جامعة الملك سعود
King Saud University

MED437
KING SAUD UNIVERSITY

HIV Human Immunodeficiency virus & AIDS Acquired immune deficiency syndrome

Objectives

- To know the modes of transmission of HIV
- To understand HIV interactions with CD4 positive helper lymphocytes
- To understand the mechanisms involved in immunodeficiency associated with HIV
- To know the course of immunological events from the time of infection with HIV until the development of AIDS

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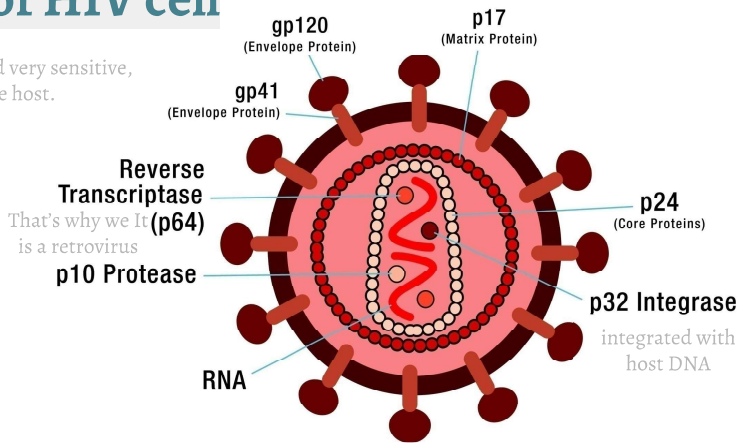
Immunology
Team 437

Color index: Important Note

Structure of HIV cell

It's an enveloped virus and very sensitive, will not survive outside the host.



Useful video (2:56)

Transmission

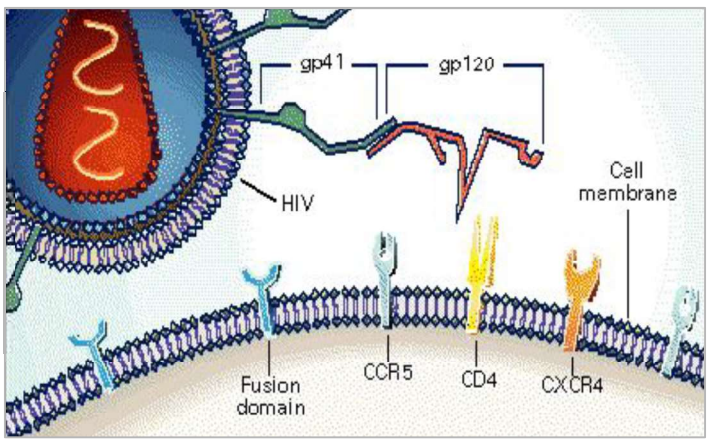
Modes of infection:

- **Sexual transmission at genital or colonic mucosa**
  - Homosexuals are more prone to injury due to high vascular supply to the anus (the receptive is at higher risk).
  - Circumcision is a protective factor
  - It is not transmitted by kissing nor by mosquito bites
- **Mother to infant**
  During pregnancy, labor & breastfeeding
- **Blood transfusions**
- **Accidental occupational exposure**
  Needle prick

How HIV enters cells?

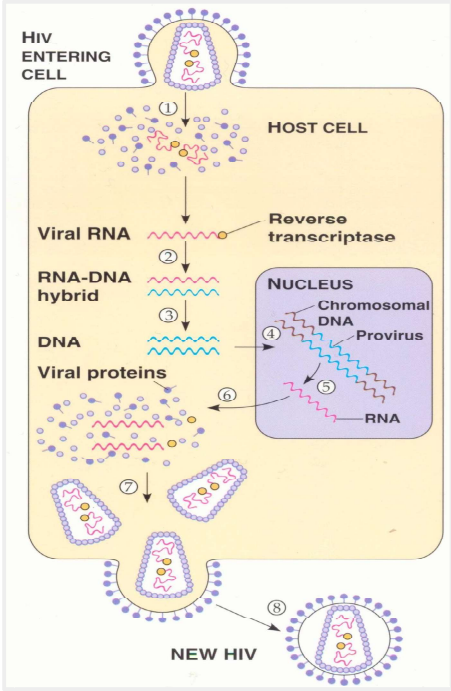
- **gp120** env protein binds to **CD4** molecule
  - CD4 found on T-cells macrophages, and microglial cells
  - Binding to CD4 is not sufficient for entry
- gp120 env protein binds to co-receptor
  - Chemokine receptors
  - CCR5 and CXCR4 receptors — Deletion of CCR5 gene will decrease the possibility to have HIV.
- Binding of virus to cell surface results in fusion of viral envelope with cell membrane
- Viral core is released into cell cytoplasm

