↑	↓[3]	↑	↓	+	↓/↓[3]	↓[3]	↓[3]	↑	↓[3]	↓[3]	↑
Sirolimus	–	↓	↓	↓	↓	+/+	+	+	↑	+	+	+
Tacrolimus	↑	↓	↓	↓	↓	+/+	+	+	↑	+	+	?[4]
Tamoxifen	↑	↓[3]	↓	↓	↓	+/↓[3]	↓[3]	+	↑	?	+	↓[4]
Vinblastine	↑	↓[3]	↓	↓	↓	+/↓[3]	↓[3]	↓[3]	↑	↓[3]	↓[3]	↓
Vincristine	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	+

[1] Active level of immunosuppressant increases; observe dose adjustment and maximum dose (according to package insert)
[2] Active level of the HIV drug increases!
[3] Active level of the HIV drug decreases!
[4] QT prolongation possible

Contraceptives

Particular caution is required when contraceptives are combined with protease inhibitors or efavirenz. In contrast, concomitant use with rilpivirine, doravirine, bictegravir, dolutegravir, cabotegravir, or raltegravir appears to be unproblematic.

Malaria/Protozoan Therapy

	DRV	DOR	EFV	ETV	NVP	CAB/ RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Artemisinin	↑	↓[1]	↓	↓	↓	+/↓[1]	↓[1]	+	↑	↓[1]	+	(↑)
Atovaquone	?	+	↓	↓	↓	+/+	+	+	+	+	+	+
Chloroquine	+	+	+	+	+	+/+	+	+	+	+	+	?[2]
Doxycycline	+	+	+	+	+	+/+	+	+	+	+	+	+
Lumefantrine	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	?[2]
Mefloquine	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	?[2]
Pentamidine	+	+	+	+	+	+/?	+	+	+	+	+	↑[2]
Primaquine	+	+	+	+	+	+/+	+	+	+	+	+	?[2]
Proguanil	↓	+	↓	↓	↓	+/+	+	+	+	+	+	+
Pyrimethamine	+	+	+	+	+	+/+	+	+	+	+	+	+

[1] Active level of the HIV drug decreases!
[2] QT prolongation possible

Phosphodiesterase type 5 inhibitors

Combining PDE5 inhibitors with a boosted protease inhibitor sometimes leads to strong increases in the PDE5 inhibitors. Therefore, they should always be given cautiously and initially at half of the lowest dose maximum every 48 to 72 hours. According to an FDA warning, sildenafil is contraindicated for treating PAH in combination with boosted ART. Tadalafil should be adjusted for treating PAH when taken concomitantly with PI. Also, be careful with EVG/c – this also significantly increases levels of PDE5 inhibitors.
The combination of sildenafil (in PAH dose) + EVG/c is contraindicated, and similarly, relevant interactions are also likely to exist for tadalafil and vardenafil. In combination with EFV, NVP, and ETV, there are usually decreased levels of PDE5 inhibitor activity. Concurrent use with DOR, RPV (caveat: QT time prolongation possible), MVC, DTG, CAB, BIC, or RAL is possible.

Statins/lipid-lowering agents

	DRV	DOR	EFV	ETV	NVP	CAB/ RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Atorvastatin	↑[1]	+	↓	↓	↓	+/+	+	+	↑[1]	+	+	↑
Clofibrate	+	+	+	+	+	+/+	+	+	+	+	+	+
Ezetimibe	↑	+	+	+	+	+/+	+	+	+	+	+	+
Fenofibrate	+	+	+	+	+	+/+	+	+	+	+	+	+
Fluvastatin	↑	+	↑	↑	+	+/+	+	+	↑	+	+	↑
Gemfibrozil	?	+	+	+	+	+/+	+	+	+	+	+	+
Lovastatin	–	+	↓	↓	↓	+/+	+	+	–	+	+	↑
Pravastatin	↑	+	↓	↓	+	+/+	+	+	↑	+	+	↑
Rosuvastatin	↑[1]	+	+	+	+	+/+	+	+	↑	+	+	↑
Simvastatin	–	+	↓	↓	↓	+/+	+	+	–	+	+	↑

[1] Always start with the lowest statin dose! Caution: rhabdomyolysis

Substitution

	DRV	DOR	EFV	ETV	NVP	CAB/ RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Buprenorphine	↑	+	↓	↓	+	+/+	+	+	+	+	+	+
Codeine	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	+
Methadone	?	+	↓	↑	↓	?/↓[1]	+	+	+	+	+	↑
Morphine	↓	+	↑	↑	+	+/+	+	+	↑	+	+	+

[1] Caution when combining methadone with RPV because of possible QT time prolongation

Virustatics/antivirals

	DRV	DOR	EFV	ETV	NVP	CAB/ RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Acyclovir	+	+	+	+	+	+/+	+	+	?	+	+	+
Adefovir	?[1]	?[1]	+	+	+	+/+	+	+	–	–	+	+
Cidofovir	+	+	+	+	+	+/+	+	+	?	+	+	+
Entecavir	+	+	+	+	+	+/+	+	+	+	+	+	+
Famciclovir	+	+	+	+	+	+/+	+	+	+	+	+	+
Foscarnet	+	+	+	+	+	+/+	+	+	?	+	+	+
Ganciclovir	+	+	+	+	+	+/+	+	+	?	+	+	+
Oseltamivir	+	+	+	+	+	+/+	+	+	+	+	+	+
Ribavirin	+	+	+	+	+	+/+	+	+	+	+	+	+
Valacyclovir	+	+	+	+	+	+/+	+	+	?	+	+	+
Valganciclovir	+	+	+	+	+	+/+	+	+	?	+	+	+
Glecaprevir/Pibrentasvir	–	+	–	–	–	+/+	+	+	+	?	+	(↑)
Elbasvir/Grazoprevir	–	+	–	–	–	+/+	+	+	–	+	+	–
Sofosbuvir/Velpatasvir	+	+	–	–	–	+/+	+	+	+	+	+	(↑)

[1] No combination of adefovir with Symtuza® or Delstrigo®.

Other

Here are listed alphabetically some more commonly used drugs that have not been assigned to individual categories.

	DRV	DOR	EFV	ETV	NVP	CAB/ RPV	MVC	DTG	EVG/c	BIC	RAL	FTR
Alendronate	+	+	+	+	+	+/+	+	+	+	+	+	+
Allopurinol	+	+	+	+	+	+/+	+	+	+	+	+	+
Budesonide	–	+	↓	↓	↓	+/+	+	+	–	+	+	+
Celecoxib	+	+	↑	↑	+	+/+	+	+	+	+	+	+
Colecalciferol	+	+	+	+	+	+/+	+	+	+	+	+	?
Dexamethasone[4]	?[1]	↓[2]	↓[2]	↓[2]	↓[2]	?/–	↓[2]	+	?[1]	↓[2]	+	+
Diclofenac	+	+	↑	↑	+	+/+	+	+	?[3]	+	+	+
Ibandronate	+	+	+	+	+	+/+	+	+	+	+	+	+
Ibuprofen	+	+	↑	↑	+	+/+	+	+	?[3]	+	+	+
Naproxen	+	+	↑	↑	+	+/+	+	+	?[3]	+	+	+
Paracetamol	+	+	+	+	+	+/+	+	+	+	+	+	+
Prednisone	↑	+	↓	↓	↓	+/+	+	+	↑	+	+	+
Theophylline	↓	+	+	+	+	+/+	+	+	+	+	+	+
Torasemide	+	+	?	?	+	+/+	+	+	?	+	+	+

[1] Dexamethasone level increases and active level of HIV drug decreases!
[2] Active level of the HIV drug decreases
[3] Caution: Check kidney values in combination with TDF
[4] No combination of CAB/RPV as injection with dexamethasone!

Literature and links

Bartlett JG; Pocket Guide Adult HIV/AIDS Treatment 2008-09. www.hopkins-hivguide.org.

Fachinformationen: Atripla®, Biktarvy®, Celsentri®, Delstrigo®, Descovy®, Emtriva®, Edurant®, Epivir®, Eviplera®, Genvoya®, Intelence®, Isentress®, Kivexa®, Norvir®, Odefsey®, Prezista®, Rekambys®, Retrovir®, Rukobia®, Stribild®, Sustiva®, Symtuza®, Tivicay®, Triumeq®, Trizivir®, Truvada®, Tybost®, Viramune®, Viread®, Vocabria®, Ziagen®.

www.hiv-druginteractions.org (Lexi-Comp Online™ Interaction Lookup).

www.hivinsite.org.

37. ART – alternative administrations

SARAH FISCHER, MARKUS UNNEWEHR

This chapter provides a brief overview of the options for ART via feeding tubes, in case of difficulties swallowing, and via parenteral administration.

Pharmaceutical aspects

Drugs must be crushed, suspended, or dissolved to facilitate ingestion in case of difficulties swallowing or for administration via a feeding tube. The manufacturer has often not studied cutting, crushing, and dissolving ART, which is not recommended. In this case, the use is off-label and constantly on a case-by-case medical decision. Whether a drug is suitable for crushing and tube administration depends on the active ingredient properties and the pharmaceutical manufacturing method. Particular attention must be paid to active ingredient stability, bioavailability, osmolarity, and interactions with food components.

The active substance's pharmacological location and absorption site must not be affected by the type and position of the feeding tube. In this case, parameters such as the pH value of the resorption site are relevant. Acid-sensitive active ingredients protected by an enteric coating must not be crushed in an acidic gastric environment; conversely, jejunal administration is possible.

Environmental influences such as light, oxidation, and moisture affect the chemical stability of the drug substance and limit its shelf life. Therefore, the medication must be applied immediately after comminution. In addition, film-coating components can swell rapidly and clog a feeding tube.

Liquid antiretroviral drugs available on the market are primarily designed for pediatrics. Adults must, therefore, take large volumes due to the low concentration of active ingredients. As a result, there is a risk of excipients accumulating and relatively high sugar and sorbitol levels, leading to increased osmolarity and causing gastrointestinal discomfort. This is why oral solutions should be diluted before application. Depending on the type and width of the tube, maximum applicable volumes must be noted.

The pharmacological processing into the solid drug form defines the possibility of crushing. In particular, in the case of sustained-release tablets, there are various ways to incorporate the drug substance and delay its release. Mechanical comminution can release too large amounts of active ingredients in too short a time. This can lead to dose-dependent side effects and insufficient duration of action.

