MEDICINE
KING SAUD UNIVERSITY

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Reproduction Block

Lecture One

AIDS

IMMUNOLOGY
436's TEAMWORK

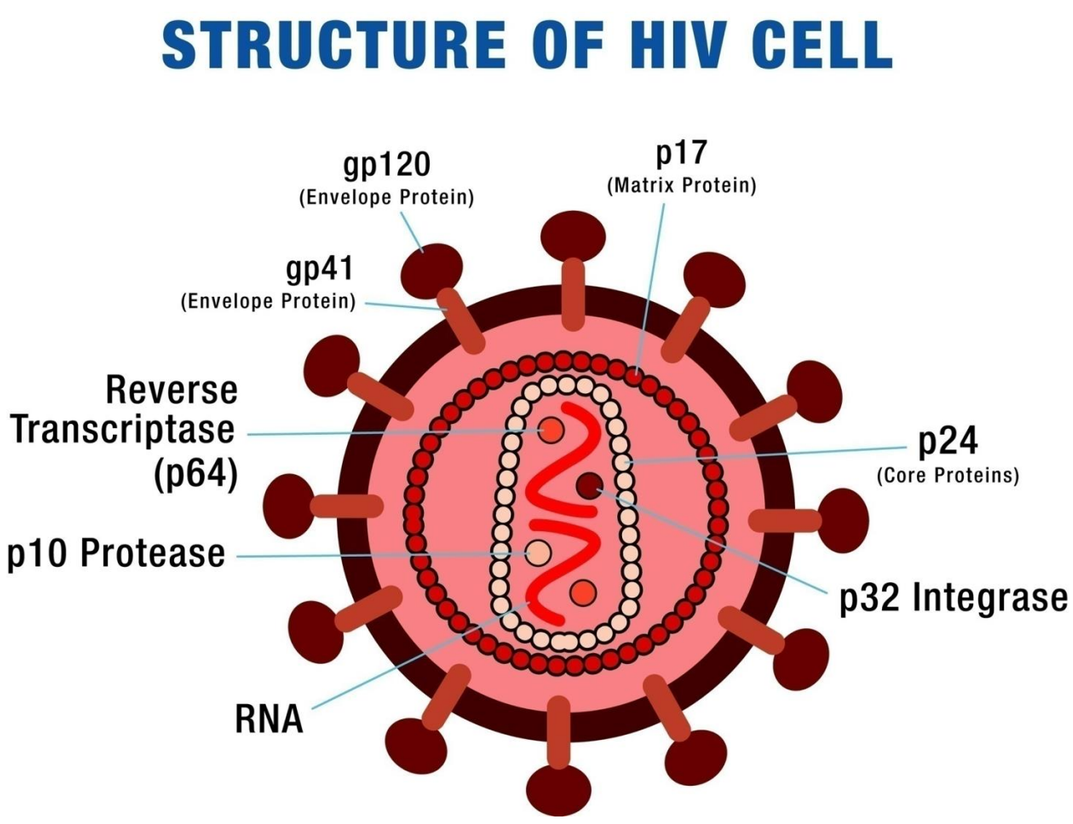
Objectives:

- 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

- **Important.**
- **Extra notes.**
- **Doctors' notes**

Structure of HIV cell:

- Retrovirus (RNA).
- Host derived envelope.
- Glycoproteins on the surface.



Transmission

Modes of infection:

