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King Saud University

MED438
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Color code:
Important in red
Extra in blue

HIV/AIDS

Immunology
MED438

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Editing file

Objectives

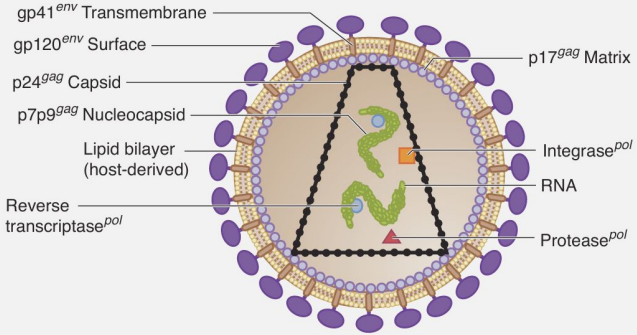
- To know the modes of transmission of HIV.
- To understand HIV interactions with CD4 positive helper lymphocytes.
- To understand the mechanisms involved in immunodeficiency associated with HIV.
- To know the course of immunological events from the time of infection with HIV until the development of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

Structure of HIV

APCs work via MHC Class II, thus they express the CD4 receptor.

- HIV is an enveloped retrovirus that infects CD4 receptor-expressing cells (CD4 cells and APCs such as macrophages).
- **Transmission:** Sexually, Parenterally (blood transfusions, needles, ,etc...), Perinatally, or through Occupational exposure.
- **Cells infected:** Lymphocytes (Lymph nodes, thymus, Bone marrow) and Macrophages (Brain, Body fluids, Skin, GIT, Lung).

Structural genes		Regulatory genes (extra)	
Gag	Matrix (p17) Conical Capsid (p24)	Tat	Transcription activator Enhances replication by upregulating transcription
Pol	**Reverse transcriptase** (synthesizes dsDNA from genomic RNA) **Integrase** (integrates the dsDNA into host DNA) **Protease** (cleaves viral polyprotein)	Nef	Auxiliary gene (not required for replication) Decreases CD4 proteins and MHC I expression on T cells **Required for progression to AIDS**
Env	GP120 (surface protein that binds to CD4 receptor + coreceptors) GP41 (transmembrane protein for **fusion** into host cell)	Rev	Regulatory protein Transports mRNA from the nucleus to the cytoplasm



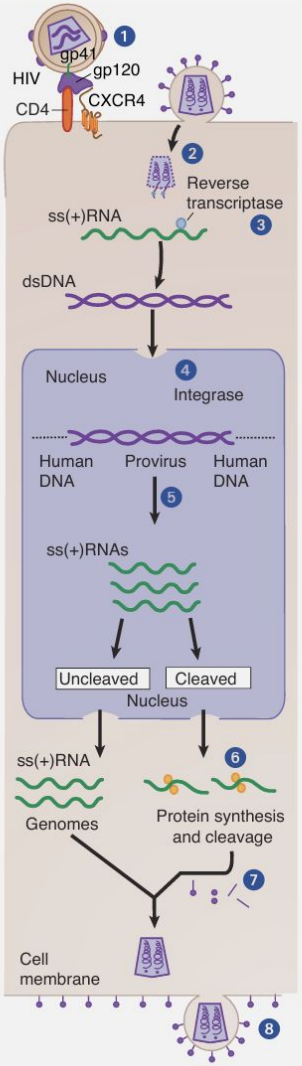
Loss of Function mutations of regulatory genes (extra):

- Nef → Slow rate or no progression to AIDS
- Tat/Rev → Virus is unable to replicate

Host cell mutation of CCR5 coreceptor (extra):

- Homozygous → **Immunity** (reason discussed in the next slide)
- Heterozygous → Slower progression to AIDS

Pathophysiology



1- Surface GP120 binds to host CD4 receptor and coreceptors (chemokines)

- Coreceptors are CXCR4 (on CD4 cells) and CCR5 (on Macrophages, microglia, dendritic cells, etc...)
- Early infection, virus binds to CCR5 (M-tropic) → hence the immunity in a homozygous mutation
- Late infection, virus binds to CXCR4 (T-tropic)

