Retroviridae (human)

Onkorvirinae  HTLV group  
HTLV-1  
HTLV-2  

Lentvirinae  Lentivirus  
HIV-1 Subtypes A-II Major  
Subtype O  
HIV-2  

Spumavirinae  Spumavirus  
human Spumaviruses  

Diagram:
- Transforming
- Cytopathic
- Bovine Leukemia Virus
- Simian STLV-I
- Human HTLV I, II
- Human HIV I, II
- Simian SIV
- Lentivirus V, C, E
Genetic organization of retroviruses

**Oncovirus**
- M-MULV
- RSV
- HTLV-1
- BLV

**Lentivirus**
- HIV

**Spumavirus**
- HFV

**Dogma:**
DNA-RNA-Protein

**retro**: RNA-cDNA-DNA-RNA-Protein

Schatzl, 1989
Discovery of human lentiviruses

1981: AIDS: 5 cases *Pneumocystis carinii* pneumonia in previously healthy man in L.A. area reported to CDC

1983 LAV: Montagnier and colleagues isolate lymphadenopathy-associated virus from lymph node cells of one patient with lymphadenopathy

1984: HTLV-III: Gallo and colleagues link Human T-Lymphotropic Virus III with AIDS, based on seroepidemiological data. *LAV and HTLV-III later named into HIV-I.*

1986: HIV-2: Clavel and colleagues isolate HIV-2 from Western Africa

2008: Nobel Prize: F. Barre-Sinoussi and L. Montagnier/H. zur Hausen (HPV)

Origin of HIV

**Zoonotic transmission (trans-species): monkey-man**

HIV-1: from SIV<sub>cpz</sub>. Evidence: Viral genetic homology, geography of viruses. At least 3 transmission events result in HIV-1 groups M, N, O. Group M viruses affected man ~1930.

HIV-2: from SIV<sub>sim</sub>. Evidence: Viral genetic homology, geography.

Key for cross-species transmission: (1) initial infection and (2) good transmission within new host (e.g., urbanization, trucking/trade, air traffic...
HIV/AIDS: bad statistics...

~40 million persons infected with HIV
~5 million persons infected in 2007
~15 thousand new HIV infections per day
(1.700 children!)
>22 million total death toll HIV/AIDS
>13 million children orphans by AIDS

HIV/AIDS continues to be important global problem!!!
Estimates of New HIV Infections in US, By Transmission Category, 2006

- MSM: 53%
- Heterosexual: 31%
- MSM-IDU: 4%
- IDU: 12%


Global distribution

HIV/AIDS

- North America: 940,000
- Western Europe & Central Asia: 560,000
- Eastern Europe & Central Asia: 1 million
- North Africa & Middle East: 440,000
- South & South-East Asia: 1 million
- East Asia & Pacific: 6.1 million
- Sub-Saharan Africa: 28.1 million
- Caribbean: 420,000
- Latin America: 1.4 million
- Australia & New Zealand: 15,000

Total: ~40 millions
Distribution, prevalence and transmission modes: “evolution”

