HIV Pathogenesis

Lecture 18
Virology W3310/W4310
Spring 2012

Nature is not human-hearted
Lao Tzu
Tao Te Ching
Pneumocystis Pneumonia — Los Angeles

As part of its commemoration of CDC's 50th anniversary, MMWR is reprinting selected MMWR articles of historical interest to public health, accompanied by a current editorial note.

On June 4, 1981, MMWR published a report about Pneumocystis carinii pneumonia in homosexual men in Los Angeles. This was the first published report of what, a year later, became known as acquired immunodeficiency syndrome (AIDS). This report and current editorial note appear below.

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.
HIV is a lentivirus

- First isolated in 1983 from the lymph node of a patient with lymphadenopathy in Paris
- Subsequently isolated at NIH and UCSF
- Electron microscopy and sequence analysis revealed them to be lentiviruses, a known group of retroviruses
Retroviridae

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

- The lymphotropic 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

• 40,000 new infections each year; 70% men, 30% women

• Half of all new infections in US occur in people 25 or younger
### Global summary of the AIDS epidemic | 2010

<table>
<thead>
<tr>
<th>Number of people living with HIV</th>
<th>Total</th>
<th>34.0 million [31.6 million–35.2 million]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults</td>
<td>30.1 million [28.4 million–31.5 million]</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>16.8 million [15.8 million–17.6 million]</td>
</tr>
<tr>
<td></td>
<td>Children (&lt;15 years)</td>
<td>3.4 million [3.0 million–3.8 million]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>People newly infected with HIV in 2010</th>
<th>Total</th>
<th>2.7 million [2.4 million–2.9 million]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults</td>
<td>2.3 million [2.1 million–2.5 million]</td>
</tr>
<tr>
<td></td>
<td>Children (&lt;15 years)</td>
<td>390 000 [340 000–450 000]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AIDS deaths in 2010</th>
<th>Total</th>
<th>1.8 million [1.6 million–1.9 million]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults</td>
<td>1.5 million [1.4 million–1.6 million]</td>
</tr>
<tr>
<td></td>
<td>Children (&lt;15 years)</td>
<td>250 000 [220 000–290 000]</td>
</tr>
</tbody>
</table>
Adults and children estimated to be living with HIV  |  2010

Total: 34.0 million [31.6 million – 35.2 million]
Estimated number of adults and children newly infected with HIV | 2010

Total: 2.7 million [2.4 million – 2.9 million]
Estimated adult and child deaths from AIDS | 2010

Total: 1.8 million [1.6 million – 1.9 million]
Children (<15 years) estimated to be living with HIV  |  2010

Total: 3.4 million [3.0 million – 3.8 million]
Estimated number of children (<15 years) newly infected with HIV | 2010

Total: 390 000 [340 000 – 450 000]
Estimated deaths in children (<15 years) from AIDS | 2010

Total: 250 000 [220 000 – 290 000]
Over 7000 new HIV infections a day in 2010

- About 97% are in low and middle income countries
- About 1000 are in children under 15 years of age
- About 6000 are in adults aged 15 years and older, of whom:
  - almost 48% are among women
  - about 42% are among young people (15-24)
<table>
<thead>
<tr>
<th>Causes of Death</th>
<th>Annual Deaths</th>
<th>Annual DALYs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower Respiratory Infections</td>
<td>4.1 million</td>
<td>94.5 million</td>
</tr>
<tr>
<td>Diarrheal Diseases</td>
<td>2.1 million</td>
<td>72.7 million</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>2 million</td>
<td>58.5 million</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1.4 million</td>
<td>34.2 million</td>
</tr>
<tr>
<td>Malaria</td>
<td>889,185</td>
<td>33.9 million</td>
</tr>
<tr>
<td>Measles</td>
<td>423,710</td>
<td>14.8 million</td>
</tr>
<tr>
<td>Neglected Diseases</td>
<td>195,098</td>
<td>19 million</td>
</tr>
<tr>
<td>Sexually Transmitted Infections</td>
<td>128,472</td>
<td>10.4 million</td>
</tr>
<tr>
<td>Polio</td>
<td>1,195</td>
<td>34,399</td>
</tr>
<tr>
<td>Other Infectious Diseases</td>
<td>1.3 million</td>
<td>28.5 million</td>
</tr>
<tr>
<td>Emerging Infectious Diseases</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*DALY = Disability-Adjusted Life Years, the years of healthy life lost due to disability, sickness or premature mortality

N/A = not available
Control of AIDS

• Triple-drug therapy has slowed the pandemic in countries with money
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
HIV-2

- Restricted primarily to populations in West Africa
- Less virulent, transmissible than HIV-1
- HIV-2 membrane proteins share homology with those of SIV
- Humans infected with HIV-2 have antibodies that cross-react with SIV
- SIV causes AIDS-like disease in macaques, but is not pathogenic in some species like African green monkeys
## Primate lentiviruses and the origin of HIV