Most hard gelatin capsules can be opened, and the content can be suspended. Some dosage forms, such as lingual tablets or soft capsules, are less suitable for crushing, division, or suspension because of their nature, shape, and release of active ingredients. In principle, the method of taking a drug should not be changed. Simultaneous food intake may affect absorption. However, this is necessary with some antiretroviral agents to achieve adequate exposure because specific dietary components (especially fat) are required, or a delayed intestinal transit time is needed. For others, this is not necessary.

Caution is advised in using magnesium- or aluminum-containing antacids or iron- and calcium-containing supplements. Complex formation can significantly reduce drug exposure.

ART administration via feeding tubes

In general, the following applies to drug administration via a feeding tube:

- There is a risk that the desired clinical effect fails due to the active ingredient becoming ineffective, the feeding tube becoming blocked, and the drug irritating the mucous membranes.
- The preparation must be finely crushed and dissolved or suspended in water. Direct dissolution in a syringe filled with water is preferable to avoid loss of the substance.
- Mortar and suspend medications only immediately before use.
- Each drug should be administered separately and not simultaneously with other medications or enteral nutrition to avoid (chemical) incompatibilities.
- If fasting ART is required, enteral nutrition boluses are preferable to continuous feeding. If continuous feeding is mandatory, it must be interrupted to administer the solubilized drug after gastric emptying.
- Rinse the feeding tube with water before and after drug administration.

Table 1

Active ingredient(s)	Trade name	To take on an empty stomach	Form[2]	Crushing possible?[3]	Note
Abacavir	Ziagen®	no matter	FCT	yes	Solution
FTC	Emtriva®	no matter	HC	no	Crushing not possible, suspension possible (solution)
3TC	Epivir®	no matter	FCT	yes	Solution
TDF	Viread®	no	FCT	yes	Granulate
AZT	Retrovir®	no matter	HC	no	Crushing not possible, suspension possible, solution
ABC/3TC	Kivexa®	no matter	FCT	no	
TAF/FTC	Descovy®	no matter	FCT	yes	
TDF/FTC	Truvada®	no	FCT	yes	
Dolutegravir	Tivicay®	no matter	FCT	yes	Tablets for the preparation of a suspension
Raltegravir	Isentress®	no matter	FCT	no	Granulate, 400 mg, 600 mg
Raltegravir	Isentress®	no matter	CT	yes	Granulate, 25 mg, 100 mg
Atazanavir	Generic	no	HC	no	Crushing not possible, suspension possible
Darunavir	Prezista®	no	FCT	yes	Suspension
Lopinavir/r	Kaletra®	no matter	FCT	no	Solution: Rinse with milk
Tipranavir	Aptivus®	no	SC	no	
Efavirenz	Sustiva®	no	FCT	yes	(crush before suspending)
Etravirine	Intelence®	no	TAB	no	Crushing not possible, suspension see product information
Nevirapine	Viramune®	no matter	TAB	yes	Suspension, 200 mg

Table 1: Continuation

Active ingredient(s)	Trade name	To take on an empty stomach	Form[2]	Crushing possible?[3]	Note
Nevirapine	Viramune RETARD®	no matter	SRT	no	400 mg
Rilpivirine	Edurant®	no	FCT	no	Barely soluble in water, bitter taste
Doravirine	Pifeltro®	no matter	FCT	no	
Maraviroc	Celsentri®	no matter	FCT	yes	
Fostemsavir	Rukobia®	no matter	SRT	no	
Efavirenz/FTC/TDF	Generics previously *Atripla®*	yes	FCT	no	
Bictegravir/FTC/TAF	Biktarvy®	no matter	FCT	yes	Results of SOLUBIC study pending; BIC insoluble in water
Doravirin/3TC/TDF	Delstrigo®	no matter	FCT	no	DOR is poorly soluble in water
Dolutegravir/3TC	Dovato®	no matter	FCT	yes	
Rilpivirine/FTC/TDF	Eviplera®	no	FCT	no	altered resorption
Dolutegravir/Rilpivirine	Juluca®	no	FCT	yes	
Rilpivirine/FTC/TAF	Odefsey®	no	FCT	no	
Elvitegravir/c/FTC/TAF	Genvoya®	no	FCT	no	Case Report
Elvitegravir/c/FTC/TDF	Stribild®	no	FCT	yes	
Darunavir/c/FTC/TAF	Symtuza®	no	FCT	yes	
Dolutegravir/Abacavir/3TC	Triumeq®	no matter	FCT	yes	
Abacavir/3TC/AZT	Trizivir®	no matter	FCT	no	
Cobicistat	Tybost®	no	FCT	no	
Ritonavir	Norvir®	no	FCT	no	Dilute suspension with milk; precipitate with water

[1] Fasting = time interval between drug and food administration (1 h before or 2 h after a meal).
[2] Dosage form: FCT – film-coated tablet, HC – hard capsule, CT – chewable tablet, TAB – tablet, SRT – sustained-release tablet, SC – soft capsule.
[3] "Crushing possible" – due to its nature, the drug can be crushed in a mortar from a pharmaceutical point of view without any altered clinical effect. This is independent of the approved method of use. Depending on the manufacturer and formulation, the indication may differ.
[4] "Suspension possible" – the previously comminuted drug, the intact drug, or the capsule contents can be dissolved or suspended in a liquid medium (including water juice) due to its nature from a pharmaceutical point of view, without an expected altered clinical effect. This is independent of the approved way of administration. Depending on the manufacturer and formulation, the indication may differ.

Parenteral administration

If enteral drug administration is not possible in the context of, for example, intensive care treatment, ART becomes problematic. This is because the number of parenterally administrable agents currently approved is very limited:

Table 2: Preparations for parenteral ART.

Active ingredient	Trade name	Administration	Dosage
Rilpivirine	Rekambys® 900 mg/3 mL	IM	900 mg every 2 months
Cabotegravir	Vocabria® 600 mg/3 mL	IM	600 mg every 2 months
Enfuvirtide	Fuzeon® 90 mg/1 mL	SC	90 mg every 12h
Zidovudine	Retrovir IV® 200 mg/20 mL	IV	1–2 mg/kg BW every 4h
Lenacapvir	Sunlenca® 463.5 mg/1.5 mL	SC	927 mg every 6 months
Ibalizumab	Trogarzo® 200 mg/1.33 mL	IV	2000 mg (initial dose), maintenance dose 800 mg every 2 weeks

IM = intramuscular, SC = subcutaneous, IV = intravenous after dilution

The two long-acting substances, rilpivirine and cabotegravir, are administered simultaneously at monthly or bimonthly injection intervals. This combination is not suitable as an acute treatment.
Intravenous AZT is a component of obstetrics in HIV-positive women.
Injectable antiretroviral therapies have not yet been adequately tested in studies on intensive care patients. Considering the significantly altered pharmacokinetics and pharmacodynamics under intensive care conditions, they are, at most, a therapeutic alternative in justified individual cases (Berruti 2021).

Literature

Berruti M, Riccardi N, Canetti D, et al. Injectable Antiretroviral Drugs: Back to the Future. Viruses 2021, 13, 228.

Fuchs C, Radziwill R. Arzneimittelgabe über Ernährungssonden. Enterale Ernährung, Braun, 2005.

Liverpool Drug Interactions Group, University of Liverpool, www.hiv-druginteractions.org. https://liverpool-hiv-hep.s3.amazonaws.com/prescribing_resources/pdfs/000/000/011/original/ARV_Swallowing_2018_Oct.pdf?1540371581

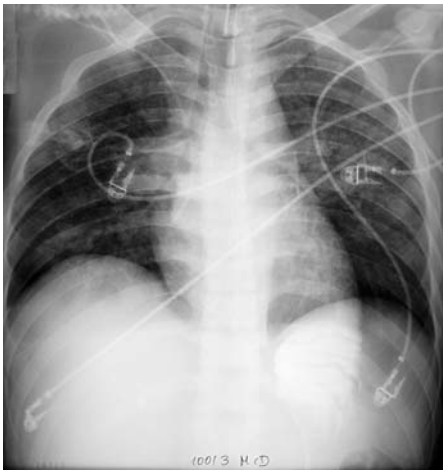
San C, Lê MP, Matheron S, et al. Management of oral antiretroviral administration in patients with swallowing disorders or with an enteral feeding tube. Médecine et Maladies Infectieuses 2020, 50, 537-44.

Tseng A, Foisy M, Hughes C. Crushing and Liquid ART Formulations. www.hivclinic.ca/main/drugs_extra_files/Crushing %20and %20Liquid %20ARV %20Formulations.pdf

Clinical Images

Clinical Images Credits

TAFEL 1: 1 JR, 2 MO, 3 CH, 4 JR, 5 MO
TAFEL 2: 1+2 CH, 3+4 HJS, 5–7 CH
TAFEL 3: 1 JR, 2–6 MO, 7+8 CH, 9+10 MO
TAFEL 4: 1 CH, 2 SU, 3+4 CH, 5 HJS, 6 CH, 7 JR, 8 MO
TAFEL 5: 1+2 CL, 3 JR, 4 HJS, 5 CH, 6 SU, 7–9 MO
TAFEL 6: 1 JR, 2+3 MO, 4 SU, 5+6 GH, 7 CH, 8 HJS, 9 MO
TAFEL 7: 1+2 CH, 3 HJS, 4 CE, 5–9 CH
TAFEL 8: 1+2 CH, 3 JT, 4 CH, 5+6 HJS, 7 CH, 8 MS, 9 HJS, 10+11 MO
TAFEL 9: 1–8 CH, 9+10 CG
TAFEL 10: 1–8 CH, 9 MO, 10 JR
TAFEL 11: 1+2 CH, 3 HJS, 4 CH, 5 HJS, 6+7 CH
TAFEL 12: 1 JR, 2 HJS, 3 CH, 4 TB, 5 SH
TAFEL 13: 1 CH, 2 JJ, 3 MO, 4–10 CH, 11 KS, 12 CH
TAFEL 14: 1 MO, 2 HJS, 3+4 RJ, 5 MO, 6–10 RJ
TAFEL 15: 1 SE, 2 MO, 3+4 SE, 5–7 JJ, 8+9 MO
TAFEL 16: 1–3 JJ, 4+5 CH, 6–9 JJ
TAFEL 17: 1+2+4 CH, 3 KS, 5+6 MS, 7–9 CH
TAFEL 18: 1–4 GS, 5–8 SF