2- HIV goes inside the cell and the RNA is uncoated

3- RNA is converted into dsDNA by Reverse Transcriptase

4- The dsDNA and Integrase migrate to the nucleus, and the DNA is integrated into the host genome

- forming the **provirus** (which can remain latent in the host DNA)

5- Transcription produces both cleaved and uncleaved +ve SSRNA

- Cleaved → used as mRNA for viral proteins
- Uncleaved → used as RNA genome of the virus

6- Translation of mRNA into polypeptides (which will be cleaved by protease)

7- Assembly of the virus

8- Maturation and release

- Note from the figure that the envelope of the virus is derived from the host cell membrane

Stages of Infection

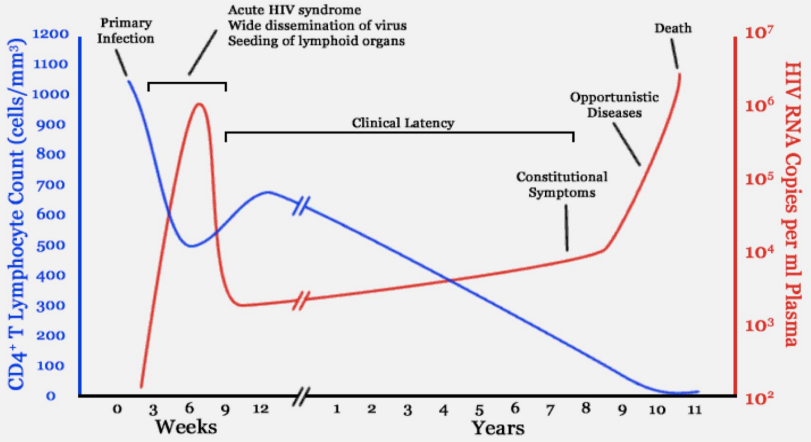
Primary (Acute)	**3-12 weeks** after exposure (2-week Incubation Period), recovery in 7-14 days 70-80 % symptomatic: **Fever**, **rash**, **cervical lymphadenopathy**, aseptic meningitis, encephalitis, myelitis, polyneuritis **Surge of viral RNA (load) to >10^6 and fall of CD4 count** to 300-400 cells/mm^3 (normal: 500-1500 cells/mm^3)
Latent (Chronic)	**Asymptomatic** and can last for 10 years No evidence of HIV infection except for **Persistent Generalized Lymphadenopathy** (enlargement of 2 or more lymph nodes other than the inguinal for at least 3 consecutive months) CD4 count falls by 50-150 cells/mm^3 per year **Gradual increase in the viral load (which is inversely proportional to the gradually decreasing CD4 count)**
AIDS	**CD4 count <200 cells/mm^3 and surge of viral RNA** Very high susceptibility to opportunistic infections

Viral-Host Dynamics:

- About 10 billion virions are produced daily
- The lifespan of an HIV virions is around 6 hours, while that of an infected CD4 cell is 1.6 days on average
- Unlike other retroviruses, HIV can lie dormant within a cell for many years **(especially memory CD4 cells)**

Viral-Host Interaction:

- Infects CD4 cells and integrates into host cell DNA
- High rate of mutation
- Hides in tissue hard for the immune system to access (e.g. microglia + Bone Marrow)



Immune Response

- HIV induces immune activation, which may seem paradoxical since it ultimately leads to severe immunosuppression.

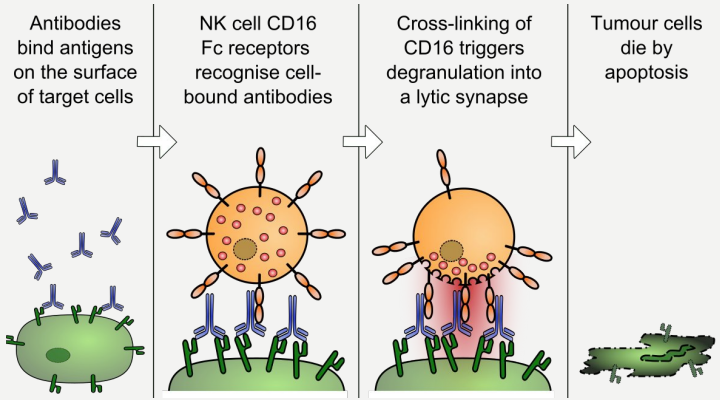
Cellular (most important)	Derived from naive CD8 T cells, which recognize viral antigens via MHC Class I to then directly destroy the infected cell Augmented by Th1 cells (they activate CD8 cells via IFN-gamma)
Humoral	Neutralization by antibodies binding to the surface of the virus, preventing its attachment to host cells **Antibody-Dependent Cell-Mediated Cytotoxicity** → Fc portion of Ab binds to **NK cell** → Stimulate it to destroy infected cell Augmented by Th2 cells (they activate B cells via IL-4)
Cytokine Dysregulation	Increased expression of **pro-inflammatory** cytokines: IL-1, IL-6, IL-10, IFN-gamma Disruption and loss of **immunoregulatory** cytokines: IL-2, IL-12 (necessary for modulating CMI response)

