Aus der Klinik für Gastroenterologie, Hepatologie und Infektiologie
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Long-term follow up study of patients initially diagnosed with the HIV infection Category C

Dissertation

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Zusammenfassung

Zwischen 2012 und 2021 wurden 253 Patienten mit HIV-Infektion CDC Kategorie C in der HIV-Ambulanz der Klinik für Gastroenterologie, Hepatologie und Infektiologie des Universitätsklinikums Düsseldorf aufgenommen. Die Daten von 238 Patienten, die sich in der Folge in regemäßigen Visiten befanden, wurden retrospektiv analysiert. Nicht alle *PLHIV (People living with HIV)* werden früh genug diagnostiziert, sodass bei diesen Menschen teilweise AIDS-definierende Erkrankungen auftreten. Auch bei Menschen, die schon länger unter einer Kombinations-Antiretroviralen Therapie (cART) stabil sind, können sich potenziell Erkrankungen der CDC Kategorie C entwickeln.

Das Ziel der Studie ist es zu analysieren, ob regelmäßige und umfassende Betreuung bei *PLHIV* mit Vorliegen AIDS-definierenden Erkrankungen die Prognose verbessern kann. Charakteristika der Patienten werden zusammengefasst. Die Kohorte war überwiegend männlich (m:w=3.56). Weibliche Patientinnen waren im Median 40 Jahre alt, männliche Patienten hingegen 45 Jahre alt. Die zwei meist häufig aufgetretenen AIDS-definierende Erkrankungen waren Soorösophagitis mit 82 Fällen sowie PCP mit 79 Fällen. 74 Patienten hatten bei der Aufnahme bereits eine bekannte HIV-Infektion, und 32 Patienten waren unter cART supprimiert. 216 Patienten (90.1%) der Kohorte erreichten eine nicht-nachweisbare Viruslast unter cART nach vier Monaten im Median. 221 Patienten (88.7%) konnten CD4-Zahl über 200 Zellen/µL in einer mittleren Zeit von zwei Monaten erreichen, und 128 Patienten (53.8%) erreichten über 500 Zellen/µL in 17 Monaten im Median. In Vergleich zur Viruslast braucht die Normalisierung der CD4-Zahl längere Zeit, und eine erfolgreiche Virussuppression hat meistens, aber nicht unbedingt die Normalisierung oder zumindest deutliche Verbesserung der CD4-Zahl zur Folge. 13 Patienten sind während des Beobachtungszeitraums gestorben, sechs waren weiblich und sieben waren männlich. Sechs Todesfälle waren definitiv AIDS-assoziiert: In fünf Fällen waren die HI-Viruslast nachweisbar und die CD4-Zahl unter 200 Zellen/µL, in einem Fall war jedoch bei bekannter HIV-Infektion unter cART keine Viruslast nachweisbar und die CD4-Zahl über 200 Zellen/µL. Die Mortalität der Kohorte während des mittleren Beobachtungszeitraums von 4 Jahren nach Auftreten eines AIDS-definierenden Ereignisses ist mit 2,5% niedrig und 172 lebende Patienten (72.3%) erreichten eine Beobachtungszeit von 5 Jahren.

Summary

Between 2012 and 2021, 253 patients were newly diagnosed with HIV infection CDC category C and presented in the HIV outpatient clinic at the Department of Gastroenterology, Hepatology and Infectious Diseases of the University Hospital of Düsseldorf. The data from 238 patients who took a part in regular outpatient visits were analyzed retrospectively. Not all people living with HIV (PLHIV) get diagnosed early enough, so that these people could develop AIDS-defining diseases at some point. Even those who are stable for a long period of time under the combined antiretroviral therapy (cART) could potentially develop the diseases belonging to CDC category C.

The aim of the study is to analyze, if regular and comprehensive care for PLHIV with AIDS-defining diseases improve their prognosis. The patients' characteristics are summarized. The cohort was male dominant (m:w=3.56). Female patients were in median age of 40. Male patients were, on the other hand, older with median age of 45. The median surveillance period was 48 months. The two most commonly occurring AIDS-defining diseases were candida esophagitis with 82 cases and pneumocystis pneumonia with 79 cases. 74 patients already had diagnosed HIV infection and progressed, and 32 patients among them were virally suppressed under cART. 216 patients (90.1%) reached non-detectable viral load under cART in four months in median. 221 patients (88.7%) could reach CD4 cell count over 200 cells/µL in median period of two months, and 128 patients (53.8%) reached over 500 cells/µL in 17 months in median. Compared to the viral load, the normalization of CD4 cell count takes longer time. The successful viral suppression leads mostly, but not always, to the normalization or at least improvement of CD4 cell count. 13 patients deceased during the surveillance period. Six were female and seven were male. Six cases of death were definitively associated with HIV infection or AIDS-defining disease. In five HIV-related deaths, the viral load was detectable, and CD4 cell count was below 200 cells/µL. In only one case of HIV-related deaths, the viral load was undetectable under cART and CD4 cell count was over 200 cells/µL. The mortality of the cohort is with 2.5% low in the median surveillance period of four years after the first diagnosis of AIDS-defining events. 172 survived patients (72.3%) reached the median surveillance period of five years.

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ARN	Acute retinal necrosis
BAL	Bronchoalveolar lavage
BMI	Body mass index
cART	Combination antiretroviral therapy
CCR	C-C chemokine receptor
CCR5	C-C chemokine receptor type 5
CD4	Cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
CMV	Cytomegalovirus
CT	Computer tomography
Decd.	Deceased
DNA	Deoxyribonucleic acid
DRK	Deutsches Rotes Kreuz
FDA	Food and drug administration
gp	Glycoprotein
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HSV	Herpes-simplex-Virus
INSTI	Integrase Inhibitor
IQR	Interquartile range
KS	Kaposi’s sarcoma
LBM	Lean body mass
LP	Late presentation
LTFU	Loss to follow-up
MDR	Multidrug resistance
MMWR	Morbidity and Mortality Weekly Report
MSM	Men who have sex with men
NHL	Non-Hodgkin lymphoma
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
OI	Opportunistic infection

PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PI	Protease Inhibitor
PIC	Pre-integration complex
PJP, PCP	Pneumocystis jirovecii (carinii) pneumonia
PML	Progressive multifocal leukoencephalopathy
PrEP	Pre-exposure prophylasis
PWID	Persons who inject drugs
RKI	Robert Koch Institute
RNA	Ribonucleic acid
TB	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Viral load
VS	Viral suppression
WHO	World Health Organization

Introduction

Epidemiology of HIV Infection

Epidemiology of HIV worldwide

According to the World Health Organization (WHO) people newly acquiring HIV has been decreasing since 2010. 1.3 million people were diagnosed with HIV in 2023. On the other hand, the number of people living with HIV (PLHIV) is globally increasing and estimated 39.9 million worldwide at the end of 2023 (Table 1). 1.4 million were children and 38.6 million were adults. The increase is due to the early detection and treatment of HIV, which have been reducing the mortality of HIV-related deaths by 51% since 2010. Africa remains the most severely affected region, but it is the region with highest rate for knowing their HIV status (90%) and receiving treatment (82%) (UNAIDS, 2024; WHO, 2024).

	PLHIV	People acquiring HIV	HIV-related deaths
Total	39.9 million [36.1-44.6 million]	1.3 million [1.0-1.7 million]	630,000 [500,000-820,000]
Adults (≥15 years)	38.6 million [34.9-43.1 million]	1.2 million [950.000-1.5 million]	560,000 [430,000-730,000]
Women	20.5 million [18.5-22.9 million]	520,000 [400,000-690,000]	240,000 [180,000-320,000]
Men	18.1 million [16.2-20.3 million]	660,000 [540,000-840,000]	320,000 [250,000-420,000]
Children (<15 years)	1.4 million [1.1-1.7 million]	120,000 [83,000-170,000]	76,000 [530,000-110,000]

Table 1 HIV global statistics 2023: Number of people living with HIV (PLHIV), their gender, age, incidence and mortality at the end of 2023 worldwide is shown (WHO, 2024).

Epidemiology of HIV in Germany

The Robert Koch Institute (RKI) is a German federal institution for public health and research. Its function is similar to the Centers for Disease Control and Prevention (CDC) in United States. According to the RKI, the number of people infected with HIV was estimated over 96,700 in Germany at the end of 2023 (Table 2). Among them, 87,200 are receiving combination antiretroviral therapy (cART) (Robert Koch-Institut, 2024b). In Germany the gender ratio (m:w) is 3.82 and is much higher in comparison to the worldwide statistics with the ratio of 0.88.

		Total
	Total number	>96,700 (91,000-102,000)
	Men	>76,700 (72,300-81,100)
	Women	>20,100 (18,600-21,400)
Ways of transmission	MSM	57,000 (53,900-60,200)
	Heterosexual	11,700 (10,700-12,500)
	PWID	9,000 (8,100-9,800)
	Blood products	~450
Countries of origin	Europe (except Germany)	>5,300 (5,000-5,700)
	Asia	>2,300 (2,100-2,500)
	Africa	>8,600 (8,000-9,300)
	America, Oceania	>1,500 (1,300-1,600)

Table 2 HIV statistics in Germany 2023: Estimated number of people living with HIV in Germany at the end of 2023, their gender, way of transmission and ethnicity are shown (Robert Koch-Institut, 2024b). MSM = Men who have sex with men; PWID = Persons who inject drugs.

The most common way of transmission was men who have sex with men (MSM). Among migrants the most common ethnic background was African (Robert Koch-Institut, 2024b). Since the war between Russia and Ukraine began in 2022 the number of PLHIV from Eastern Europe, more specifically from Ukraine, increased rapidly. From the end of 2021 to the end of 2023 the number of PLHIV from European countries except Germany increased by 1,900 (Robert Koch-Institut, 2022, 2024a).

In 2023, there were 3,500 people newly diagnosed with HIV infection in Germany. One third of them presented with CD4 cell count below 200 cells/µL. 620 people had been already progressed to acquired immunodeficiency syndrome (AIDS) at the time of HIV diagnosis. 730 people died with HIV-related diseases (Robert Koch-Institut, 2024b).

Year of diagnosis	HIV confirmed	Status unknown	Total
2012	2,954	1.096	4,050
2013	3,245	831	4,076
2014	3,533	633	4,166
2015	3,648	623	4,271
2016	3,396	671	4,067
2017	3,171	654	3,825
2018	2,886	747	3,633
2019	3,126	539	3,665
2020	2,468	438	2,906
2021	2,258	479	2,737
2022	3,279	700	3,979
2023	3,321	693	4,014

Table 3 Number of HIV antibody tests performed each year in Germany: Number of performed HIV antibody tests, confirmed tests as well as tests with unknown status each year from 2012 to 2023 are presented (Robert Koch-Institut, 2013, 2023a, 2024a).