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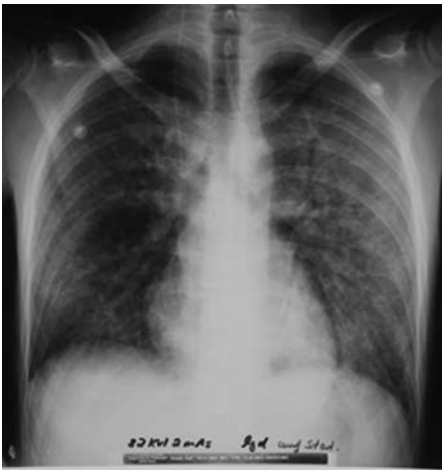

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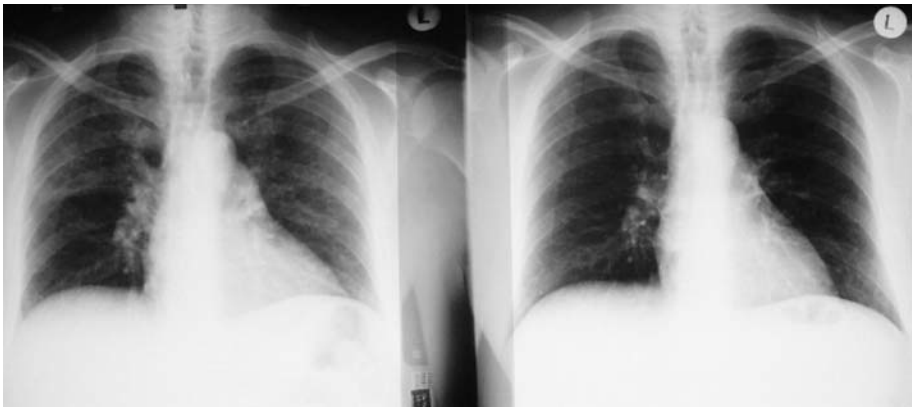

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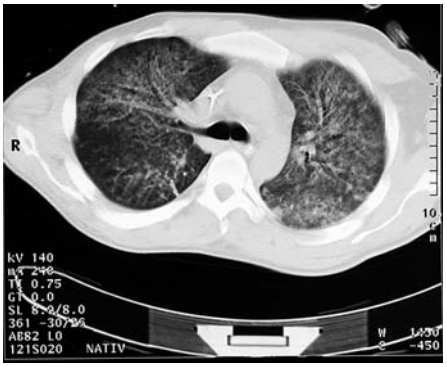

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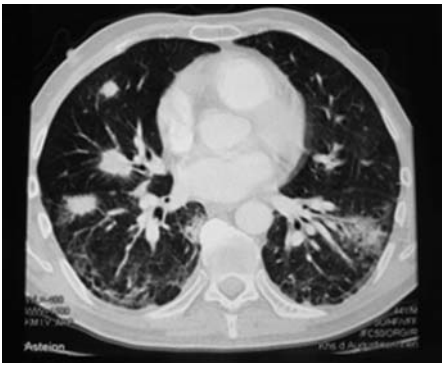

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1. Pneumocystis pneumonia

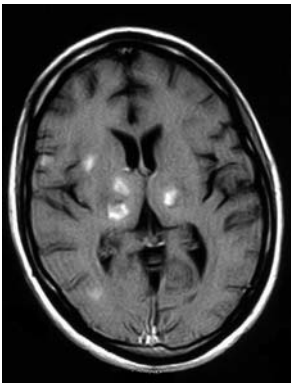
1 Chest X-ray with interstitial infiltrates. The patient is intubated and ventilated.

2 Pneumocystis pneumonia, confirmed in BAL.

3 Chest X-ray before and three weeks after cotrimoxazole therapy.

4 CT chest in PCP.

5 CT chest, multiple Kaposi's sarcomas simultaneously (in the setting of IRIS).



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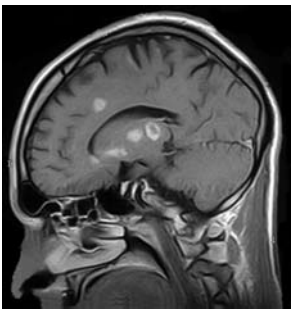

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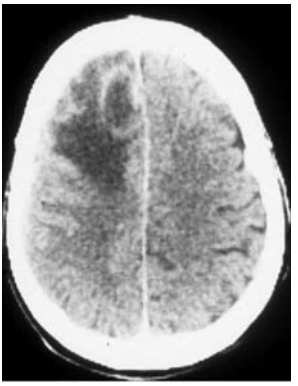

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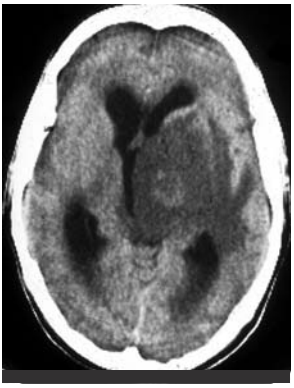

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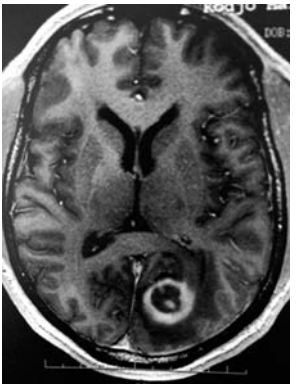

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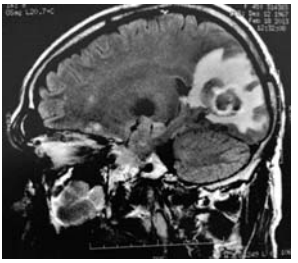

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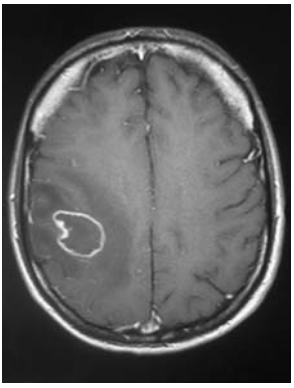

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2. Cerebral toxoplasmosis

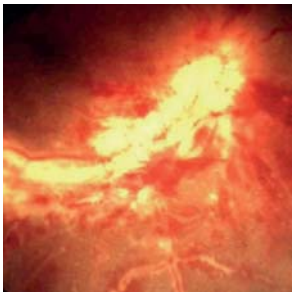
1/2 MRI scan of the same patient, two planes. Multiple, small lesions.

3 Solitary lesion with typical ring-shaped contrast enhancement (CCT).

4 CCT with large, solitary lasing and extensive edema.

5/6 Large occipital lesion in two planes.

7 Typical ring-shaped contrast enhancement.



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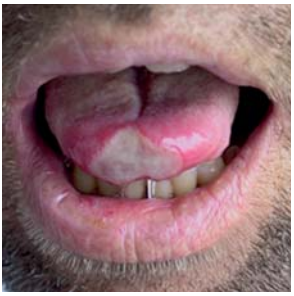

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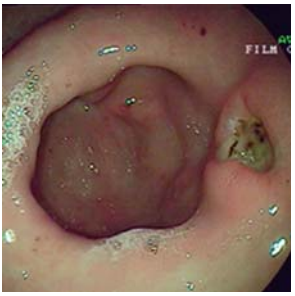

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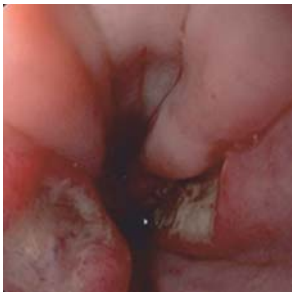

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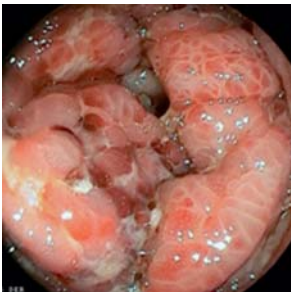

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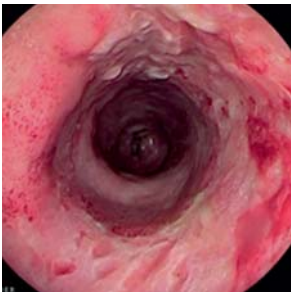

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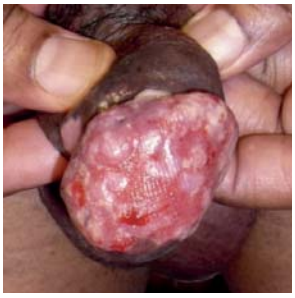

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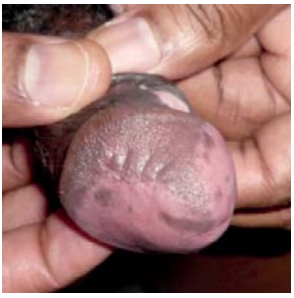

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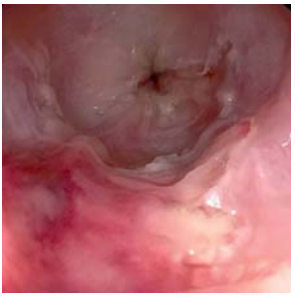

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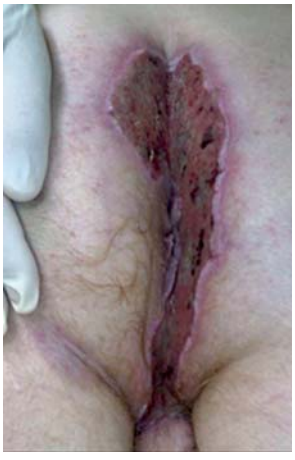

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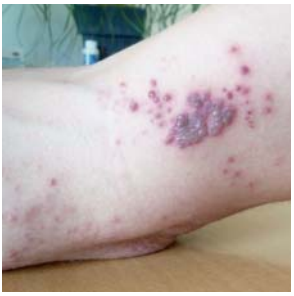
3. Herpes diseases (CMV, HSV)

1 Typical funduscopic findings, CMV retinitis.
2 Large CMV ulcer on the tongue, severe immunodeficiency.
3 CMV-associated gastric ulcer.
4 CMV ulcers in the esophagus.
5 CMV colitis.
6 CMV proctitis.
7/8 Herpes simplex infection in a patient with massive immunodeficiency, refractory to acyclovir, resolving with foscarnet therapy.
9 Herpes simplex esophagitis.
10 Large HSV-associated ulcer.