HIV and cellular receptors



Viral-host Dynamics

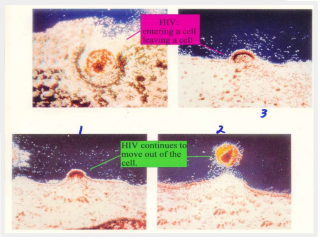
- About 10^{10} (10 billion) virions are produced daily
- Average lifespan of an HIV virion in plasma is ~6 hours
- Average life-span of an HIV-infected CD4 lymphocytes is ~1.6 days
- HIV can lie dormant within a cell for many years, especially in resting (memory) CD4 cells, unlike other retroviruses



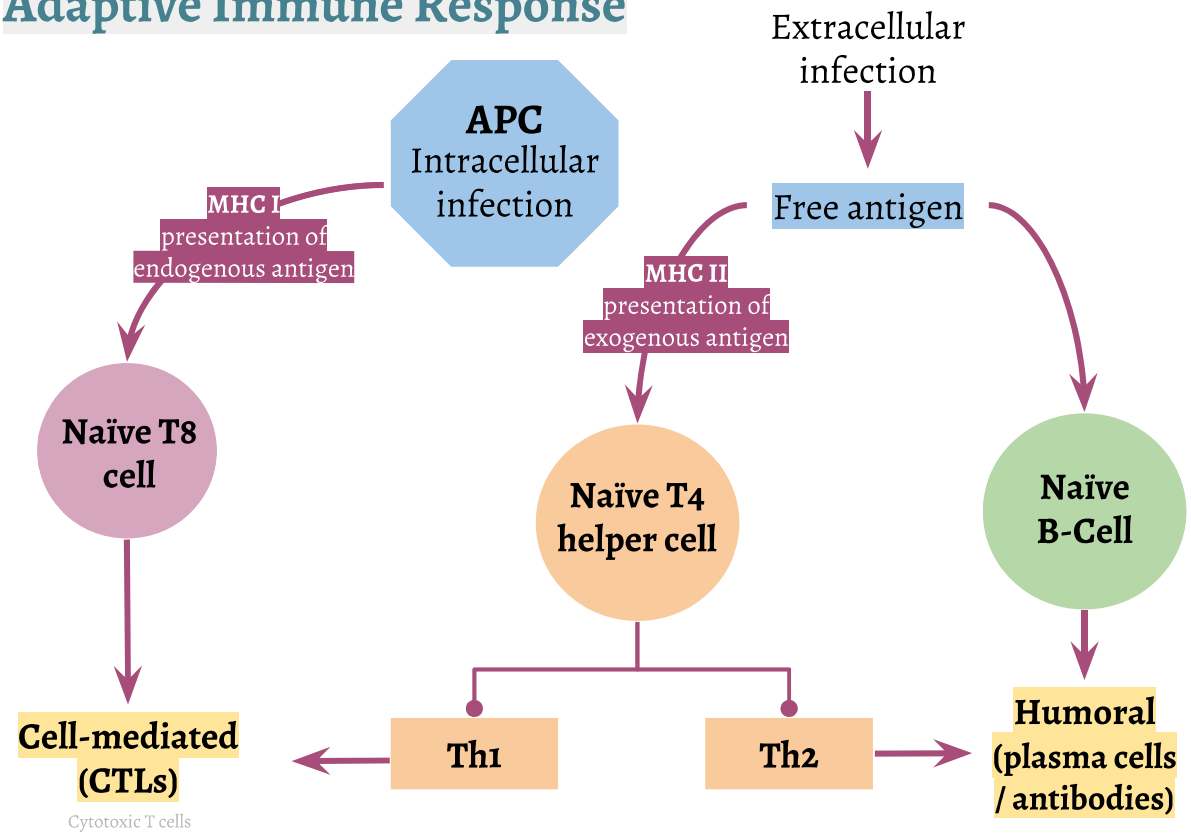
1. HIV (retrovirus) enters cell ①
2. Reverse Transcriptase makes DNA copy of RNA ③
3. Viral DNA forms provirus with host DNA ⑦