<table>
<thead>
<tr>
<th>Region</th>
<th>Epidemic onset</th>
<th>Adults &amp; children living with HIV/AIDS</th>
<th>Adults &amp; children newly infected with HIV</th>
<th>Adult prevalence of HIV</th>
<th>% of HIV-positive adults who are female</th>
<th>Main mode(s) of transmission for those living with HIV/AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>late '70s</td>
<td>18.1 million</td>
<td>2.4 million</td>
<td>3.8%</td>
<td>50%</td>
<td>Hetero</td>
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<tr>
<td>North Africa &amp; Middle East</td>
<td>early '80s</td>
<td>480,000</td>
<td>30,000</td>
<td>0.2%</td>
<td>40%</td>
<td>Hetero, IDU</td>
</tr>
<tr>
<td>South and South-East Asia</td>
<td>late '80s</td>
<td>6.1 million</td>
<td>800,000</td>
<td>0.6%</td>
<td>35%</td>
<td>Hetero, IDU</td>
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<tr>
<td>East Asia &amp; Pacific</td>
<td>late '80s</td>
<td>1 million</td>
<td>270,000</td>
<td>1.1%</td>
<td>20%</td>
<td>Hetero, IDU, MSM</td>
</tr>
<tr>
<td>Latin America</td>
<td>late '70s</td>
<td>1.4 million</td>
<td>130,000</td>
<td>0.5%</td>
<td>35%</td>
<td>MSM, IDU, Hetero</td>
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<tr>
<td>Caribbean</td>
<td>late '70s</td>
<td>420,000</td>
<td>40,000</td>
<td>2.3%</td>
<td>50%</td>
<td>Hetero, MSM</td>
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<tr>
<td>Eastern Europe &amp; Central Asia</td>
<td>early '80s</td>
<td>1 million</td>
<td>250,000</td>
<td>0.5%</td>
<td>20%</td>
<td>Hetero</td>
</tr>
<tr>
<td>Western Europe</td>
<td>early '80s</td>
<td>500,000</td>
<td>30,000</td>
<td>0.3%</td>
<td>25%</td>
<td>IDU</td>
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<tr>
<td>North America</td>
<td>late '70s</td>
<td>940,000</td>
<td>45,000</td>
<td>0.6%</td>
<td>20%</td>
<td>MSM, IDU, Hetero</td>
</tr>
<tr>
<td>Australia &amp; New Zealand</td>
<td>early '80s</td>
<td>15,000</td>
<td>500</td>
<td>0.1%</td>
<td>10%</td>
<td>MSM</td>
</tr>
<tr>
<td>TOTAL</td>
<td>early '80s</td>
<td>46 million</td>
<td>5 million</td>
<td>1.2%</td>
<td>40%</td>
<td>Hetero</td>
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</tbody>
</table>

Impact of HIV on life expectancy

- Predicted life expectancy
- Loss in life expectancy due to HIV/AIDS
Course of disease

Primary infection: mostly normal, sometimes flu-like, +/- exanthema

Phase of latency: no symptoms, can last several years

Lymphadenopathy syndrome (LAS): palpable lymph nodes on at least 2 different sites for more than 3 months

AIDS-related-Complex (ARC): Lymphadenopathy, fever, chronic diarrhea...

Full AIDS: last phase of HIV disease, characterized by (total) failure of cellular immunity, malignant tumors (lymphoma) and spread of pathogenic agents (viruses, bacteria, fungi…) causing finally death

“opportunistic infections”

10 most frequent AIDS diagnoses
(in % from 1045 AIDS diagnoses)

1. Candida-oesophagitis 12%
2. Kaposi 10,8%
3. Tuberculosis 10,7%
4. MAI 10,2%
5. NHL 8,1%
6. PcP 7,4%
7. Wasting 5,5%
8. Toxoplasmosis 5,3%
9. Encephalopathy 5,2%
10. CMV 5,1%

CD4 count, clinical symptoms, later viral load

**Laboratory categories 1 to 3**

1: above 500/µl CD4 lymphocytes

2: 200-499/µl CD4 lymphocytes

3: < 200/µl CD4 lymphocytes
Clinical Categories A to C

- Category A: no symptoms
- Category B: symptoms, no AIDS
- Category C: symptoms, AIDS
Pathogenesis
- HIV infects macrophages or Langerhans cells
- Propagation and transport from these cells to lymph nodes
  ➢ There new infection of monocytes, macrophages and T lymphocytes (CNS!)
  ➢ Such cells are always newly built from stem cells; body supplies steadily fresh host cells for infection...

Course of HIV infection

Primary infection. 10 hr doubling time, with peak viremia at 21 days; each infected cell seeds roughly 20 infected cells. Virus loads drop rapidly as the immune response kicks in.

Asymptomatic phase. Approx. $10^{10}$ virus particles made and eliminated daily; approx. $10^9$ CD4+ T cells made and eliminated daily. Virus replication and elimination are very nearly in equilibrium ("steady-state").