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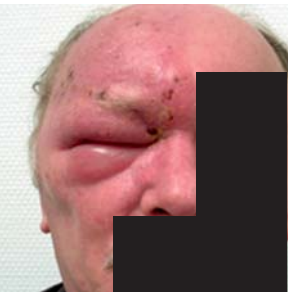

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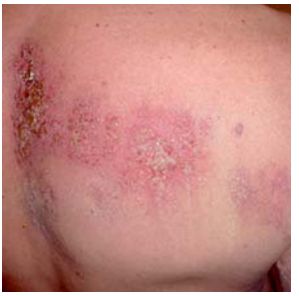

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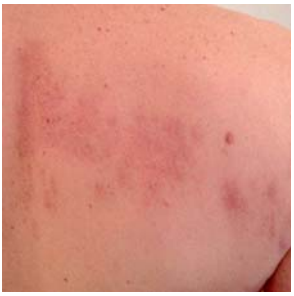

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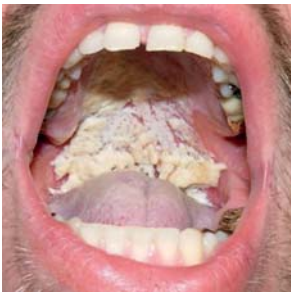

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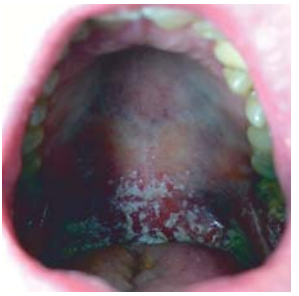

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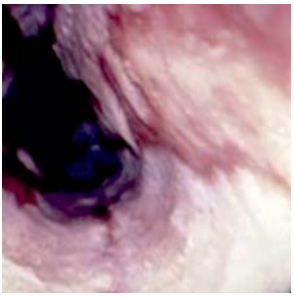

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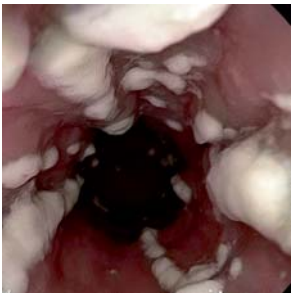

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4. Herpes zoster infections and candidosis

1 Herpes zoster at the right arm, hemorrhagic.

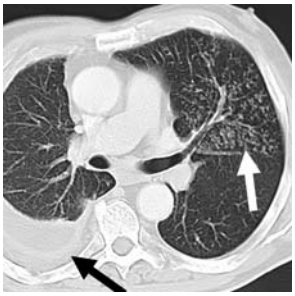
2 Zoster ophtalmicus.

3/4 Herpes zoster before treatment and three weeks later.

Candidosis

5/6 Oral candidiasis (oral thrush).

7/8 Esophageal candidiasis, endoscopic images



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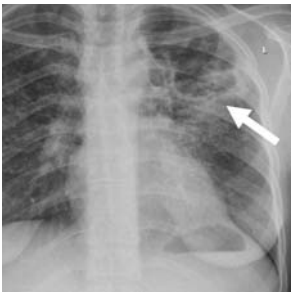

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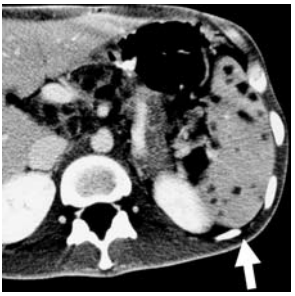

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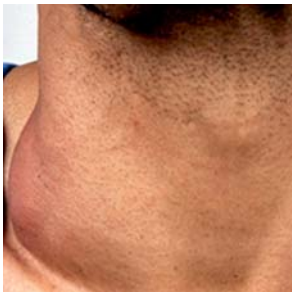

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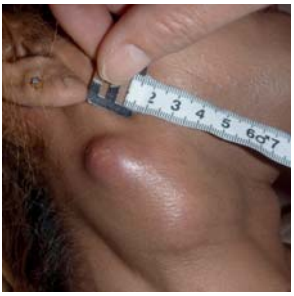

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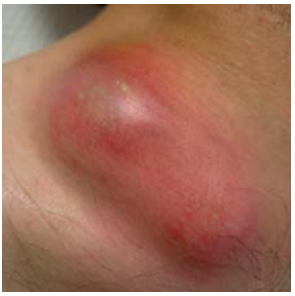

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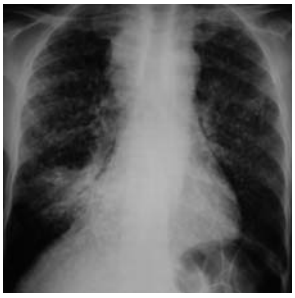

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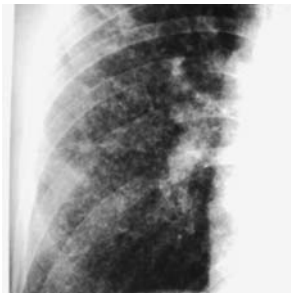

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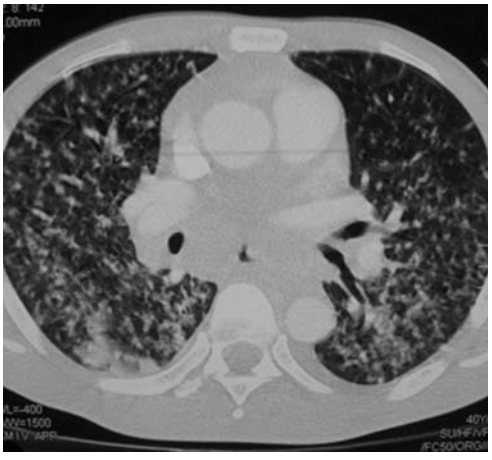

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5. Tuberculosis, various manifestations

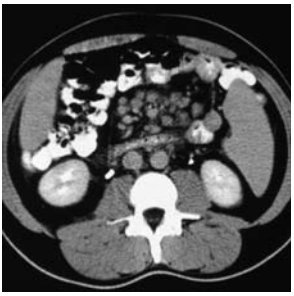
1 Tuberculosis pleuritis with right-sided pleural effusion. Left-sided "Tree-in-bud" phenomenon as seen in the bronchial spread of tuberculosis.

2 Tuberculosis cavities in the left upper lobe. Miliar nodules on the right.

3 Tuberculosis with splenic involvement.

4–6 Lymph node tuberculosis, abscessing, in the context of an IRIS.

7–9 Miliary tuberculosis. Chest X-ray and CT findings.



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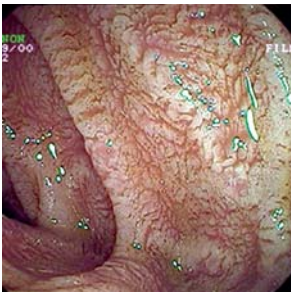

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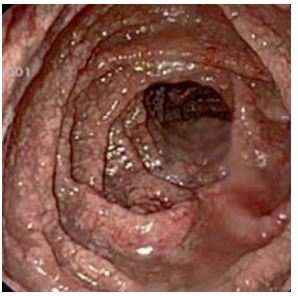

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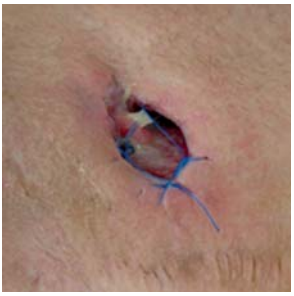

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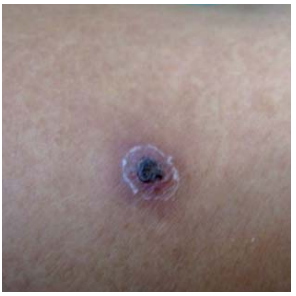

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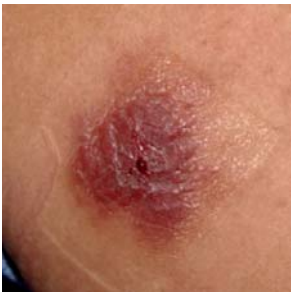

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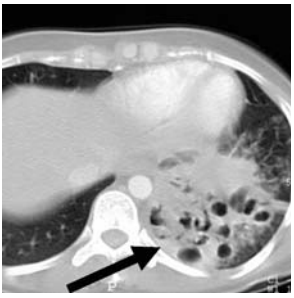

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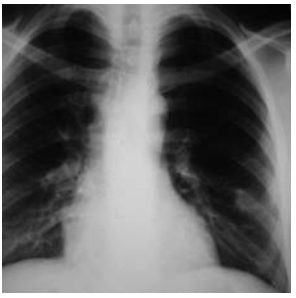

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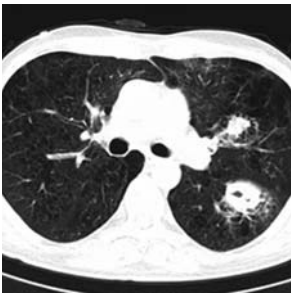

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6. Atypical mycobacterial infections and mycoses

1 CT scan of the abdomen with multiple lymph nodes, infection with *M. avium intracellulare* (MAI) infection.

2/3 Intestinal MAI infection (coloscopy)

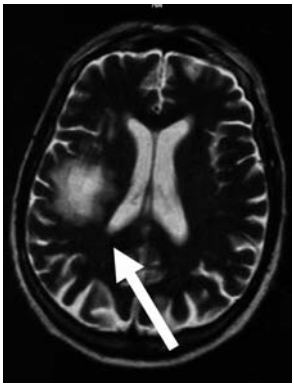
4 Abscess, detection of *M. xenopi* (manifestation as IRIS)

5/6 Cutaneous infection with *Talaromyces marneffii* (not AIDS-defining, but common in Southeast Asia!).

