HIV - AIDS

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HIV - AIDS

- HIV - Human Immunodeficiency Virus
  - virus affecting T-lymphocytes

- AIDS - Acquired Immune Deficiency Syndrome
  - syndrome, disease, stage
  - caused by the HIV
History

- **1981 - AIDS first recognized in the US**
  - unexplained occurrence of Pneumocystis jiroveci (P. carinii) pneumonia and Kaposi’s sarcoma
    - Los Angeles, New York “epidemic” in previously healthy
    - homosexual men, injection drug abusers (male and female)
    - later recipients of blood transfusion and hemophiliacs
- **1983 - isolation of HIV in patient with lymphadenopathy**
- **1984 - confirmed as causative agent of AIDS**
- **1985 - sensitive ELISA diagnostic test was developed (anti-HIV antibodies)**
- **1987 - approved zidovudine (first treatment available)**
- **1996 - HAART – highly active antiretroviral therapy**
History

- 1959 the earliest, well-documented case of HIV
  - Leopoldville (Belgian Congo, Kinshasa Congo)
  - Blood sample of patient later confirmed HIV
- Reconstruction of HIV genetic history shows that the HIV pandemic almost certainly originated in Kinshasa, Congo, around 1920
- HIV-1 and HIV-2 are believed to have originated in non-human primates in West-central Africa
  - HIV-1: SIVcpz (Simian Immunodeficiency Virus in chimpanzees)
  - HIV-2: SIVsmm (Simian Immunodeficiency Virus in sooty mangabey - monkey)
- Species barrier jump at least 3 times
  - Bushmeat
  - High-risk transmission channels allows to adapt to humans and spread
History

- previous names for HIV
  - AIDS associated retrovirus (ARV)
  - in 1986 LAV and HTLV-III (the same virus) were renamed HIV

- AIDS
  - GRID - gay-related immune deficiency
  - the 4H disease - homosexuals, heroin users, hemophiliacs, and Haitians
  - AIDS was introduced in 1982 (CDC)
Epidemiology - world

- global pandemic
- 37.9 millions infected (2017) worldwide
  - 77.3 millions totally (included deaths - 35.4 milions)
  - 57% men, 1.8 millions <15 years old
  - 21.7 on treatment
- 770 thousand deaths from AIDS yearly (2018)
  - declining
  - 2.1 millions in the year 2005
- new infections
  - peaked in 1997: 3.3 millions per year
  - declined to 2005: 2.6 millions per year
  - retained stable
  - only 1.8 millions in 2017
Epidemiology - world

- Sub-Saharan Africa is the region most affected
- Western and central Europe and North America low and declining incidence of HIV and mortality
  - prevalence ratio fall from 0.06 in 2000 to 0.03 in 2017
- South Africa has the largest population of people with HIV of any country in the world, at 7.06 million (2017)
- Tanzania, HIV/AIDS was reported to have a prevalence of 4.5% among Tanzanian adults aged 15–49 (2017)
- In 2017, approximately 1 million people in the United States had HIV; 14% did not realize that they were infected
Epidemiology - Slovakia

- 1046 HIV infections (2018)
  - 884 Slovak citizens
  - 162 foreigners
  - transmission:

  - MSM sexual contact: 64.3%
  - Heterosexual contact: 23.5%
  - Injection drug use: 2.2%
  - Unknown/other: 10.0%
Epidemiology - Slovakia

- 1046 HIV infections (2018)
  - newly diagnosed < 100 yearly
- 93 AIDS cases (1985 - 2017)
HIV - virology

- genus Lentivirus
- family Retroviridae
- single-stranded positive-sense enveloped RNA virus
- reverse transcriptase
- viral DNA integrated into cellular DNA (integrase)
HIV - virology

- two types
  - HIV 1
    - initially recognized (LAV, HTLV-III)
    - more virulent and more infective
    - majority of infections globally
  - HIV 2
    - lower infectivity, poor transmission
    - confined to West Africa
HIV - virology