The number of performed HIV antibody tests decreased in 2020 and in 2021, most likely due to the corona pandemic and reduced accessibility to the medical service. The number of positive results increased slightly after corona pandemic with 2,547 in 2022 and 2,799 in 2023 without people coming from Ukraine (Robert Koch-Institut, 2024a).

The 95-95-95 targets

The 95-95-95 targets is a part of 2025 HIV targets announced by the Joint United Nations Programme on HIV/AIDS (UNAIDS) to end the HIV pandemic by 2030.

The targets include three following goals to be achieved by the end of 2025:

- 95% of PLHIV to know their HIV status
- 95% PLHIV who know their status to receive antiretroviral treatment
- 95% of PLHIV who are on cART to be virally suppressed

At the end of 2023 worldwide, 86% of PLHIV knew their HIV status, 77% of those who knew their status received cART and 72% of those who received cART were virally suppressed. The WHO defines six regions to compare the regional statistics: African region, Region of the Americas, South-East Asian region, European region, Eastern Mediterranean region and Western Pacific region. Among all WHO regions, the African region is the closest to achieve these targets with 90-82-76 (UNAIDS, 2024; WHO, 2024).

Botswana, Eswatini, Rwanda, the United Republic of Tanzania, and Zimbabwe have achieved the 95-95-95 targets by the end of 2022. Denmark, Kenya, Kuwait, Malawi and Namibia are likely to achieve these targets by 2025 (Maheu-Giroux & Mishra, 2024; UNAIDS, 2023).

HIV Infection

Definition and History of HIV

The CDC published the report of five young previously healthy men diagnosed with Pneumocystis carinii (jirovecii) pneumonia (PCP, PJP) in 1981. All patients were homosexual, used either intranasal or intravenous drug, had a history of cytomegalovirus (CMV) infection and candida mucosal infection in common. Two of them were reported dead (Centers for Disease Control and Prevention, 1981b). On the same year, there were additional 26 cases of Kaposi's sarcoma (KS) diagnosed in young homosexual men. Eight of them died within 24 months (Centers for Disease Control and Prevention, 1981a).

The term "acquired immune deficiency syndrome (AIDS)" was used in the CDC's report in 1982 to describe 593 patients who presented with PCP, KS and/or other opportunistic infections (OOI) as an indicator of immune defect. 243 of 593 (41%) reported cases resulted in death (Centers for Disease Control and Prevention, 1982).

A retrovirus called human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-III/LA V), later known as human immunodeficiency virus (HIV), was isolated from individuals with AIDS. The antibody detection is since then the main strategy to identify the virus infection (Centers for Disease Control and Prevention, 1983). The further research led us to a profound understanding of the viral mechanism und provided necessary information such as predicted early symptoms and common risk factors, which will be discussed later in chapter.

HIV-1 and HIV-2

There are two subtypes of HIV: HIV type 1 (HIV-1) and HIV type 2 (HIV-2). The thesis focuses on patients with HIV-1 infection, which is explained in further chapter. The genomic organization and viral particle of HIV-2 is similar to HIV-1. HIV-2 is less virulent compared to HIV-1 and the VL is often undetectable without ART. Therefore, the negative HIV-2 PCR does not exclude HIV-2 infection. The genotypic resistance should be testet before the initiation of ART if possible. Even in the absence of VL and symptoms, the CD4 cell counts, especially the rate of CD4 cell count decline, should be monitored closely to determine the right moment to initiate ART. Although HIV-2 infection is endemic in West Africa, it may be diagnosed rarely in other regions, or they can co-infect with HIV-1 as well. About 1-2 million people are living with HIV-2

infection. The highest prevalence in Europe is reported in Portugal (Azevedo-Pereira & Santos-Costa, 2016; Berzow et al., 2020; Kapoor & Padival, 2025).

Mechanism of HIV infection

HIV-1 infects different kinds of cells, primarily activated CD4 T lymphocytes. Besides resting memory T lymphocytes, which is the main cellular reservoir of latent HIV-1 infection, macrophages, (follicular) dendritic cells, astrocytes and epithelial cells can be also infected by HIV-1 (Table 4). Organs such as liver, brain, lungs, spleen, lymph nodes and gastrointestinal tract are tissue reservoirs of latent HIV-1. These reservoirs makes it impossible to eliminate HIV under ART, and viral replication rebounds as soon as cART is stopped (Chen, 2022; Coffin, 1997; Kandathil et al., 2016).

HIV-1 uses its envelope glycoprotein gp160 to fuse and to enter the host cell. The precursor gp160 undergoes trimerization and cleavage to form two fragments of gp120 and gp41. Three copies of gp120/gp41 function all together as the viral spike, as gp120 bind to the primary receptor CD4 and a coreceptor CCR or CXCR4 (Chen, 2019; Xiao et al., 2021). The binding of gp120 to the CD4 receptor induces the fusion of gp41 to the target cell membrane by inserting its N-terminal fusion peptide (Murakami & Ono, 2021).

Viral type	Characteristic	Target
R5 T cell-tropic	• Detected in early stages of HIV-1 infection • Enter cells with high density of CD4	CD4 cells
X4 T cell-tropic	• Detected in late stages of HIV-1 infection • Correlate with disease progression	CD4 cells
R5 M-tropic	• Enter cells with low density of CD4 • Detected in brain tissue and CSF	Macrophages

Table 4 Three types of HIV-1: Each type of HIV-1 has its preferred target depending on the density of CD4 (Murakami & Ono, 2021).

The core of HIV consists of the replication enzymes, integrase and viral genomic RNA, and is enclosed in a shell called viral capsid. Once the HIV-1 fuse with the host cell, the capsid shell uncoats itself to reveal the viral core for reverse transcription, producing viral DNA molecules (Pre-integration complex, PIC). PIC enters the host cell nucleus, and form provirus in association with integrase. Provirus exit the nucleus to the cytoplasm, where it is translated into viral mRNAs. Lastly, assembled viral particle form a bud and is released from the host cell to proceed with its maturation (Di Nunzio et al., 2023; Engelman, 2012; Turner, 1999).

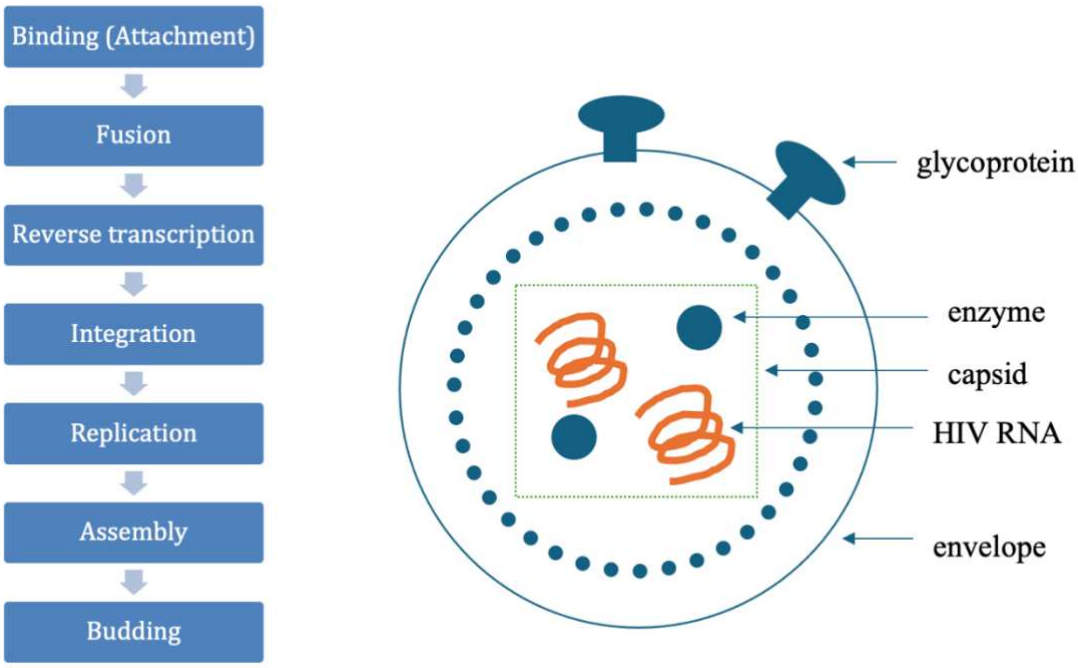


Figure 1 Simplified HIV structure and its life cycle 1. Binding, 2. Fusion, 3. Reverse transcription, 4. Integration, 5. Replication, 6. Assembly, 7. Budding and 8. Maturation (HIVinfo.NIH.gov, 2021a)

Diagnostic algorithm for HIV

HIV immunoassay

The HIV screening test uses the enzyme-linked immunosorbent assay (ELISA) technique to detect the IgM and IgG antibodies both for HIV-1 and HIV-2 in blood from needle stick. The improvement to detect IgM antibodies in 3rd generation screening test allows the detection of HIV infection during early seroconversion. Further improvement was made in 4th generation to detect p24 antigens, which allows the detection of HIV-1 before seroconversion. It has 99.1-100% sensitivity and 98.9-100% specificity (aidsmap, 2022; Branson, 2014; Deutsche Aidshilfe, 2024).

Nucleic acid test (NAT)

The nucleic acid test is a molecular technique to detect viral nucleic acids, which is used to screen donated blood for HIV-1, Hepatitis B and Hepatitis C infections in many countries. HIV-1 NAT does not detect HIV-2. It is a useful tool in detecting acute HIV infection, if the differentiation immunoassay for HIV-1 is not reactive (Branson, 2014; Hans & Marwaha, 2014).

Western blot

The western blot or immunoblot is one of the HIV confirmation tests, which isolates and detects HIV antibodies from blood sample. Disadvantages of the test are the time-consuming laboratory process and potential misclassification of HIV-2. The test is ideal to confirm the reactive result of the HIV-1/HIV-2 antibody differentiation immunoassay (Branson, 2014; Huang et al., 2018; Meles et al., 2002)

Polymerase chain reaction (PCR) test

The PCR is a laboratory technique, which mimics natural viral replication process to amplify short viral DNA segments in blood sample. In case of HIV-RNA detection, reverse transcriptase PCR (RT-PCR) is used. This is another confirmation test useful in acute HIV infection, when there is still no detectable antibody (Deutsche Aidshilfe, 2024; Khehra, 2005).