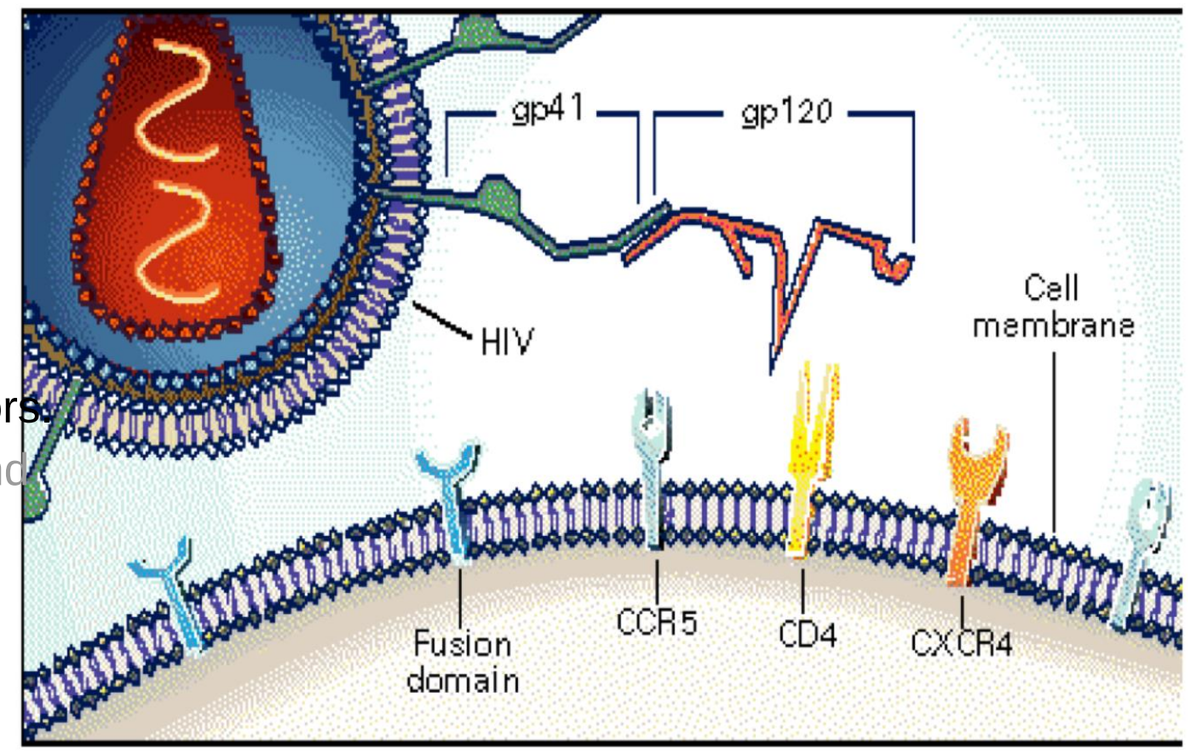
- Sexual transmission at genital or colonic mucosa. the most common and most important way. common in homosexuals because the anal canal is highly vascularized and easily ruptured.
- Blood transfusion. IV drug users (the virus can stay in the needle for up to 40 days).
- Mother to infant. Breastfeeding can transmit it as well.
- Accidental occupational exposure.

How HIV Enters Cell

- Any cell that expresses CD4 can get HIV.
- gp120 envelope protein binds to CD4 molecule
  -CD4 found on T-cells macrophages, and microglial cells.
  -Binding to CD4 is not sufficient for entry.
- gp120 envelope protein binds to co-receptor
  -Chemokine receptors: CCR5 and CXCR4 receptors.

CXCR4 are mainly found on T cells while CCR5 are found on T cells, Macrophages and dendritic cells.

- Binding of virus to cell surface results in fusion of viral envelope with cell membrane.
- Viral core is released into cell cytoplasm
- gp120 binds to CD4 but it needs chemokine CCR5 or CXCR4 to gain access into the cell.
- Some people have mutation in CCR5 gene these individuals cannot develop HIV.



