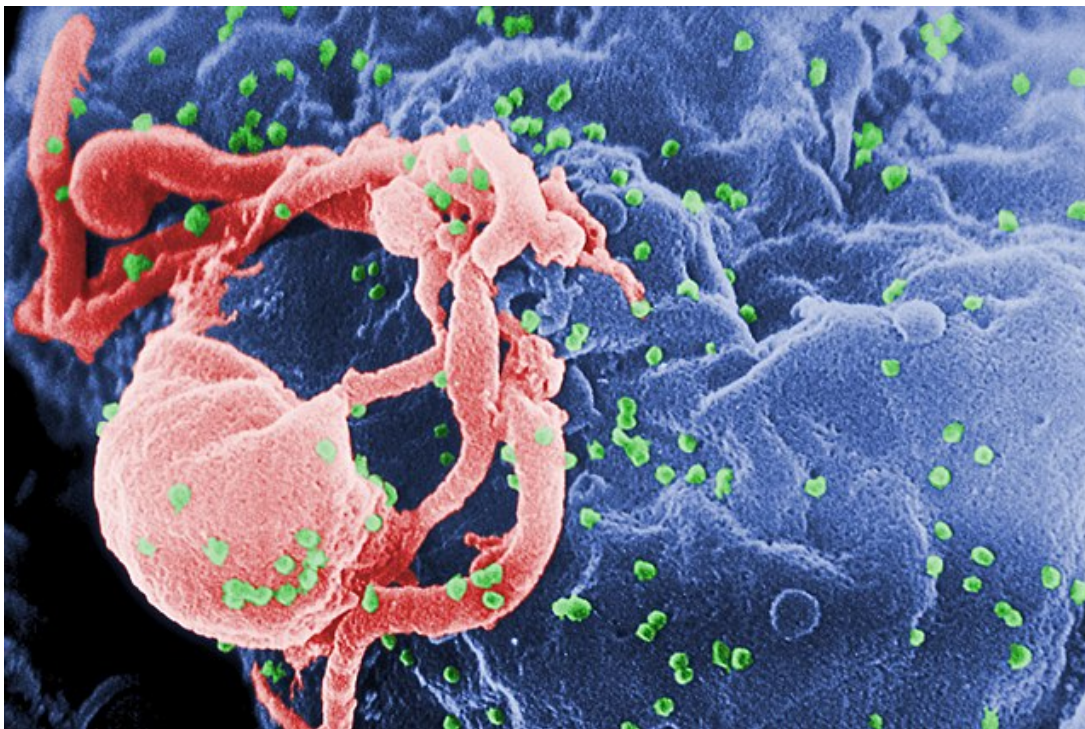


AIDS (Human Immunodeficiency Virus, HIV) — Etiology, Stages and Prognosis

[See online here](#)

Human immunodeficiency virus (HIV) infection is caused by a single-stranded RNA virus of the *retroviridae* family. It is transmitted through the exchange of body fluids such as semen and blood. The presentation is marked by a deterioration of the immune system beginning with constitutional symptoms, such as lymphadenopathy, and advancing into AIDS-defining illnesses, such as opportunistic infections.



Definition and Overview of AIDS

HIV (Human Immunodeficiency Virus) is a blood-borne virus transmitted through unprotected sexual contact, infected intravenous injections or transfusion and mother to child during birth process and breastfeeding. It causes an acquired immune deficiency and has different latency periods from individual to individual. Immune deficiency depends primarily on the progressive destruction of CD-4 Helper T cells.

Acquired Immune Deficiency Syndrome (AIDS) describes the late stages of HIV infection and is characterized by opportunistic diseases (AIDS-defining diseases). To date, there is no causal therapy for the disease.

The **antiretroviral therapy HAART** has presented at the world AIDS congress in

Vancouver in 1996, 15 years after the first report about AIDS in the “Morbidity and Mortality Weekly Report”. Due to further development and increased availability of the treatment, the worldwide morbidity rate was able to be massively reduced. There were 1.5 million deaths due to the disease in 2013, whereas in the middle of the previous decade, that figure was still 2.2 million.

Epidemiology of AIDS

Strong prevalence of AIDS in West Africa

According to [UNAIDS](#), the last major wave of infection in the USA occurred in the 1980s. Large-scale campaigns promoting “Safer Sex” helped to reduce the number of new cases by 1990. An estimate in 2010 suggested there were 33 million infected people worldwide, and 2.6 million new cases each year (UNAIDS).

