HIV and the Immune System

May 13, 2009
HIV/AIDS HISTORY

- **1926-46** - HIV possibly spreads from monkeys to humans. Newer data suggest viral ancestor appeared 1884-1924.
- **1959** - First proven AIDS death.
- **1981** - The Centers for Disease Control and Prevention (CDC) notices high rate of otherwise rare cancer.
- **1982** - The term AIDS is used for the first time.
- **1983/84** - American and French scientists each claim discovery of the virus that will later be called HIV.
- **1985** - The FDA approves the first HIV antibody test for blood supplies.
- **1987** - AZT is the first anti-HIV drug approved by the FDA.
- **1996** - FDA approves first protease inhibitors.
- **2005** - >3 million deaths in one year world wide.
- **2008** - Luc Montagnier wins Nobel Prize.
GLOBAL TOTALS
- People living with HIV/AIDS, December 2005: 40.3 million
- New infections in 2005: 4.9 million
- Deaths due to HIV/AIDS: In 2005: 3.1 million
  Cumulative: More than 25 million

North America 1.2 million
Caribbean 350,000
Latin America 1.8 million
North Africa/Mideast 510,000
Sub-Saharan Africa 25.8 million
Western Europe 720,000
East Europe/Cen Asia 1.6 million
East Asia 870,000
South Southeast Asia 7.4 million
Oceania 74,000
Australia/New Zealand 15,000

Male: female proportions

Figure 20-8
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Figure 20-7
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Transmission of HIV infection requires contact with

Blood
Milk
Semen
Vaginal fluid
Wound exudates from an infected individual.

Saliva, tears and sweat do not transmit HIV
Structure of HIV-1

CD4 - CD4+ T lymphocytes, monocytes, DCs, brain microglia

CCR5 - mononuclear phagocytes, T cells (M-tropic) - 1st to be infected

CXCR4 - naïve T cells, B cells, monocytes (T-tropic) (2%) - 50% switch late in infection
### Table 1

Patient characteristics and distribution of class I HLA alleles associated with disease progression.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Elite controllers</th>
<th>Viremic controllers</th>
<th>Chronic progressors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects, no.</td>
<td>66</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>Age, mean (range), years</td>
<td>47 (22-75)</td>
<td>48 (32-67)</td>
<td>36 (18-70)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (64)</td>
<td>47 (78)</td>
<td>24 (80)</td>
</tr>
<tr>
<td>Female</td>
<td>24 (36)</td>
<td>13 (22)</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>36 (54)</td>
<td>35 (58)</td>
<td>17 (57)</td>
</tr>
<tr>
<td>Black</td>
<td>19 (29)</td>
<td>13 (22)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9 (14)</td>
<td>5 (8)</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (3)</td>
<td>7 (12)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Plasma HIV RNA level, median (IQR), copies/mL</td>
<td>Below detection</td>
<td>770 (348-1500)</td>
<td>152,000 (67,050-278,000)</td>
</tr>
<tr>
<td>CD4+ cell count, median (IQR), cells/mm³</td>
<td>884 (641-1149)</td>
<td>602 (451-786)</td>
<td>295 (203-455)</td>
</tr>
<tr>
<td>Duration of HIV diagnosis, median (IQR), years</td>
<td>15 (9-22)</td>
<td>17 (13-25)</td>
<td>5.5 (1-17)</td>
</tr>
<tr>
<td>CCR5Δ 32 genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>57 (86)</td>
<td>47 (78)</td>
<td>NA</td>
</tr>
<tr>
<td>HT</td>
<td>9 (14)</td>
<td>13 (22)</td>
<td>NA</td>
</tr>
<tr>
<td>CCR2-64I genotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>56 (85)</td>
<td>47 (78)</td>
<td>NA</td>
</tr>
<tr>
<td>HT</td>
<td>9 (14)</td>
<td>9 (15)</td>
<td>NA</td>
</tr>
<tr>
<td>HM</td>
<td>1 (1)</td>
<td>4 (7)</td>
<td>NA</td>
</tr>
<tr>
<td>HLA-B*57</td>
<td>29 (44)</td>
<td>20 (33)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>HLA-B*27</td>
<td>10 (15)</td>
<td>12 (20)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>All protective HLA alleles</td>
<td>45 (68)</td>
<td>36 (60)</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Combined protective HLA alleles and chemokine receptors</td>
<td>48 (73)</td>
<td>43 (72)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Note. Data are no. (%) of subjects, unless otherwise indicated. See Methods for details about the 3 study groups. WT, wild type; HT, heterozygous; HM, homozygous; NA, not applicable.

a Elite controllers compared to viremic controllers, $P < .001$ by nonparametric Mann-Whitney test.

b Includes B*57, 27, 5801, 1503, 13 and 51.
Analysis of viral isolates

• Considerable variations in envelope glycoproteins.
• M (major group) >90% of all infections
  – Clades (subtypes) A through K.