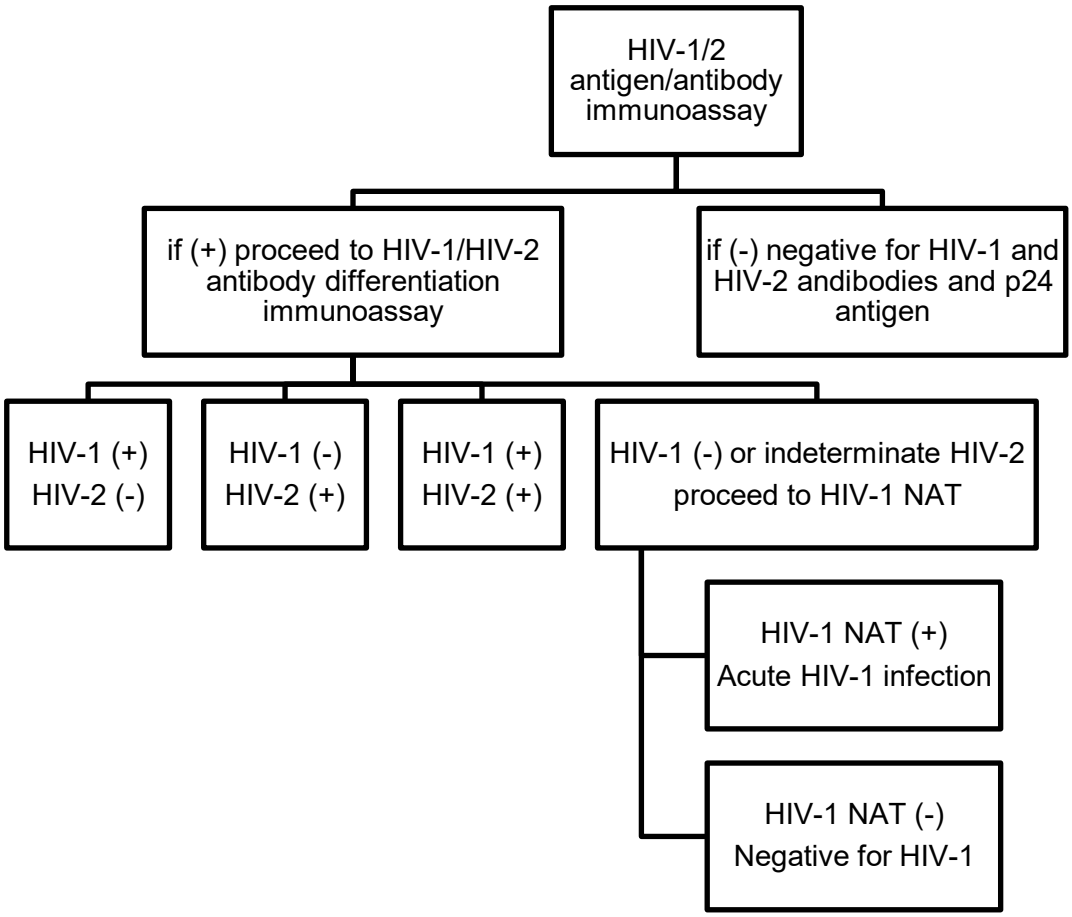


Figure 2 Algorithm for HIV diagnosis NAT = nucleic acid test; (+) = test is reactive; (-) = test is not reactive (Centers for Disease Control and Prevention, 2018)

The CDC recommends a HIV testing at least once between age of 13 and 64. Pregnant women should be tested for HIV as early as possible. In Germany, it is a part of prenatal care. Transgender people who are sexually active should consider more frequent HIV testing (Centers for Disease Control and Prevention, 2024; Deutsche Aidshilfe, 2024).

Following groups of people should get tested once a year (Centers for Disease Control and Prevention, 2024):

- MSM
- Persons who inject drugs (PWID)
- People who had sex with more than one partner
- People who had sex with PLHIV
- Sex workers
- People diagnosed with sexually transmitted diseases (STDs) such as syphilis
- People diagnosed with hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection or tuberculosis (TB)

HIV transmission and its prevention

HIV is transmitted by parenteral route, blood-to-blood contact, blood exposure to mucous membrane or sexual contacts.

People at higher risk of obtaining HIV infection (UNAIDS, 2024):

- MSM
- PWID
- Sex workers
- Transgender people
- People in prisons
- Young women and girls (15-49 years old) in African region

Blood products

In Germany the prevention against the HIV transmission through blood transfusion started in 1983 with screening out the people at high risks of obtaining HIV infection such as MSM and PWID. The HIV-1 antibody test of donated blood began in 1985 (Flegel et al., 1996). The RKI reported up to 450 HIV infections through blood products by the end of 2023 (Robert Koch-Institut, 2024a). The *Deutsches Rotes Kreuz* (German red cross) provides questionnaires online and on site to pre-screen people whether they are eligible to spend blood.

Persons who inject drugs (PWID)

For those who consume intravenous drugs, there are also available resources to prevent HIV infection such as needle exchange service, syringe vending machines or methadone substitution program. The Syringe Services Programs (SSP) plays an important role in reducing the incidence of HIV and HCV infection by about 50 % (Centers for Disease Control and Prevention, 2023).

Vertical transmission

Vertical transmission is mentioned separately in the later chapter for HIV infection and pregnancy.

Pre-exposure prophylaxis (PrEP)

PrEP is classically a combination of antiretroviral agents, emtricitabine and tenofovir disoproxifumarate (TDF/FTC). The long-acting agents such as cabotegravir and lenacapavir became available in injectable form and are well-accepted worldwide (Liegeon & Ghosn, 2023; WHO, 2025). The individuals who have undetectable HIV viral load under cART cannot transmit HIV sexually. People with a sex partner, who might have HIV or has an HIV infection with detectable viral load, are recommended to take PrEP. Sex workers also profit from taking PrEP It is not only useful in preventing sexual transmission of HIV, but also among PWID. Unfortunately, the awareness of PrEP among PWID is low (Deutsche AIDS-Gesellschaft, 2024; Sayood et al., 2022).

Post-exposure prophylaxis (PEP)

PEP should be initiated optimally within 2 to 24 hours, and within 72 hours at the latest, after exposition to HIV. It should be continued for over 30 days. TDF/FTC and raltegravir (RAL), TDF/FTC and dolutegravir (DTG), or bictegravir, emtricitabine and tenofovir alafenamide (TAF/FTC/BIC) are commonly used regime. PEP is recommended for people, who got injured with HIV contaminated object such as scalpel and needle, and the index person has HIV viral load over 50 copies/µL. Needle stick injury (NSI) is commonly reported among health care workers and often associated with recapping. PEP is also recommended in case of needle sharing among PWID, or after unprotected sexual intercourse with a partner, who have HIV infection and viral load over 1000 copies/µL (Deutsche AIDS-Gesellschaft, 2022; Perumal & Shanmugam, 2024).

Clinical stages and features of HIV infection

There are three clinical stages of HIV infection. The first stage is acute or primary HIV infection, which develops within two to four weeks after HIV infection. In this stage HIV replicate rapidly and is highly contagious. People may experience flu-like symptoms such as fever, skin rash and lymphadenopathy. These are signs of seroconversion. The second stage is chronic or asymptomatic HIV infection, which can last, if untreated, for about eight to ten years. The third stage is late-stage HIV infection or AIDS. In this stage CD4 cells are depleted, and immune system is severely compromised. The body can no longer fight against opportunistic infections. If cART is started early, most people remain in the second stage for many years (HIVinfo.NIH.gov, 2021b; Terrence Higgins Trust, 2022).

Clinical signs of acute HIV infection (seroconversion syndrome):

- Fever, usually >3 days
- Malaise
- Myalgia
- Pharyngitis
- Maculopapular rash
- Headache
- Arthralgia
- Diarrhea
- Meningoencephalitis (rare)

Prolonging fever and skin rash are strongly associated with primary HIV infection. General symptoms are mistaken as a flu, Epstein-Barr virus (EBV) or cytomegalovirus (CMV) infections. It is therefore important to assess the risk factors of HIV infection (Anderson, 2003; Department of Health, 2023; Hecht et al., 2002).

Elite controllers (ECs) remain asymptomatic over many years without cART by being able to suppress viral activity with their natural immune response. The study from Batohi et al. revealed, that ECs have higher level of CD69-expressing natural killer cells compared to PLHIV under cART or people without HIV infection (Batohi et al., 2024).

CDC Categories

There are two classification systems in the 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. The first classification system uses clinical signs and opportunistic infections to classify HIV infection into three categories: A, B and C (Table 5). The second classification system uses the level of CD4 cell counts to classify HIV infection into three categories: 1, 2 and 3 (Table 6). The new definition of AIDS was expanded in 1993 with CD4 cell counts under 200 cells/μL, CD4 cell percentage below 14% of total lymphocytes, pulmonary tuberculosis, recurrent pneumonia and invasive cervical cancer. Classifying patients into categories allows clinicians to establish optimal treatment and surveillance strategies (Centers for Disease Control and Prevention, 1992).

Category A

- Asymptomatic HIV infection
- Persistent generalized lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Category B

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5 C) or diarrhea lasting greater than 1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
- Peripheral neuropathy

Category C

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis carinii pneumonia
- Pneumonia, recurrent (two or more episodes within a year)
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV

Table 5 The clinical categories of HIV infection Pulmonary tuberculosis, recurrent pneumonia, and invasive cervical cancer were added to the category C (Centers for Disease Control and Prevention, 1992).

	CD4 cell count
Category1	≥500 cells/μL
Category 2	200-499 cells/μL
Category 3	<200 cells/μL

Table 6 CD4 T lymphocyte categories CD4 cell count is normal in category 1 (Centers for Disease Control and Prevention, 1992)

In 2008 CDC added another classification system based on laboratory and clinical evidence: stage 1 to 3 and unknown (Table 7). Stage 0 was added to the classification in 2014 to define the primary HIV infection, when CD4 cell counts are diminished, and AIDS-defining condition is not present. In stage 0, a negative or indeterminate HIV test is followed by a positive test result within six months (Centers for Disease Control and Prevention, 2014).

	Laboratory evidence	Clinical evidence
Stage 1	CD4 cell counts ≥500 cells/μL or CD4 percentage ≥29	None
Stage 2	CD4 cell counts 200-499 cells/μL or CD4 percentage 14-28	None
Stage 3 (AIDS)	CD4 cell counts <200 cells/μL or CD4 percentage <14	AIDS-defining condition
Stage unknown	No information	No information

Table 7 Surveillance case definition for HIV infection – 2008 For all stages, it is required to have laboratory confirmation of HIV infection (Centers for Disease Control and Prevention, 2008).

