HIV Pathogenesis

Lecture 24
Biology W3310/W4310
Virology
Spring 2014

Nature is not human-hearted
Lao Tzu
Tao Te Ching
This tragedy was facilitated (or even caused) by human interventions: colonization, urbanization, and probably well-intentioned public health campaigns

**Pneumocystis Pneumonia --- Los Angeles**

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed *Pneumocystis carinii* pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.

Patient 1: A previously healthy 33-year-old man developed *P. carinii* pneumonia and oral mucosal candidiasis in March 1981 after a 2-month history of fever associated with elevated liver enzymes, leukopenia, and CMV viremia. The serum complement-fixation CMV titer in October 1980 was 256; in May 1981 it was 32.* The patient's condition deteriorated despite courses of treatment with trimethoprim-sulfamethoxazole (TMP/SMX), pentamidine, and acyclovir. He died May 3, and postmortem examination showed residual *P. carinii* and CMV pneumonia, but no evidence of neoplasia.

Patient 2: A previously healthy 30-year-old man developed *P. carinii* pneumonia in April 1981 after a 5-month history of fever each day and of elevated liver-function tests, CMV viremia, and documented seroconversion to CMV, i.e., an acute-phase titer of 16 and a convalescent-phase titer of 28* in anticomplement immunofluorescence tests. Other features of his illness included leukopenia and mucosal candidiasis. His pneumonia responded to a course of intravenous TMP/SMX, but, as of the latest reports, he continues to have a fever each day.

**Editorial Note:** *Pneumocystis pneumonia in the United States is almost exclusively limited to severely immunosuppressed patients* (1). The occurrence of pneumocystosis in these 5 previously healthy individuals without a clinically apparent underlying immunodeficiency is unusual. The fact that these patients were all homosexuals suggests an association between some aspect of a homosexual lifestyle or disease acquired through sexual contact and *Pneumocystis pneumonia* in this population. All 5 patients described in this report had laboratory-confirmed CMV disease or virus shedding within 5 months of the diagnosis of *Pneumocystis* pneumonia. CMV infection has been shown to induce transient abnormalities of in vitro cellular-immune function in otherwise healthy human hosts (2,3). Although all 3 patients tested had abnormal cellular-immune function, no definitive conclusion regarding the role of CMV infection in these 5 cases can be reached because of the lack of published data on cellular-immune function in healthy homosexual males with and without CMV antibody. In 1 report, 7 (3.6%) of 194 patients with pneumocystosis also had CMV infection* 40 (21%) of the same group had at least 1 other major concurrent infection (1). A high prevalence of CMV infections among homosexual males was recently reported: 179 (94%) had CMV viremia; rates for 101 controls of similar age who were reported to be exclusively heterosexual were 54% for seropositivity and zero for viremia (4). In another study of 64 males, 4 (6.3%) had positive tests for CMV in semen, but none had CMV recovered from urine. Two of the 4 reported recent homosexual contacts. These findings suggest not only that virus shedding may be more readily detected in seminal fluid than urine, but also that seminal fluid may be an important vehicle of CMV transmission (5).

All the above observations suggest the possibility of a cellular-immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystosis and candidiasis. Although the role of CMV infection in the pathogenesis of pneumocystosis remains unknown, the possibility of *P. carinii* infection must be carefully considered in a differential diagnosis for previously healthy homosexual males with dyspnea and pneumonia.
AIDS

- Clusters of PCP and Kaposi’s sarcoma observed in other urban centers
- CDC established case definition of KS or opportunistic infections
- 1982 disease was called AIDS (formerly GRID)
- Found transmitted at birth and heterosexually
HIV is a lentivirus

- First isolated in 1983 from the lymph node of a patient with lymphadenopathy in Paris
- 1984 blood test developed
- Electron microscopy and sequence analysis revealed HIV to be a lentivirus, known group of retroviruses
Retroviridae

• Orthoretrovirinae (subfamily)
  - Alpharetrovirus
  - Betaretrovirus
  - Gammaretrovirus
  - Deltaretrovirus
    ▶ HTLV-1, HTLV-2, HTLV-3
  - Epsilonretrovirus
  - Lentivirus
    ▶ HIV-1, HIV-2
Two evolutionarily distinct groups of human retroviruses

