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

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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

Human immunodeficiency virus (HIV) is a blood-borne virus transmitted through unprotected sexual contact, infected intravenous injections or blood transfusion, and during birth and breastfeeding. It induces acquired immune deficiency with the latency period varying between individuals. Immune deficiency depends primarily on the progressive destruction of CD-4 T-helper cells.

Acquired immune deficiency syndrome (AIDS) refers to the late stages of HIV infection and is characterized by opportunistic (AIDS-defining) diseases. To date, there is no causal therapy for the disease.

Antiretroviral therapy HAART was first presented at the 1996 World AIDS congress.
held in Vancouver, 15 years after the first report about AIDS was published in the ‘Morbidity and mortality weekly report’. Due to advances in research and treatment of AIDS, the worldwide morbidity rate has been massively reduced. Compared with nearly 2.2 million AIDS-related deaths in the middle of the last decade, 1.5 million deaths were recorded in 2013.

Epidemiology of AIDS

Increased 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’ led to a reduction in the number of new cases by 1990. In 2010, there were an estimated 33 million infected patients worldwide, with 2.6 million new cases recorded each year (UNAIDS).

Worldwide: Sub-Saharan Africa is the most affected area in the world with 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 dramatically increased by 21% in the last few years. Swaziland has the highest overall prevalence of HIV infection.

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

Age, gender, and race-related differences in incidence

HIV infection is the highest among 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 disease exposure as they engage in unprotected sexual intercourse. Children acquire infection from mother at birth and subsequent breastfeeding.
Etiology and Pathogenesis of AIDS

AIDS pathogens

- **HIV virus** is a single-stranded RNA virus belonging to the genus *Lentivirus* under family Retroviridae. HIV-1 is the most common species causing AIDS worldwide unlike HIV-2, which is restricted almost completely to West Africa and does not lead to AIDS.
- It is found in body fluids, especially **blood, semen, vaginal secretions, and breast milk**.
- The **three modes of HIV transmission** are:
  - Sexual transmission via unprotected sex responsible for 80% of infections
  - Parenteral transmission via intravenous drug use and sharing needles, and accidental needle puncture by medical professionals
  - Vertical transmission from mother to child during pregnancy, delivery, or breastfeeding

**Biological factors**

- Viral load < 400 copies/mL reduces the chances of viral transmission, which is almost impossible at < 50 copies/mL.
- Type of sexual contact: Receptive anal sex is the most high-risk biological factor, and circumcision reduces the risk.
- Mucosal damage including inflammation, tears, infection (STIs), and irritation of the genital mucous membranes increases the risk.
- Recent HIV infection elevates the 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-stranded) RNA. Genetic information is stored in the RNA, which is transcribed to protein-coding DNA by **reverse transcriptase** in the host (human) cells.

The target cells are all CD4 receptor-bearing cells:

- **T-helper cells**
- **CD4-positive monocytes**, macrophages, and dendritic cells

HIV enters the Langerhans cells via a defective mucous membrane and is then 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 via lymphatic vessels, resulting in severe immune deficiency, which increases the risk of major opportunistic infections.

**Note**: Sufficient immune response can no longer be generated at counts of < 400/µl.
**HIV transmission**

Upon infection, all body fluids carry 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 viral load.

**Sexual transmission**

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

**Note**: The ejaculate 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 via intravenous drug abuse (7,800) using shared needles. Transmission within the medical profession may occasionally occur through accidental needle puncture with an infected needle.

**Vertical transmission**

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

**Incubation period**

The incubation period varies 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**

According to the Centers for Disease Control and Infection (CDC, USA), the HIV stages are used to classify the progression of disease in combination with the T-helper cell count. The normal T-helper lymphocyte count ranges between **650 and 1250/μl**.

<table>
<thead>
<tr>
<th>Stage</th>
<th>T-helper lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1, B1, C1</td>
<td>&gt; 500/μl</td>
</tr>
<tr>
<td>A2, B2, C2</td>
<td>200 - 499/μl</td>
</tr>
<tr>
<td>A3, B3, C3</td>
<td>&lt; 200/μl</td>
</tr>
</tbody>
</table>

**Stage A**

There are three stages. Stage A is 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 and symptoms of exhaustion such as tiredness and lethargy.

**Lymphadenopathy syndrome** is defined as generalized lymph node swelling lasting longer than three months.
Stage B

Stage B is asymptomatic and chronic in nature. The patient does not exhibit any symptoms. HIV is still active and reproduced at a very low level. The disease is still transmitted in this stage. Patients who are on ART may remain in this stage for decades and are not contagious.