- Viral DNA makes mRNA
- mRNA makes HIV proteins
- HIV proteins become HIV capsid
- mRNA is collected inside of HIV capsid forming new HIV
- New HIV leaves cell and wraps itself in host membrane (envelope)

HIV entering and leaving a human cell



Overview of Adaptive Immune Response



General principles of viral-host interactions

- **Host**: mounts HIV-specific immune responses CD8 & CTLs mainly
  - Cellular (cell-mediated) - most important
  - Humoral (antibody-mediated)

- **Virus**: subverts the immune system
  - Infects CD4 cells that control normal immune responses
  - Integrates into host DNA
  - High rate of mutation this is why we use a lot of drugs
  - Hides in tissue not readily accessible to immune system

Cellular immune response to HIV

CD8 Cytotoxic T lymphocyte (CTL) once get exhausted ⇒ patient will reach the end stage "AIDs"

- Derived from naïve T8 cells, which recognize viral antigens in context of MHC class **I** presentation
- Directly destroy infected cell
- Activity augmented by Th1 response

CD4 Helper T Lymphocyte (Th)

- Plays an important role in cell-mediated response
- Recognizes viral antigens by an antigen presenting cell (APC)
  - Utilizes major histocompatibility complex (MHC) class **II**
- Differentiated according to the type of "help"
  - Th1 - activate Tc (CD8) lymphocytes, promoting cell-mediated immunity
  - Th2 - activate B lymphocytes, promoting antibody mediated immunity

Humoral immune response to HIV

Antibodies response is less effective than the cellular

- **Neutralization**
  - Antibodies bind to surface of virus to prevent attachment to target cell
- **Antibody-dependent cell-mediated cytotoxicity (ADCC)**
  - Fc portion of antibody binds to NK cell
  - Stimulates NK cell to destroy infected cell

Cells infected by HIV

➢ Numerous organ systems are infected by HIV:

- Brain: macrophages and glial cells
- Lymph nodes and thymus: lymphocytes and dendritic cells
- Blood, semen, vaginal fluids: macrophages
- Bone marrow: lymphocytes (important in trans-plantation)
- Skin: langerhans cells
- Colon, duodenum, rectum: chromaffin cells
- Lung: alveolar macrophages

General principles of immune dysfunction in HIV

- All elements of immune system are affected
- Advanced stages of HIV are associated with substantial disruption of lymphoid tissue
  - Impaired ability to mount immune response to new antigen
  - Impaired ability to maintain memory responses
  - Susceptibility to opportunistic infections

Mechanisms of CD4 depletion and dysfunction

Direct	Indirect
• Elimination of HIV-infected cells by virus-specific immune responses • Loss of plasma membrane integrity because of viral budding	1. Syncytium formation 2. Apoptosis 3. Autoimmunity

Syncytium formation

★ Observed in HIV infection, most commonly in the **brain**

★ Uninfected cells may then bind to infected cells due to **viral gp 120** (Infected and non-infected cells will adhere together)

★ This results in **fusion** of the cell membranes and subsequent **syncytium formation.**

★ These syncytia are highly unstable and die quickly

Role of Cellular Activation in Pathogenesis of HIV

- HIV induces immune activation
  - Which may seem paradoxical because HIV ultimately results in severe immunosuppression
- Activated T-cells support HIV replication
  - Intercurrent infections are associated with transient increases in viremia
  - Accounts for why TB worsens underlying HIV disease