7 Cryptococcosis, CT findings.

8 Cryptococcosis, pulmonary cryptococcoma.

9 Aspergilloma (and CMV pneumonia, both microbiologically confirmed).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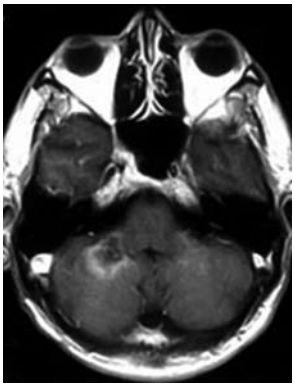
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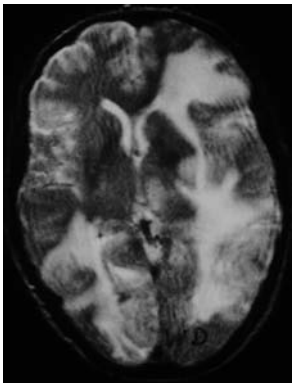
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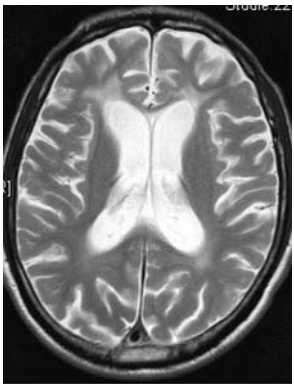
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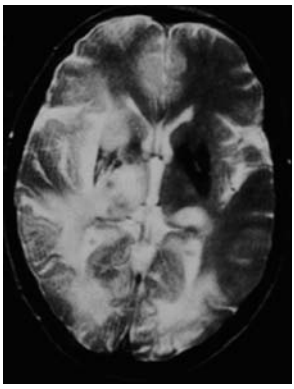
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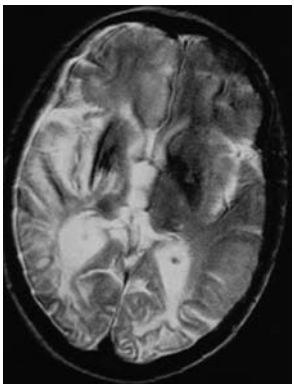
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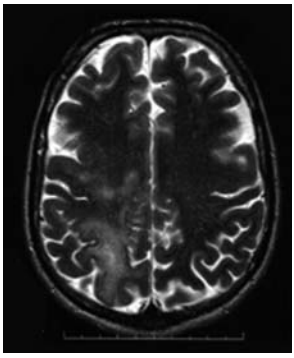
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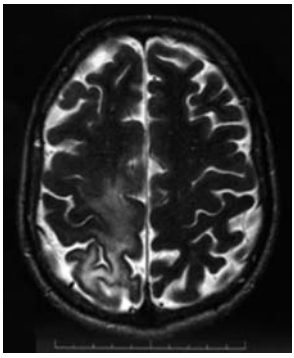
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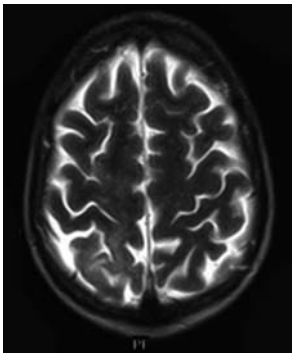
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7. PML and HAND

1 MRI scan with a relatively small PML lesion (arrow). JCV was detected in CSF.

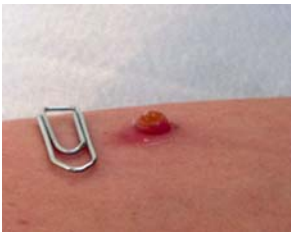
2 Cerebellar involvement of PML

3 Extensive PML lesions on MRI.

4 Axial T2-weighted MRI of a 60-year-old patient with HAND. Moderate atrophy, hyperintense lesions at the rostral and caudal end of the cella media of lateral ventricles (typical but not specific for HAND)

5/6 PML, MRI findings before and six months after initiation of ART. Partial regression (T2-weighted scan).

7–9 PML during ART. On the left, manifestation of occipital lesion two months after starting ART, then maximum manifestation two months later. On the right, regression, a further three months later. No specific PML therapy was given.



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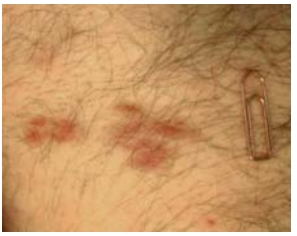

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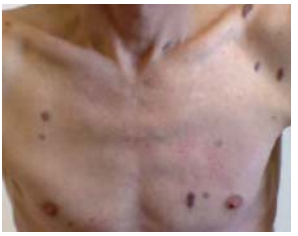

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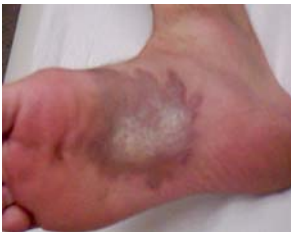

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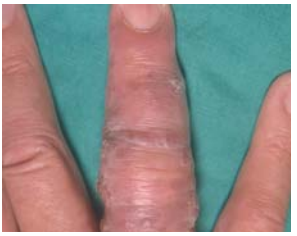

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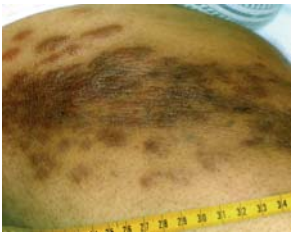

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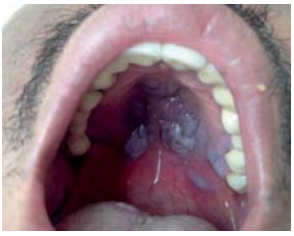

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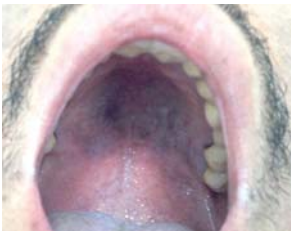

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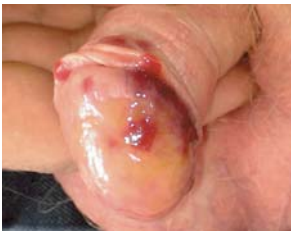

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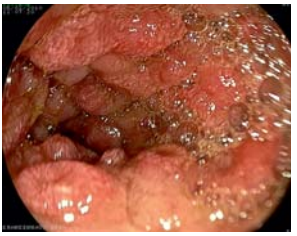

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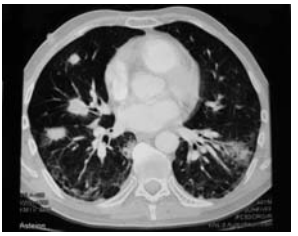

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8. Kaposi's sarcoma (KS)

1–5 Miscellaneous cutaneous findings.

6 Plate-like involvement in the groin, often with accompanying lymphodema of the affected extremity.

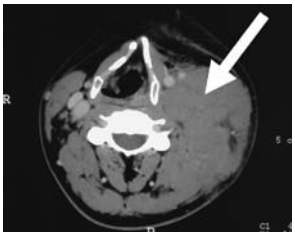
7a/b Mucocutaneous involvement of the hard palate before and after four cycles of chemotherapy.

8 Penile lesion.

9 Conjunctival lesions.

10 Visceral disease.

11 Pulmonary KS.



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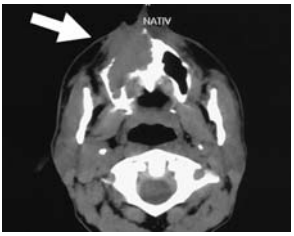

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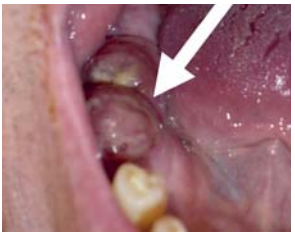

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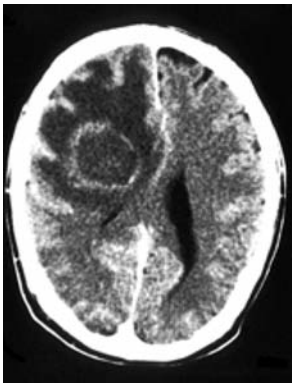

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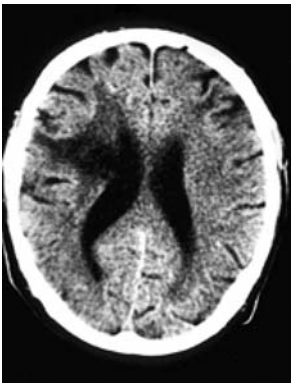

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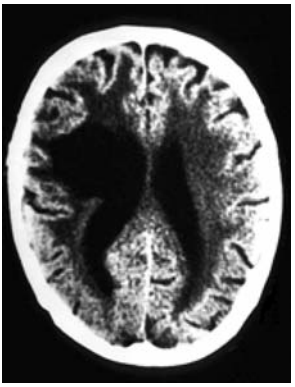

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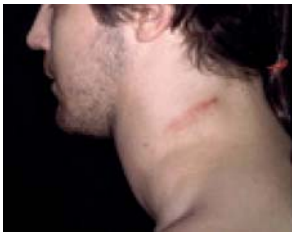

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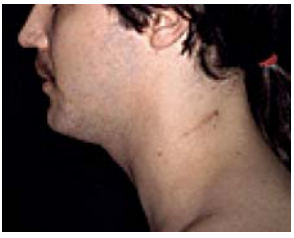

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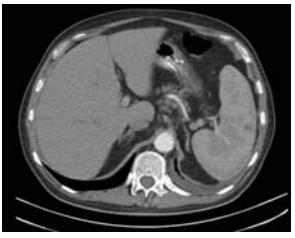

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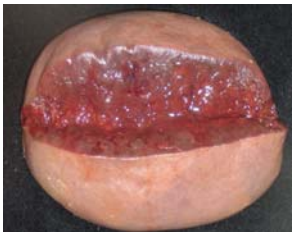

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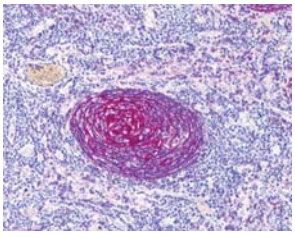

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9. Malignant lymphomas

1 Burkitt's lymphoma, rapidly growing, cervical location.

2 Diffuse large B cell lymphoma, destructive of the nasal area.

3 Plasmablastic lymphoma of the oral cavity (rare subtype, almost exclusively occurring in PLWH).

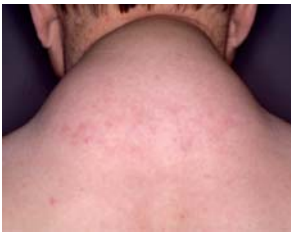
4–6 Primary CNS lymphoma. On the left, a large solitary lesion with contrast enhancement. In the middle, the same patient, complete remission after radiotherapy. On the right, the same patient, almost three years later. Marked atrophy due to radiotherapy (clinical dementia)

7/8 Hodgkin's disease with typical cervical manifestation before and after chemotherapy (complete remission).