Viral-host Dynamics

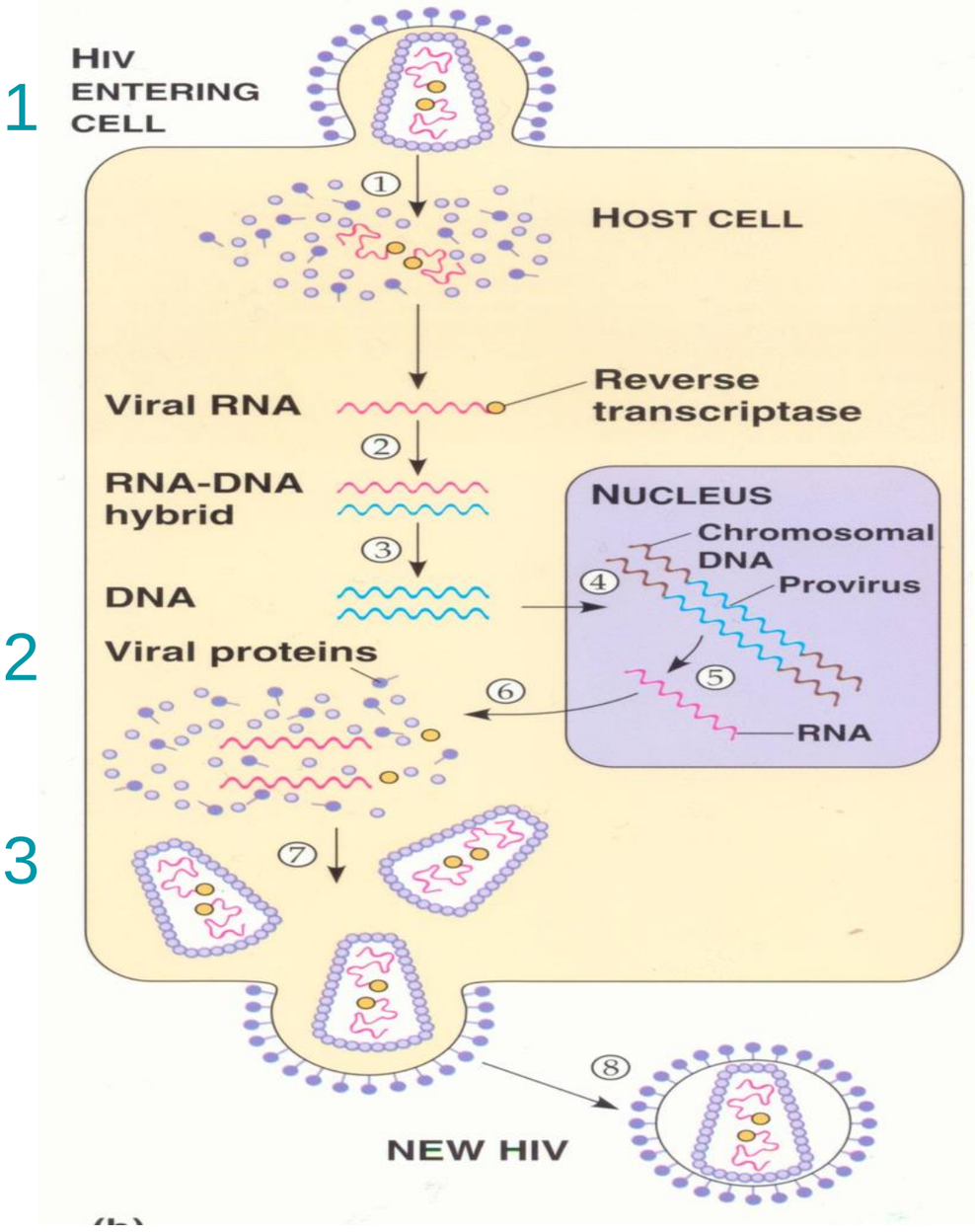
- About 10^{10} (10 billion) virions are produced daily
- Average life-span of an HIV virion in plasma is ~6 hours
- Average life-span of an HIV-infected CD4 lymphocytes is ~1.6 days
- HIV can lie dormant within a cell for many years, especially in resting (memory) CD4 cells, unlike other retroviruses

1-Retrovirus enters cell.