• O (outlier group) - restricted to west-central Africa
• N group - (“new”) extremely rare - discovered in Cameroon
Mechanism of HIV entry into a cell

Molecular basis of HIV entry into host cells. Interactions with CD4 and a chemokine receptor ("coreceptor"). (Adapted by permission from Macmillan Publishers Ltd, from Wain-Hobson S: HIV. One on one meets two. Nature 384:117, copyright 1996.)
Pathogenesis of HIV

1. **Primary infection of cells in blood, mucosa**
   - CD4+ T cell
   - Dendritic cell

2. **Drainage to lymph nodes, spleen**

3. **Infection established in lymphoid tissue, e.g., lymph node**

4. **Acute HIV syndrome, spread of infection throughout the body**

5. **Viremia**

6. **Immune response**
   - Anti-HIV antibodies
   - HIV-specific CTLs

Kumar et al: Robbins Basic Pathology 8e - www.studentconsult.com 5-32
Partial control of viral replication

Proivirus

Clinical latency

Latent infection  Low-level infection

Other microbial infections; cytokines (e.g., TNF)

Extensive viral replication and CD4+ cell lysis

AIDS

Destruction of lymphoid tissue: depletion of CD4+ T cells
Mechanisms of CD4 cell loss

1. HIV infection of CD4+ T cells
   - Viral replication in infected CD4+ T cells
   - Death of infected cells (cytopathic effect of virus)

2. Chronic T-cell activation
   - Activation of uninfected CD4+ T cells
   - Activation-induced cell death (apoptosis)

3. Expression of HIV peptides on infected CD4+ T cells
   - Killing of infected cells by virus-specific CTLs
Normal CD4 = 500-1600

Start antiretroviral therapy when CD4<350
Nonprogressors

I. Seroconvert - immune competence maintained - low levels of virus

II. Seronegative and disease-free

III. CCR5 deficient (CCR5− 32-32-nucleotide deletion - 1% of the caucasian population

IV. HLA-B*27 and HLA-B*57 slow progression
Latently infected quiescent CD4+ T cells that contain non-integrated proviral DNA are important long-living reservoirs.
<table>
<thead>
<tr>
<th>Stage of infection</th>
<th>Typical abnormalities observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Infection and destruction of dendritic cells; some structural disruption</td>
</tr>
<tr>
<td>Late</td>
<td>Extensive damage and tissue necrosis; loss of follicular dendritic cells and germinal centers; inability to trap antigens or support activation of T and B cells</td>
</tr>
</tbody>
</table>
Lymph Node Fibrosis in HIV Infection

Normal  HIV infected


Table 20-4

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### TABLE 20-4  Immunologic abnormalities associated with HIV infection

<table>
<thead>
<tr>
<th>Stage of infection</th>
<th>Typical abnormalities observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Increased levels of some cytokines</td>
</tr>
<tr>
<td>Late</td>
<td>Shift in cytokine production from $T_H^1$ subset to $T_H^2$ subset</td>
</tr>
</tbody>
</table>

### CYTOKINE PRODUCTION

<table>
<thead>
<tr>
<th>Stage of infection</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>Highly significant reduction in proliferative capacity of $T_H^1$ cells and reduction in skin-test reactivity</td>
</tr>
<tr>
<td>Late</td>
<td>Elimination of DTH response; complete absence of skin-test reactivity</td>
</tr>
</tbody>
</table>

**DELAYED-TYPE HYPERSENSITIVITY**
Altered APC function, chemotaxis, and cytokine production

FIG. 1. Alterations of phagocytic and opsonic activities of monocytes/macrophages and PMNLs against intracellular and extracellular organisms induced by HIV.
MECHANISMS OF IMMUNE EVASION

High mutation rate - replication of retroviruses is prone to error - opportunity for accumulation of undesirable mutations

Downregulation of class I MHC molecules

Preferential inhibition of CMI
• Acute stage: HIV preferentially replicates within activated, or recently activated memory, CD4+ T cells that express CCR5. Most CD4+ T cells in the intestine (particularly in the lamina propria) express this phenotype - favored target for virus.

• Chronic activation: disruption of organization of the immune system.

Gut-Associated Lymphoid Tissue (GALT) Is a Reservoir of HIV Infection in Patients on ART

Gastrointestinal CD4$^+$ T cells harbor a greater viral burden than PB CD4$^+$ T cells during acute and early HIV-1 infection.

Migration of T cells to GALT is mediated by $\alpha 4\beta 7$. gp120 binds to an activated form of $\alpha 4\beta 7$.