- The lymphotrophic viruses: HTLV 1, 2, 3, 4
- The immunodeficiency viruses: HIV-1, HIV-2
  - Lentiviruses, not new or unique to humans
  - Equine infectious anemia virus, causes fatal immunodeficiency of horses, isolated early 1900s
HIV and AIDS: Acquired ImmunoDeficiency Syndrome

- Syndrome: the occurrence together of a characteristic group or pattern of symptoms
- HIV-1 is the etiological agent of epidemic AIDS
- AIDS denialists: the hypothesis that HIV causes AIDS has been tested by inadvertent infection of people with HIV-contaminated blood
HIV/AIDS pandemic

- In the US, HIV has killed over 600,000, exceeding all US combat-related deaths in all wars fought in the 20th century
- >1 million in the US are infected; 25% unaware
- 51,000 new infections 2011; 70% men, 30% women
- Half of all new infections in US occur in people 25 or younger
## Global summary of the AIDS epidemic | 2012

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of people living with HIV</td>
<td>35.3 million</td>
<td>[32.2 million – 38.8 million]</td>
</tr>
<tr>
<td>Adults</td>
<td>32.1 million</td>
<td>[29.1 million – 35.3 million]</td>
</tr>
<tr>
<td>Women</td>
<td>17.7 million</td>
<td>[16.4 million – 19.3 million]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>3.3 million</td>
<td>[3.0 million – 3.7 million]</td>
</tr>
<tr>
<td>People newly infected with HIV in 2012</td>
<td>2.3 million</td>
<td>[1.9 million – 2.7 million]</td>
</tr>
<tr>
<td>Adults</td>
<td>2.0 million</td>
<td>[1.7 million – 2.4 million]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>260 000</td>
<td>[230 000 – 320 000]</td>
</tr>
<tr>
<td>AIDS deaths in 2012</td>
<td>1.6 million</td>
<td>[1.4 million – 1.9 million]</td>
</tr>
<tr>
<td>Adults</td>
<td>1.4 million</td>
<td>[1.2 million – 1.7 million]</td>
</tr>
<tr>
<td>Children (&lt;15 years)</td>
<td>210 000</td>
<td>[190 000 – 250 000]</td>
</tr>
</tbody>
</table>
Adults and children estimated to be living with HIV | 2012

Total: 35.3 million [32.2 million – 38.8 million]
Estimated number of adults and children newly infected with HIV | 2012

- **Western & Central Europe**: 29,000 [25,000 – 35,000]
- **Eastern Europe & Central Asia**: 130,000 [89,000 – 190,000]
- **Middle East & North Africa**: 32,000 [22,000 – 47,000]
- **Sub-Saharan Africa**: 1.6 million [1.4 million – 1.8 million]
- **Eastern Europe & Central Asia**: 130,000 [89,000 – 190,000]
- **South & South-East Asia**: 270,000 [160,000 – 440,000]
- **Caribbean**: 12,000 [9,400 – 14,000]
- **Latin America**: 86,000 [57,000 – 150,000]
- **East Asia**: 81,000 [34,000 – 160,000]
- **Oceania**: 2,100 [1,500 – 2,700]
- **North America**: 48,000 [15,000 – 100,000]

**Total: 2.3 million [1.9 million – 2.7 million]**
Estimated adult and child deaths from AIDS | 2012

- Western & Central Europe: 7,600 [6,900 – 8,300]
- Eastern Europe & Central Asia: 91,000 [66,000 – 120,000]
- Middle East & North Africa: 17,000 [12,000 – 26,000]
- South & South-East Asia: 220,000 [150,000 – 310,000]
- Sub-Saharan Africa: 1.2 million [1.1 million – 1.3 million]
- Eastern Europe & Central Asia: 91,000 [66,000 – 120,000]
- East Asia: 41,000 [25,000 – 64,000]
- Caribbean: 11,000 [9,400 – 14,000]
- Latin America: 52,000 [35,000 – 75,000]
- North America: 20,000 [16,000 – 27,000]
- South & South-East Asia: 220,000 [150,000 – 310,000]
- Sub-Saharan Africa: 1.2 million [1.1 million – 1.3 million]
- East Asia: 41,000 [25,000 – 64,000]
- Caribbean: 11,000 [9,400 – 14,000]
- Latin America: 52,000 [35,000 – 75,000]
- North America: 20,000 [16,000 – 27,000]

Total: 1.6 million [1.4 million – 1.9 million]
Children (<15 years) estimated to be living with HIV | 2012