Worldwide: The most affected area in the world is sub-Saharan Africa approximately 5.2 % of the population. HIV-1 is a pandemic and is primarily found in West Africa. In Eastern Europe, the number of new cases has dramatically increased by 21 % in the last few years. Swaziland has the highest overall prevalence of HIV infection.

USA: (2017) Although more females are infected worldwide, bisexual males are primarily affected in the USA. Each year there are approximately 38,700 new cases diagnosed in the United States alone.

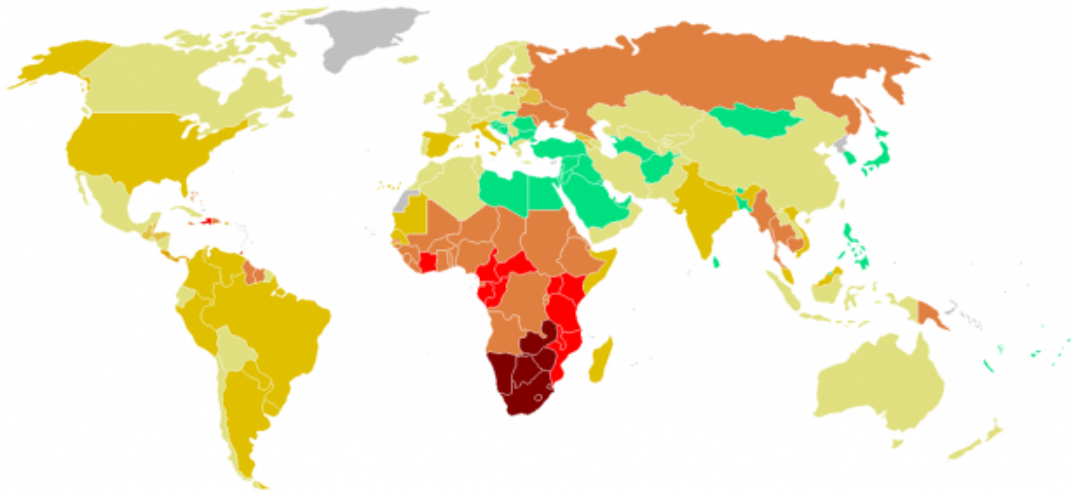
Germany: Men are the most affected with about 65,000 infected (Germany, 2013), women 15,000. About 3,000 women are newly diagnosed each year.

Age-sex race-related differences in incidence

HIV infection is observed highest among the Hispanic persons probably due to socioeconomic factors rather than genetic causes.

Males are more likely to acquire HIV infection in the United States. In developing countries, males have more predilection towards HIV infection.

Young adults are at the highest risk of the disease exposure as they are highly involved in unprotected sexual intercourse. Children acquire infection through mother by trans parental transmission and breastfeeding.



Percentage of adults that are infected with HIV per country at the end of 2005. Dark red: 15-50% (15-50 people out of 100), Red: 5-15% (5-15 people out of 100), Orange: 1-5% (1-5 people out of 100), Dark yellow: 0.5-1.0% (1-2 people out of 200), Yellow: 0.1-0.5% (1-5 people out of 1000), Green: < 0.1% (less than 1 person out of 1000), Grey: Greenland no data

Etiology and Pathogenesis of AIDS

AIDS pathogens



Picture: "Stereoview of superposition of the C α atoms of the HIV-1 PR protomer (PDB entry 3hvp, red) on monomer A of M-PMV PR in the crystal structure (green)." by Openi. License: [CC BY 2.0 UK](https://creativecommons.org/licenses/by/2.0/)

- **HIV virus:** genus *Lentivirus*, family *Retroviridae*, single-stranded, enveloped RNA. HIV-1 is the most common species worldwide, while HIV-2 is restricted almost completely to West Africa and doesn't lead to AIDS.
- [See Retroviridae: HIV](#)
- It is found in bodily fluids, especially **blood, sperm, vaginal secretions and breast milk.**
- There are **3 methods of HIV transmission:**
 - Sexual: unprotected sex is responsible for 80% of infections
 - Parenteral: intravenous drug use and sharing needles, accidental needle punctures in medical professionals
 - Vertical: mother to child during pregnancy, delivery, or breastfeeding
- **Biological factors:**
 - Viral load: transmission unlikely if < 400 copies/ml, nearly impossible <50 copies/ml
 - Type of sexual contact: receptive anal sex is the most high-risk, circumcision reduces risk
 - Mucosal damage: inflammation, tears, infection (STIs), and irritation of the genital mucous membranes increase risk
 - Recent HIV infection: high risk of transmission due to high viral load

HIV-1 and **HIV-2** are **retroviruses** belonging to the lentivirus genus. They are cuboid, enveloped viruses with linear (single strand) RNA. Genetic information is stored in the

RNA: **reverse transcriptase** from the human host is used to transcribe the RNA into protein-coding DNA.

