MED 443
King Saud University

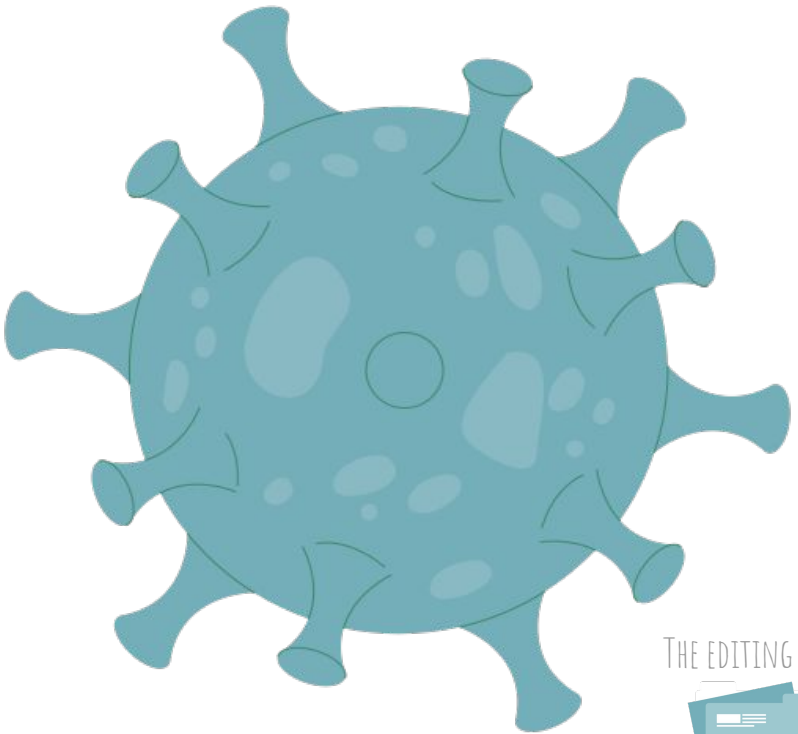
443
IMMUNOLOGY TEAM

Reviewed by
Mohammed AlEssa
Abdulaziz AlFuhayd
Lama AlMutairi

HIV & AIDS

REPRODUCTIVE BLOCK

THE LAST IMMUNOLOGY LECTURE IN BASIC YEARS!



THE EDITING FILE:

OBJECTIVES

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

Playlist (Osmosis+Armando+Others)

Lecture was presented by Dr. Reem Sghiri and Prof. Zahid Shakoor

COLOR INDEX

- Main text
- Female slides
- Male slides
- Important
- Drs' notes
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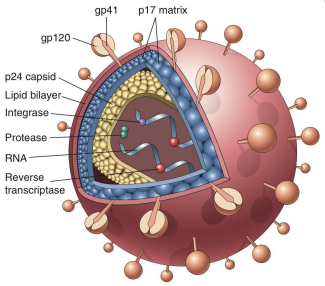
Structure of HIV

Introduction

➥ HIV is an **enveloped (sensitive to the environment) retrovirus Lentivirus** that infects **CD4 receptor-expressing cells**; this includes: CD4 T cells and APCs such as macrophages and dendrites.

➥ **Target cells of HIV infection:**

- **Lymphocytes** (Lymph nodes, thymus, bone marrow)
- **Macrophages** (Brain, body fluids, Skin, GIT, Lung)



➥ Transmission:

- **Sexually** (most common) especially from male to female
  - Genital or colonic mucosa
- Parenterally:
  - Blood transfusions
- Perinatally: **mother to infant** (around delivery, breastfeeding)
- Accidental occupational exposure
- **Not** transmitted through kissing, **mosquitoes**, sharing things with AIDS patients because virus is **very weak and can't resist the environment**

HIV Structure

	Structure	Function
Genome	**2 molecules of ss-RNA**	-
Envelope Protein	**gp120**	Attaches to host CD4+ T-cells
	gp41	Assists in fusion and entry of the virus into the host cell
Matrix Protein	**p17**	-
Core Protein	**p24**	-
Enzymes	**Reverse Transcriptase**	Converts viral RNA into DNA
	Integrase	Integrates viral DNA with host DNA forming provirus, persisting infection.
	Protease	Cleaves viral polyprotein

Pathophysiology (How HIV Enters Cells?)