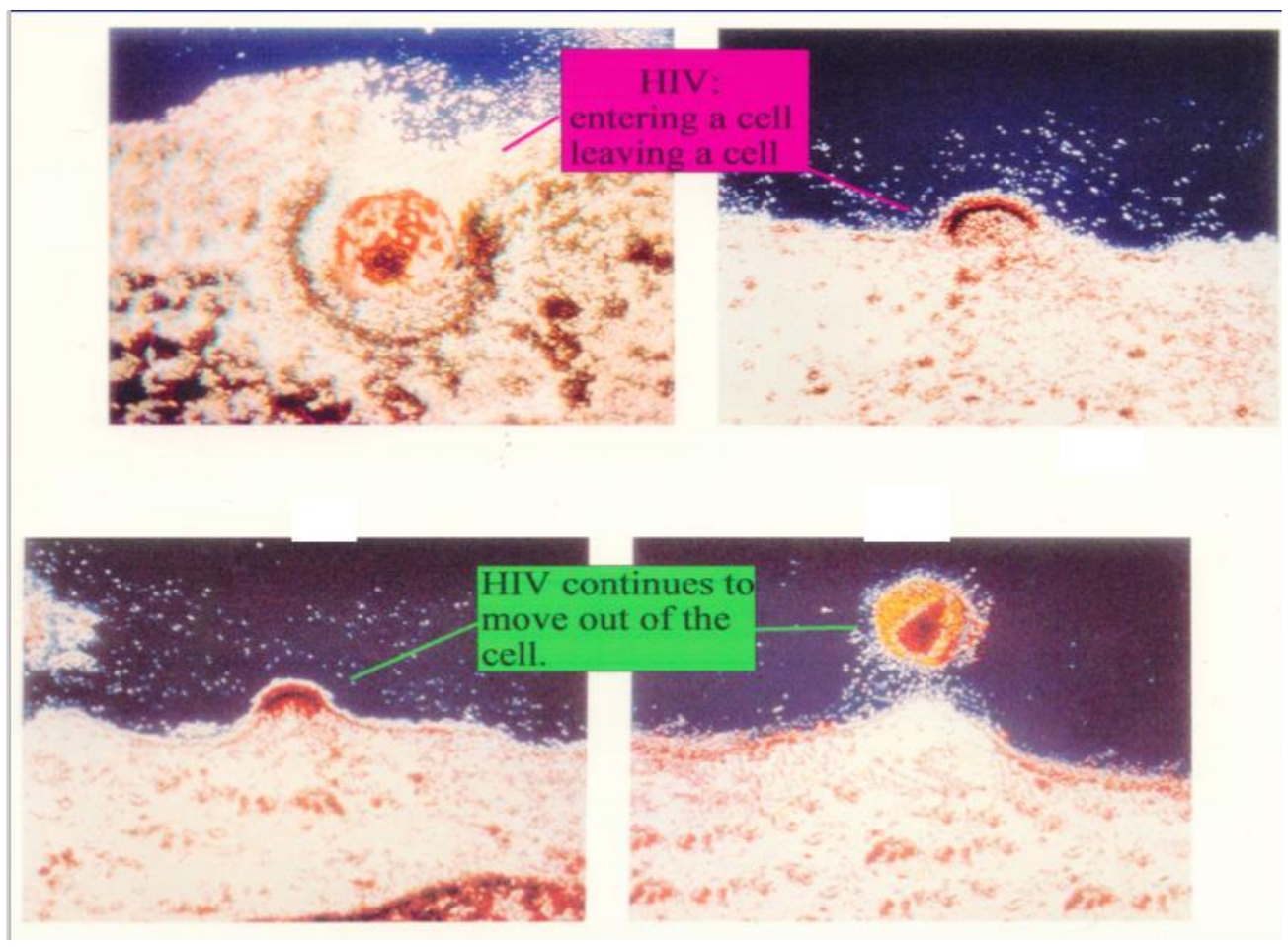
2- Reverse Transcriptase makes DNA copy of RNA.

3-Viral DNA forms provirus with host DNA:

- 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

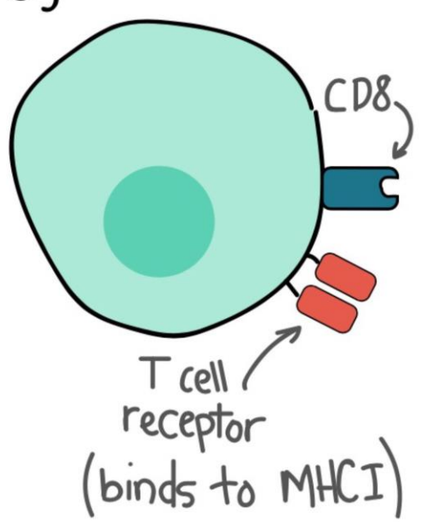
dendritic cell

APC or any cell

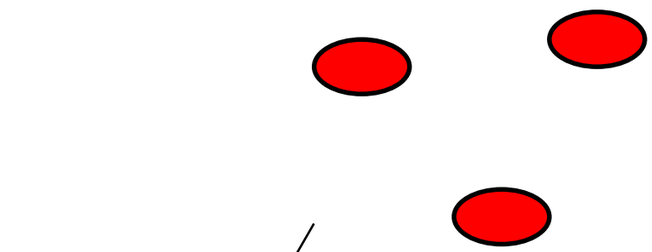
(intracellular infection)