The target cells are all CD4 receptor-carrying cells:

- **T-Helper Cells**
- **CD4 positive monocyte cells:** Monocytes, macrophages, and dendritic cells.

HIV enters the Langerhans cells through mucous membrane defects and is then further transported to the lymph nodes. The virus penetrates the T-Lymphocytes through their CD4 receptors and destroys them. The virus spreads through the rest of the body through lymphatic vessels. This results in severe immune deficiency with the risk of contracting major opportunistic infections.

Note: A sufficient immune response can no longer be raised at counts of $< 400/\mu\text{l}$.

Transmission of HIV

All bodily fluids contain the Human Immunodeficiency Virus in varying quantities. The most significant amounts are found in **blood, sperm, vaginal secretions** and **breast milk**. The likelihood of transmission depends upon the virus load.

Sexual Transmission

The most common route of infection is homosexual intercourse in males followed by infection via heterosexual intercourse. In these cases, the risk of infection depends on the size of the virus load in the secretions exchanged.

Note: the Ejaculated fluid has a significantly higher concentration of HIV than vaginal secretion, so women have a higher risk of contracting the virus through unprotected sexual intercourse

Parenteral Transmission

The third most common method of transmission is from intravenous drug abuse (7,800) with the practice of sharing needles. Transmission within medical professions may occasionally occur through accidental needle puncture with an infected needle.

Vertical Transmission

Trans-placental mother-child transmissions are infrequent (1 in 1 million). It occurs during pregnancy or birth.

Incubation period for HIV

The incubation period is between **three and six months** and is usually not apparent during the first two months. In 6 % of infections, the disease becomes AIDS after around two years.

CDC Stages of HIV Infection

The CDC (Center for Disease Control) stages allow for classification of the progression of the disease in combination with the Helper T-Cell count. The normal value for helper T-lymphocytes is **650 - 1250/ μl** .

| | |
|------------|---|
| A1, B1, C1 | Helper T Lymphocytes $> 500/\mu\text{l}$ |
| A2, B2, C2 | Helper T Lymphocytes 200 - 499/ μl |
| A3, B3, C3 | Helper T Lymphocytes $< 200/\mu\text{l}$ |

Stage A

There are three stages. Stage A can be accompanied by an influenza-like symptom complex (50—90 % also suffer from **acute retroviral syndrome** – fever, angina, lymphadenopathy, exanthema, muscle and joint pain), however, even completely asymptomatic patients (**latent phase**) suffer from reduced performance, symptoms of exhaustion such as tiredness and lethargy.

Lymphadenopathy syndrome is defined as generalized lymph node swelling for longer than three months.

Stage B

This stage is asymptomatic and chronic in nature. The patient does not exhibit any symptom. HIV is still active and reproduced at a very low level. The disease is still transmittable in this stage. Those patients who are on ART can remain in this stage for decades and are not contagious.

Stage C: AIDS-defining diseases

AIDS is the most severe phase of HIV infection with a deteriorated immune system and severe illness. Patients having AIDS can exhibit a high viral load and can be highly infectious. The pathogen spectrum of opportunistic infections that do not cause infection in immunocompetent people is far reaching.

- **Wasting Syndrome** with significant cognitive and vigilance impairment, depression and ataxia
- **Encephalopathy associated with HIV:** slowly progressing dementia with deficits in emotion, cognition and motor skills due to progressive CNS inflammation

Amongst the known AIDS-defining diseases are :

- Herpes Zoster
- **Candidiasis**
- Oral hairy leukoplakia
- Chronic **diarrhea**
- Changes in the blood count with **anemia**, **thrombocytopenia**, and neutropenia
- Infections with **molluscum contagiosum**
- Tubo-ovarian abscesses
- Listeriosis

Bacterial infections

- **Tuberculosis**
- Cerebral **Toxoplasmosis** (most common neurological AIDS Manifestation)
- Salmonella septicemia

Mycotic and parasitic infections



Picture: "This patient presented with a secondary oral pseudomembranous candidiasis infection." by Sol Silverman, Jr., D.D.S.. License: [Public Domain](#)