Pathophysiology

1. **Envelope protein gp120 (Main Protein) binds to host CD4 molecule**
   a. CD4 found on: T cells, macrophages, and microglial cells
   b. **Binding to CD4 is <u>not sufficient</u> for entry,** co-receptor binding is essential

2. **Envelope protein gp120 binds to co-receptor. Co-receptor = chemokine receptors which are: CXCR4 and CCR5.**

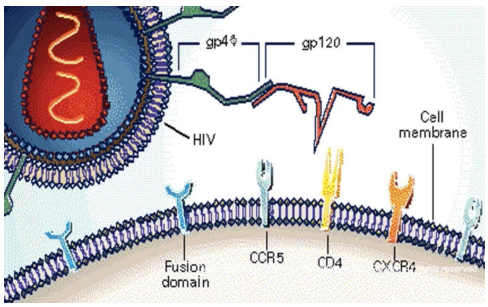
3. Binding of virus to cell surface results **in <u>fusion</u> of viral envelope** with cell membrane. Viral core is released into cell cytoplasm –> **HIV (Retrovirus) enters cell**

4. **Inside the cell:** Reverse transcriptase makes DNA copy of RNA. By action of integrase enzyme, viral DNA forms provirus with host DNA

5. Forming new HIV:
   a. Viral DNA makes mRNA
   b. mRNA makes HIV proteins
   c. HIV proteins become HIV capsid
   d. mRNA is collected inside of HIV capsid forming new HIV

6. New HIV leaves cell and wraps itself in host membrane forming its envelope by budding

FIGURE A



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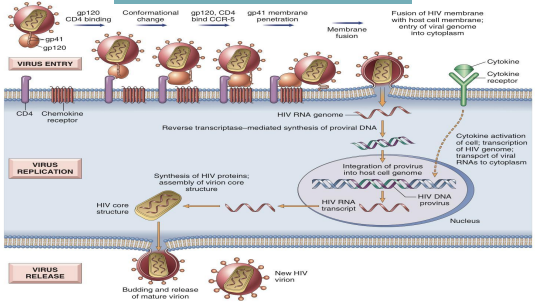


FIGURE A: shows HIV's attachment and entry into a host cell.
- ❖ **gp120** protein attaches to a CD4 receptor
- ❖ **gp41** is exposed for attachment to the host cell, and fusion of the cell membrane with the viral envelope starts

- A **mutant CCR5 receptor gene** that prevents the virus from binding to the cell has been discovered. **Homozygosity** for this mutant gene is strongly protective against HIV infection. Heterozygous people are not protected from infection but the disease may take longer to develop.

General Principles of Viral-Host Interaction

Viral-Host Dynamics

- About 10 billion virions are produced **daily.** Extremely high rates of viral replication results in every possible point mutation in the viral genome. In any given patient, the virus usually varies by 1-6% in the envelope gene.
- Average lifespan of an HIV virions <u>in plasma</u> is around **<u>6 hours</u>**
- Average lifespan of infected CD4 cell is **<u>1.6 days</u>** (live longer inside cells)
- Unlike other retroviruses, **HIV can lie dormant** within a cell for many years, especially in resting (memory) CD4 cells (patient is asymptomatic) lie dormant: من أسباب: resistant to the drugs

Viral-Host Interaction

Host	Host mounts HIV-specific immune responses: 1. **Cellular (cell-mediated immunity) -** عمادها : CD8 T cells 2. Humoral (antibody-mediated) عمادها : Antibodies
Virus	HIV virus subverts the immune system. How? 1. It **infects CD4** cells that control normal immune responses 2. Integrates into host DNA 3. **High rates of mutation** (#micro: HIV-1 is HIGHLY susceptible to mutations) by RNA transcriptase 4. **Hides in tissue** not readily accessible to immune system e.g: CNS (lies dormant in cells like in: glial cells and lymphocytes)

Cells infected by HIV

➥ Numerous organ systems are infected by HIV, all in which **their cells express CD4 receptor. Such as:**

- **Brain:** macrophages and glial cells
- **Skin:** langerhans cells
- **Lung:** alveolar macrophages
- **Lymph nodes and thymus:** lymphocytes and dendritic cells
- **Blood, semen, vaginal fluids:** macrophages
- **Bone marrow:** lymphocytes
- **Colon, duodenum, rectum:** chromaffin cells

Immune Response to HIV

Cellular Immune Response to HIV

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

CD8 Cytotoxic T Lymphocyte (CTL)	• Derived from naïve T8 cells, which recognize viral antigens in context of MHC class I presentation • **Directly destroy infected cell** CD4 • Activity augmented by Th1 response

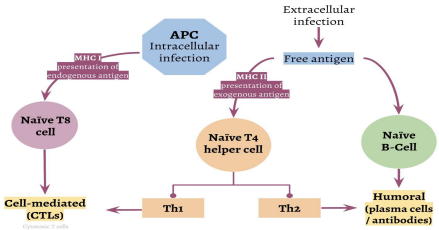
Humoral Immune Response to HIV

(Less effective in controlling HIV infection compared to cellular immunity)

