Human Immunodeficiency Virus (HIV)

Chapter 37

Retroviridae
Retroviridae

- RNA
- Single Stranded
- Positive
- DNA Step in Replication
- Enveloped
Artist’s Images of HIV

Cutaway Image

External Image
Acquired Immune Deficiency Syndrome (AIDS)

- caused by human immunodeficiency virus (HIV)
  - occurs worldwide, causing the great pandemic of the second half of the twentieth century
  - retrovirus
- theories on origin of disease
  - HIV-1 evolved from chimp virus SIVcpz
  - use of human blood products in chimps infected animals with HIV-1 precursor that evolved into SIVcpz
HIV
HIV video

Figure 37.8
Figure 37.9

**HIV replication**

(a) Docking and fusion.

(b) Immune stimulus.

(c) HIV exits by viral budding.

Steps show activity of one strand of viral DNA.
HIV
Figure 37.7

Map showing the distribution of HIV cases worldwide with specific numbers for each region:

- North America: 1.0 million
- Caribbean: 440,000
- Western Europe: 610,000
- Eastern Europe and Central Asia: 1.4 million
- Eastern Asia/South Asia and Southeast Asia: 8.2 million
- Latin America: 1.7 million
- North Africa/Middle East: 540,000
- Sub-Saharan Africa: 25.4 million
- Oceania: 35,000

Total: >46 million
Transmission

- acquired and can be passed from person to person
  - when infected blood, semen or vaginal secretions come in contact with uninfected person’s broken skin or mucous membranes
Groups Most at Risk

- in descending order
  - men who have sex with other men
  - intravenous drug users
  - heterosexuals who have intercourse with drug users and prostitutes
  - children born of infected mothers, as well as their breast-fed infants
  - transfusion patients and transplant recipients
Serological changes during infection

Figure 37.11
HIV pathogenesis

- once inside host, HIV gp120 envelope protein binds to host CD4+ glycoprotein plasma membrane receptor on CD4+ cells
- after entry into host cells, viral RNA is reverse transcribed into DNA, then second strand of DNA is synthesized to produce proviral DNA
  - integrates into host cell’s DNA as a provirus which can remain latent or, alternatively, can direct synthesis of viral RNA $\rightarrow$ synthesis of new viral particles
HIV pathogenesis

- involves depletion of T cells, possibly by:
  - disruption of plasma membrane permeability
  - destruction by immune system cells due to presence of gp120 in membrane
  - syncytia formation
  - integration and transposition of HIV provirus
  - apoptosis

- may cause disruption of balance between different T cell populations
- may destroy or disable dendritic cells
- HIV mutates rapidly, so that it evades immune system
Figure 37.12

Apoptosis

Indirect

HIV

gp120

Antibody

Infected CD4⁺ cell

Non-activated uninfected CD4⁺ cell

Direct

Infected CD4⁺ cell

Activated uninfected CD4⁺ cell

Activation

Antigen(s) or superantigens

Apoptosis of uninfected cell

(a)

CD4⁺
gp120

(b)
Clinical manifestations

• four types of pathological changes
  – AIDS-related complex (ARC)
  – AIDS
  – central nervous system disease
  – AIDS-related cancers
ARC

- fever, malaise, headaches, macular rash, weight loss, lymph node enlargement, oral candidiasis, and presence of antibodies to HIV
- occurs in first few months after infection; lasts 1 to 3 weeks
- can develop to full-blown AIDS
AIDS

- progressive destruction of CD4+ cells leads to collapse of immune system
- patient susceptible to opportunistic infections
Course of Disease

• some patients rapidly develop clinical AIDS; die within 2-3 years
• some patients remain relatively healthy for at least 10 years post infection
• in majority of patients HIV infection progresses to AIDS in 8-10 years
CDC Classification System for Stages of HIV-Related Conditions

- **acute**
  - 2-8 weeks after infection
  - most individuals experience a brief illness called acute retroviral syndrome
  - rapid multiplication and dissemination of virus throughout body
  - stimulation of immune response

- **asymptomatic**
  - may last from 6 months to 10 or more years
  - levels of detectable HIV in blood decrease, although viral replication continues
  - effects on immune functions may occur
CDC Classification System for Stages of HIV-Related Conditions

- chronic symptomatic
  - formerly called AIDS-related complex or ARC
  - can last for months to years
  - viral replication continues
  - numbers of CD4+ cells in blood significantly decrease

- results in patients developing a variety of illnesses often caused by opportunistic pathogens
CD4 + T Cell Depletion by HIV

• possible mechanisms
  – direct cytopathic effects of HIV on T cells
  – formation of syncytia
  – immune-mediated destruction of HIV-infected cells
  – effects of viral products (e.g., gp120) on uninfected cells
Other Mechanisms for CD4+ T Cell Depletion by HIV