Total: 3.3 million [3.0 million – 3.7 million]
Estimated number of children (<15) newly infected with HIV | 2012

Total: 260 000 [230 000 – 320 000]
Estimated deaths in children (<15 years) from AIDS | 2012

Total: 210 000 [190 000 – 250 000]
About 6,300 new HIV infections a day in 2012

- About 95% are in low- and middle-income countries
- About 700 are in children under 15 years of age
- About 5,500 are in adults aged 15 years and older, of whom:
  - almost 47% are among women
  - about 39% are among young people (15-24)
New HIV infections and AIDS-related deaths

Globally new HIV infections peaked in 1997
Control of AIDS

Triple-drug therapy has slowed the pandemic in countries with money
Number of people receiving antiretroviral therapy in low- and middle-income countries
Number of people eligible for antiretroviral therapy in low- and middle-income countries based on the epidemic and response status at the end of 2012

Updated fig 1.23 (Global update on HIV treatment 2013: results, impact and opportunities: WHO report in partnership with UNICEF and UNAIDS, page 41).
But...

• There is as yet no cure
  - Can’t clear virus from an infected individual
• There is no vaccine
  - Can’t block primary infection
• Can’t stop taking antiviral drugs
  - Reservoirs: latently infected hematopoietic progenitor cells (TWiV 133: The HIV hideout)
• Drug resistant viruses appear
• Drugs are expensive
• AIDS is becoming a Third World disease
  - Spreading unabated in sub-Saharan Africa
First studies in Africa, in Zaire and Rwanda, showed that AIDS was common in Kinshasa and Kigali, where nearly 90% of sex workers were infected.
• Testing of archival samples suggested that HIV-1 was present in the 1960s and 1970s in several locations in central Africa but not in West or East Africa

• Serum sample ZR59 from a DRC adult male (1959) found positive for HIV-1 in 1998

• Lymph node sample from DRC adult female (1960)
• DRC60 and ZR59 differed by about 12%

• No doubt that HIV-1 was present in Léopoldville (Kinshasa today) by 1959–60
HIV-1 diversity

- Four groups based on sequence alignment
- Group M (main): 99% of all HIV-1 infections
- Group O (outlier): <1% of infections, limited to Cameroon, Gabon, neighboring countries
- Group N: Only 13 cases, Cameroon
- Group P: Only 2 cases, Cameroon
- Each from an independent transmission event of SIV to humans
HIV-1 diversity

- HIV-1 group M further divided into 9 subtypes
- High-risk individuals multiply infected, recombinants emerge (CRFs) 48 so far
- No clear cut difference between subtypes in propensity to cause AIDS, except that those infected with D die faster
- Shedding of subtype C in female genital tract is higher, perhaps higher female to male transmission, extensive spread in Africa
HIV-1 subtypes

- HIV-1 evolves in one direction to numerous subtypes and recombinants
- Therefore can reconstruct sequence of progress in region or country by examining local distribution of subtypes
- Facilitated in 1990s by new tools enabling examination of nucleotide sequences from large number of isolates
- Extreme diversity of HIV-1 in central Africa, clearly the origin as had more time to diversify
HIV-1 subtypes

- Some subtypes associated in specific locations with modes of transmission
- Founder effect: subtype will *predominate* in at-risk group
- Example: subtype B found in 96% of white homosexuals in South Africa (imported from US); subtype C accounts for 81% of infections of black heterosexuals
• Subtype C (50%), B and A (10-12%), G (6%), CRF02_AG (5%), CRF01_AE (5%), D (2.5%) of all HIV-1 infections

• Subtypes F, H, J, K limited transmission (<1%)
What was the source of HIV-1?

- SIV first isolated from chimpanzee in 1989 (SIVcpz)
- Analysis of >7,000 chimpanzee fecal samples from 90 field sites confirmed natural SIVcpz reservoir
- Only *Pan troglodytes troglodytes* and *P. T. schweinfurthii* harbor SIVcpz
SIVcpz

- Transmitted among chimpanzees by sexual intercourse; mother to child; possibly blood-blood during aggression
- Estimated transmission probability per coital act 0.008 - 0.0015, similar to humans (0.0011)
- SIVcpz is pathogenic in natural host, similar to AIDS
The diagram illustrates the evolutionary relationship between simian immunodeficiency virus (SIV) and human immunodeficiency virus (HIV). SIV is found in various species of monkeys and apes, and it is believed to have evolved into HIV. The diagram shows several species of monkeys and apes, each labeled with their respective SIV strain:

- Sykes's monkey: SIVsyk
- Sooty mangabey: SIVsmm
- Mantled guereza: SIVcol
- Mona monkey: SIVmon
- Chimpanzee: SIVcpz
- Red-capped mangabey: SIVrcm
- Vervet monkey: SIVver
- L'Hoest's monkey: SIVlho
- Mandrill: SIVmnd
- Western gorilla: SIVgor

The diagram also indicates the origin of HIV-1 subtypes M, N, and O, which are found in different species of monkeys and apes. HIV-2 is believed to originate from a SIV strain in central Africa (P. t. t. of central Africa).
Phylogenetics

- Phylogenetic trees measure the genetic distance between organisms, and identify the nearest relatives.
- Each division in the tree is a ‘node’, the common ancestor of the organisms or the isolates identified to its right.
- After such branching, the organisms and their sequences evolve independently. The ‘root’ (at the extreme left) is the assumed common ancestor of all organisms in the tree.
- To construct a phylogenetic tree, compare differences in nucleotide sequences of many isolates of putatively related organisms.
- Confidence increases if same findings obtained for multiple genes.
When did SIV infect humans?

- Four separate crossover events
- M, O: First three decades of 20th century
- N, P: more recently but not enough data
- Suggested that Kinshasa was epicenter, early spread concurrent with development of colonial cities
How did SIVcpz infect humans?

- The cut hunter: bushmeat hunting
- Cutaneous or mucous membrane exposure to infected chimpanzee blood, body fluids
- Calculations suggest that in 1921 number of people infected with SIVcpz was <10, but probably only one spread and multiplied
- Such cross-species infections probably have occurred many times previously
- Why did this one spread?
Why did HIV-1 spread?

- European colonization of Africa beginning end of 19th century
- Establishment of large population centers, movement of adult males for labor - large scale prostitution
- Introduction of health care - colonial medicine - injections and transmission of viruses
- Egypt at turn of 20th century - well intentioned treatment for schistosomiasis spread HCV to millions
- Large scale amplification of HIV-1
• **Spread of HIV-1**

- Leopoldville was the most dynamic city in the region, attracted large numbers of migrants and traders
- The cut hunter might have traveled there, visited a brothel, then a STD clinic
- Then amplification by non-sterile syringes, sex (some women had 1,000 clients/yr)
- Haiti and the Belgian Congo
HIV-2

- First isolated Guinea-Bissau, 30-40% identity HIV-1
- Restricted primarily to populations in West Africa
- Less virulent (most infections do not progress to AIDS), transmissible than HIV-1, no mother-infant spread
- Crossover from sooty mangabey
- 8 distinct lineages, each arose from separate infection
Transmission

- HIV is not a particularly infectious virus, not contagious like measles virus ($R_0$ 2-5)
- Not spread by respiratory, alimentary, or vector routes
<table>
<thead>
<tr>
<th>Fluid</th>
<th>Virus isolation</th>
<th>Estimated quantity of virus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell-free fluid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>21/40</td>
<td>10–10,000</td>
</tr>
<tr>
<td>Ear secretions</td>
<td>1/8</td>
<td>5–10</td>
</tr>
<tr>
<td>Feces</td>
<td>0/2</td>
<td>None detected</td>
</tr>
<tr>
<td>Milk</td>
<td>1/5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Plasma</td>
<td>33/33</td>
<td>1–5,000&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Saliva</td>
<td>3/55</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Semen</td>
<td>5/15</td>
<td>10–50</td>
</tr>
<tr>
<td>Sweat</td>
<td>0/2</td>
<td>None detected</td>
</tr>
<tr>
<td>Tears</td>
<td>2/5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Urine</td>
<td>1/5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vaginal-cervical fluid</td>
<td>5/16</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Infected cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial fluid</td>
<td>3/24</td>
<td>Not determined</td>
</tr>
<tr>
<td>PBMC</td>
<td>89/92</td>
<td>0.001–1%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Saliva</td>
<td>4/11</td>
<td>&lt;0.01%</td>
</tr>
<tr>
<td>Semen</td>
<td>11/28</td>
<td>0.01–5%</td>
</tr>
<tr>
<td>Vaginal-cervical fluid</td>
<td>7/16</td>
<td>Not determined</td>
</tr>
</tbody>
</table>
Probability of HIV Transmission per Coital Act in Monogamous, Heterosexual, HIV-Discordant Couples in Rakai, Uganda