Neutralization	• Antibodies against viral proteins bind to surface of virus to prevent attachment to target cell (Coating)
Antibody-dependant cell-mediated cytotoxicity (ADCC)	• Fc portion of antibody binds to NK cell • Stimulates natural killer cell to indirectly destroy infected cell

General Principles of Immune Dysfunction due to 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**



Adaptive Immune Response

Overview of Adaptive Immune Response

- This is an important slide representing the **adaptive immune response, which is the main response to HIV** (as opposed to the innate immune response).
- The adaptive immune response is divided into 2 types: cell-mediated (cytotoxic t-cell) type and humoral (antibody-mediated) type. In general, location of the infection (intracellular or extracellular) determines the type of adaptive immune response.
- **Intracellular** infections stimulate a cell-mediated response that will ultimately kill the infected cell. This is **mediated by T8 cells, and utilizes the MHC I system.**
- In **extracellular** infection, humoral response will be stimulated helping in containing free antigens which will be picked up by APCs, **presented by MHC II to the Th 1 or 2 cells**

Immune Dysfunction in HIV

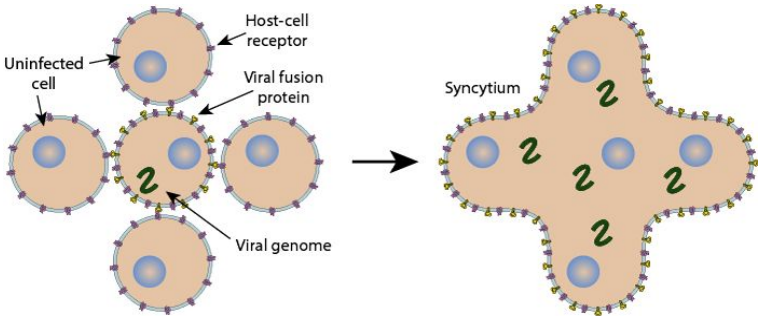
Mechanisms of CD4 Depletion and Dysfunction

Direct

- Elimination of HIV-infected cells by **virus-specific** immune responses
- **Loss of plasma membrane integrity** because of **viral budding**

Indirect

- **Apoptosis**
- **Autoimmunity** (HIV increases autoantibodies which increases incidence of autoimmune diseases)
- **Syncytium formation**
  - Observed in HIV infection, **most commonly in the brain** (Neuronal tissue is seen, but nonfunctional)
  - **Uninfected** cells may then bind to infected cells due to **viral gp120**. 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

لما يصير فيه infection وش تسوي CD4؟ multiply
بنفس الوقت تسوي multiply للـ virus

Role of Cytokine Dysregulation in Pathogenesis of HIV

Increased expression

HIV is associated with **increased** expression of **pro-inflammatory cytokines:**

- **—TNF-alpha, IFN-gamma, IL-1,IL-6, IL-10 , IL-8** Chronic inflammation

Disruption and loss

HIV results in disruption and **loss of immunoregulatory cytokines:**

- **—IL-2, IL-12**
- Necessary for **modulating effective cell-mediated immune responses** (CTLs and NK cells)

Stages of HIV Infection

Primary Infection (Acute)

Clinical features

ممكن تكون totally asymptomatic

- **70- 80% are symptomatic, 3 - 12 weeks** after exposure (incubation period)
- **Symptoms include:**
  - **Fever, rash, cervical lymphadenopathy,** aseptic meningitis, encephalitis, myelitis, polyneuritis

Lab markers

- **Surge** in **viral RNA** copies to >1 million. (high viral load)
- **Fall** Acute drop in CD4 T cell count to 300-400 cells/mm^3 (normal: 500-1500 cells/mm^3)
- **Recovery** in 7-14 days (2 weeks)

Latent/Asymptomatic phase (Chronic)

Clinical features

- Remain well with no evidence of HIV disease except for **generalized lymphadenopathy.**

Lab markers

- **Fall** of CD4 T cell count by about 50-150 cells per year (note that it's still above 200 but the pattern of decline is 50-150)

End-stage: CD4 T-cell count and Progression to Acquired Immunodeficiency Syndrome (AIDS)

Clinical features

- Any **depletion in numbers of CD4** cells renders the body susceptible to **Opportunistic infections:** لما العدد أقل من 200
  - **Tumors: such as kaposi sarcoma, B-cell lymphoma** (mainly in the brain, mostly associated with EBV) **(imp for MCQ)**