9 Multicentric Castleman's disease (MCD) with hepatosplenomegaly on CT abdomen.

10 MCD, large spleen (autopsy finding).

11 MCD, characteristic histological findings, germinal center with a typical “onion-skin” pattern



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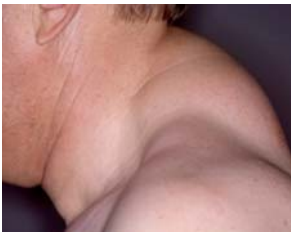

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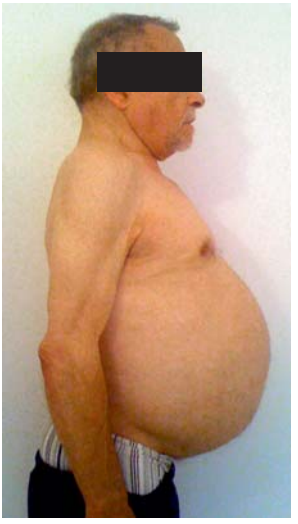

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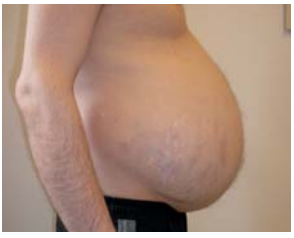

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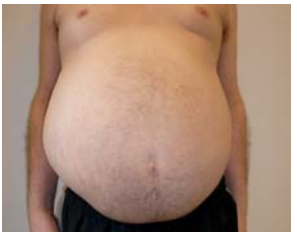

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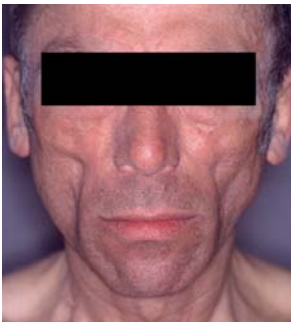

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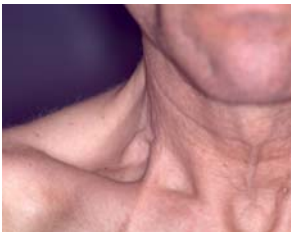

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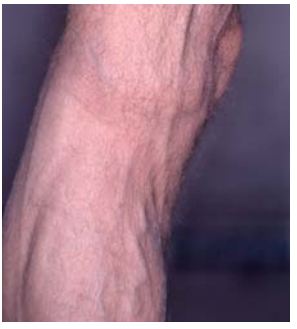

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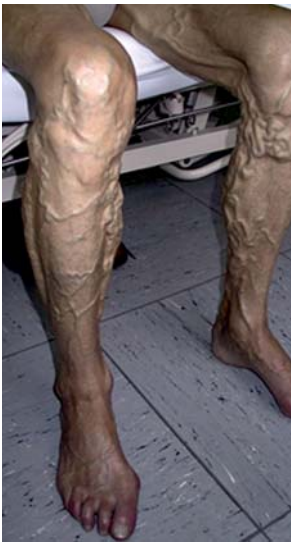

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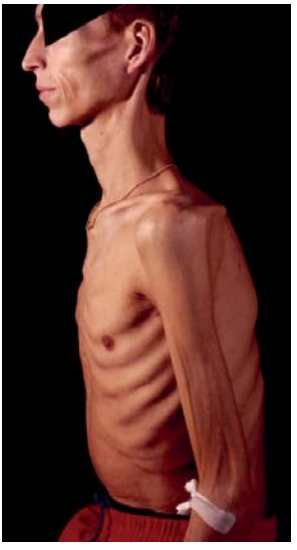

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10. Lipodystrophy

1/2 Buffalo Hump.

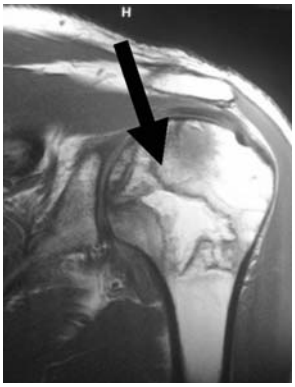
3–5 Extended abdominal fat accumulation.

6 Facial lipoatrophy.

7 Lipoatrophy. Due to the subcutaneous fat loss, a Port-a-Cath system (used for CMV treatment) is visible

8/9 Subcutaneous fat loss at the lower extremities with bulging veins, occurring after years of NRTI therapy (“D-drugs”, DDI, and D4T)

10 Classic wasting syndrome.



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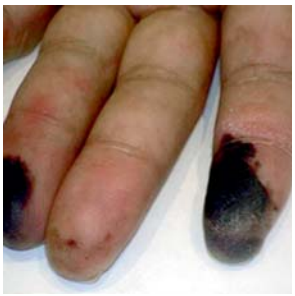

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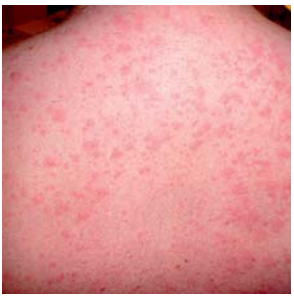

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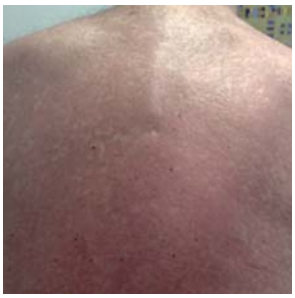

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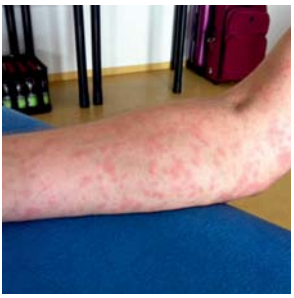

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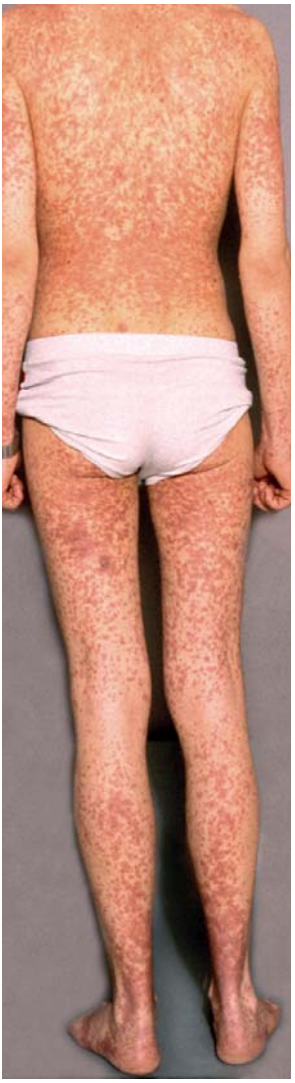

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11. Other side effects of antiretroviral therapies.

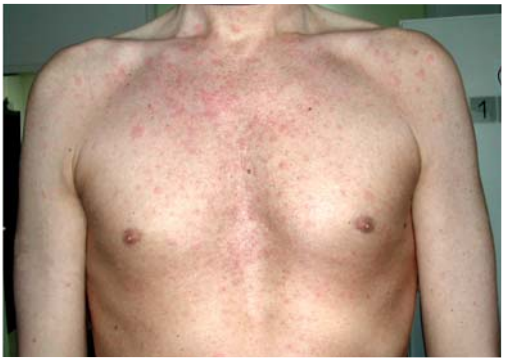
1 Avascular necrosis of the humerus (possibly due to PI therapy)

2 Serum sample from a patient with hypertriglyceridemia> 3,000 mg/dl, caused by PI-based therapy with saquinavir/r (resolved after switching to PI-free regimens).

3 Gangrenous ergotism: finger necrosis occurring under the combination of lopinavir/r and ergotamine.

4,5,7 NNRTI rash in patients treated with nevirapine (1–3 weeks after onset).

6 Exanthema, occurring with darunavir (clinically indistinguishable from NNRTI rash).



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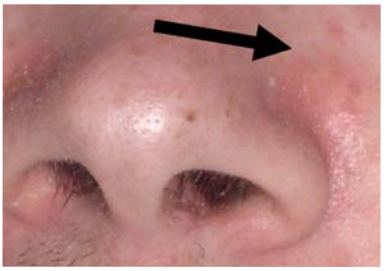

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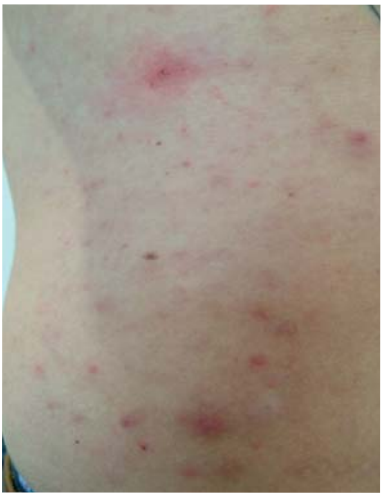

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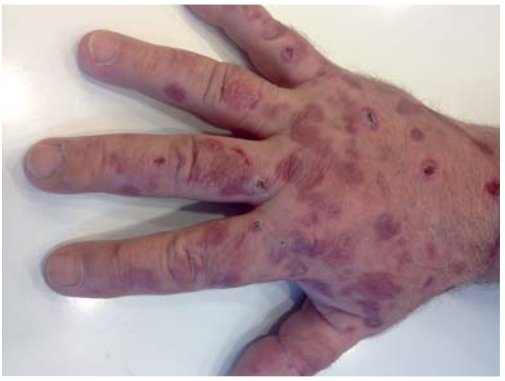

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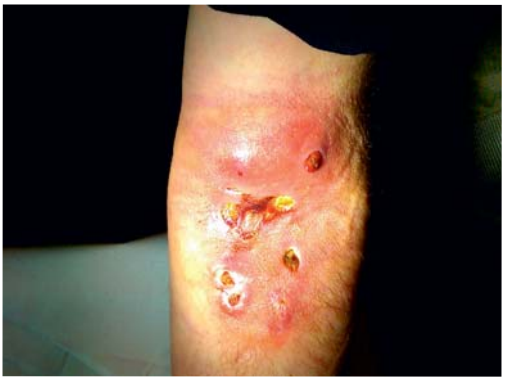

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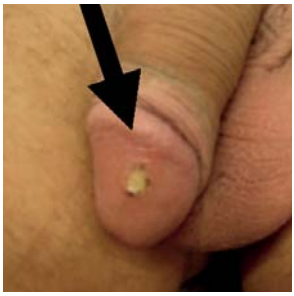
12. Various cutaneous manifestations in PLWH

1 Macular exanthema in acute HIV infection.
2 Seborrheic exanthema (indicator disease!).
3 Cutaneous porphyria (extrahepatic manifestation of hepatitis C, resolving after HCV treatment).
4 Scabies infection.
5 Multiple abscesses after chemsex (mephedrone) in an HIV-infected MSM.