Activated T cells support HIV-replication:

- Intercurrent infections are associated with transient increase in viremia
  (activated immunity → more T cells to infect)
- Accounts for why TB worsens an underlying HIV disease
  (HIV can also reactivate a latent TB as immunosuppression develops)

HIV-immune dysfunction:

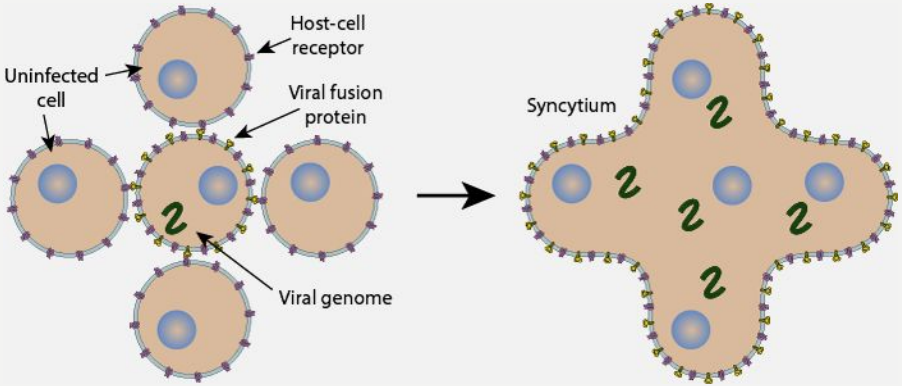
- All elements of the immune system are affected
- Advanced stages have substantial lymphoid tissue disruption
- Impaired ability to initiate an immune response or to even maintain memory responses



CD4 Depletion/Dysfunction

- Any depletion in numbers of CD4 cells renders the body susceptible to opportunistic infections
- There are 2 mechanisms by which CD4 cells are depleted and dysfunctioned:

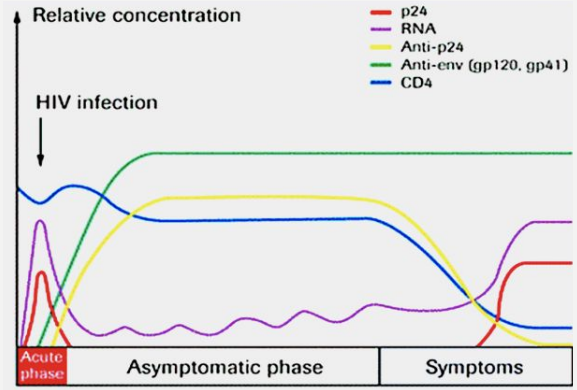
Direct	Elimination of HIV-infected cells by virus-specific immune responses (using up the CD4 cells to fight the infection) Loss of plasma membrane integrity because of viral budding (recall that the virus derives its envelope from the host cell membrane)
Indirect	**Syncytium** formation (a syncytium is a single cell containing several nuclei formed by fusion of cells or by division of nuclei) - Most commonly in the **brain** (microglia) - Infected cells express GP120, and adjacent uninfected cells may then bind to the expressed GP120, which results in **fusion of the cell membranes** and subsequent syncytium formation → highly unstable and quickly die Apoptosis Autoimmunity