Source: Gray et al., Lancet 2001;257:1149
Transmission

- HIV-1 infectivity reduced by air drying (99%/24 hr)
- By heating (56°C/30 min)
- By 10% bleach or 70% alcohol
- By pH extremes (<6 or >10)
- STD/IVDU bypass these!
Co-receptors

HIV (X4) interacts with CD4 and α-chemokine receptor (Cxcr4) on the CD4+ target cell. Sdf-1 binds to Cxcr4.

HIV (R5) interacts with CD4 and β-chemokine receptor (Ccr5) on the CD4+ target cell. β-chemokine (Rantes, Mip-1α, Mip-1β) binds to Ccr5.
Primary HIV Infection

- Virus-dendritic cell interaction (no activation)
  - Infection typically with CCR5 binding strains
  - Importance of DC-SIGN (dendritic cell-specific, Icam-3 grabbing nonintegrin)

- Delivery of virus to lymph nodes

- Active replication in lymphoid tissue

- High levels of viremia and dissemination

- Down-regulation of virus replication by immune response

- Viral set point reached after ~6 months
Primary HIV Infection: Clinical Characteristics

- 50-90% of infections are symptomatic
- Symptoms generally occur 5-30 days after exposure
- Symptoms and signs
  - Fever, fatigue, malaise, arthralgias, headache, nausea, vomiting, diarrhea
  - Lymphadenopathy, pharyngitis, rash, weight loss, mucocutaneous ulcerations, aseptic meningitis
  - Leukopenia, thrombocytopenia, elevated liver enzymes
- Median duration of symptoms: 14 days
GI associated lymphoid tissue following acute infection

Absence of lymphoid cell aggregates in terminal ileum
Established HIV Infection

• Active viral replication throughout course of disease

• Major reservoirs of infection exist outside of blood
  - Lymphoreticular tissues (Gastrointestinal tract - GALT)
  - Central nervous system
  - Genital tract

• At least $10 \times 10^9$ virions produced and destroyed each day

• $T_{1/2}$ of HIV in plasma is <6 h and may be as short as 30 min
Blood compartment

Productively infected CD4+ lymphocytes

Uninfected, activated CD4+ lymphocytes

HIV-1

Latently infected CD4+ lymphocytes

Uninfected CD4+ lymphocytes

CD4+ lymphocytes infected with defective viruses

Long-lived cell populations

1.6 days per generation

93–99%

<1%

1–7%

6 h

$\frac{t_{1/2}}{\text{blood}} \sim 1.1$ days

$\frac{t_{1/2}}{\text{other compartments}} \sim 8.5$ days

$\frac{t_{1/2}}{\text{other compartments}} \sim 14.1$ days

multipotent hematopoietic progenitor cells - latent reservoir
The Variable Course of HIV-1 Infection

**Typical Progressor**

- Primary HIV Infection
- Clinical Latency
- AIDS

**Rapid Progressor**

- Primary HIV Infection
- AIDS

**Nonprogressor**

- Primary HIV Infection
- Clinical Latency

Graphs showing the progression of viral replication and CD4 levels over time for different stages of HIV-1 infection.
Elite HIV Controllers

- Individuals who maintain normal CD4 counts and undetectable viral loads (<50 copies HIV RNA/ml of plasma) for >10 years in the absence of antiretroviral therapy
  - Estimated at 1/300 infected persons

- Associated with favorable HLA types (esp HLA B57 and B27) and T-cell responses (CD4 and CD8) to Gag

- Persistent viremia (1-30 copies of RNA/ml) demonstrable

- Not associated with attenuated viruses

http://www.twiv.tv/2010/05/16/twiv-82-immunology-in-silico/
# Immune cell dysfunction in AIDS