Lab markers

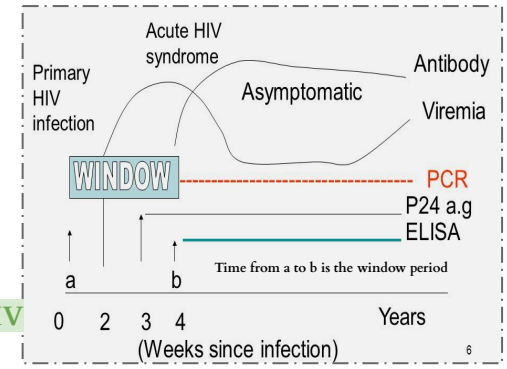
- **Gradual** reduction in number of circulating **CD4** cells is **inversely** correlated with the **viral load.** High RNA: probably progress more fast to AIDS than other person

Clinical Course of HIV Infection

Seroconversion

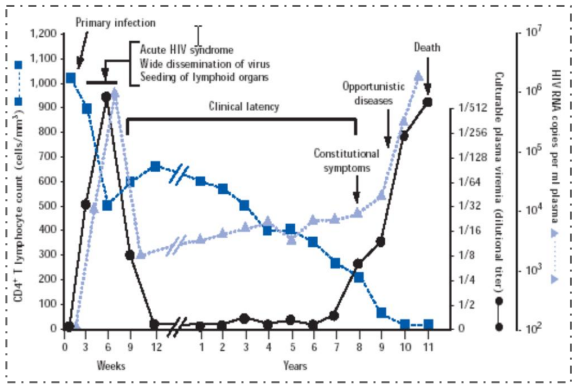
- Definition: it is the time period during which **a specific antibody develops and becomes detectable in the blood.**
- In HIV, seroconversion occurs **median 8 weeks after infection**
- **Levels of viral load post sero-conversion correlates with risk of progression of disease.**

FIGURE A



Window Period: Untreated Clinical Course

FIGURE B



Natural History of HIV

Why is it imp? To diagnose HIV during this period. أهميته الحين صارت أقل لأن صار عندنا: PCR

FIGURE A

Shows infection course in relation to antibody formation and diagnostic approach

#438: **Untreated Clinical Course**

Note that ELISA is positive only after the 4th week

- In HIV, it takes 4-8 weeks after infection for seroconversion (according to drs notes and slides, but figure shows 4w). The time it takes for seroconversion to occur is called the **window period**
- **Window period: The time between infection and detectability of HIV antibodies (very imp), begins at the time of infection and can last 4 to 8 weeks.**
- **In other words:** During this period, a person is infected, with a high viral load and a **negative** HIV antibody test (from week 0-4), the point when the HIV antibody test becomes positive is called the point of **seroconversion**
- The level of viral load post seroconversion correlates with risk of progression of disease (hence why PCR is used for follow up)

FIGURE B

Shows infection course in relation to symptoms, viral load (HIV RNA), and CD4 T cell count

- Acute (primary) retroviral syndrome is the initial event after infection, which is **characterized by a rapid decline in CD4 cell count and high plasma viremia**
- Development of cytotoxic T-cell (CTL) response results in clinical recovery of acute infection and a reduction in plasma viremia. The virus reaches "set point" as a result of this immune response. The viral load at this "set point" correlates with the rate of CD4 decline and disease progression. Overtime, HIV RNA levels gradually increase.
- **When the CD4 count falls below 200, patients develop opportunistic infections, tumors, and neurological complications.** The median survival after the CD4 count has fallen to <200 is 3.7 years, if untreated.

Diagnosis and Management

Laboratory Markers of HIV Infection

- **Viral load:** Marker of **HIV replication rate**
- **CD4 count:** Marker of **immunologic damage**

How to monitor the patient?
-viral load
- CD4

Diagnosis

أغلبية البلدان الغنية تستخدم directly:
RNA detection

1. Antibody test, ELISA
2. Conformation
   Western blot
3. HIV RNA viral load

Management

Treatment recommended **as soon as possible.** It can't cure HIV but help to keep HIV patients healthier and **prevent HIV transmission**

- Anti- retroviral therapy (ART)
- Reverse transcriptase inhibitors
- Protease inhibitors
- Fusion inhibitors
- Post exposure prophylactic treatment (PEP): within max 72 hours after exposure for 28 days

Take Home Message

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

HIV mode of transmission

EXTRA

- Sexually (genital od colonic mucosa)
- **Perinatally** (mother to infant)
- Parenterally (blood transfusions, needles, ,etc...)
- Accidental occupational exposure