Common AIDS defining diseases

Esophageal candidiasis

Candida is a yeast which colonizes the surface epithelium of the alimentary tract. In healthy individuals it is a part of the normal flora and does not lead to clinical manifestation. Candida mucosal infection due to its overgrowth may occur in individuals with impaired immune system such as people living with HIV and people taking immune suppressants or receiving chemotherapy. Candida, most commonly *Candida albicans*, grow on the esophageal mucosa and initially form small and round plaques, which as the infection progresses begin to thicken, then eventually form confluent plaques and cause ulceration of esophageal mucosa. The common clinical manifestations are dysphagia, epigastric pain, and oral candidiasis. The diagnosis is made endoscopically. The Kodsi classification shown below on the table may be used to describe the severity of esophageal candidiasis (Fitting, 2024; Mohamed et al., 2019). The intravenous administration of fluconazol for at least 14 days is required to treat esophageal candidiasis effectively. The oral administration of fluconazol or itraconazol is also possible if patients are able to swallow medications (Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV, 2024).

Kodsi grade	Description
Grade I	• Plaques ≤2 mm • No edema, no ulceration
Grade II	• Plaques ≥2mm • Edema possible, no ulceration
Grade III	• Linear and confluent plaques and/or • Ulceration
Grade IV	• As for grade III, plus • Detachment of mucous membranes and luminal narrowing

Table 8: Kodsi classification of esophageal candidiasis (Fitting, 2024)

Pneumocystis jirovecii (carinii) pneumonia (PJP, PCP)

The *Pneumocystis carinii* is a type of fungus, which infects rats and was named after the person who discovered the specie, Antonio Carini. The name of the subspecies causing PJP was changed later to *Pneumocystis jirovecii*. PCP is suggested to be an airborne disease transmitted human-to-human and is one of the most common opportunistic infections among individuals with HIV infections. The typical radiological findings are diffuse bilateral ground-glass opacities (Shibata & Kikuchi, 2019). The gold standard of PCP diagnosis is microscopic visualization of *Pneumocystis jirovecii* in sputum or in bronchoalveolar lavage (BAL) (Centers for Disease Control and Prevention, 2017).

The clinical symptoms of PCP in HIV patients are prolonged, rather slowly progressing dyspnea and fatigue (Table 9), which in severe case results in respiratory distress and necessity to mechanical ventilation.

	HIV	Non-HIV
Common symptoms	Fever, dyspnea, nonproductive cough	
Severity of symptoms	Moderate	Severe
Onset	Subacute	Acute
Course of disease	Slow	Rapid
Progression	In weeks	In days

Table 9: Characteristics of PCP in HIV and non-HIV patients (Shibata & Kikuchi, 2019)

During the Corona pandemic, there were reported cases of SARS-CoV-2 infection with PCP superinfection or misdiagnosis and delayed diagnosis of PCP because of nonspecific symptoms and inconclusive CT scans (Hadavand et al., 2023; Su, 2023).

The first-line treatment is high-dose rimethoprim/sulfamethoxazole, commonly combined with an additive steroid therapy in case of respiratory insufficiency ($PaO_2 < 10$ kPa or < 70 mmHg or alveolar/arterial O_2 gradient > 35 mmHg), which should be initiated if PCP is clinically suspected (Behrens, 2020; EACS, 2025a).

Wasting syndrome

The HIV-associated wasting syndrome is defined as a combination of involuntary loss of more than 10% of body weight and longer than 30 days of either diarrhea, weakness or fever (IAPAC, 2024). The pathogenesis is multifactorial and affected by metabolic changes, endocrine dysfunction, immune dysregulation and gastrointestinal changes. The wasting causes degradation of protein and loss of lean body mass (LBM), which does not only include skeletal muscles but also organ tissues. The loss of LBM eventually leads to muscle fatigue and reduces physical endurance (HIV-associated Wasting, 2024). Bioelectrical impedance analysis (BIA) is an accurate method to determine the LBM. This analysis allows to diagnose wasting syndrome in patients whose BMIs are still in normal range (Bruce et al., 2004).

Specific treatments for HIV-associated wasting syndrome include:

- Testosterone replacement therapy,
- Recombinant human growth hormone,
- Anabolic steroids,
- Progressive resistance exercise,
- Nutritional supplements, and
- Cytokine modulation.

CMV diseases and retinitis

Cytomegalovirus (CMV, HHV-5) is a double-stranded DNA virus that belongs to the Herpesviridae family and is the most popular congenital viral infection. It's seroprevalence in the whole German population is unknown, yet among those who donated blood the seroprevalence was as high as 46%, and among pregnant women also about 47%. The transmission occurs through bodily fluids and blood. Most infections are asymptomatic and self-limited in immunocompetent individuals (Robert Koch-Institut, 2023b). The CMV infections may manifest in multiple organs such as brain, lungs, liver, intestine and eyes.

CMV manifestations in the alimentary tract occur in following sites (in order of frequency):

- Colon
- Stomach
- Esophagus
- Small intestine

The colon is the most frequent and the stomach is the second frequent site of CMV manifestation in the gastrointestinal (GI) tract. The most common endoscopic finding is ulcer, but it may also appear as polypoid mass or inflammation (Yeh et al., 2022). CMV and HSV esophagitis are differentiated by gross appearance and histological findings. HSV esophagitis appear as multiple small, shallow ulcers with a "volcano" appearance, on the other hand, CMV ulcers are deeper and larger (AMA, 2024).

The ocular manifestations may appear as decreased visual acuity, visual field defect, floaters and photophobia. The diagnosis is made by dilated fundus examination. The treatment includes antiviral treatment with ganciclovir and corticosteroid therapy. In severe case of ocular manifestation, the acute retinal necrosis (ARN) may occur, and the loss of vision is not reversible (Lee et al., 2017).

Kaposi's sarcoma (KS)

The Kaposi's sarcoma is a cancer caused by infection with Kaposi Sarcoma-associated herpesvirus (KSHV) or human herpesvirus 8 (HHV-8), the double-stranded DNA virus with six subtypes and 13 genetic variations, transmitted through saliva. The gold standard for its diagnosis is tissue biopsy. (Schneider & Dittmer, 2017) The HIV-associated KS responds well to the cART, especially if the patients are new to the cART. The tumor regress with immune reconstruction. Otherwise, the liposomal anthracycline is the gold standard for KS treatment since early 1990 (Dalla Pria et al., 2019).

Location of lesion	• Lymph nodes • Internal • Cutaneous
Clinical stage	• Patch • Plaque • Nodular
Epidemiology	• Classic KS in elder men • Endemic KS in younger African men and children from central Africa • Iatrogenic KS in transplant patients and in immune suppressed patients • Epidemic KS in HIV patients

Table 10 Clinicopathological variation of KS (Schneider & Dittmer, 2017)

Staging	Early stage	Late stage
Tumor (T)	T0: Confined to skin, lymph nodes or minimal oral disease (T0)	T1: Tumor-associated edema Ulceration Extensive oral disease Visceral disease (non-nodal)
Immune status (I)	I0: CD4 >150/mL	I1: CD4 <150/mL

Table 11 Staging of Kaposi's sarcoma depending on tumor characteristics (T0 or T1) and CD4 cell counts (I0 or I1) (Dalla Pria et al., 2019)

Antiretroviral Therapy (ART)

The first approved antiretroviral substance was zidovudine (ZDV, or azidothymidine as AZT), which inhibits nucleoside reverse transcriptase. It was used in 1987 as a monotherapy, and patients still progressed to AIDS within a couple of years. Two more nucleoside reverse transcriptase inhibitors (NRTIs), didanosine and zalcitabine, were approved. It was shown that the combination of two NRTIs could slow down the progression to AIDS and reduce the mortality compared to the monotherapy. The second substance class, protease inhibitors (PIs) including ritonavir, showed remarkable reduction in AIDS mortality. Another substance nevirapine from the third substance class, non-nucleoside reverse transcriptase inhibitors (NTRTIs), was then approved in 1997. The incidence of AIDS in Europe was able to be reduced from 30.7 per 100 patient years in 1994 to 2.5 per 100 patient years in 1998 (Cameron et al., 1998; Delta Coordinating Committee, 1996; Hoffmann & Rockstroh, 2022; Mocroft et al., 2000). The CDC published the first guideline for antiretroviral treatment in 1998. Without the initiation of cART, patients in developed country progress to AIDS approximately within 10-11 years. It is rare to sustain a long-term asymptomatic HIV infection over 10 years without cART (Centers for Disease Control and Prevention, 1998).

There are 24 single antiretroviral medicines, and 23 combined antiretroviral medicines approved for HIV treatment by the United States Food and Drug Administration (FDA). Substance classes with their function as well as approved medicines in each substance class are summarized below (Beccari et al., 2019; Chen et al., 2002; Hitchcock et al., 2024; HIVinfo.NIH.gov, 2024; Mandala, 2016; Segal-Maurer et al., 2022; Tseng et al., 2017).

Nucleoside reverse transcriptase inhibitors (NRTIs)

NRTIs bind to reverse transcriptase and inhibit the copying process of viral RNA into complementary DNA (cDNA). FDA-approved NRTIs are:

- abacavir (ABC),
- emtricitabine (FTC),
- lamivudine (3TC),
- tenofovir disoproxil fumarate (TDF), and
- zidovudine (ZDV) or azidothymidine (AZT).

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTIs inhibit viral replication also by blocking reverse transcriptase, like NRTIs, but by binding to different sites. FDA-approved NNRTIs are:

- doravirine (DOR),
- efavirenz (EFV),
- etravirine (ETR),
- nevirapine (NVP), and
- rilprivirine (RPV).

Protease inhibitors (PIs)

PIs inhibit viral maturation by blocking protease. Ritonavir (RTV) is a pharmacokinetic enhancer or booster, which only be used in combination with other drugs, typically with other PIs to prolong their efficacy. FDA-approved PIs are:

- ritonavir (RTV, r),
- atazanavir (ATV),
- darunavir (DRV),
- fosamprenavir (FPV), and
- tipranavir (TPV).

Entry inhibitors

- Enfuvirtide (T-20) is a fusion inhibitor, which bind to gp41 of HIV envelope to block the fusion of HIV with CD4 T lymphocytes.
- Maraviroc (MVC) is a CCR5 antagonist, which attach to the CCR5 coreceptor to inhibit HIV entry into CCR5 presenting cells.
- Fostemsavir (FTR) is an attachment inhibitor, which bind to the gp120 of HIV envelope to block the entry of HIV into CD4 lymphocytes.
- Ibalizumab is a post-attachment inhibitor, which is used against multidrug-resistant (MDR) HIV. It is a recombinant humanized monoclonal antibody, which interfere the conformational changes of gp120 and CD4 coreceptors. Unlike other HIV medications, it is administered intravenously and in 14 days interval.

Integrase strand transfer inhibitors (INSTIs)

INSTIs inhibit the HIV enzyme called integrase, which inserts viral cDNA into the DNA of CD4 lymphocytes. As a result, viral cDNA is unable to replicate. FDA-approved INSTIs are:

- bictegravir (BIC),
- cabotegravir (CAB),
- dolutegravir (DTG), and
- raltegravir (RAL).