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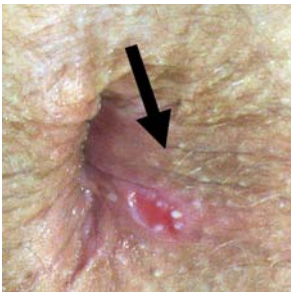

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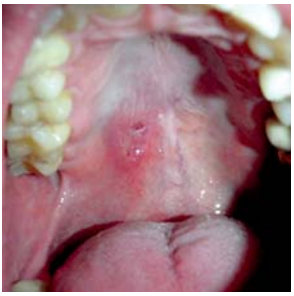

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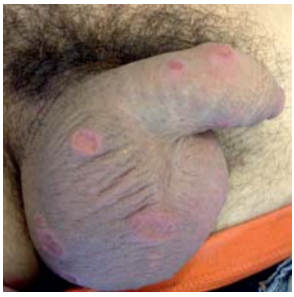

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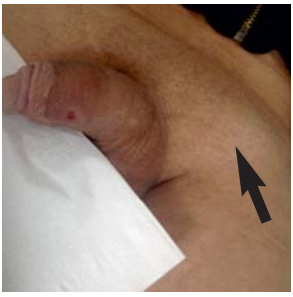

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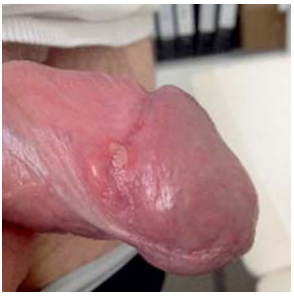

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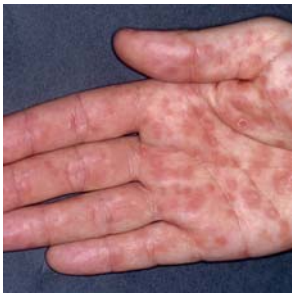

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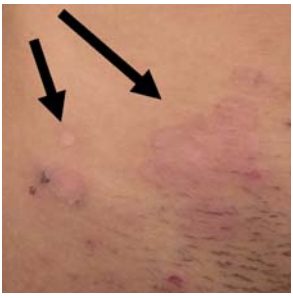

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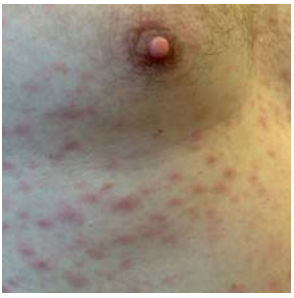

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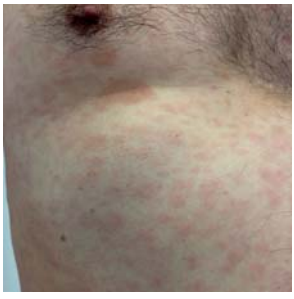

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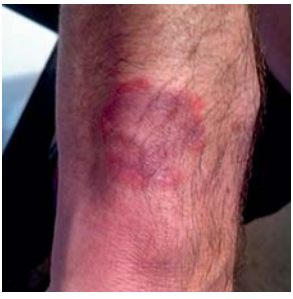

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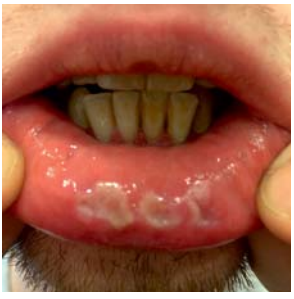


12

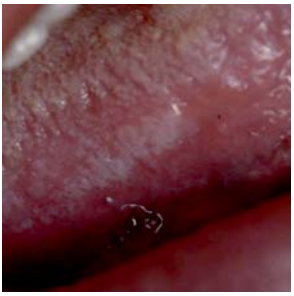
13. Sexually transmitted diseases (Syphilis and LGV)

1–4 Primary syphilis.

5 Painful ulcer caused by chlamydia L3, lymphogranuloma venerum (LGV), swollen lymph nodes (arrow).

6 LGV ulcer.

7–12 Various findings (no pain, no pruritus!) in lues II.



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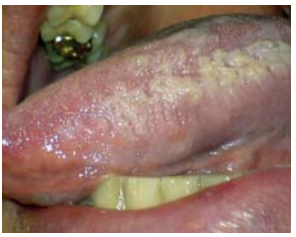

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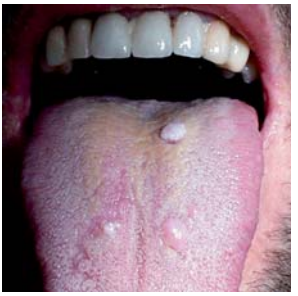

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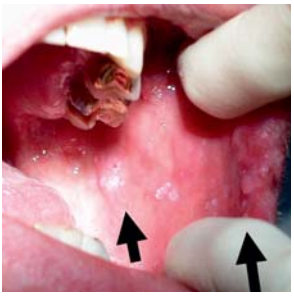

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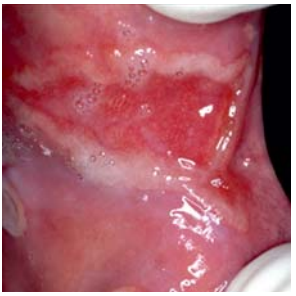

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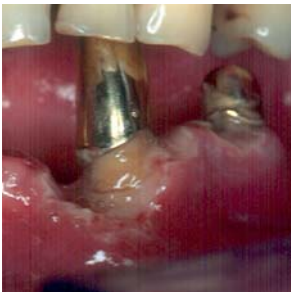

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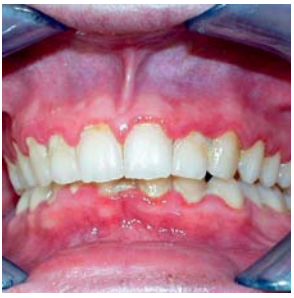

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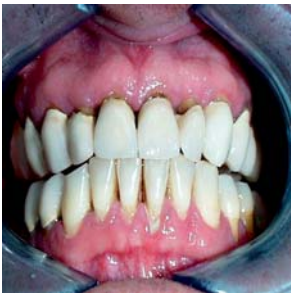

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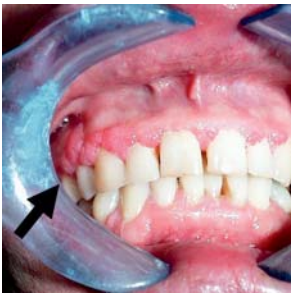

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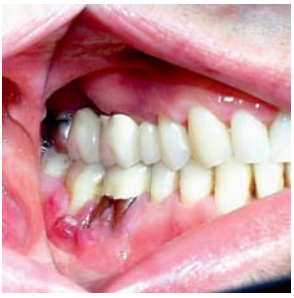

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14. Oral manifestations in PLWH (thrush see candidiasis)

1/2 Oral hairy leukoplakia (OHL), typical plaques which cannot be scraped off

3 Solitary oral warts on the tongue

4 Solitary oral warts on the oral mucosa

5 "Plaque muqueuses" (oral manifestation of syphilis)

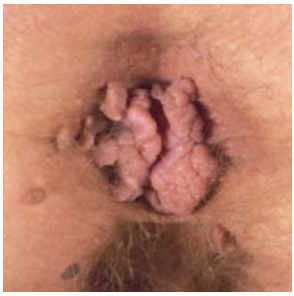
6 Necrotizing ulcerative periodontitis at teeth 33 and 35.

7 Linear gingival erythema on the vestibular gingiva.

8 Generalized chronic periodontosis.

9 Disseminated oral warts on the vestibular gingiva.

10 Oral vestibular ulcers at tooth 37.



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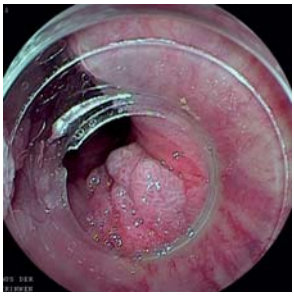

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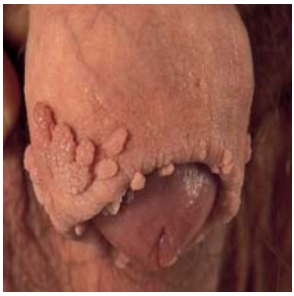

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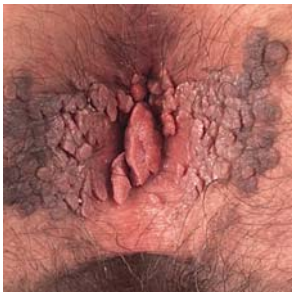

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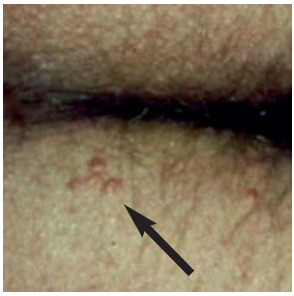

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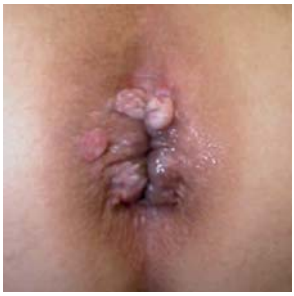

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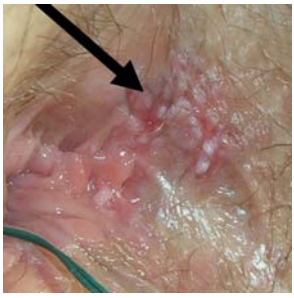

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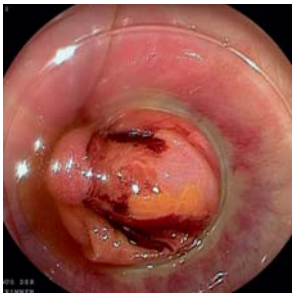

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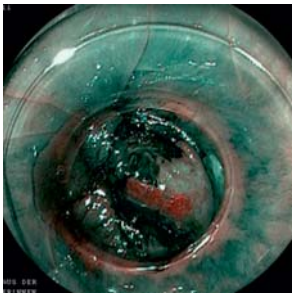

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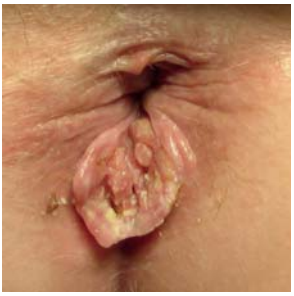
15. HPV-associated diseases

1/2 Anal condylomata acuminata.
3 Genital condyloma.
4 Bowenoid papulosis.
5 Perianal infection with *molluscum contagiosum* virus (not HPV-related!).
6 Anal intraepithelial neoplasia (AIN) III.
7 AIN III with the transition to anal carcinoma (green Siton drainage of a fistula).
8 Anal dysplasia (yellow areas).
9 Anal dysplasia, FICE technique (red areas).