Diagnosis and Management

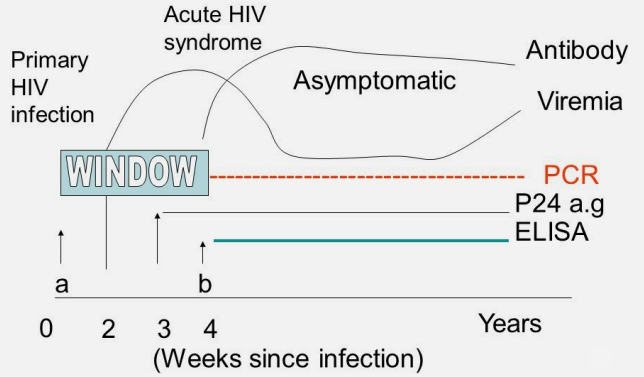
Lab markers:

- Viral load (RNA) → Marker of **replication rate**
- CD4 count → Marker of immunologic damage



Diagnosis:

- **ELISA**: Detects the p24 antibody using the p24 antigen
- **Western blot**: Detects HIV antibodies via gel electrophoresis and subsequent blotting (Used for confirmation if ELISA is positive)
- **PCR**: Detects viral RNA (used for monitoring and following up)



Note that ELISA is positive only after the 4th week

- This is due to Seroconversion → The development of detectable antibodies in the blood
- Median 8 weeks after infection (according to the slides….)
- The time it takes for seroconversion to occur is called the Window Period (during which an infected person tests negative)
- The level of viral load post seroconversion correlates with risk of progression of disease (**hence why PCR is used for follow up)**

Management:

- Antiretroviral therapy: Reverse Transcriptase inhibitors, Protease inhibitors, and Fusion inhibitors
- Post exposure prophylactic treatment (PEP): within max 72 hours after exposure for 28 days

Diagnosis and Management (EXTRA)

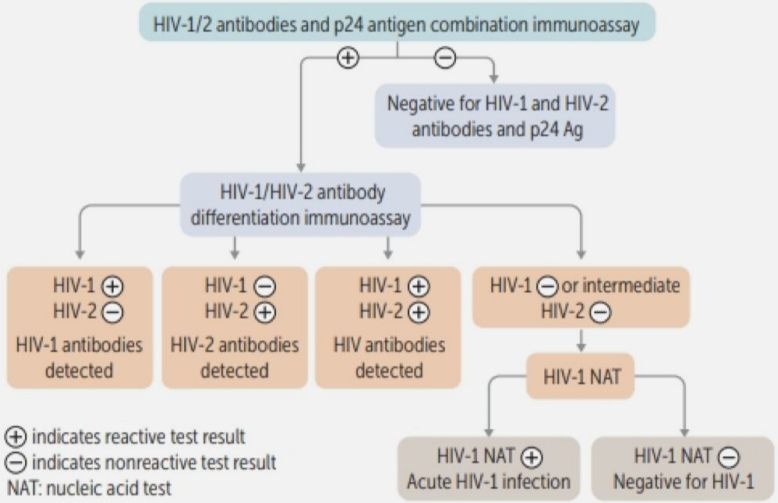
Western blots are no longer recommended for testing

Presumptive diagnosis is made with HIV-1/2 Ag/Ab immunoassays

These immunoassays detect viral p24 Ag capsid protein and IgG Abs to HIV-1/2 (Very high sensitivity and specificity)