- free gp120 proteins released from infected cells may bind to CD4 on uninfected cells inducing them to undergo apoptosis
- immune system components may contribute to continuing destruction of virus-infected CD4+ cells
- HIV may inhibit or destroy dendritic cells
- rapid mutation rate of virus may overwhelm immune system
- may alter immune system integrity by disrupting balance between various T cell phenotypes
Back to CDC Classification System for Stages of HIV-Related Conditions

• AIDS – fourth and last stage
  – immune system no longer able to defend against virus

• definition of AIDS
  – all HIV-infected individuals who has fewer than 200 CD4\(^+\) T cells/microliter of blood or a CD4\(^+\) cell percentage of lymphocytes of less than 14
<table>
<thead>
<tr>
<th>Table 37.3</th>
<th>Disease Processes Associated with AIDS</th>
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<tbody>
<tr>
<td></td>
<td>Candidiasis of bronchi, trachea, or lungs</td>
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<td></td>
<td>Candidiasis, esophageal</td>
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<td></td>
<td>Cervical cancer, invasive</td>
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<tr>
<td></td>
<td>Coccidioidomycosis, disseminated or extrapulmonary</td>
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<td></td>
<td>Cryptosporidiosis, chronic intestinal (&gt;1 month’s duration)</td>
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<td></td>
<td><em>Cyclospora</em>, diarrheal disease</td>
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<td></td>
<td>Cytomegalovirus disease (other than liver, spleen, or lymph nodes)</td>
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<td>Cytomegalovirus retinitis (with loss of vision)</td>
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<td>Encephalopathy, HIV-related</td>
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<td></td>
<td>Herpes simplex: chronic ulcer(s) (&gt;1 month’s duration); or bronchitis, pneumonitis, or esophagitis</td>
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<td></td>
<td>Histoplasmosis, disseminated or extrapulmonary</td>
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<td>Isosporiasis, chronic intestinal (&gt;1 month’s duration)</td>
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<td></td>
<td>Kaposi’s sarcoma</td>
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<td>Lymphoma, Burkitt’s (or equivalent term)</td>
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<td></td>
<td>Lymphoma, immunoblastic (or equivalent term)</td>
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<td>Lymphoma, primary, of brain</td>
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<td></td>
<td><em>Mycobacterium avium</em> complex or <em>M. kansasii</em></td>
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<td><em>Mycobacterium tuberculosis</em>, any site</td>
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<td><em>Mycobacterium</em>, other species or unidentified species</td>
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<td></td>
<td><em>Pneumocystis</em> pneumonia</td>
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<td>Pneumonia, recurrent</td>
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<td>Progressive multifocal leukoencephalopathy</td>
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<td><em>Salmonella</em> septicemia, recurrent</td>
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<td>Toxoplasmosis of brain</td>
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<td>Wasting syndrome due to AIDS</td>
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</tbody>
</table>

*Source: Data from MMWR 41 (No. RR17). 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults.*
Central nervous system disease caused by HIV

- headaches, fever, subtle cognitive changes, abnormal reflexes, and ataxia
- dementia and severe sensory and motor changes observed in advanced cases
- autoimmune neuropathies, cerebrovascular disease, and brain tumors are common
AIDS-related cancers

- Kaposi’s sarcoma
  - caused by human herpesvirus 8
- carcinoma of mouth and rectum
- B-cell lymphomas
AIDS Associated Diseases

Thrush

*Candida albicans*

Karposi’s sarcoma
Diagnosis

- viral isolation and culture
- assays for reverse transcriptase activity or viral antigens
- most commonly done by detection of specific anti-HIV antibodies in the blood
  - routine screening tests use ELISA assays which have many false positive results which are retested using western blot technique
- most sensitive test uses polymerase chain reaction
Treatment

- no cure for AIDS
- treatment directed at reducing viral load, disease symptoms, and treating disease and malignancies
- most successful treatment involves a combination of drugs
Antivirals used

- **nucleoside reverse transcriptase inhibitors**, e.g., AZT
- **nonnucleoside reverse transcriptase inhibitors**, e.g., delavirdine
- **protease inhibitors**, e.g., indinavir
- **fusion inhibitors** (FIs) – prevent entry of HIV into cells, e.g., enfuvirtide
Prevention and control

• achieved primarily through education
• barrier protection from blood and body fluids
• not sharing intravenous needs or syringes
• continued screening of blood and blood products
Vaccine

- not available
- ideal vaccine
  - would stimulate the production of neutralizing antibodies which would bind to virus preventing it from entering host cells
  - promote formation of cytotoxic T cells capable of destroying cells infected with virus
- problems with development of vaccine
  - envelope proteins of virus continually change their antigenic properties
Long Term Nonprogressors

- HIV-infected people who
  - maintain CD+ T cell counts of at least 600 cells/µl of blood
  - have <5,000 copies of HIV RNA/ml of blood
  - have remained this way for > 10 years after documented infection

- explanations of phenomena
  - effective immune response to relatively conserved proteins
  - initial infection was with attenuated strain
  - predisposing genetic differences