- spherical shape, 60 times smaller than erythrocyte (120 nm)
- 2 copies of positive-sense single-stranded RNA
- 9 genes
- capsid: 2000 copies of protein p24
- enzymes
  - reverse transcriptase
  - proteases
  - ribonuclease
  - integrase
- envelope: lipid bilayer (from the human host cell)
  - glycoprotein gp120, gp41
  - envelope protein: attach to target cells and fuse viral envelope with cell’s membrane, release
HIV - virology

● tropism - type of cells infected
  ○ immune cells
    ■ CD 4+ T cells
    ■ macrophages
    ■ microglial cells
  ○ HIV entry
    ■ interaction envelope gp120 with CD4 molecule on target cells
    ■ and also chemokine co-receptors

● macrophage-tropic strains (early stages)
  ○ beta-chemokine receptors CCR5
  ○ both macrophages and CD4 T cells
  ○ macrophages are first cells infected by HIV, play a key role in several aspects of HIV infection
HIV - virology

- **T-tropic strains**
  - replicate primary in CD4+ T cells
  - alfa-chemokine receptor CXCR4
- **dual-tropic strains**
  - transitional strains
- **M-tropic strains** predominantly transmitted
- **T-tropic strains** replicate more aggressively with heightened virulence
- **viral adaptation to use CXCR4 (T-tropic) instead of CCR5 (M-tropic) may be key step in the progression to AIDS**
HIV - virology

- replication cycle 1
  - entry to the cell
    - virion enters Ma/T-ly gp - receptors, fusion of envelope
    - RNA is transcribed into double-strand DNA (reverse transcription)
    - genome is integrated into host chromosome
HIV - virology

- replication cycle 2
  - replication and transcription
    - integrated viral DNA may lie dormant (latent stage) or actively produce the virus
    - transcription factors upregulated when T cells become activated
    - DNA transcription to mRNA
    - protein production and new copies of viral RNA
HIV - virology

- replication cycle 3 recombinaton
  - 2 RNA genomes in each HIV particle
  - possible recombination between two genomes
  - "copy choice"
  - genetic variation - evolution of resistance to therapy and overcome the immune system
HIV - virology

- replication cycle 4
  - assembly and release
    - final step of viral cycle in general - new virion
    - at plasma membrane of cell
    - gp120, gp41 to membrane
    - budding the membrane, pushes out new virions
    - spread:
      - cell-free (blood, extracellular fluid)
      - cell-to-cell spread (antigen presenting, virological synapses)
HIV

- genetic variability
  - fast replication cycle
  - high mutation rate
  - recombinogenic properties of reverse transcriptase
    - 2 or more strains of HIV in one cell
    - hybrid virion with RNA of 2 strains
    - reverse transcriptase randomly jumping between different RNA templates
HIV - transmission

- sexual contact
  - homosexual (male-male)
  - heterosexual

- blood and blood products
  - healthcare
  - intravenous drug use
  - occupational transmission

- mother to child
  - intrapartum
  - perinatally
  - breastfeeding
HIV - transmission

Percentages of Stage 3 (AIDS) Classifications among Adults and Adolescents with Diagnosed HIV Infection, by Transmission Category and Year of Classification 1985–2015—United States and 6 Dependent Areas

Note: Data have been statistically adjusted to account for missing transmission category.

a Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

b Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.
HIV - transmission

- predominantly sexually transmitted disease
  - developed countries male-to-male > heterosexual
  - worldwide the most common mode of infection, particularly in developing countries is heterosexual transmission (and increasing also in developed countries)

- seminal fluid, cervical smear, vaginal fluid
  - mononuclears and cell-free
  - especially in genital inflammatory states (urethritis, epididymitis - other STDs)

- anal sexual practices
  - traumatize the rectal mucosa, direct inoculation into blood
  - susceptible target cells - Langerhans cells in the mucosal layer even in absence of trauma