Capsid inhibitors

- Lenacapavir is a capsid inhibitor, which interferes with the HIV capsid. It does not only disrupt the uncoating process of viral core in early HIV life cycle, but also the reassembly of viral particle in late HIV life cycle. It is a long-acting agent and can be administered either orally in weekly interval or subcutaneously in six-month interval. It is suitable to treat MDR-HIV.

Pharmacokinetic enhancers

- Cobicistat (COBI, c) is a pharmacokinetic enhancer or booster, which is combined with PIs to maximize their efficacy. In contrast to RTV, it does not have its own antiretroviral activity.

HIV cure is possible only under certain circumstance, in which PLHIV also have leukemia and need bone marrow transplantation. Initially it was assumed to only work, if the donor has a homozygous CCR5Δ32 mutation. The first case of HIV cure in a patient, who received a transplant from a wild-type CCR5 donor, was reported in 2024 (Dickter et al., 2024; Jensen et al., 2023; Noy, 2019; Sáez-Cirión et al., 2024). cART is not able to achieve cure, yet the most efficient, noninvasive and available treatment for PLHIV at this point.

HIV infection and pregnancy

Vertical transmissions of HIV from mother to child occur during pregnancy, through giving a birth and through nursing. The HIV screening test is strongly recommended for every pregnant woman and should be repeated during the pregnancy, if the partner has HIV infection. Every pregnant woman with HIV infection should be treated with cART. Early cesarean section is recommended if viral load at 36 weeks of pregnancy is not suppressed (Behrens, 2020). The risk of mother-to-child transmission can be minimized to below 0.1% if the viral load is undetectable, and below 1% if viral load is 50-400 copies/mL (Townsend et al., 2014).

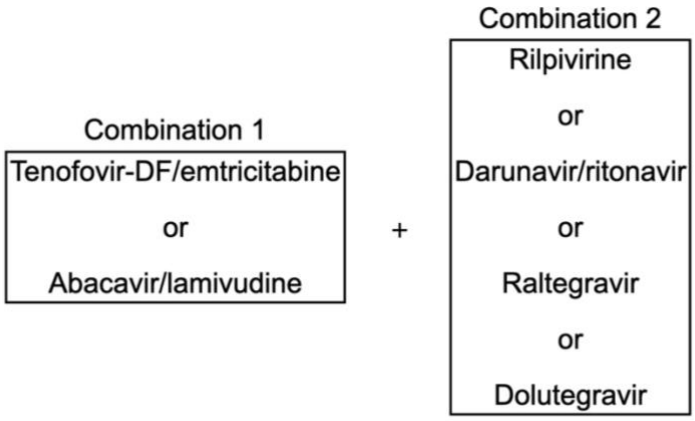


Figure 3 Examples of recommended cART regimen during pregnancy Tenofovir-DF=tenofovir disoproxil fumarate; cART in pregnancy consists of the combination 1 and combination 2. The combination of tenofovir disoproxil fumarate, emtricitabine and rilpivirine is available as single-drug regime (Behrens, 2020).

The breastfeeding should be supported if all following criteria are met (EACS, 2025b):

1. Maternal cART adherence
2. Suppressed viral load
3. Availability of regular multidisciplinary team support
4. Regular viral load monitoring during breastfeeding (every two to four weeks)

Late diagnosis

About 30% to 50% to of PLHIV are diagnosed by health care services at very late stage. Here are two definitions to identify late diagnosis (Croxford et al., 2022).

- *Late diagnosis* means that PLHIV are diagnosed with CD4 cell count below 350 cells/μL or with AIDS-defining diseases.
- *Advanced HIV disease* means that PLHIV are diagnosed with CD4 cell count below 200 cells/μL or with AIDS-defining diseases.

Purpose of the study and questions to be answered

The study focuses on the patients with advanced HIV infection, more specifically CDC Category C, to observe the surveillance outcomes. The long-term surveillance of the HIV disease under the proper treatment with cART and close clinical observation will minimize the progression of the disease and allow those patients to achieve a better prognosis. The improvement may be indicated by the reduction of viral loads followed by increase of CD4 cell counts. Another interest of the study is to reveal the cause of death and to answer if the rate of death could be reduced through surveillance in outpatient clinic.

Material and Methods

Location of the Study

The study took place in the Department of Gastroenterology, Hepatology and Infectious Diseases of the Düsseldorf University Hospital. The HIV outpatient clinic was established in 1988 and treats over 1000 patients continuously. The outpatient clinic works closely with other departments for consultations.

Severely ill patients are admitted to the infectious disease ward (MX01), to the intermediate care unit (MI03) or to the intensive care unit (MI01/MI02). The inpatient ward MX01 offers 15 beds including seven isolation rooms with negative pressure and double doors, which enable the treatment of airborne diseases such as tuberculosis.

Regular outpatient visits are offered every three months to assess clinical and laboratory findings, to prescribe medications including cART, and to switch regimens if necessary. Visits are offered in monthly interval for patients with complex cases and during pregnancy. The outpatient clinic also offers evening consultation hours.

Study Population

The cohort comprises PLHIV treated in the Department of Gastroenterology, Hepatology and Infectious Diseases of the Düsseldorf University Hospital. There are two inclusion criteria. The first criterium is to be diagnosed with HIV infection in category C according to the CDC clinical categories of HIV infection between January 1, 2012, and December 31, 2021. This also includes PLHIV who progressed to category C during above mentioned recruiting period. The second criterium is at least one outpatient visit. Exclusion criterium is lack of at least two laboratory results from two different days regarding CD4 cell count and viral load. 253 patients were recruited, and 15 patients were excluded due to the lack of sufficient laboratory results to assess the surveillance. The data from 238 patients were collected and analyzed.

Collected Data

The duration of the study, from now on called surveillance period, is ten years starting from January 1, 2012, and ending on December 31, 2021. Patients' data are obtained from electronic and paper-based hospital records and analyzed retrospectively. If HIV infection in CDC clinical category A or B was diagnosed prior to or during the surveillance period, only the data within the surveillance period and from the point of category C diagnosis are obtained.

Data obtained are listed below:

- Gender (biological)
- Onset of HIV infection
- Onset of CDC clinical category C
- Age at the onset of category C
- Beginning of surveillance (year and month)
- cART regimens
- Duration of surveillance (months)
- Cause of death
- Age at death
- Frequency AIDS defining diseases
- Viral loads (VLs)
- CD4 cell counts (CD4 counts)
- Numbers and results of pregnancies

There are three end points: 1. survived, 2. deceased (decd.) and 3. loss to follow-up (LTFU). Survived patients are those who made at least one outpatient visit in 2021 and not reported as decd. until December 31, 2021. Patients who were diagnosed with category C in 2021 and not reported as decd. are grouped into survived. Deceased patients are those, whose deaths were reported or documented with exact dates between the surveillance period, with or without causes of deaths. LTFU are those who stopped coming to outpatient visits until December 31, 2020.

Statistic

Two programs were used for statistic purpose. Microsoft 365 Excel was used for grouping, simple calculation and counting purposes.

GraphPad Prism Version 10.4.2 was used to calculate fraction of total, survival rate (Kaplan-Meier), P value (Mann-Whitney test and ordinary one-way ANOVA), and median with its interquartile range (IQR). The term “statistically significant” is used for a P value <0.05.

In case of successful viral suppression, the HIV-RNA-PCR results are shown as <20 copies/mL or <40 copies/mL. If CD4 counts are unmeasurable (low), they are omitted from laboratory results. For statistical purposes, undetectable viral loads and unmeasurable CD4 counts are entered as zero.

Approval of the Ethic Commission

All data and results obtained were treated respectfully and analyzed pseudonomously. The application for the study was handed in and approved before the data collection by the ethics committee of the Heinrich-Heine-Universität Düsseldorf with the study number 2022-1910.

Results

Overview

HIV infection in CDC clinical category C is defined by the presence of at least one AIDS-defining disease. The total of 253 patients were newly diagnosed with one or more AIDS-defining diseases and presented in the outpatient clinic in the Department of Gastroenterology, Hepatology and Infectious Diseases of the Düsseldorf University Hospital between January 1, 2012, and December 31, 2021. Among them, 15 patients were excluded by lacking two sets of laboratory results on two different days, specifically CD4 cell counts and viral loads. 238 patients were diagnosed with HIV infection in category C and visited the outpatient clinic regularly.

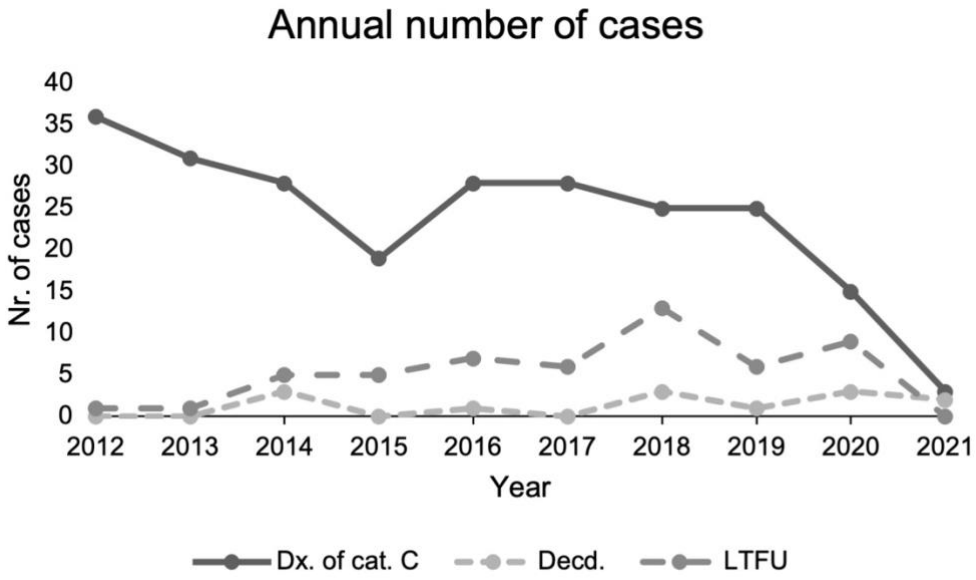


Fig. 4 Annual number of diagnosed HIV infection in category C, deaths and loss to follow-up: x-axis shows the surveillance year and y-axis shows the number (Nr.) of cases; Dx. of cat. C = Diagnosis of category C; Decd. = Deceased; LTFU = Loss to follow-up.

The number of patients who were diagnosed with HIV infection in CDC category C had a decreasing tendency, and dropped rapidly in 2020 and 2021(Fig. 4).

There are three endpoints in this study: 1. survived, 2. Loss to follow-up (LTFU) and 3. deceased (decd.). 53 patients became LTFU and 13 patiens deceased during the surveillance period, leaving 172 patients who completed the surveillance. Characteristics of patients are listed (Table 12).