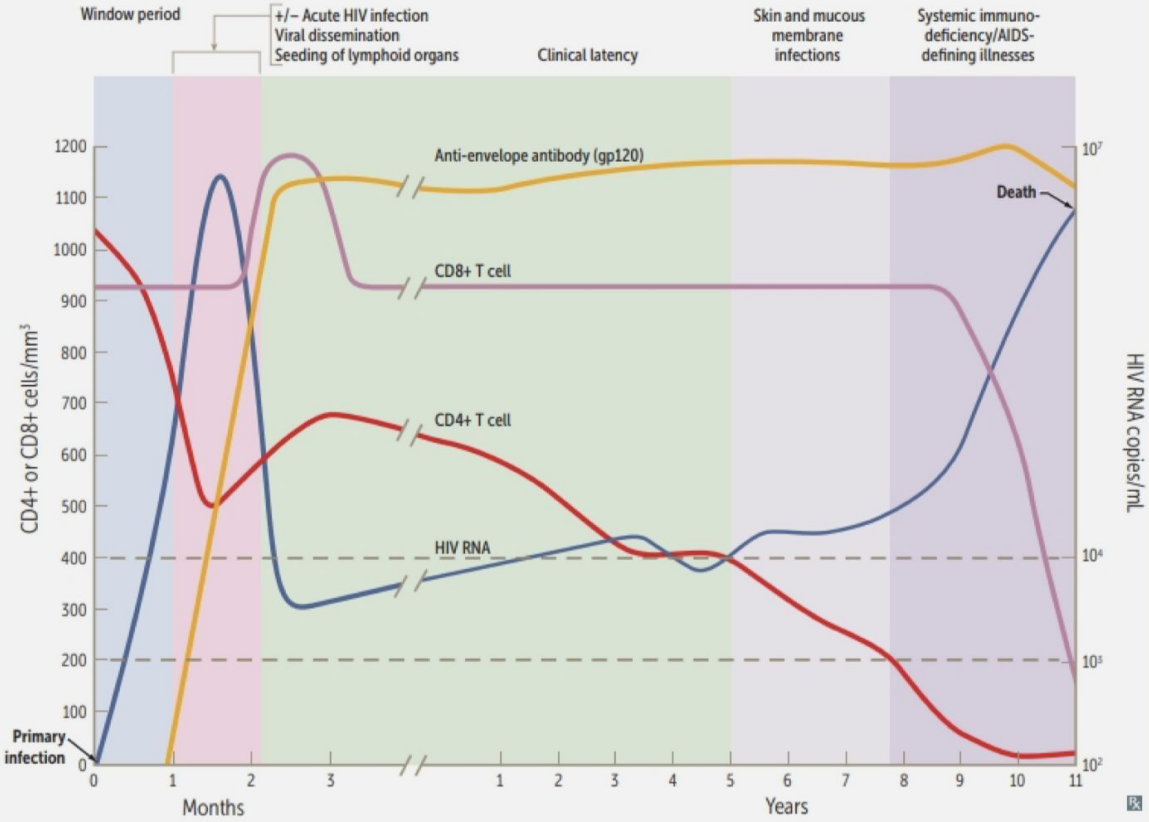
- They are not recommended in babies with suspected HIV due to maternally transferred antibodies. Use HIV viral load

Use HIV genotyping to determine appropriate therapy (Recall that there are two types of HIV, and Non-Nucleoside RTIs do not work on HIV-2)



Prophylaxis is indicated based on CD4 count:

Disease Agent	Begin Prophylaxis	Drug
Pneumocystis Jirovecii	CD4 <200	TMP-SMX
Toxoplasma Gondii	CD4 <100	TMP-SMX
Histoplasma Capsulatum (endemic areas)	CD4 <100	Itraconazole
Mycobacterium Avium	CD4 <50	Azithromycin



Dashed lines on CD4+ count axis indicate moderate immunocompromise (< 400 CD4+ cells/mm^3) and when AIDS-defining illnesses emerge (< 200 CD4+ cells/mm^3).

Most patients who do not receive treatment eventually die of complications of HIV infection.

Four stages of untreated infection:

1. Flu-like (acute)
2. Feeling fine (latent)
3. Falling count
4. Final crisis

During clinical latency phase, virus replicates in lymph nodes

Take Home Messages

- 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. Which of the following binds to the CD4 receptor upon entry of HIV to the host cell?

a) CXCR4
b) GP120
c) GP41
d) CCR5

2. Which of the following is a target cell for HIV?

a) Plasma cell
b) RBC
c) Neutrophil
d) Microglial cell

3. What does HIV additionally bind to upon entry to the host cell?

a) Glycoprotein receptor
b) Chemokine receptor
c) TNF-alpha receptor
d) IFN-gamma receptor

4. What is the most common site of syncytium formation?

a) Bones
b) Brain
c) Lymph nodes
d) Lungs

5. Which of the following tests is used to monitor HIV patients?

a) ELISA
b) Western blot
c) HIV RNA
d) Tuberculin test

6. The time between an HIV infection and a positive antibody test is known as?

a) Seroconversion
b) Window period
c) Door period
d) Latent period

1.B 2.D 3.B 4.B 5.C 6.B

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