- vaginal intercourse
  - thicker mucosal layers
  - less likely to be traumatized
  - possible route, but in lower rate, route of transmission
HIV - transmission

- vaginal intercourse
  - thicker mucosal layers
  - less likely to be traumatized
  - can be, but in lower rate, route of transmission
  - male-to-female > female-to-male risk
    - prolonged exposure
  - presence of other STD significantly increases the risk
    - e.g. Syphilis, Haemophilus ducreyi, Herpes simplex, Trichomonas vaginalis, Neisseria gonorrhoeae, Chlamydia trachomatis
    - genital ulcerations
      - both infectivity and susceptibility to infection
HIV - transmission

- blood and blood products, transplantations, intravenous drug abuse
  - US (1982 - 2005) totally 9300 confirmed AIDS cases caused by blood, blood products
    - virtually all infected before the year 1985
      - mandatory testing of donated blood (anti-HIV antibodies, later p24 or RNA)
  - 1 case in Slovakia
    - very low HIV incidence in the 1980-1990s
    - even this case was in diagnostic window (2007)
  - transfusion safety
    - screening: RNA, p24, anti-HIV antibodies
    - self-deferral of donors - risk-behavior
    - actual risk: 1 in 1.5 millions blood donations
      - first 2 weeks current technology can not detect HIV RNA (very low viremia)
HIV - transmission

- blood and blood products, occupational transmission
  - exposure with infectious body fluids
    - percutaneous injuries (needle stick, cut)
    - contact of mucous membrane or non-intact skin
  - risk:
    - skin puncture from a needle contaminated with blood: 0.3%
    - mucous membrane: 0.09%
  - blood and also: semen, vaginal secretions, cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, amniotic fluid
  - not potentially infectious: feces, nasal secretion, saliva, sputum, sweat, tears, urine, vomitus (unless visibly bloody)
  - rare cases: human bite
HIV - transmission

- maternal-fetal/infant transmission
  - during pregnancy
  - during delivery (most commonly)
  - by breastfeeding
- in the absence of prophylaxis
  - pregnancy, labor and delivery: total 15-35% risk (developing countries >> developed)
- <5% (some studies 0%) among women with <1000 HIV-RNA/ml
- combination antiretroviral therapy and cesarean section rate < 1% risk rate
- prophylactic antiretroviral regimens to the infant up to 12 months
  - discontinue after negative results
HIV - transmission

- HIV is not a very resistant virus
  - during drying loses 99% infectivity within hours
  - inactivated by temperature > 56°C during 30 minutes
  - pH sensitive >9, <6
  - common disinfectants, also detergents
### HIV - transmission rates

<table>
<thead>
<tr>
<th>Activity</th>
<th>Transmission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>iv drug use, sharing needles (with HIV + persons)</td>
<td>0.6%</td>
</tr>
<tr>
<td>sc or im penetration with used needle (HIV+ blood)</td>
<td>0.3%</td>
</tr>
<tr>
<td>sexual intercourse - anal passive (w/ HIV+)</td>
<td>0.5%</td>
</tr>
<tr>
<td>sexual intercourse - anal active (w/ HIV+)</td>
<td>0.06%</td>
</tr>
<tr>
<td>sexual intercourse - vaginal female (w/ male HIV +)</td>
<td>0.3%</td>
</tr>
<tr>
<td>sexual intercourse - vaginal male (w/ female HIV +)</td>
<td>0.05%</td>
</tr>
<tr>
<td>small skin injury - HIV + body fluid/blood</td>
<td>0.4%</td>
</tr>
<tr>
<td>mother (HIV +) - infant</td>
<td>30%</td>
</tr>
<tr>
<td>blood transfusion (HIV +)</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>
HIV - not transmitted by
HIV - clinical course

The diagram illustrates the clinical course of HIV, showing the progression from acute infection to sub-clinical immune dysfunction, skin and mucous membrane immune defects, and systemic immune deficiency. Key events include the increase in virus (p24 antigen) and CD4 T cells concentration over time (months after infection). Anti-HIV antibody (gp120) is also indicated.
HIV - clinical course

