Ch19
Disorders Associated with the Immune System: AIDS
LEARNING OBJECTIVES

- Explain the attachment of HIV to a host cell
- List two ways in which HIV avoids the host’s antibodies
- Describe the stages of HIV infection
- Describe the effects of HIV infection on the immune system
- Describe how HIV infection is diagnosed
- List the routes of HIV transmission
- Identify geographic patterns of HIV transmission
- List the current methods of preventing and treating HIV infection
Acquired Immunodeficiency Syndrome (AIDS)

Origin and History

- **1981**: In US, cluster of *Pneumocystis* pneumonia and Kaposi's sarcoma in young homosexual men discovered. The men showed loss of immune function.

- **1983**: Discovery of virus causing loss of immune function.

- **1986**: Scientists started to identify the virus with "HIV" abbreviation.

HIV is thought to have crossed the species barrier into humans in central Africa in the 1930s.

- Patient who died in 1959 in Congo is the oldest known case.

- Virus spread in Africa as result of urbanization. World-wide spread through modern transportation and unsafe sex.

- Norwegian sailor who died in 1976 is the first known case in Western world.
HIV Infection – Review from Ch 13

Fig 13.19

1. Retrovirus enters by fusion between attachment spikes and the host cell receptors.

2. Uncoating releases the two viral RNA genomes and the viral enzymes reverse transcriptase, integrase, and protease.

3. Reverse transcriptase copies viral RNA to produce double-stranded DNA.

4. The new viral DNA is transported into the host cell’s nucleus, where it is integrated into a host cell chromosome as a provirus by viral integrase. The provirus may be replicated when the host cell replicates.

5. Transcription of the provirus may also occur, producing RNA for new retrovirus genomes and RNA that encodes the retrovirus capsid, enzymes, and envelope proteins.

6. Viral proteins are processed by viral protease; some of the viral proteins are moved to the host plasma membrane.

7. Mature retrovirus leaves the host cell, acquiring an envelope and attachment spikes as it buds out.

8. Host cell

9. Viral proteins

10. Identical strands of RNA

11. RNA

12. Provirus

13. Reverse transcriptase

14. Viral DNA

15. Viral RNA
Pathogenesis: HIV cellular targets

- **T<sub>h</sub> cells**
- APCs
- Brain cell
- Intestinal epithelium

Infection of intestinal epithelium and lymphoid tissue probably contributes to chronic diarrhea and weight loss.

Infection of several types of brain cells probably contributes to lethargy and HIV dementia.

CD<sup>+</sup> Th1 inflammatory cells are the principal target of HIV. These cells are normally responsible for macrophage activation and cell-mediated immunity through CD8 cytotoxic cell activation.

CD<sup>+</sup> macrophages, dendritic and other antigen-presenting cells harbor HIV but are not usually killed by it. The cells are a continuing source of the virus and can carry it into the brain.

CD<sup>+</sup> Th2 helper cells normally control antibody production by B cells.
HIV: Retrovirus with ssRNA, RT, and envelope with gp120 spikes.

Gp120 attach to CD4 on _________ cells, MΦ, dendritic cells.

Function of RT?

Provirus latent or directs active viron synthesis

HIV evades IS via latency, vacuoles, antigenic change

HIV Infection – AIDS is Final stage of HIV Infection
HIV Attachment, Fusion, and Entry

Fig 19.13

- CD4 receptor
- gp120
- gp41
- CCR5 or CXCR4 coreceptor
- Viral envelope
- Envelope remains behind
Latent vs. Active HIV Infection in CD4+ T Cells

Proviruses

CD4 receptors

CCR5 or CXCR4 receptors

CD4+ T Cell

Chromosomal DNA

Viral RNA

mRNA

Core with viral RNA

Envelope

Virus beginning to bud from T cell

Progeny HIV

Fig 19.14b
Active HIV Infection in Macrophages

Fig19.15
The Stages of HIV Infection

- **Phase 1**: Asymptomatic or chronic lymphadenopathy
- **Phase 2**: Symptomatic; early indications of immune failure
- **Phase 3** is AIDS: Characterized by indicator conditions, such as: CMV, TB, *Pneumocystis*, toxoplasmosis, and Kaposi's sarcoma (see Table 19.5)