	All N=238	Survived n=172	LTFU n=53	Decd. n=13
Male	186/238 (78.2%)	135/172 (79.7%)	42/53 (79%)	7/13 (54%)
Female	52/238 (21.8%)	35/172 (20.3%)	11/53 (21%)	6/13 (46%)
HIV-to-AIDS progression	74/238 (31.1%)	46/172 (26.7%)	19/53 (36%)	9/13 (69%)
Late presentation	164/238 (68.9%)	126/172 (73.3%)	34/53 (64%)	4/13 (31%)
Age in median (IQR) [years old]	44 (36-51)	45(37-51)	42 (34-48)	48 (43-56)
Surveillance period in median (IQR) [months]	48 (24-82)	62.5 (36.25-96.25)	15 (5.5-39.5)	19 (9.5-44)
VL entry in median (IQR) [copies/mL]	100,969 (3,435-380,762)	123,546 (11,187-502,997)	89,379 (358.5-212,784)	32,219 (0-234,112)
VL exit in median (IQR) [copies/mL]	0 (0-33.5)	0 (0-29)	0 (0-48.5)	0 (0-75.5)
CD4 count entry in median (IQR) [cells/μL]	79 (16.5-218)	60.5 (15-185)	120 (31.5-330)	73 (11-395)
CD4 count exit in median (IQR) [cells/μL]	435 (223-623.3)	474.5 (287.3-684.8)	247 (129-558.5)	91 (12.5-451.0)
CD4 count ≥200 achieved in median (IQR) [months]	2 (0-8)	2 (1-9)	0.5 (0-4)	0 (0-3)
CD4 count ≥500 achieved in median (IQR) [months]	17 (1-32.75)	20 (2-37)	2 (0-22)	17 (0-26.5)
VS achieved in median (IQR) [months]	4 (2-6.75)	4 (2-7)	3.5 (0.75-6)	2 (0-4)

Table 12 Characteristics of patients grouped for each endpoint: LTFU = loss to follow-up; Decd. = deceased; VL = viral load; entry = beginning of surveillance; exit = end of surveillance; IQR = interquartile range; VS = viral suppression, undetectable viral load.

The gender ratio (m:w) of the study population was 3.56 and resembles that of the German cohort for PLHIV. The study population is male dominant with 78.2% (186/ 238). The female population is 21.8% (52/238). The group of deceased patients had the gender ratio of 1.17, which is closer to the ratio of 0.88 from worldwide statistics for PLHIV.

Age of patients were measured at the beginning of surveillance. There is a significant difference (P=0.0210) in the age distributions between two genders (Fig. 5). Female patients were 40 (IQR 32.25-50.75) years old in median. Male patients were 45 (IQR 39-51) years old in median. The distributions in all three endpoints are comparable.

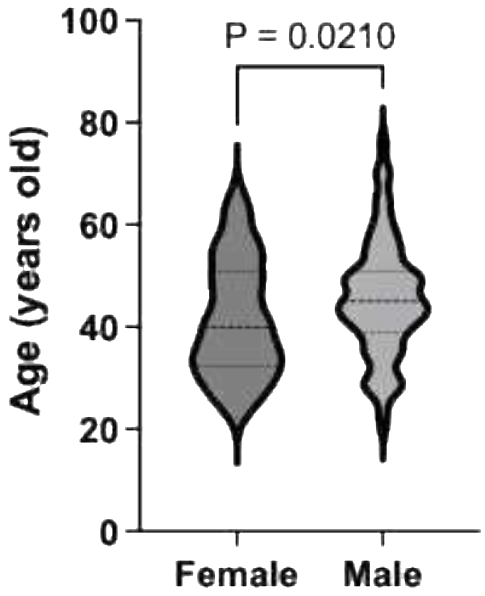


Fig. 5 Age distributions in each gender: Significant difference in age distribution between male and female population (P=0.0210)

Progressors and late presenters

The study population was divided into two groups: progressors and late presenters. The majority (164/238, 68.9%) of study population were diagnosed late and entered specialized medical services for the first time with manifesting AIDS-defining diseases. The number of late diagnoses in each endpoint group were compared. The group of survived patients comprised the largest proportion (126/164, 76.8%) of late diagnosis, and the group of deceased patients the least (4/164, 2.4%).

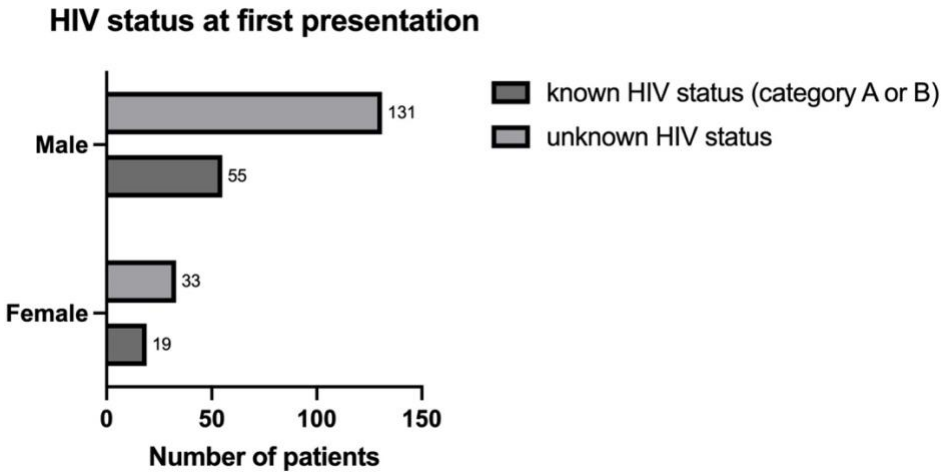


Fig. 6 HIV status at first presentation: A majority in both genders presenting with AIDS-defining diseases are not aware of their HIV status.

31.1% (74/238) of the study population fell into the group of progressors. The largest proportion (9/13, 69%) of progressors was seen in the group of deceased patients. The median rate of progression from the diagnosis of HIV infection to the onset of AIDS-defining diseases was 10.5 (IQR 3-16) years. Of the 74 progressors, 43% (32/74) of patients had undetectable VLs under cART. The proportion was the largest (4/13, 31%) in the group of deceased patients and the smallest (20/172, 11.6%) in the group of surviving patients (Table 13).

	Survived	LTFU	Decd.
Progressors	46/172 (26.7%)	19/52 (37%)	9/13 (69%)
Patients with VS	20/172 (11.6%)	8/52 (15%)	4/13 (31%)

Table 13 Proportion of virally suppressed patients among progressors in each endpoint: LTFU= loss to follow-up; Decd.=deceased; VS = viral suppression.

	25% Percentile	Median	75% Percentile
VL LP entry	38,469	131,883	585,528
VL LP exit	0.0	0.0	33
VL progressors entry	0.0	9,393	188,203
VL progressors exit	0.0	0.0	42
CD4 LP entry	18	64	172
CD4 LP exit	226	410	567
CD4 progressors entry	27	120	450
CD4 progressors exit	174	445	692

Table 14 Median viral loads (unit: copies/mL) and CD4 counts (unit: cells/μL) at the beginning and the end of surveillance: VL=viral load; LP=late presentation; entry=beginning of surveillance; exit=end of surveillance.

Surveillance period

The surveillance period was analyzed for each endpoint. The median surveillance period for all patients was 48 (IQR 24-82) months. Among survived patients, the median surveillance period was the longest with 62.5 (IQR 36.25-96.25) months. The difference among means of all endpoints was significant (P=<0.0001).

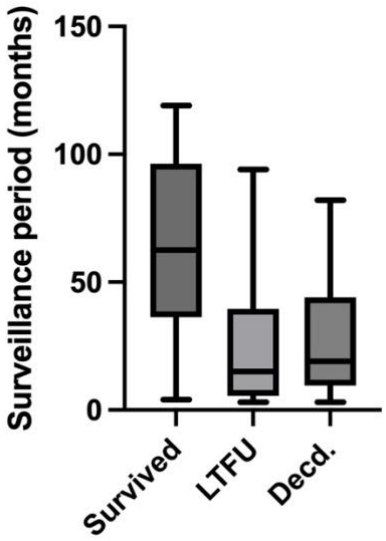


Fig. 7 Surveillance period for each endpoint: LTFU=lost to follow-up; Decd.=deceased.

Viral load

The successful viral suppression (VS) refers to undetectable viral load (VL) by HIV-1-PCR method. The median VLs at the beginning of surveillance was the highest in survived group with 123,546 (IQR 11,187-502,997) copies/mL and the lowest in deceased group with 32,219 (IQR 0-234,112) copies/mL. The median (IQR) VLs at the end of surveillance were 0 (0-29) in survived group, 0 (0-48.5) in LTFU, and 0 (0-75.5) in deceased patients. The difference among means of all endpoints was significant both at the beginning of surveillance (P=0.0001) and at the end of surveillance (P= 0.0143).

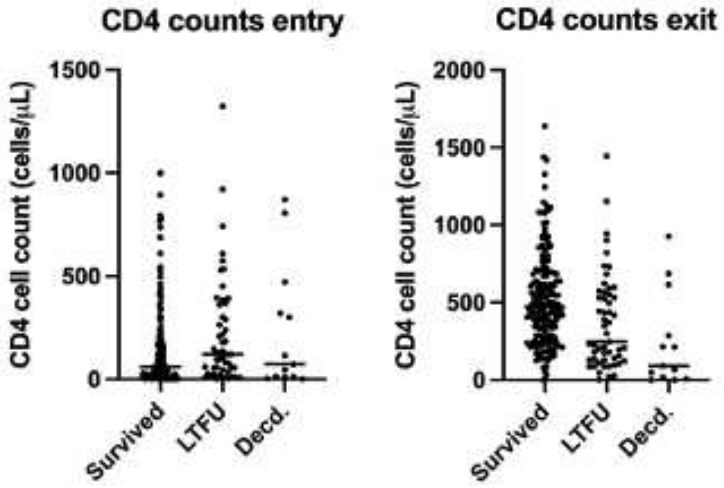
	Survived	LTFU	Decd.
VL at entry (copies/mL)			
25% Percentile	11187	359	0.0
Median	123546	89379	32219
75% Percentile	502997	212784	234112
VL at exit (copies/mL)			
25% Percentile	0.000	0.000	0.000
Median	0.000	0.000	0.000
75% Percentile	29.00	48.50	75.50

Table 15 Viral loads in median and IQR at the beginning and the end of surveillance: LTFU=loss to follow-up; Decd.=deceased; VL=viral load.