Following HAART in pts with undetectable blood HIV RNA (>4 yrs), T cell numbers (sigmoid colon) increased.
Development of AIDS is like an impending train wreck

Viral Load = Speed of the train
CD4 count = Distance from cliff

"tap-and-drain" model

J. Coffin, XI International Conf. on AIDS, Vancouver, 1996
A Modified Coffin Model

Developing AIDS is like an impending train wreck:

- The CD4 count is the distance from the cliff
- Viral load is the fuel
- Speed of the train depends on:
  - Engine gear ratio (host factors)
  - Fuel mix (i.e., immune activation driven by viremia and other factors – e.g., other microbial TLR ligands)

Rodriguez, Lederman
Possible causes of immune activation:

1. Innate and adaptive immune response to HIV and its antigens
2. Direct effect of HIV proteins to bind to cellular proteins and induce immune activation (e.g., Env-binding to CD4 and/or CCR5; nef ability, or lack thereof, to down-modulate CD3-TCR)
3. Translocation of microbial products across the intestinal mucosa with resultant stimulation of TLR-2/4/5/6 on numerous immune cell types
4. Concomitant infections, either opportunistic or nonopportunistic (i.e., intestinal helminths)
5. Increased levels of pro-inflammatory and/or pro-apoptotic cytokines resulting in activation of bystander (i.e., non-HIV specific) T cells
6. Depletion and/or dysfunction of regulatory CD4 T cells (T<sub>reg</sub>).

AIDS 22(4) 439-446, 2008
Immune Reconstitution Disease (IRD)
(Immune Reconstitution Inflammatory Syndrome (IRIS))

Immune reconstitution - reversal of HIV-related immune system decline to increase functional CD4+ T cells

Anti-retroviral treatment triggers inflammatory responses to pathogens - hypersensitivity reaction

Many cases resolve within a few weeks
Diseases and Pathogens Associated With IRIS

- Castleman disease
- *Cryptococcus neoformans*
- cytomegalovirus (CMV)
- eosinophilic folliculitis
- Graves' disease
- Hansen's disease (leprosy)
- hepatitis B virus (HBV)
- hepatitis C virus (HCV)
- herpes simplex virus (HSV)
- herpes zoster (shingles)
- *Histoplasma capsulatum*
- human papillomavirus (HPV)
- Kaposi's sarcoma (KS)
- *Mycobacterium avium* complex (MAC)
- myopathy
- non-Hodgkin's lymphoma (NHL)
- *Pneumocystis carinii (P. jiroveci)* pneumonia (PCP)
- progressive multifocal leukoencephalopathy
- sarcoidosis
- systemic lupus erythematosus
- tuberculosis
Opportunistic Infections

• Protozoa
  – Cryptosporodium

• Bacteria
  – Toxoplasma, Mycobacterium avium, Nocardia, Salmonella

• Fungi
  – Candida, Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum, Pneumocystis (carinii) jiroveci

• Viruses
  – Cytomegalovirus, herpes simplex, varicella-zoster
Laboratory Diagnosis

• Serology is the usual method for diagnosing HIV infection. Serological tests can be divided into screening and confirmatory assays.

• Screening assays - ELISAs are the most frequently used screening assays. The sensitivity and specificity approaches 100% but false positive and negative reactions occur.

• Confirmatory assays - Western blot is regarded as the gold standard for serological diagnosis. However, its sensitivity is lower than screening ELISAs.
Diagnosis in Children

- Positive HIV antibody test - not used in children <18 months because of the possibility of maternal antibodies - use PCR - treat with triple therapy.
  - Controversy - should HIV negative infants with HIV-positive mothers be treated? Early treatment of asymptomatic infants prevents or delays progression of the disease

- Positive HIV antibody test in child >18 months usually indicates infection
Treatment and Prevention of AIDS and Vaccine Development

Antiviral drugs used in combination (HAART)
  Nucleoside analogues - inhibit reverse transcriptase activity
  Viral protease inhibitors - block processing of precursor proteins into mature viral capsid and core proteins
  Newer reverse transcriptase inhibitors

NEW RECOMMENDATION: TREAT BEFORE HAART IS ABSOLUTELY NECESSARY

Inhibitors of viral entry - chemokine receptor antagonists and inhibitors of viral-cell membrane fusion

Integrase inhibitors - prevent integration of proviral DNA into host DNA

Prevention - screening blood supply, public health awareness

Vaccine development

Antibiotics
Box 1 | Challenges in the development of a prophylactic HIV-1 vaccine