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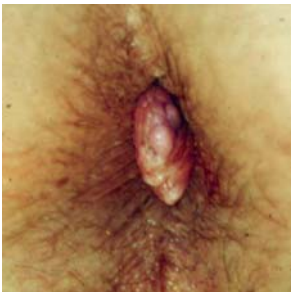

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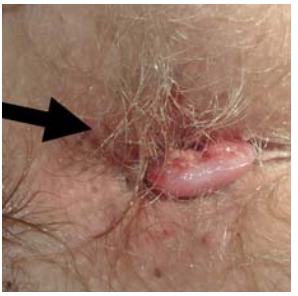

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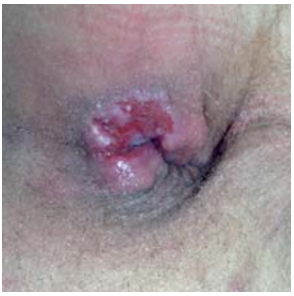

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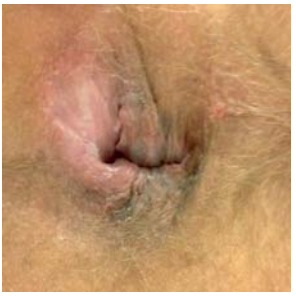

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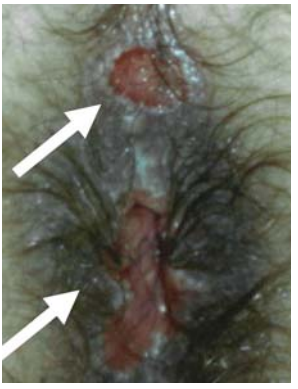

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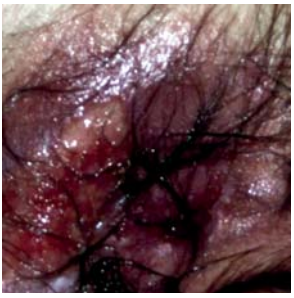

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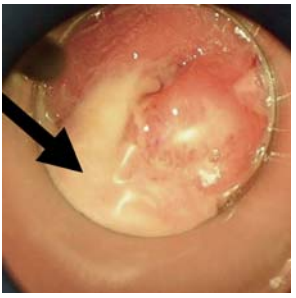

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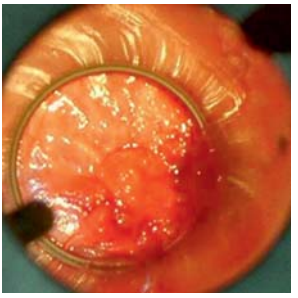

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16. Anal carcinomas and differential diagnoses

1 HIV-positive woman presenting with "hemorrhoids". Diagnosis: Invasive anal carcinoma (stage T2).

2 Verrucous anal carcinoma, prolapsing from the anal canal.

3 HIV-positive man with a three-week history of a growing tumor. Chlamydial proctitis was initially misdiagnosed as anal carcinoma.

4/5 Painful ulcer due to lymphogranuloma venerum (LGV), initially misinterpreted as anal carcinoma, resolving after three weeks of doxycycline.

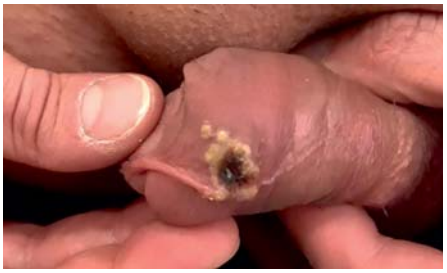
Inflammatory proctological findings

6 Anal CMV infection with extremely painful ulcers.

7 Anal HSV infection, also painful ulcers.

8 Purulent (purulent!) gonococcal proctitis.

9 Painful purulent proctitis with induration (detection of gonococci and chlamydia L3 serotype).



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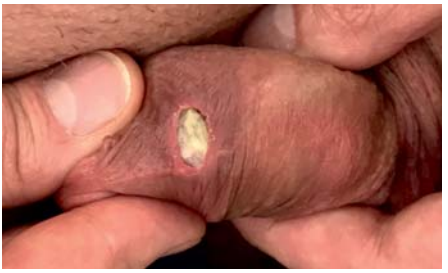

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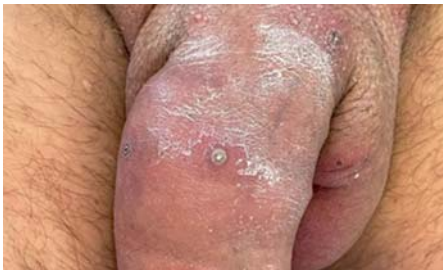

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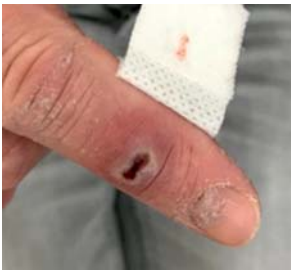

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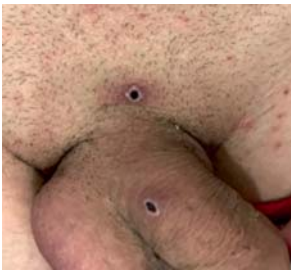

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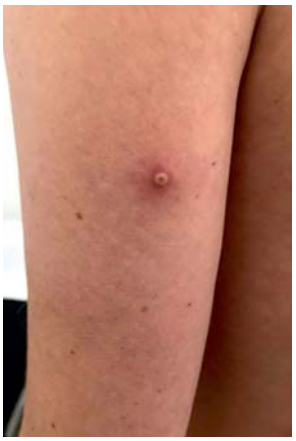

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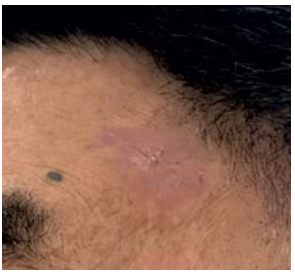

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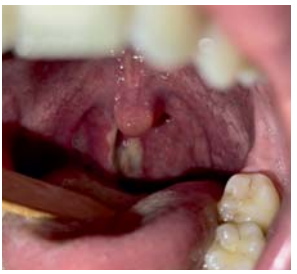

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17. Mpox

1/2 Isolated necrotic lesion on the penis. On the right, five weeks later (of note, still positive MPXV PCR).

3 Genital lesion with edema.

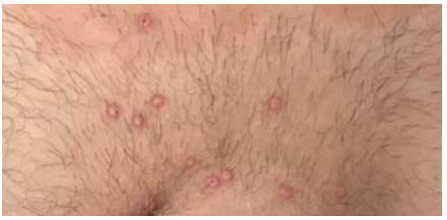
4 Very painful perianal lesions; hospitalization required (analgesia).

5/6 Isolated lesions on fingers, genital, note the central necrosis.

7 Isolated lesion on upper extremity.

8 Unusual, painless, flat-like lesion temporal.

9 Extremely painful pharyngeal ulcer.



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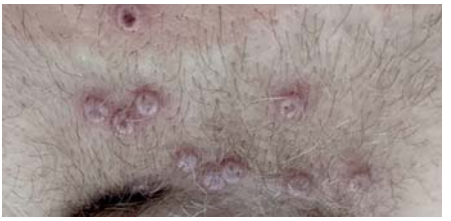

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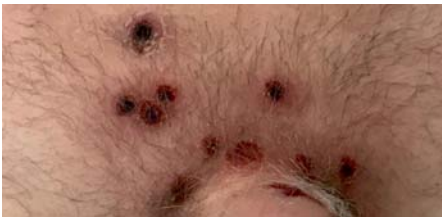

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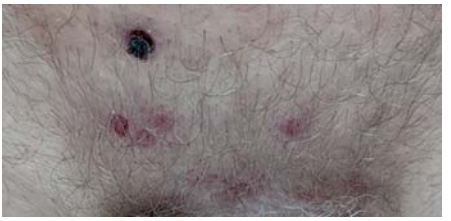

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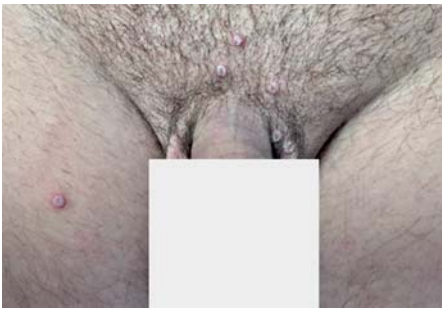

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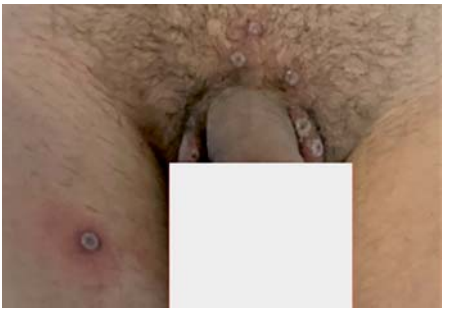

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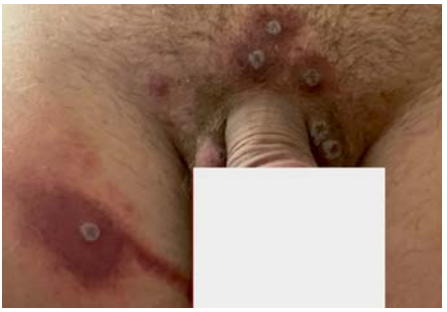

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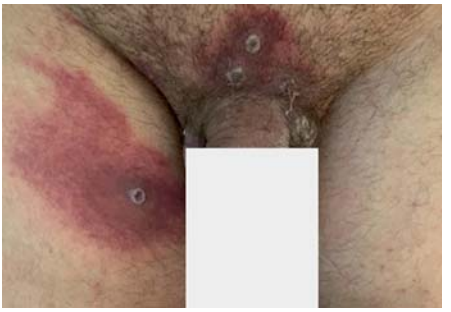

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Hoffmann | **Rockstroh**

HIV 2023/2024

What to start with? When to switch? How can a failing antiretroviral drug combination be improved? How to treat pregnant women and children, patients with tuberculosis or other AIDS events, with hepatitis coinfections or with HIV-2? What about STDs, Mpox and COVID-19? How should PrEP be taken and monitored?

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