Cell targets of HIV

Cells which express **CD4 receptor, such as:**

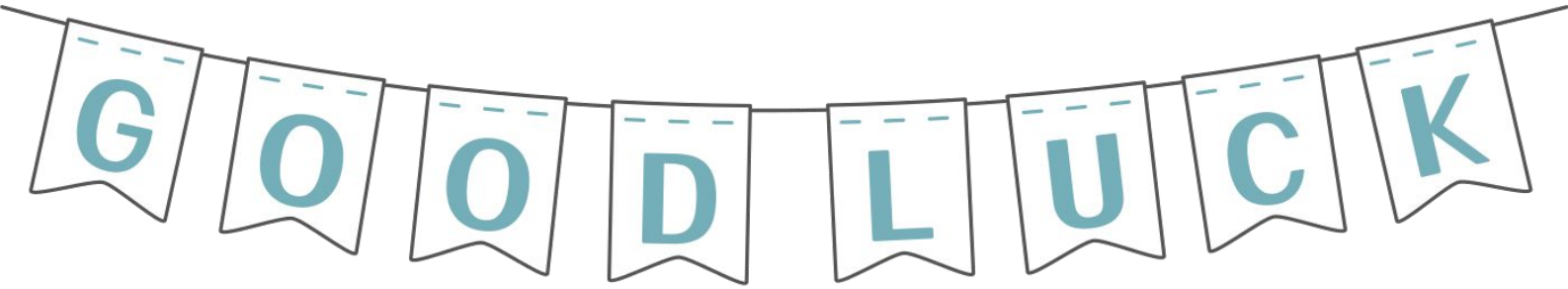
- **Brain:** macrophages and glial cells
- **Skin:** langerhans cells
- **Lung:** alveolar macrophages
- **Bone marrow:** lymphocytes
- **Lymph nodes and thymus:** lymphocytes and dendritic cells
- **Blood, semen, vaginal fluids:** macrophages
- **Colon, duodenum, rectum:** chromaffin cells

Properties of HIV

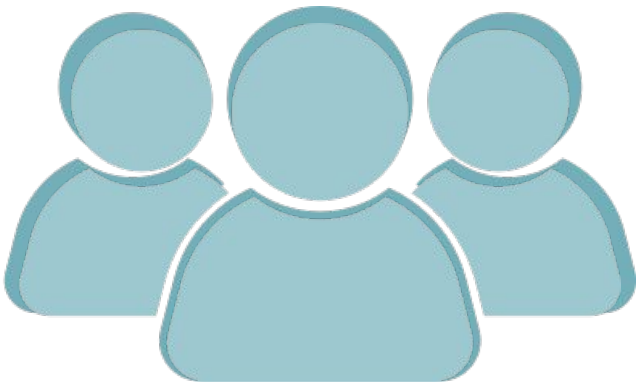
Structure	**Envelope proteins: 1) gp120 2) gp41** **Capsid protein: p24** (anti-HIV antibodies are against p24, anti-p24 antibodies)	
Pathogenesis	1. **Envelope protein gp120 binds to host CD4 receptor AND coreceptor. CXCR4 and CCR5 (chemokine receptors)** 2. **HIV (Retrovirus) enters cell** 3. Reverse transcriptase makes DNA copy of RNA 4. Integrase enzyme integrates viral DNA with host DNA 5. HIV makes it own proteins 6. New HIV forms and leaves the cell (budding process)	
CD4 depletion & dysfunction	**Direct**	• Elimination of infected cells **by virus-specific immune responses** • Loss of plasma membrane integrity because of **viral budding**
	Indirect	• Apoptosis • **Autoimmunity** • **Syncytium formation: most commonly in the brain**
Cytokine dysregulation	**Increase**	Increased expression of pro-inflammatory cytokines: • TNF-alpha, IL-1,IL-6, IL-10, IFN-gamma
	Decrease	Disruption and loss of immunoregulatory cytokines: • IL-2, IL-12 • CD8 and NK
Infection Course	• Seroconversion: it takes 4 - 8 weeks after HIV infection for the antibodies to appear. • **Window period: The time between infection and detectability of HIV antibodies, begins at the time of infection and can last 4 to 8 weeks.** • **Levels of viral load post seroconversion correlate with risk of progression of disease.**	

Progression of infection to AIDS

- **Increased viral load**
- **Significant reduction in CD4 lymphocytes:** CD4+ T cell count **less than 200** cells/mm^3
- **Opportunistic infections** & tumors **(kaposi's sarcoma)**



TEAM LEADERS



ابو عويد فيصل الشويعر ألين الكليه

Special Thanks to 439 Immunology team

443
IMMUNOLOGY TEAM

immunologyteam443@gmail.com