Role of Cytokine Dysregulation in Pathogenesis of HIV

- HIV is associated with increased expression of pro-inflammatory cytokines
  - TNF-alpha, IL-1,IL-6, IL-10, IFN-gamma
- HIV results in disruption and loss of immunoregulatory cytokines
  - IL-2, IL-12 very imp. to compact the infection
  - Necessary for modulating effective cell-mediated immune responses (CTLs and NK cells)

Primary infection

flu-like manifestations

- 70-80% symptomatic, 3-12 weeks after exposure
- Fever, rash, cervical lymphadenopathy, aseptic meningitis, encephalitis, myelitis, polyneuritis
- Surge in viral RNA copies to >1 million
- Fall in CD4 count to 300-400
- Recovery in 7-14 days

Seroconversion

- Median 8 weeks after infection
- Level of viral load post seroconversion correlates with risk of progression of disease

The time when antibodies can be detected in the serum, may happen in 28 days or 3 months.

Asymptomatic phase

- Remain well with no evidence of HIV disease except for generalized lymphadenopathy
- Fall of CD4 count by about 50-150 cells per year

Balance between HIV & immune system but it will not stop infecting the CD4 cells, gradually decrease every year until reach the end stage.

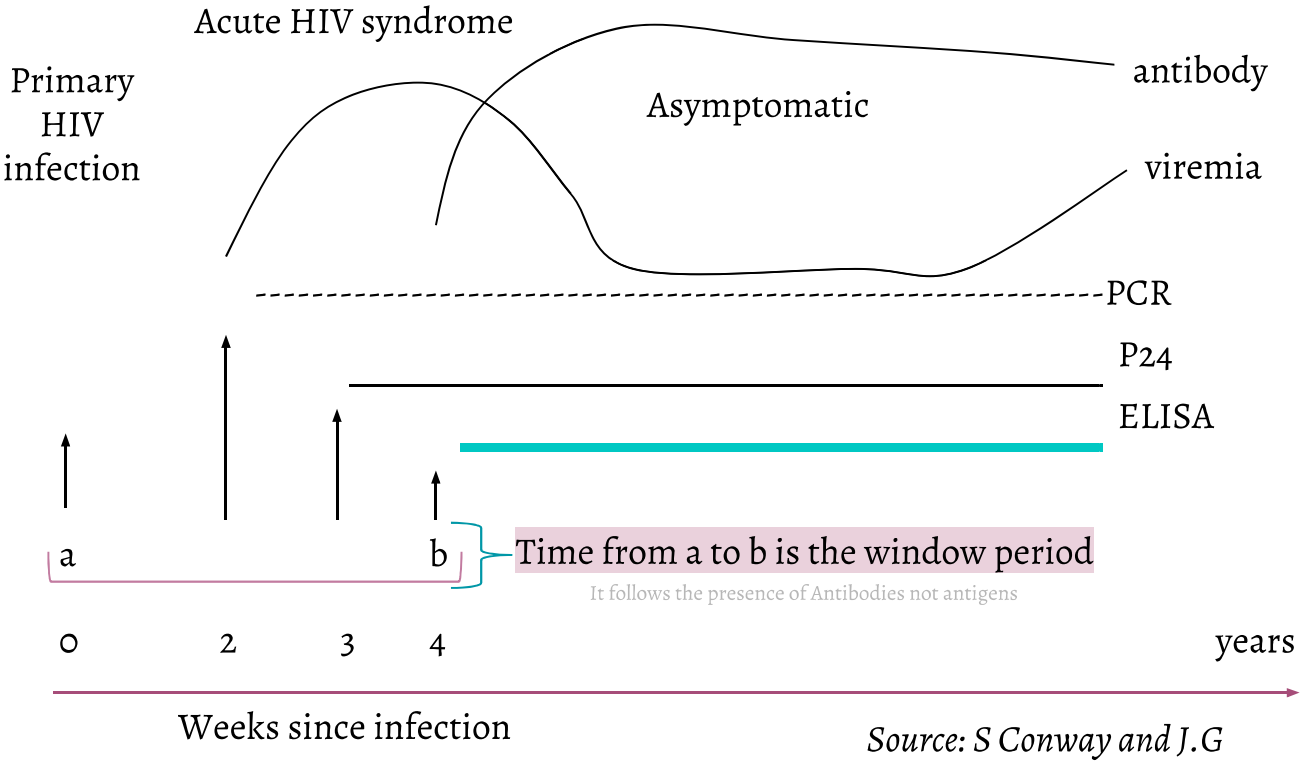
CD4 T-cell Count and Progression to AIDS