Stage C: AIDS-defining diseases

AIDS is the most severe phase of HIV infection characterized by a deteriorated immune system and severe illness. Patients with AIDS exhibit a high viral load and are highly infectious. The spectrum of opportunistic infections that do not cause disease in immunocompetent people is diverse.

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

Some of the known AIDS-defining diseases are:

- Herpes Zoster
- **Candidiasis**
- Oral hairy leukoplakia
- Chronic **diarrhea**
- Changes in 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**

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

**Viral infections**

- Cytomegalic manifestations
- **Herpes simplex encephalitis**
- Progressive multifocal leukoencephalopathy (triggered by John Cunningham virus, which is a type of human polyomavirus (formerly known as papovavirus))

**AIDS-defining malignancies**

- **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**

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. Enzyme-linked immunosorbent assay (ELISA) has a high sensitivity but not 100% specificity. A positive result requires further testing to confirm the findings.
- **Confirmatory test**: Western blot has very high specificity; however, a second positive confirmatory test is required before providing the results to the patients.

**Direct virus identification**
HIV can be identified directly by electron microscopy, virus isolation, and polymerase chain reaction (PCR) testing.

**Virus quantification**

PCR represents a diagnostic modality and is also used for monitoring purposes. The PCR detection limit is 20–50 copies/mL.

**Determination of CD4 T-helper lymphocyte count**

The number of CD4 T-helper lymphocytes can be determined via flow cytometry. The CD4 count is part of the CDC classification.

**Note:** The CD4 T-helper lymphocyte count and virus quantification are parameters used to ascertain the extent of immune deficiency.

### Differential Diagnosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Possible differential diagnosis</th>
<th>Landmark studies</th>
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</table>
| Acute retroviral syndrome  | • Mononucleosis
• Unspecified viral infection
• Drug allergy            | • EBV-serology
• HIV-PCR
• Drug anamnesis          |
| Lymphadenopathy syndrome   | • Tuberculosis
• Malign lymphoma
• Toxoplasmosis            | • Lymph node biopsy
• Toxoplasmosis serology   |
| Opportunistic infections   | • Primary (congenital) immune defect
• Secondary (acquired) immune defect of other origins | • Anamnesis
• Exclusion of other causal diseases such as immunosuppressive therapy or hematologic neoplasia |

### AIDS Therapy

**Antiretroviral treatment for AIDS prevention**

In the USA, around 57% of the HIV/AIDS budget is used for antiretroviral treatment.

The current recommendation for the initiation of HAART is a lower T-helper cell count of 200/µl. It has been argued that it should begin as early as 200-350/µl.

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 currently being replaced by **cART (combined antiretroviral therapy)** to better describe the combination of drugs used.

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

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

The ‘Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents’ provides a detailed overview of antiretroviral therapy.

**Side effects**

The undesirable side effects of antiretroviral therapy include:

- Bone marrow depression
- Polyneuropathy
- Headaches, nausea
- Hypersensitivity reactions
- Diarrhea
- Nephrotoxicity
- Elevated transaminases
- Exanthema

**Complications**

**Metabolic changes** are most commonly observed during treatment with cART/HAART: lipoatrophy, lipodystrophy, impaired **glucose tolerance** (IGT), **diabetes mellitus**, and hyperlipidemia or dyslipidemia. These changes increase cardiovascular risk.

**Prophylaxis**

**How AIDS can be avoided?**

- ‘Safer sex’ (using condoms)
- General public education
- Avoiding sexual intercourse with unknown and promiscuous partners
- Use of sterile instruments for drug abuse
- Use of protective gloves, face masks, and protective glasses by health care professionals

**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 odds of infection due to percutaneous injury is 1 in 300. Immediate PEP with antiretroviral drugs has been proven to be effective in case-control studies. PEP not only plays an important role in HIV prevention among medical professionals, but it has also been successfully used after unprotected sexual intercourse (i.e. following a rape) or after sharing needles during drug abuse.

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

### Prognosis of AIDS

The mortality rate of untreated HIV is higher than 90%. The average survival time from infection to death is 8 to 10 years in untreated cases. The survival time of patients with full-blown AIDS is 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, improved life expectancy of patients is possible with:**

- Access to drugs
- Compliance

The **Swiss cohort study (SHCS)**, initiated in 1988 reported that only 9% of HIV patients died from AIDS, while 24% died from AIDS-defining cancers. The **SHCS** is a longitudinal study conducted within Swiss university hospitals, Canton hospitals and practicing doctors who treat HIV patients. Its primary aim was to ‘provide optimal patient care, reduce HIV transmission and to conduct research’, which is naturally inconsistent with the global scenario, where the majority of patients still have no access to the necessary drugs.

### References


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