- **Pneumocystis jirovecii pneumonia**
- Cryptococcal meningitis
- **Candidiasis**
- Coccidioidomycosis (extrapulmonary/disseminated)

Viral infections

- Cytomegalic manifestations
- **Herpes Simplex Encephalitis**
- Progressive multifocal Leukoencephalopathy (triggered by the JC virus, John Cunningham virus, a type of human polyomavirus (formerly known as papovavirus))

AIDS-defining malignancies



- **Kaposi's sarcoma** on the skin of an AIDS patient." by National Cancer Institute. License: [Public Domain](#)

Non-Hodgkin's Lymphoma of the B Cell type

- **Cervical carcinoma**
- Kaposi sarcoma (associated HHV8)
- Invasive cervical carcinoma and anal carcinoma

Diagnosis of AIDS

Anamnesis and clinical examination of AIDS

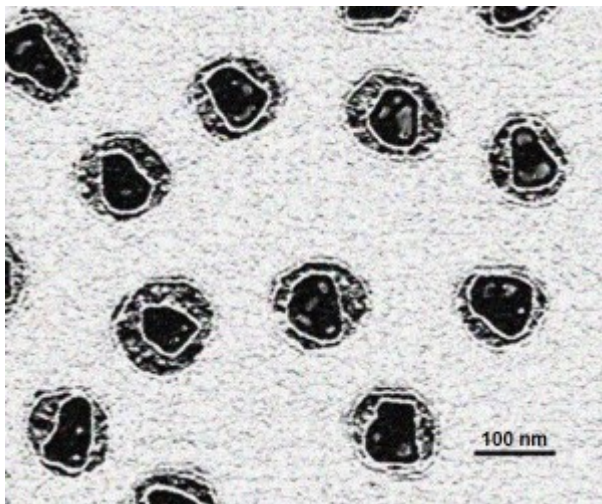
The anamnesis should focus in particular on health complaints, medication, travel, and sexual history. The clinical examination should particularly focus on weight, lymph node status and opportunistic infections.

Pathogen identification and CD4 cell count

Indirect viral screening

- **Screening test:** Antibody screening with HIV ELISA. ELISA has a high sensitivity but not 100 % specificity. A positive test result requires further testing to confirm the findings.
- **Confirmatory test: Western blot.** The western blot test has a very high specificity but despite that, **a second positive confirmatory test should be performed** before giving the results back to the patients.

Direct virus identification



Picture: "Micrograph from a transmission electron microscope of HIV Retrovirus, sample taken of diluted infectious serum, isolated" by [PhD Dre](#) at [en.wikipedia](#). License: [CC BY-SA 3.0](#)

Direct identification of HIV can be done by electron microscopy, virus isolation, and **PCR testing**.

Virus quantification

Virus quantification via PCR serves as a therapeutic device and also for monitoring purposes. The **detection limit is 20–50 copies/ml**.

Determination of the CD4 Helper T Lymphocyte count

The amount of CD4 Helper T Lymphocytes can be determined via flow cytometry. The CD4 count is a component of CDC classification.

Note: The CD4 Helper T Lymphocyte count and virus quantification are parameters which allow a judgment of the extent of the immune deficiency.

Differential Diagnosis

| Stage | Possible differential diagnosis | Landmark studies |
|---------------------------|---|--|
| Acute retroviral syndrome | <ul style="list-style-type: none"> • Mononucleosis • Unspecified viral infection • Drug allergy | <ul style="list-style-type: none"> • EBV-Serology • HIV-PCR • Drug anamnesis |
| Lymphadenopathy syndrome | <ul style="list-style-type: none"> • Tuberculosis • Malign lymphoma • Toxoplasmosis | <ul style="list-style-type: none"> • Lymph node biopsy • Toxoplasmosis serology |
| Opportunistic infections | <ul style="list-style-type: none"> • Primary (congenital) immune defect • Secondary (acquired) immune defect of other origins | <ul style="list-style-type: none"> • Anamnesis • Exclusion of other causal diseases such as immunosuppressive therapy or hematologic neoplasia |

Source: Genzwürker et al. (2014): *AlLEX – Alles fürs Examen*. Thieme Verlag, p. 533.

Therapy of AIDS

Antiretroviral Treatment for AIDS prevention

In the USA, around 57 % of the HIV/AIDS budget is used for antiretroviral treatment. The current recommendation for initiation of HAART is a lower limit for the Helper T-Cell value of **200/ μ l**. It has been argued that it should begin as early as **200—350/ μ l**.