Virus reservoir. Approx. $10^6$-$10^7$ T cells sustain the HIV-1 infection (productively infected, activated T cells). *The size of the latent HIV-1 reservoir (mostly in resting T cells) is similar.*
Target cells for HIV/The lymphoid system

- T-cells
- Monocytes
- Natural killer cells
- Dendritic cells
- Macrophages

HIV genome

LTR  gag  vif  rev  nef  LTR
pol  tat
vpr  vpr  env

http://listen.to/hiv
Fig. 1. An overview of the organization of the 5-flanked genome of the HIV provirus and a summary of the function of its nine genes encoding 15 proteins.
**THERAPY:**
- No vaccine feasible, due to high variability of HIV
  (*quasi-species*)
- Inhibitors of reverse transcriptase: Nucleoside analogs (e.g. azidothymidin) are used which bind to active center of enzyme and are incorporated into DNA strands, resulting in chain termination (problem: induction of mutations, no more effect of inhibition)
- Inhibitors of viral protease
- However: **No cure possible**, i.e. elimination of viral DNA out of cells in body does not take place.

**HIV infection and pregnancy**
- **worldwide**: ~800,000 new infections per year
- **Germany**: < 20 new infections per year
- **Transmission:**
  - in 15-30% from HIV-pos. mother to child
  - >30% when seroconversion of mother in pregnancy
  - 30% prenatal (in utero)
  - 70% during delivery
  - 14% via breast feeding

**Procedure:** Reduce viral load mother, C-sectio, no breast feeding, mono-therapy (AZT) child
Antiviral drug resistance

Monotherapy. HIV becomes genetically resistant to all known monotherapies (i.e., single drug treatments). *This is due to the rapid viral mutation rate and the existence of a huge pool of genetically distinct viral quasispecies.*

Combination therapy. Simultaneous use of multiple drugs makes it harder for the virus to develop drug resistance since several mutations must happen at the same time, in order for the virus to replicate.

**HAART: highly active anti-retroviral therapy**
- combination of 3 or more drugs

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**Anti-retroviral therapy: substances**

- Nucleoside: chain termination reverse transcription  
  - NRTI
- Non-nucleoside: steric inhibition RT at binding center  
  - NNRTI
- Protease inhibitor: inhibition viral maturation: poly-protein - structural proteins  
  - PI
AZT structure

![AZT structure diagram](image-url)
New developments

• Therapy breaks: no!!!
  – Problem of in DNA-integrated mutants (archive)
• Immunization („vaccine“): no effect/quasi-species
• Prophylactic, therapeutic…
  – Induction of antibodies
    • in „sterilizing“ quantity
    • Neutralizing epitopes
  – Cellular immunity (T cells)
  – Drug prophylaxis!!! (Africa)
  – BMT: Donor Co-receptor negative!!! (1 case worldwide/G)

Risk of side effects

• Acute side effects: Diarrhea, skin rushes etc.

• Chronic: Diab. mell., hypertension, lipids ↑

• Long-term: Lipodystrophy, heart attack (myocardial infarction)
Long-term side effects

- Lipodystrophy
  - Lipoatrophy
  - Lipohypertrophy
  - Lipoatrophy + -hypertrophy
Cardiovascular events

Loss of fat - Lipoatrophy
Is HAART effective???

**Human T cell leukemia virus**

**HTLV-1**

**Taxonomy:** Family Retroviridae, Subfamily Onkovirinae

**Epidemiology:** endemic in Japan, Caribbean, S. America, Africa

**Transmission:** Blood transfusion, intra-uterine, sexual, via breast milk

**Klinics:** adult T cell leukemia
HTLV-associated myelopathy
Tropical spastic paresis

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**Selected animal retroviruses**

**Avian leukosis virus ALF:** α-retrovirus, high prevalence, disease (osteopetrosis, lymph. leukemia) rare

**Feline leukemia virus FeLV**
γ-retrovirus, worldwide, vaccine available, feline sarcomavirus

**Bovine leukemia virus BLV**
σ-retrovirus, worldwide

**Meadi-visna virus,** caprine arthritis-encephalitis virus **CAEV**

**Feline immunodeficiency virus FIV**