- Gradual reduction in number of circulating CD4 cells is inversely* correlated with the viral load
- Any depletion in numbers of CD4 cells renders the body susceptible to opportunistic infections

Window period: Untreated clinical course

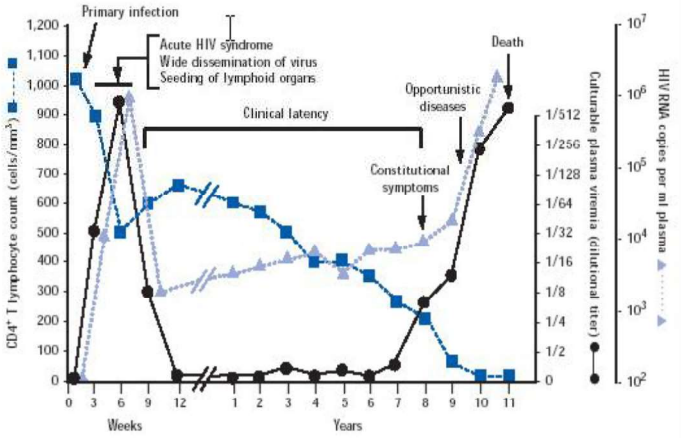
The period between getting HIV infection and appearing of the antibodies.

Viremic & contiguous period, but we can't tell that the patient is infected!



Source: S Conway and J.G Bartlett, 2003

Natural history of HIV



Laboratory markers of HIV infection

Viral load	CD4 count
• Marker of HIV replication rate Increased viral load ⇒worse prognosis	• Marker of immunologic damage

Diagnosis

most sensitive ⇒ PCR

Antibody test, ELISA	Western blot	used for monitoring HIV RNA viral load

Management

- Treatment recommended when symptomatic or CD4 count below 200
- Earlier if high viral load, rapidly falling CD4 count, hepatitis C co-infection
  - Antiviral therapy
    - Reverse transcriptase inhibitors
    - Protease inhibitors
    - Fusion inhibitors

Take home message

Dr. Reem said: window period and CD4 are the most important

- ➢ Infection with HIV usually occurs by sexual transmission, blood transfusion, mother to infant or accidental exposure.
- ➢ HIV targets the immune system and primarily infects CD4 positive lymphocytes
- ➢ Immunodeficiency associated with HIV infections is mainly due to reduction in CD4 positive helper lymphocyte numbers.
- ➢ Increased viral load, significant reduction in CD4 lymphocytes and opportunistic infections are the hallmarks of progression to AIDS.

Quiz

1- Naïve T8 cells recognize viral antigens by:

A- MHC I
B- MHC II
C- A&B
D- None of the above

2-Syncytium Formation is commonly observed in which organ?

A- Lung
B- Duodenum
C- Brain
D- Bone marrow

3- Th2 activate which type of immunity?

A- Cell mediated immunity
B- Antibody mediated immunity

4- HIV is results in loss of:

A- IL-1
B- IL-2
C- IL6
D- IL-10

5- Which of the following is a direct mechanism of CD4 depletion?

A- Elimination of HIV-infected cells by virus-specific immune responses
B- Syncytium formation
C- Apoptosis
D-Autoimmunity

Answers:
1. A
2. C
3. B
4. B
5. A

Thanks for checking our team