The VLs fluctuate during surveillance period. The time required to achieve VS was shorter in deceased group (Table 15). A vast majority (216/238, 90.8%) of the study population reached undetectable viral load at least once during the surveillanve period, which could be achieved in median (IQR) of 4 (2-6.75) months. At the end of surveillance, however, fewer (156/238, 65.5%) patients had successful VS. Moreover, 28.2% (67/238) of patients had detectable VLs under 200 copies/mL.

CD4 cell count

CD4 cell counts at the beginning (entry) and at the end (exit) of the surveillance of each endpoint were compared. At the entry, the median (IQR) CD4 cell count was 79 (16.5-218) cells/μL. There there was no significant difference among means of all endpoints (P=0.1782). CD4 cell counts could be improved through the surveillance, and the median (IQR) at the exit was 435 (223-623.3) cells/μL. Unlike the CD4 cell counts at the entry, the difference was significant (P=0.0002) at the end of surveillance among three endpoints.



	Survived	LTFU	Decd.
CD4 cell counts at entry (cells/μL)			
25% Percentile	15.00	31.50	11.00
Median	60.50	120.0	73.00
75% Percentile	185.0	330.0	395.0
CD4 cell counts at exit (cells/μL)			
25% Percentile	287.3	129.0	12.50
Median	474.5	247.0	91.00
75% Percentile	684.8	558.5	451.0

Fig. 8 Comparison of CD4 cell counts at the beginning and the end of surveillance: entry=beginning of surveillance; exit=end of surveillance; LTFU=loss to follow-up; Decd.=deceased. P=0.1782 at entry and P=0.0002 at exit.

There are two major goals for CD4 cell counts. The first goal is CD4 cell counts over 200 cells/μL, which is category 2 according to the CDC lymphocyte categories (Table 6). The second goal is CD4 cell counts over 500 cells/μL, which is category 1 of the CDC lymphocyte categories.

A vast majority (211/238, 88.7%) of the study population could achieve CD4 cell counts over 200 cells/μL, and the majority (128/238, 53.8%) achieved over 500 cells/μL. The time required to achieve CD4 cell counts over 200 cells/μL and over 500 cells/μL was measured in each endpoint group. The median (IQR) to achieve over 200 cells/μL was 2 (0-8) months for the entire study population. Zero month required means, that the patients already had CD4 cell counts over 200 cells/μL at the beginning of surveillance. More time was required to achieve CD4 cell counts over 500 cells/μL, and the median (IQR) was 17 (1-32.5) months. There was no significant difference between three endpoints for achieving CD4 cell counts over 200 cells/μL (P=0.2807) and over 500 cells/μL (P=0.0513).

Achievement	Survived	LTFU	Decd.
VS	167/172 (97.1%)	38/53 (72%)	11/13 (85%)
CD4 counts ≥200 cells/μL	162/172 (94.2%)	38/53 (72%)	11/13 (85%)
CD4 counts ≥500 cells/μL	103/172 (59.9%)	19/53 (36%)	6/13 (46%)

Table 16 Proportion of patients in each endpoint for achieving CD4 goals and viral suppression

Proportions of patients who achieved VS and CD4 cell counts over 200 cells/μL are nearly identical in all endpoints.

Mortality and causes of deaths

Characteristics of seven male and six female patients, who deceased during the surveillance, were analyzed. Male patients deceased at the median age of 56 (IQR 48-66). Female patients deceased younger than male patients at the median age of of 46 (IQR 38.75-56.25). There was no significant difference (P=0.07) between two genders (Fig. 9).

The majority (9/13, 69%) of patients had known HIV infection for variable time (7-28 years). 31% (4/13) of patients progressed to category C with undetectable VL under cART.

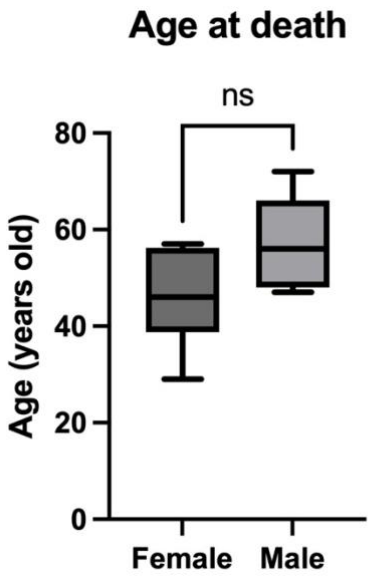


Fig. 9 Age of deceased patients in both genders

Compared to survived group, fewer percentage of deceased patients could achieve CD4 cell counts over 200 cells/µL and over 500 cells/µL, but faster with the median (IQR) of 0 (0-3) months and 17 (0-26.5) months accordingly. This, rather implausible results, may be due to the fact that the number of patients in the group is small and that about a half of them might not have died of HIV-related events.

Each deceased case was individually analyzed, if the cause of death was related to HIV infection (Table 17). Two cases of sepsis and four cases of respiratory distress could be confirmed to be related to HIV infection based on hospital records. Four cases with unknown cause could not be further determined. There were two cases of cerebral hemorrhage. The correlation of cerebral hemorrhages to HIV infection could not be confirmed. The first patient had diagnosed esophageal candidiasis, and the second patient

had non-Hodgkin lymphoma (NHL). There was no documentation of cerebral tumors in both patients. Likewise the correlation of epiglottis carcinoma to HIV infection could not be confirmed. The overall mortality of PLHIV with AIDS-defining diseases was low (13/238, 5.5%). The rate of HIV-related deaths was even lower (6/238, 2.5%).

Cause of death	Number of patients
Unknown	4
Sepsis	4
Respiratory distress	2
Cerebral hemorrhage	2
Epiglottis carcinoma	1

Table 17 Reported number and causes of death

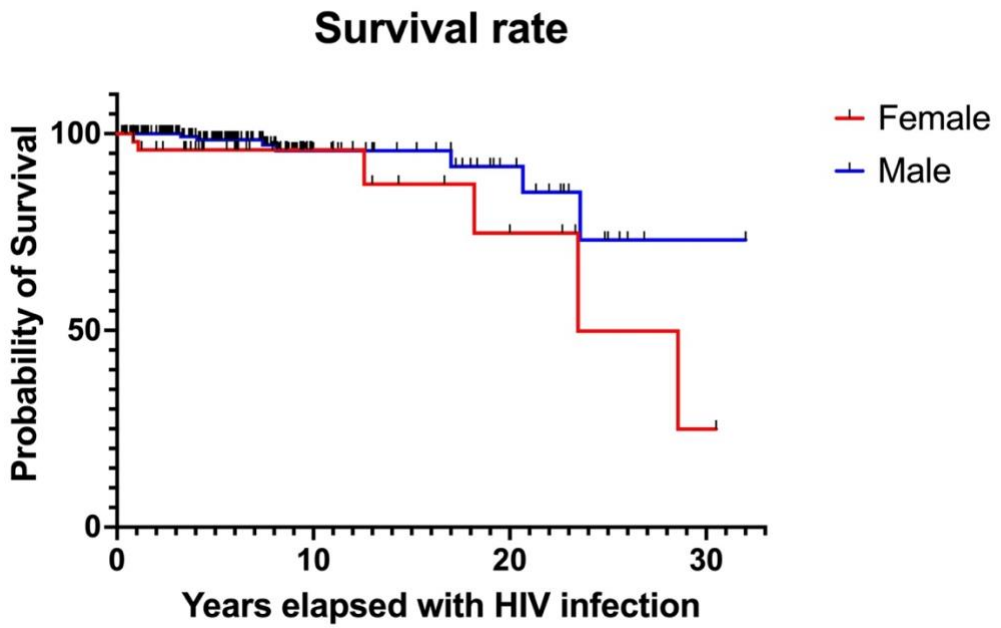


Figure 10 Survival rate for each gender since the first diagnosis of HIV infection. At year 0: male population (n= 186), female population (n= 52). At year 30: male population (n= 135), female population (n= 35).

Male patients have higher survival rate than female patients, yet both groups show survival above 30 years since the diagnosis of HIV infection.

AIDS-defining diseases

424 cases of AIDS-defining diseases were diagnosed for 238 patients during surveillance. Each AIDS-defining disease is counted only once per patient. Esophageal candidiasis has the highest rate (82/238, 34.5%). Pneumocystis jirovecii pneumonia (PJP) has the second highest rate (79/238, 33.2%).

Diagnosis	Cases	%
Esophageal candidiasis	82	34.5
Pneumocystis jirovecii pneumonia (PJP)	79	33.2
Wasting syndrome	33	13.9
Cytomegalovirus (CMV) disease: other than liver, spleen, or nodes	33	13.9
Kaposi's sarcoma	31	13.0
Herpes simplex: chronic ulcers, bronchitis, pneumonitis, or esophagitis	29	12.2
Mycobacterium tuberculosis of any site	26	10.9
Non-Hodgekin lymphoma	21	8.8
HIV related encephalopathy	18	7.6
Progressive multifocal leukoencephalopathy (PML)	17	7.1
Cerebral toxoplasmosis	16	6.7
Atypical Mycobacteriosis	8	3.4
CMV retinitis	7	2.9
Cryptococcosis	7	2.9
Recurrent pneumonia	6	2.5
Candidiasis of bronchi, trachea, or lungs	4	1.7
Chronic intestinal Cryptosporidiosis	4	1.7
Invasive cervical carcinoma	2	0.8
Talaromycosis (Penicilliosis)	1	0.4

Table 18 Occurrence of diagnosed AIDS-defining diseases in order of frequency

cART regimen

Only one patient was not prescribed cART because of tuberculosis and CD4 cell counts >50 cells/μL. 237 patients were treated with cART immediately.

Frequency of regimen changes	Number of patients	%
No change	76	31.9
Once	61	25.6
Twice	63	26.5
Three times	18	7.6
Four times	9	3.8
Five times	7	2.9
Six times	4	2.5

Table 19 Frequency of regimen changes

76 patients did not have any changes in their cART from the beginning to the end of surveillance. Among them, the three most popular regimens were:

1. Biktarvy® (TAF, FTC, BIC)
2. Truvada® + Tivicay® (TDF, FTC, DTG), and
3. Descovy® + Tivicay® (TAF, FTC, DTG).

These three regimens are also most likely to be prescribed as first-line treatment. It is common to go through the regimen change once (61/238, 25.7%) or twice (63/238, 26.5%). The reasons for switching the regimens among the study population:

- (Planning) pregnancy
- Nephrotoxicity, hepatotoxicity
- Adverse effects (allergic reaction, weight gain, hair loss, nausea, headache)
- Icterus
- Simplifying the treatment
- Intensifying the treatment
- Patient's wish
- Interaction with co-medications, chemotherapy
- Resistance, treatment failure
- Cardiovascular risk factors
- Encephalopathy

The treatment adherence is crucial for the successful viral suppression, hence the better prognosis. Simplifying the regimens is a strategy to gain treatment adherence. Patients' wishes should be respected. Patients who are suffering from severe adverse effects are also likely to stop taking their medications. Switching regimens can reduce or eliminate the adverse effect and reduces the risk of treatment discontinuation.