- hallmark of HIV pathogenesis is immunodeficiency resulting primarily from a progressive quantitative and qualitative deficiency of T helper lymphocytes (CD4+)
  - direct destruction
  - apoptosis
  - immune clearance
  - immune exhaustion
- characterized by opportunistic infections and neoplasms
  - AIDS-defining illnesses
  - e.g. Tuberculosis, Kaposi sarcoma, Toxoplasmosis, Pneumocystosis, Cryptococcosis
- immune system is target of the virus
HIV - clinical course

- mechanism and course is multifactorial and multiphasic
- primary HIV infection - acute HIV syndrome (stage 1)
  - early dissemination to lymphoid organs, particularly GIT lymphoid tissue
  - burst of viremia, rapid replication in lymphoid organs
- chronic and persistent infection - clinical latency (stage 2)
  - virus escapes robust cellular and humoral immune response
  - various degree of continual replication
  - level of CD4- lymphocytes decreases progressively (gradual or abrupt decline)
  - untreated median duration 10 years
- advanced HIV disease (stage 3 - 4)
  - usually after critical threshold of CD4 count < 200/ul
  - AIDS (stage 4)
HIV - clinical manifestations

- Acute HIV syndrome
  - 50-70% 3-6 weeks after primary infection, duration - weeks
  - various degree of clinical severity
  - along with burst of plasma viremia
  - typical acute viral syndrome
    - fever, pharyngitis, lymphadenopathy, headache, arthralgia, myalgias, lethargy, malaise, anorexia, weight loss, nausea, vomiting, diarrhea
    - meningitis, encephalitis, peripheral neuropathy, myelopathy
    - erythematous maculopapular rash, mucocutaneous ulcerations
  - spontaneous recovery
HIV - clinical manifestations

● Clinical latency - The asymptomatic stage
  ○ median time for untreated 10 years
  ○ HIV disease is ongoing, with active replication, progressive CD4+ lymphocyte decline
    ■ rate of progression is directly correlated with HIV RNA level
HIV - clinical manifestations

- Symptomatic disease
  - CD4+ T cell count < 200/ul (AIDS definition)
  - or HIV-associated indicative of severe defect in cell-mediated immunity (AIDS definition):
    - candidiasis of bronchi, trachea, lungs
    - candidiasis esophageal
    - invasive cervical cancer
    - coccidiomycosis, disseminated
    - cryptococcosis, extrapulmonary
    - cytomegalovirus disease (other than LAP)
    - encephalopathy HIV
    - herpes simplex chronic ulcers, pneumonia
    - histoplasmosis, disseminated
    - isosporiasis, chronic intestinal
    - Kaposi’s sarcoma

- Burkitt’s lymphoma
- Brain lymphoma
- Mycobacterium avium, M. kansasii
- Mycobacterium tuberculosis
- Pneumocystis jiroveci pneumonia
- Pneumonia recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome due to HIV
HIV - clinical presentation
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## HIV - Classification

<table>
<thead>
<tr>
<th>CD4+ cell category (cell/ul)</th>
<th>A asymptomatic or acute HIV syndrome</th>
<th>B symptomatic, but not A, not C</th>
<th>C AIDS indicative conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500 (&gt;29%)</td>
<td>A1</td>
<td>B1</td>
<td>C1</td>
</tr>
<tr>
<td>&lt;500 &gt;200 (&lt;28% &gt;14%)</td>
<td>A2</td>
<td>B2</td>
<td>C2</td>
</tr>
<tr>
<td>&lt;200 (&lt;14%)</td>
<td>A3</td>
<td>B3</td>
<td>C3</td>
</tr>
</tbody>
</table>
HIV - diagnosis

- antibodies anti-HIV
  - window period 3 weeks - 6 months (seroconversion); influenced by treatment, immune state
  - ELISA (enzyme-linked immunosorbent assay)
  - western blot