MHC I presentation of endogenous antigen

Cytotoxic T cell



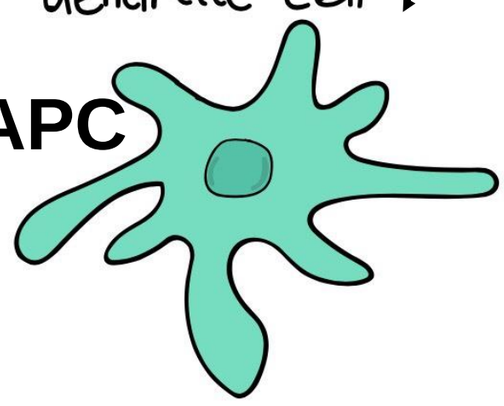
Extracellular infection



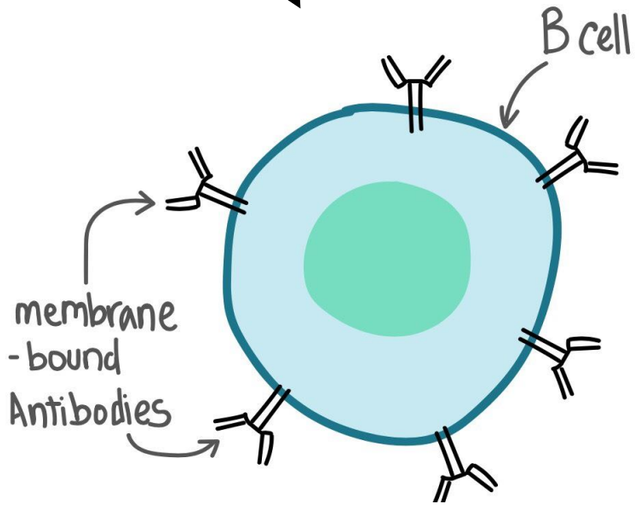
Free antigens

dendritic cell

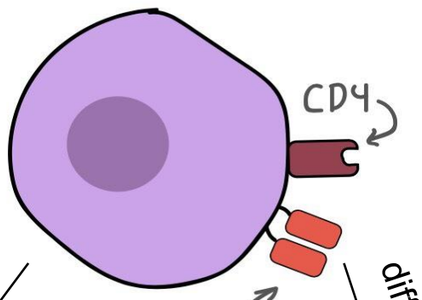
Only APC



MHC II presentation of exogenous antigen



Helper T cell



differentiates

differentiates

Helper T cell

Helper T cell

augments

augments

Cell mediated
(cytotoxic t lymphocytes)

General Principles of Viral-host Interactions

- **Host**: mounts HIV specific immune responses .
  -Cellular (cell mediated) most important. Cytotoxic cells.
  -Humoral (antibody mediated).

- **Virus**: subverts the immune system
  -Infects CD4 cells that control normal immune responses
  -Integrates into host DNA
  -High rate of mutation
  -Hides in tissue not readily accessible to immune system

Immune Responses to HIV

Cellular Immune Responses to HIV	Humoral Immune Response to HIV
CD8 Cytotoxic T lymphocyte (CTL) (protective during HIV) -Derived from naive 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 **The Th1 response is mediated by IL-2, (IFN- gamma), and (TNF-beta)**	**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 **Less effective in controlling HIV infection compared to cellular immunity.**

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
Skin: Langerhans cells
Colon, duodenum, rectum: chromaffin cells
Lung: alveolar macrophages

Decline in immune status parallels the decline in CD4 number and function. Loss of these cells results in failure of normal Th1 response and cell-mediated immunity that is necessary for controlling intracellular infections.

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** (1ry response)

Impaired ability **to maintain memory responses** (2ry response)

Susceptibility to opportunistic infections (in immunocompromised patients)

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	**Syncytium formation** - Observed in HIV infection, most commonly in **the brain** -Uninfected cells may then bind to infected cells due to viral gp120 (bind to CD4 of uninfected cells) -This results in **fusion** of the cell membranes and subsequent **syncytium formation.** - These syncytia are highly unstable and **die** quickly	Apoptosis	Autoimmunity

Role of Cellular Activation in Pathogenesis of HIV

HIV induces immune activation: **HIV induce (infection) -> increase HIV replication and worsen it**

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

Not only does the virus destroy and disrupt the immune system, it can manipulate the immune system to its own replicative advantage. This is achieved by immune activation. Clinically, this is demonstrated by the observation that viral load transiently increases in the presence of intercurrent illnesses, such as TB.

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

Associated with up-regulation of HIV replication

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)

Primary infection:

- 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. Because of CD8 activation.