Regimen at the beginning of surveillance	Nr. of tabl.	Nr. of pat.	%
TDF, FTC, DTG (Truvada®+Tivicay®)	2	47	19.7
TAF, FTC, BIC (Biktarvy®)	1	33	13.9
TAF, FTC, DTG (Descovy®+Tivicay®)	2	33	13.9
TDF, FTC, DRV, r (Truvada®+Prezista®+Norvir®)	3	28	11.8
TDF, FTC, RAL (Truvada®+Isentress®)	2	15	6.3

Table 20 The popular regimens (n≥10) at the beginning of surveillance

Regimen at the end of surveillance	Nr. of tabl.	Nr. of pat.	%
TAF, FTC, BIC (Biktarvy®)	1	69	29.0
ABC, 3TC, DTG (Triumeq®)	1	26	10.9
TDF, FTC, DTG (Truvada®+Tivicay®)	2	22	9.2
TAF, FTC, DRV, c (Symtuza®)	1	18	7.6
DTG, 3TC (Dovato®)	1	13	5.5
TAF, FTC, DTG (Descovy®+Tivicay®)	2	13	5.5
TDF, FTC, RAL (Truvada®+Isentress®)	2	10	4.2

Table 21 The popular regimens (n≥10) at the end of surveillance

Two tables above (Table 20, Table 21) show that one-drug or two-drug regimens became more popular at the end of surveillance. Biktarvy® (TAF, FTC, BIC) is a single-drug regime, which was most chosen (69/238, 29%).

Pregnancy and delivery form

HIV outpatient clinic offers monthly clinical and laboratory monitoring throughout the pregnancy. Six pregnancies from five women were documented (Table 22). All of them were treated with TDF/FTC/RAL and were virally suppressed. Two pregnancies resulted in miscarriages and four babies were delivered by cesarean section. There was no vaginal delivery. There was no documentation regarding breast feeding. Three patients became loss to follow-up and two patients remained in care until the end of surveillance.

Type of delivery	Cases	%
Miscarriage	2	33
Vaginal delivery	0	0
Cesarean section	4	67

Table 22 Reported cases of pregnancy and their delivary type

Discussion

Recap

The aim of the study was to analyse, how much long-term surveillance through regular outpatient visits improves the outcome of PLHIV with AIDS-defining diseases i.e. CDC clinical category C. The data from 238 patients, who were diagnosed with HIV infection category C between January 1, 2012, and December 31, 2021, were analyzed. The number of patients who were diagnosed with HIV infection in CDC category C each year had a decreasing tendency, and declined rapidly in 2020 and 2021. The decline in the number of PLHIV with AIDS-defining diseases in 2020 and 2021 may be affected by corona pandemic. Limited access to elective medical counsultation, limited social contact and limited mobility are possible factors (Robert Koch-Institut, 2024a). The number of confirmed HIV tests in Germany also declined in 2020 and in 2021, followed by an increase in 2022 (Table 3). Moreover, the diagnosis of HIV infection could have been delayed due to the similarity of initial flu-like symptoms (Suchacz et al., 2022).

The study population was divided into two groups: late diagnosis and progressors. The majority (164/238, 68.9%) of study population were diagnosed late. In Germany, the proportion of late presenters in PLHIV, who are diagnosed with HIV for the first time, reaches nearly 50%. PLHIV with late diagnosis are known to have worse prognosis, hence higher mortality, than those who are diagnosed and receive cART at early stage of HIV infection (Delpech & Lundgren, 2014; Zoufaly et al., 2012). The data from this study shows that PLHIV with late diagnosis do not necessarily have higher mortality. Of 172 patients who survived and achieved surveillance period of 62.5 (36.25-96.25) months in median (IQR), 126 patients were diagnosed late (73.3%). Most patients who are diagnosed late with category C require an intensive in-patient treament. The fact that this study only includes the population who recovered and could be discharged should be taken in consideration to interpret the result. Only 1.7% (4/238) of the study population have been diagnosed late and deceased. Rather the majority (9/13, 69%) of those who deceased were progressors. Unfortunately, the progression of HIV disease can occur even for patients who are virally suppressed (Pantke et al., 2023). Of 72 progressors, 43% (32/74) had undetectable VLs. The median rate of progression from the diagnosis of HIV infection to the onset of AIDS-defining diseases was 10.5 (IQR 3-16) years.

Viral load is used to monitor HIV infection to observe treatment failure. VL is used to predict disease progression, and higher baseline viral load at the initiation of cART or higher viral exposition during surveillance is related with higher mortality in PLHIV (Palella et al., 2021; Zhou et al., 2022). Opposingly, in this study, higher baseline VL was not associated with higher mortality in PLHIV. The median VL at the beginning of surveillance was the highest in survived group of patients with 123,546 (IQR 11,187-502,997) copies/mL and the lowest in deceased group of patients with 32,219 (IQR 0-234,112) copies/mL. This unexpected result may be due to the huge difference in the number of patients in two cohort and also due to the very small number of deceased patients. This also applies to the interpretation of CD4 cell baseline. Most (216/238, 90.8%) patients reached undetectable VLs in median (IQR) of 4 (2-6.75) months.

Likewise, a vast majority (211/238, 88.7%) of patients achieved CD4 cell counts over 200 cells/μL in median (IQR) of 2 (0-8) months. The number of patients who achieved CD4 cell counts over 200 cells/μL resembled the number of patients who achieved viral suppression (VS). Compared to the threshold of 200 cells/μL, it took longer to achieve CD4 cell counts over 500 cells/μL. Fewer, but the majority (128/238, 53.8%) of patients achieved CD4 cell counts over 500 cells/μL in median (IQR) of 17 (1-32.5) months. The achievement of VS and CD4 cell count over 200 cells/μL seems to correlate. Similar to VL, CD4 cell count has a predictive value in HIV surveillance. Higher baseline CD4 cell count is associated with greater chance of achieving normal CD4 cell count and reducing mortality in PLHIV (Palella et al., 2016). Contrariwise, the study population showed the lowest baseline CD4 cell counts in the group of survived patients with median (IQR) of 60.5 (15-185) cells/μL. In the group of deceased patients, it was 73 (11-395) in median (IQR). Interestingly, CD4 cell counts in deceased patients barely improved although VL was undetectable. On the other hand, CD4 cell counts in the group of survived patients made clear improvement. Rather than the baseline CD4 cell count, the resulting CD4 cell count under cART showed correlation to mortality (Maduna et al., 2015).

The mortality of PLHIV with AIDS-defining diseases was 5.5% (13/238) in median surveillance period of 48 (IQR 24-82) months. Of 13 cases, only 2.5% (6/238) were defined as HIV-related deaths. Unknown causes of death could not be further investigated retrospectively. The gender ratio of deceased patients in the study population was 1.17. In european cohort including Germany, deceased patients have similar gender ratio to that

of overall PLHIV. It is shown that PLHIV who started on ART at the age of 40 with CD4 cell count < 50 cells/uL has a life expectancy of 24.9 years for female population and 23.7 years for male popukation. The life expectancy depends on gender, CD4 cell count, the way of transmission, the age at the initiation of ART and the year of the ART initiation (Trickey et al., 2023). Male patients deceased at the median age of 56 (IQR 48-66), and female patients deceased younger than male patients at the median age of 46 (IQR 38.75-56.25). The study population deceased much younger than it was expected.

The two most common occuring AIDS-defining diseases were esophageal candidiasis and Pneumocystis jirovecii pneumonia (PJP), affecting 34.5% (82/238) and 33.2% (79/238) of study population accordingly. In German cohort between 1999 and 2018, who developed AIDS-defining events under cART, the most common AIDS-defining diseases were esophageal candidiasis and wasting syndrome. PJP could have been reduced due to the prophylactic treatment (Pantke et al., 2024).

Biktarvy® (TAF, FTC, BIC) was the most chosen regime (69/238, 29%) at the end of surveillance, which is a single-drug regime consisting of two non-nucleoside reverse transcriptase inhibitors and one integrase inhibitor. Concerning the forgiveness, which is the ability of a HIV drug to assure viral suppression in case of incomplete adherance to the treatment, Biktarvy can maintain VS in patients who miss up to 30% of their medication intake. This could be a useful strategy to reduce the treatment failure in case of partial adherence to the cART (Maggiolo F et al., 2022).

Six pregnancies were reported during the surveillance period. All pregnant patients were treated with TDF/FTC/RAL and virally suppressed. Two pregnancies resulted in miscarriages and four babys were born by cesarean sections. Current guideline in Germany suggests to support vaginal delivary, if maternal VL is suppressed under cART, but there was no vaginal delivary reported (Behrens, 2020; Eke et al., 2023). Other medical indications to cesarean section could not be obtained retrospectively. Furthermore, causes of miscarriage could not be determined.

Limitations

The data collection was limited by its retrospective mode of analysis. The population of deceased patients was extremely small compared to the survived group. This is mainly because the patients who deceased during the first hospitalization and never made it to the out-patient clinic are not included in the study. Because of that, all patients included in the study are “survived” patients who recovered at least once from severe AIDS-defining diseases. Causes of death could not be sufficiently analyzed, but only few of them died obviously of HIV- or AIDS-associated causes. For those who knew their HIV status and progressed to category C, the timing of cART initiation was uncertain or documented only partially. The median surveillance period was 48 (IQR 24-82) months, which suggests that the surveillance for patients who were diagnosed with category C between 2018 and 2021 was most likely to be incomplete.

Conclusion

As a result of comprehensive surveillance through regular outpatient visits, the median surveillance period of 48 (IQR 24-82) months could be achieved. Knowing that PLHIV with low CD cell counts could have a life expectancy over 20 years from the age of 40 if treated, the surveillance period was much shorter and most likely incomplete. The rate of HIV-related deaths in PLHIV with AIDS-defining diseases was low with 2.5% (6/238). Higher baseline viral load does not indicate higher mortality, which suggests that baseline VL is not a good mortality predictor. Viral suppression and improvement of CD4 cell count over 200 cells/µL can both be achieved quickly and have a strong correlation to each other. In this study, lower baseline CD4 cell count indicated neither higher mortality nor lower resulting CD4 cell count at the end of surveillance. This may be due to the very small number of deceased patients with less variable CD4 cell counts compared to the survived patients. Deceased patients have, however, hardly improved their CD4 cell count under cART, resulting in lower CD4 cell count at the time of death. Future work should focus on characterizing patients, whose CD4 cell count does not improve under cART, for instance, comorbidity, co-infections, co-medications, body-mass-index, physical activity and so on.

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