<table>
<thead>
<tr>
<th>Affected cell type</th>
<th>Dysfunction</th>
<th>Known or postulated causes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Direct</td>
</tr>
<tr>
<td><strong>CD4⁺ T cells</strong></td>
<td>Colony formation ↓</td>
<td>Direct killing by HIV-1</td>
</tr>
<tr>
<td></td>
<td>Proliferative response to antigen ↓</td>
<td>CD4 is down-regulated in infected cells (by SU, Vpu, Nef)</td>
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<tr>
<td></td>
<td>Expression of IL-2 and IL-2R ↓</td>
<td>Trapping of infected cells in lymphoid organs</td>
</tr>
<tr>
<td></td>
<td>Total number in circulation ↓</td>
<td>Destruction of infected cells by anti-HIV-1 CD8⁺ CTLs</td>
</tr>
<tr>
<td><strong>CD8⁺ T cells</strong></td>
<td>Abnormally large numbers following acute phase</td>
<td>Infection and killing of progenitor CD4⁺/CD8⁺ and CD8⁺ immature thymocytes</td>
</tr>
<tr>
<td></td>
<td>Loss of anti-HIV CTL activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loss in numbers toward end stage</td>
<td></td>
</tr>
<tr>
<td><strong>Monocytes</strong></td>
<td>Defects in chemotaxis</td>
<td>Only a few circulatory cells are infected, but changes in cytokine production by such cells (e.g., Tnf-α, IL-1 ↓) can cause apoptosis of CD4⁺ cells and other abnormalities</td>
</tr>
<tr>
<td><strong>(dendritic cells)/macrophages</strong></td>
<td>Monocyte-dependent T-cell proliferation ↓</td>
<td></td>
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<tr>
<td></td>
<td>Antigen-presenting cell activity ↓</td>
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<tr>
<td></td>
<td>Fc receptor function ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complement C3 receptor-mediated clearance/oxidative burst ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decrease in numbers</td>
<td></td>
</tr>
<tr>
<td><strong>B cells</strong></td>
<td>Abnormal proliferation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypergammaglobulinemia</td>
<td></td>
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<tr>
<td></td>
<td>Poor response to additional antigen signals</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Production of autoantibodies</td>
<td></td>
</tr>
<tr>
<td><strong>NK cells</strong></td>
<td>NK cytotoxicity function ↓</td>
<td></td>
</tr>
</tbody>
</table>
AIDS

• <200 CD4+ T cells/ml

• Protozoal: *Pneumocystis, Toxoplasma, Isospora, Cryptosporidium*, microsporidia

• Bacterial: *Mycobacterium, Treponema*

• Fungal: *Candida, Cryptococcus, Histoplasma*

• Viral: CMV, HSV

• Immune activation: HIV replicates better in activated T cells

• Malignancies: EBV lymphoma, Kaposi’s sarcoma, anogenital carcinoma

• Neurological symptoms: aseptic meningitis, myelopathies, neuropathies, AIDS dementia complex
HIV and cancer

- HIV-1 infection leads to increase incidence of malignancy: 40% of infected individuals
- An indirect effect of dysregulation of the immune system
  - Absence of proper immune surveillance
  - High levels of cytokines leads to inappropriate cell proliferation, replication of oncogenic viruses, angiogenesis
Kaposi’s sarcoma

• Described 1872 by Hungarian physician
• Pre-AIDS: mainly in older Mediterranean men
• Occurs in 20% of HIV-1 infected homosexual men, 2% of HIV-1 infected women, transfusion recipients
• Infection with human herpesvirus 8 is necessary for development of KS
Is an HIV-1 vaccine possible?

How does HIV-1 persist despite effective anti-viral immunity?
How does it eventually outstrip immune control?

HIV-1 superinfection occurs less frequently than initial infection
HIV-1 escape from neutralizing antibody
Broadly neutralizing antibodies

- Have been identified in 20% of HIV-1 infected individuals
- Neutralize broadly across subtypes
- Recognize conserved epitopes on Env glycoprotein
CD8$^+$ CTL are important for control of HIV-1

- Kinetics of early CTL response peak as early viremia falls
- Adverse effect of removing CD8$^+$ T cells in SIV-infected macaques, CTL correlate with slower disease in humans
- Viral escape, CD4 T cell loss contributes to dysfunction
RV144

- Prime-boost: ALVAC-HIV (env, gag, pol in canarypox vector) and AIDSVAX B/E (recombinant gp120 protein)
- 16,000 adult volunteers in Thailand
- 6 prime, 6 boost injections
- Lowered rate of HIV-1 infection by 31.2% compared with placebo
- n=51 vs n=74
~1921: Patient zero

SIV

HIV

60,000,000 infections
25,000,000 deaths