1. Extensive viral clade and sequence diversity.
2. Early establishment of latent viral reservoirs.
3. Immune correlates of protection unclear.
5. Antibody responses typically type-specific.
6. No method exists to elicit broadly reactive neutralizing antibodies.
7. Attenuated viruses unsafe for human use.
8. Lack of a small-animal model.
9. Little pharmaceutical interest.
<table>
<thead>
<tr>
<th>Generic name (other names)</th>
<th>Typical dosage</th>
<th>Some potential side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REVERSE TRANSCRIPTASE INHIBITORS: NUCLEOSIDE ANALOGUES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine (Videx, ddI)</td>
<td>2 pills, 2 times a day on empty stomach</td>
<td>Nausea, diarrhea, pancreatic inflammation, peripheral neuropathy</td>
</tr>
<tr>
<td>Emtricitabine (Emtriva, FTC)</td>
<td>1 pill, 1 time a day</td>
<td>Headache, diarrhea, nausea, rash</td>
</tr>
<tr>
<td>Lamivudine (Epivir, 3TC)</td>
<td>1 pill, 2 times a day</td>
<td>Usually none</td>
</tr>
<tr>
<td>Stavudine (Zerit, d4T)</td>
<td>1 pill, 2 times a day</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Zalcitabine (Hivid, ddC)</td>
<td>1 pill, 3 times a day</td>
<td>Peripheral neuropathy, mouth inflammation, pancreatic inflammation</td>
</tr>
<tr>
<td>Zidovudine (Retrovir, AZT, ZDV)</td>
<td>1 pill, 2 times a day</td>
<td>Nausea, headache, anemia, neutropenia (reduced levels of neutrophil white blood cells), weakness, insomnia</td>
</tr>
<tr>
<td>Pill containing lamivudine and zidovudine (Combivir)</td>
<td>1 pill, 2 times a day</td>
<td>Same as for zidovudine</td>
</tr>
<tr>
<td>Abacavir (Ziagen)</td>
<td>2 pills, 1 time a day</td>
<td>Nausea, vomiting, diarrhea, lactic acidosis (severe liver disease)</td>
</tr>
<tr>
<td>Tenofovir (Viread)</td>
<td>1 pill, 1 time a day</td>
<td>Nausea, vomiting, increased risk of bone breakage</td>
</tr>
<tr>
<td><strong>REVERSE TRANSCRIPTASE INHIBITORS: NONNUCLEOSIDE ANALOGUES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delavirdine (Rescriptor)</td>
<td>4 pills, 3 times a day (mixed into water); not within an hour of antacids or didanosine</td>
<td>Rash, headache, hepatitis</td>
</tr>
<tr>
<td>Nevirapine (Viramune)</td>
<td>1 pill, 2 times a day</td>
<td>Rash, hepatitis</td>
</tr>
<tr>
<td>Efavirenz (Sustiva)</td>
<td>1 pill, 1 time a day</td>
<td>Dizziness, insomnia, rash</td>
</tr>
<tr>
<td><strong>PROTEASE INHIBITORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir (Crixivan)</td>
<td>2 pills, 3 times a day on empty stomach or with a low-fat snack and not within 2 hours of didanosine</td>
<td>Kidney stones, nausea, headache, blurred vision, dizziness, rash, metallic taste in mouth, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance</td>
</tr>
<tr>
<td>Nelfinavir (Viracept)</td>
<td>3 pills, 3 times a day with some food</td>
<td>Diarrhea, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance</td>
</tr>
<tr>
<td>Ritonavir (Norvir)</td>
<td>6 pills, 2 times a day (or 4 pills, 2 times a day if taken with saquinavir) with food and not within 2 hours of didanosine</td>
<td>Nausea, vomiting, diarrhea, abdominal pain, headache, pricking sensation in skin, hepatitis, weakness, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance</td>
</tr>
<tr>
<td>Saquinavir (Invirase, a hard-gel capsule; Fortovase, a soft-gel capsule)</td>
<td>6 pills, 3 times a day (or 2 pills, 2 times a day if taken with ritonavir) with a large meal</td>
<td>Nausea, diarrhea, headache, abnormal distribution of fat, elevated triglyceride and cholesterol levels, glucose intolerance</td>
</tr>
<tr>
<td>Atazanavir (Reyataz)</td>
<td>2 pills, 1 time a day</td>
<td>Must be used with at least two other drugs</td>
</tr>
<tr>
<td>Fosamprenavir calcium? (Lexiva)</td>
<td>2 pills, 2 times a day</td>
<td>Appetite loss, malaise, diarrhea, nausea, vomiting</td>
</tr>
<tr>
<td><strong>FUSION INHIBITORS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide (Fuzeon, T-20)</td>
<td>Subcutaneous injection</td>
<td>Soreness at injection site, dizziness, loss of sleep, numbness in feet and legs</td>
</tr>
</tbody>
</table>

Table 20-5
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Therapeutic Strategies to Modulate Expression of Chemokine Receptors

• Monoclonal abs to receptor
• Chemokines that stay within the cytoplasm are able to capture and bind to their corresponding receptor on the way to the cell surface.
• Short interfering RNA (siRNA) - selectively inactivate target genes