- antigen test p24 (capsid protein of HIV)
  - p24 rises soon after infection relative to antibodies
  - covers part of antibodies window period (< 2 weeks)
  - p24 diminished with the increase production of antibodies

- nucleic acid based tests
  - detection of target sequences of viral RNA
  - shortening window period to a median < 17 days
  - RNA - PCR

- CD4+ lymphocyte count
  - stage of disease, followup
HIV - treatment

● only suppressing replication - control of HIV infection, can not be cured
  ○ multiple antiretroviral drugs available
  ○ highly active antiretroviral therapy (HAART)
    ■ decreases the patient's total burden of HIV, maintains function of the immune system, and prevents opportunistic infections
    ■ also prevents the transmission of HIV between serodiscordant same sex and opposite sex partners so long as the HIV-positive partner maintains an undetectable viral load
    ■ treatment has been so successful that in many parts of the world, HIV has become a chronic condition in which progression to AIDS is increasingly rare

● treatment of complications - opportunistic infections
  ○ T cells < 200/ul: prophylactic treatment against Pneumocystis jirovecii
  ○ T cells <100ul: prophylactic treatment against mycotic infections
  ○ T cells <50/ul: prophylactic treatment against Mycobacterium avium
HIV - antiretroviral treatment

Classes of medication:

1. Entry inhibitors
2. Fusion inhibitor (CCR5 inhibitors)
3. Nucleoside/nucleotide reverse-transcriptase inhibitors
4. Non-nucleoside reverse-transcriptase inhibitors (1st and 2nd generation)
5. Integrase inhibitors
6. Protease inhibitors
HIV - treatment

- The standard of care is to use combinations of antiretroviral drugs
  - three drugs from at least two different classes
    - 2 nucleoside reverse-transcriptase inhibitors as a “backbone”
    - with 1 of non-nucleoside reverse-transcriptase inhibitor, protease inhibitor, or integrase inhibitor
  - fixed-dose combinations of antiretrovirals combined into a single pill

- Once initiated, antiretroviral therapy should never be stopped

- Recommended for all HIV-infected individuals to reduce the risk of disease progression
  - Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors

- Recommended for HIV-infected individuals also for the prevention of transmission of HIV
HIV - treatment

- Rapid mutation can lead to antiretroviral drug resistance
  - multi-drug resistant mutation
  - combination therapy - suppress HIV replication and thus also mutation rate
  - If a mutation that conveys resistance to one of the drugs being taken arises, the other drugs continue to suppress reproduction of that mutation
HIV - management

- vaccination: Streptococcus pneumoniae, Influenza, Hepatitis B
- screening/follow up
  - syphilis
  - toxoplasma
  - CMV
  - tuberculosis
HIV - prophylaxis

● HIV postexposure prophylaxis (PEP)
  ○ The sooner after exposure ART is started the better
  ○ US Public Health Service Guidelines recommending starting prophylaxis up to a week after exposure
  ○ Recommend treating for a duration of four weeks (based on animal studies)
    ■ emtricitabine + tenofovir + raltegravir
    ■ tolerable, potent, and conveniently administered
  ○ Follow up HIV testing at six, 12, and 24 weeks

● wound
  ○ keep bleeding, disinfection (e.g. Iodine)
  ○ start PEP ASAP
HIV - treatment

- HIV postexposure prophylaxis (PEP)
  - guideline recommendation
    - subcutaneous or intramuscular penetration with needle or intravascular device;
      - HIV positive or recent serostatus unknown but presence of HIV risk factors
    - percutaneous injury with sharp instrument im or sc needle, suture needed
    - contact > 15min of mucous membrane or non intact skin
      - HIV positive
    - anal or vaginal sex
      - viraemic HIV positive or serostatus unknown but presence of HIV risk factors
    - receptive oral sex with ejaculation
      - viraemic HIV positive
    - intravenous drug use - exchange of syringe, needle, preparation material
      - HIV positive
The End.