<table>
<thead>
<tr>
<th>Virus</th>
<th>Host infected</th>
<th>Primary cell type infected</th>
<th>Clinical disorder(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equine infectious anemia virus</td>
<td>Horse</td>
<td>Macrophages</td>
<td>Cyclical infection in the first year, autoimmune hemolytic anemia, sometimes encephalopathy</td>
</tr>
<tr>
<td>Visna/maedi virus</td>
<td>Sheep</td>
<td>Macrophages</td>
<td>Encephalopathy/pneumonitis</td>
</tr>
<tr>
<td>Caprine arthritis-encephalitis virus</td>
<td>Goat</td>
<td>Macrophages</td>
<td>Immune deficiency, arthritis, encephalopathy</td>
</tr>
<tr>
<td>Bovine immunodeficiency virus</td>
<td>Cow</td>
<td>Macrophages</td>
<td>Lymphadenopathy, lymphocytosis</td>
</tr>
<tr>
<td>Feline immunodeficiency virus</td>
<td>Cat</td>
<td>T lymphocytes</td>
<td>Immune deficiency</td>
</tr>
<tr>
<td>Simian immunodeficiency virus</td>
<td>Primate</td>
<td>T lymphocytes</td>
<td>Immune deficiency and encephalopathy</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>Human</td>
<td>T lymphocytes</td>
<td>Immune deficiency and encephalopathy</td>
</tr>
</tbody>
</table>

4Adapted from Table 1.1 (p. 2) of J. A., Levy, *HIV and the Pathogenesis of AIDS*, 3rd ed. (ASM Press, Washington, DC, 2007), with permission.
Origin of HIV

• Current thinking, based on sequence analysis, is that HIV-1 and HIV-2 came from separate colonization events of simian lentiviruses in humans
HIV-1 clades or subtypes

- Four groups (four separate colonizations of humans with SIV)
- Group M: at least 9 distinct clades
- Assignment based on sequence of ENV and GAG genes
• Clades A, C, D, E predominate in areas with highest rates of infection
  - Most clades are found in central Africa
• Elsewhere, one or two clades predominate
  - Clade B predominates in the US and Western Europe
• HIV spread changing with time
  - Spread of the C-clade in Africa
Sequence comparisons provide insight on HIV origins

- Chimpanzee (SIV CPZ) and Mandrill (SIV MND) viruses: closely related to HIV-1
- Sooty mangabey virus group (SIV SM): closely related to HIV-2
Earliest records of HIV-1 infection

- Serum sample ZR59 from a DRC adult male (1959) found positive for HIV-1 in 1998
- Lymph node sample from DRC adult female (1960)
- HIV in tissue from US teenager died 1969
- HIV in tissue from Norwegian sailor died 1976
- Viral genome amplified by PCR and DNA sequence determined
When did SIV infect humans?

- 1931 (+/- 15 yr)
- 1884 - 1924, comparing 1959 and 1960 sequences
- Suggested that Kinshasa was epicenter, early spread concurrent with development of colonial cities
- Hunter, colonialism, contaminated needle theories
Transmission

• HIV is not a particularly infectious virus, not contagious like measles virus

• Not spread by respiratory, alimentary, or vector routes
<table>
<thead>
<tr>
<th>Fluid</th>
<th>Virus isolation $^b$</th>
<th>Estimated quantity of virus $^c$</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$^d$</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%$^d$</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)
Co-receptors

T cell-tropic strain of HIV-1

- HIV (X4)
- α-chemokine receptor (CxcR4)
- CD4
- Sdf-1
- CD4+ target cell

Macrophage-tropic strain of HIV-1

- HIV (R5)
- β-chemokine receptor (Ccr5)
- CD4
- β-chemokine (Rantes, Mip-1α, Mip-1β)
- CD4+ target cell
Primary HIV Infection

• Virus-dendritic cell interaction
  - Infection is typically with CCR5 (M-tropic) 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

• Downregulation 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
  - Adenopathy, 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
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
# 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><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>
</tr>
<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>Attempt of the immune system to establish homeostasis results in higher production of CD4⁺ and CD8⁺ cells as CD4⁺ cells are depleted</td>
</tr>
<tr>
<td><strong>Monocytes (dendritic cells)/macrophages</strong></td>
<td>Defects in chemotaxis</td>
<td>Loss of IL-2 production as CD4⁺ pool is depleted</td>
</tr>
<tr>
<td></td>
<td>Monocyte-dependent T-cell proliferation ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antigen-presenting cell activity ↓</td>
<td></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>Exposure to noninfectious virions (SU and TM), down-regulates chemotactic ligand receptors and causes abnormal secretion of certain chemokines</td>
</tr>
<tr>
<td></td>
<td>Hypergammaglobulinemia</td>
<td>Decreased expression of costimulatory molecules (e.g., B7)</td>
</tr>
<tr>
<td></td>
<td>Poor response to additional antigen signals</td>
<td>Cells killed by eliciting cytotoxic response in CTLs</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>Exposure to noninfectious virions (TM) causes polyclonal activation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of CD4⁺ T-cell helper function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Molecular mimicry of host proteins by viral proteins</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of IL-2 as CD4⁺ pool is depleted</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

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

• Neurological symptoms: aseptic meningitis, myelopathies, neuropathies, AIDS dementia complex
Neurological symptoms
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
B-cell lymphomas

- 60-100 times more common in AIDS patients than general population
- Tumors in lymph nodes, intestine, CNS, liver
- Often associated with infection by HHV-8 or Epstein-Barr virus
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 escape from neutralizing antibody
Broadly neutralizing antibodies

- Have been identified in some HIV-1 infected individuals
- Neutralize broadly across clades
- 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
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/