Currently, **HAART (highly active antiretroviral therapy)** consists of at least three antiretroviral drugs used to treat HIV infection: two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). The term HAART is presently being replaced by **cART (combined anti-retroviral therapy)** as this term better describes the combination of drugs used.

- **2 Nucleoside reverse transcriptase inhibitors (NRTI):** Zidovudine (AZT), Lamivudine, Abacavir
- **1 Non-nucleoside reverse transcriptase inhibitor (NNRTI):** Nevirapine, Efavirenz
- **1 Protease Inhibitor (PI):** Indinavir, Ritonavir, Nelfinavir, Lopinavir
- **1 Integrase Inhibitor:** Raltegravir

Chemoprophylaxis: In order to avoid an outbreak of opportunistic infections, chemoprophylaxis is carried out consisting of co-trimoxazole (for *pneumocystis jirovecii* pneumonia and toxoplasmosis) and isoniazid (for tuberculosis)

A detailed overview of antiretroviral therapy can be found in “Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents”.

Side effects

Among the undesirable side effects of antiretroviral therapy are:

- Bone marrow depression
- Polyneuropathy
- [Headaches](#), nausea
- [Hypersensitivity reactions](#)
- [Diarrhea](#)
- Nephrotoxicity
- Transaminases
- Exanthema

Complications

Metabolic changes are most commonly observed during treatment with cART/HAART: Lipoatrophy, lipodystrophy, impaired **glucose tolerance** (IGT), [diabetes mellitus](#) and hyper- or dyslipidemia. These changes are associated with an increased cardiovascular risk.

Prophylaxis

How AIDS can be avoided

- “Safer sex” (Using condoms)
- Education for the general public
- Avoiding sexual intercourse with unknown and promiscuous partners
- Use of sterile instruments for drug abuse
- In medical professions: protective gloves, face masks, and protective glasses

Post-Exposure Prophylaxis (PEP)

In the case of **accidental** contact with exposure to the mucous membranes or parenteral contact with potentially HIV containing materials, PEP can be considered within 72 hours of exposure to HIV. The risk of infection due to a percutaneous injury: 1 in 300.

Immediate PEP with antiretroviral drugs has been proven to be effective in case-control studies. PEP does not only play an important role in medical professionals, but it has also been successfully used after unprotected sexual intercourse (i.e. following a rape) or after patients have shared needles during drug abuse.

Note: The risk of HIV infection following a needlestick injury can be reduced by 80 % if the antiretroviral therapy is started within 2 hours of the accident.

Prognosis of AIDS

The mortality rate of untreated HIV is poor up to more than 90 %. The average survival time from infection to death is 8-10 years in untreated cases. Once it has advanced to AIDS, the survival time reduces to less than 2 years. Mortality is higher in intravenous drug users.

Access to drugs determines the progression of AIDS

Since the introduction of **antiretroviral therapy**, the life expectancy of HIV patients has drastically changed.

However, this is only the case if two main points are observed in patients:

- Access to drugs
- Compliance

The **Swiss Cohort Study**, initiated in 1988 was able to determine that only 9 % of HIV patients died from AIDS, while 24 % died from AIDS-defining cancers. The [Swiss Cohort Study \(SHCS\)](#) is a longitudinal study within Swiss university hospitals, Canton hospitals and practicing doctors who treat HIV patients. Its primary aim is to “provide optimal patient care, reduce HIV transmission and to conduct research”. This progress is naturally not in line with the global situation, where the majority of patients still have no access to the necessary drugs.

Review Questions

Answers can be found below the references.

1. Which of the following groups of drugs does not belong to the antiretroviral AIDS treatments?

- A. Nucleoside Reverse Transcriptase Inhibitors

- B. Non-Nucleoside Reverse Transcriptase Inhibitors
- C. Transferase Inhibitors
- D. Protease Inhibitors
- E. Integrase Inhibitor

2. Which of these diseases is typical for stage C in the CDC stage classification system for HIV infection?

- A. Oral hairy leukoplakia
- B. Chronic diarrhea
- C. Tubo-ovarian abscesses
- D. Listeriosis
- E. Cryptococcal Meningitis

3. HIV is a retrovirus. Which group do retroviruses belong to?

- A. Hantaviruses
- B. Lentiviruses
- C. Flaviviruses
- D. Rhadinoviruses
- E. Rubiviruses

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U.S. Statistics -<https://www.hiv.gov/hiv-basics/overview/data-and-trends/statistics>

Correct answers: 1C, 2E, 3B

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