- Phases 1 and 2 are reported as AIDS if CD4+ T cells <200 cells/µl; Phase 3 always reported as AIDS
- Progression from HIV infection to AIDS: ~ 10 y
- The life of an AIDS patient can be prolonged by the proper treatment of opportunistic infections
- People lacking CCR5 are resistant to HIV infection
Several **chemokine receptors** can function as viral coreceptors, but CCR5 is likely the most physiologically important. ⇒ new experimental HIV drugs, called **entry inhibitors**
The Progression of HIV Infection

**Phase 1: Asymptomatic or chronic lymphadenopathy**

1. About 2 months following initial infection, the population of HIV in blood peaks at about 10,000,000/ml.

2. Population of CD4+ T cells plunges during acute phase of HIV infection, then recovers as immune response appears.


4. HIV in blood stabilizes at steady state of 1000 to 10,000/ml.

5. CD4+ T cell population declines steadily.

**Phase 2: Symptomatic; early indications of immune failure**

6. Huge but indefinite numbers of HIV are present in lymphoid tissue, many in latent or proviral form (see Figure 19.14). At least 100 billion HIV are generated each day for years, mostly by infected T cells.


8. HIV levels in blood rise as immune system breaks down.

**Phase 3: AIDS indicator conditions**

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**KEY**

- **CD4+ T cell population**
- **HIV population in blood**
Exposed, but not infected

- CCR5 mutation
- Effective CTLs

Survival with HIV Infection

Long-term nonprogressors

- Mechanism not known
Pneumocystis jirovecii

Normal lung

Infection of lungs by Pneumocystis carinii

Pneumocystis jirovecii
Diagnostic Methods

- **Seroconversion** takes up to 3 months
- HIV antibodies detected by ELISA
- HIV antigens detected by Western blotting
- HIV antigens detection for diagnosis of congenital HIV infection, needle stick accidents and to monitor drug therapy: **Plasma viral load tests** (PCR or Western blot)
- **Plasma viral load** (PVL) is determined by PCR or nucleic acid hybridization
To be conclusive (HIV-positive), a Western Blot must have 5 horizontal stripes.

Figure:
Examples of reactions by an HIV-1 Western blot:

1. Positive control (strong)
2. Positive control (weak)
3. Negative control
4. Indeterminate profile
5. Indeterminate profile (highly suggestive)
HIV Transmission

HIV survives 6 h outside a cell and < 1.5 d inside a cell. Infected body fluids transmit HIV via:

- Sexual contact
- Breast milk
- Transplacental infection of fetus
- Blood-contaminated needles
- Organ transplants
- Artificial insemination
- Blood transfusion

In developed countries, blood transfusions are not a likely source of infection anymore.
AIDS Worldwide

- Heterosexual intercourse (85%)
- Injected drug use (IDU)
- Women comprise 42% of infected

*Fig 19.17

= 100,000 persons living with HIV/AIDS

*Estimates are that India now has in excess of 5 million cases; data for China are weak, but AIDS cases are estimated at more than 1 million and are entering a phase of rapid increase.
AIDS Prevention

- Condoms and sterile needles!
- Health care workers use Universal Precautions:
  - Wear gloves, gowns, masks, and goggles
  - Do not recap needles
  - Risk of infection from infected needlestick injury is 0.3%

- Vaccine difficulties due to
  - Mutations
  - Geographical clades
  - Antibody-binding sites “hidden”
  - Infected cells not susceptible to CTLs
  - Proviruses
  - Latent viruses

(2099 last phase III trial in Thailand)
AIDS Chemotherapy

Treatment has much improved with **HAART** (Highly Active Anti-Retroviral Therapy - cocktail)

- *Nucleoside reverse transcriptase inhibitors* (mostly nucleoside analogs, e.g.: AZT)
- *Non-nucleoside reverse transcriptase inhibitors*
- Protease inhibitors
- Fusion inhibitors