Seroconversion

"**seroconversion** is the time period during which a specific antibody develops and becomes detectable in the blood."

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

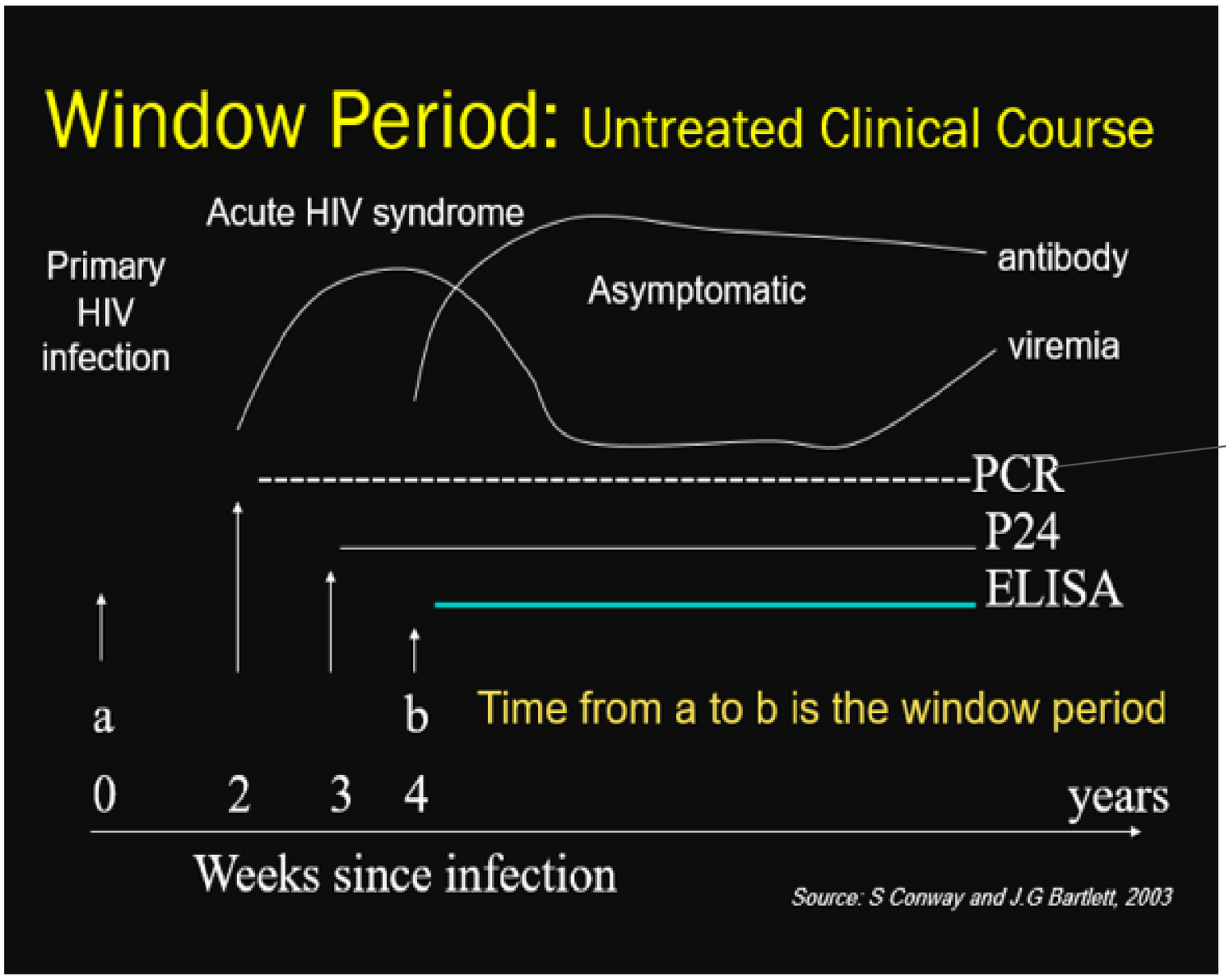
Asymptomatic Phase

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

CD4 T-cell Count and Progression to AIDS

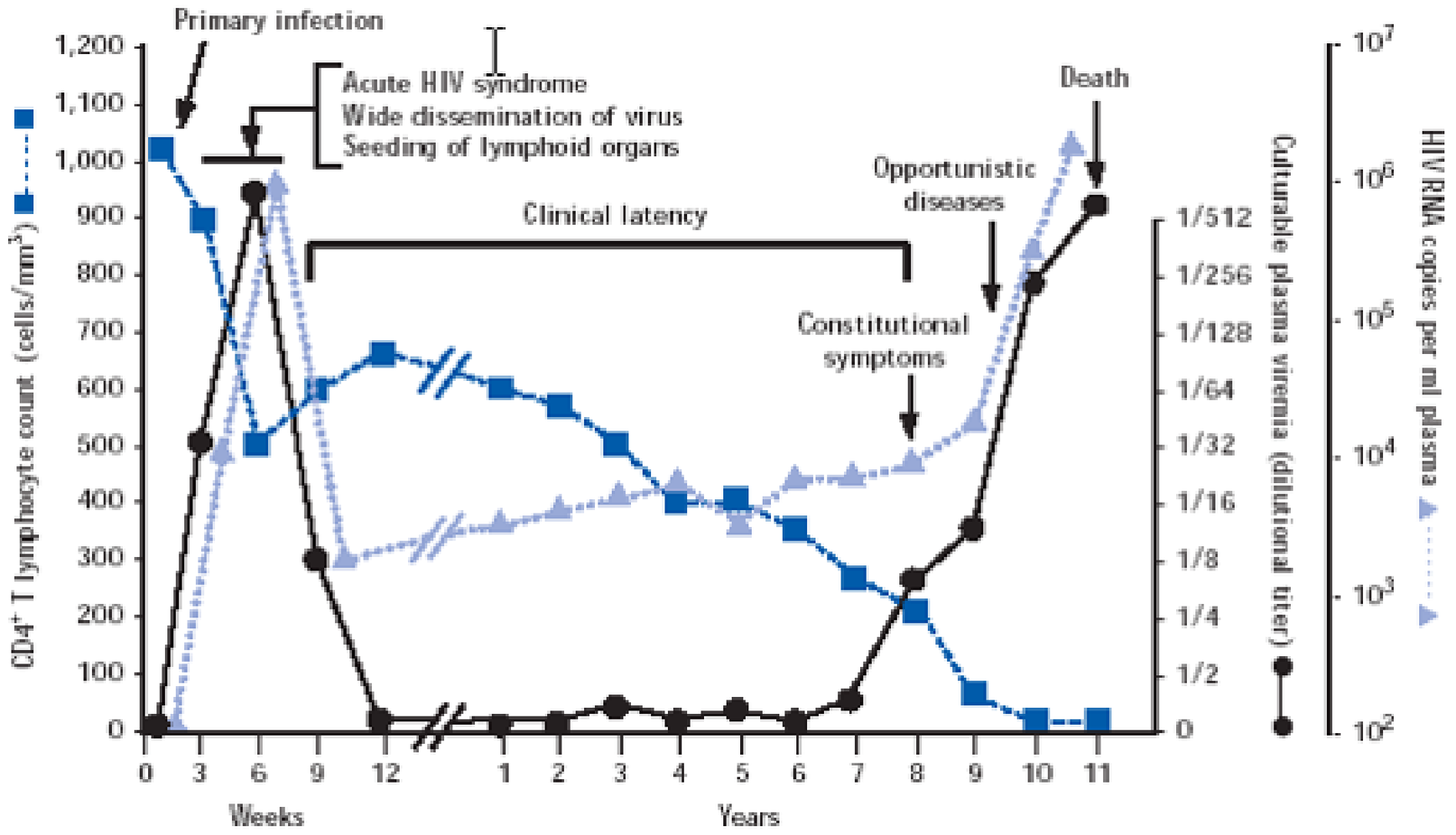
- Gradual reduction in number of circulating CD4 cells is **inversely correlated** with the viral load
- Any depletion in numbers of CD4 cells renders the body susceptible to **opportunistic infections**

in short, the less the CD4 T cell count the stronger the progression to AIDS



- window period:
  is the time between first infection and when the test can reliably detect the antibodies
- can last up to 8 weeks.
- a high viral load and a negative HIV antibody test.
- what is the test that will detect the early evidence of the disease? PCR,

Natural History of HIV



- CD4: At first a rapid decline then. Increases but, continuing to progressively decreases.
- Development of cytotoxic T-cell (CTL) response results in clinical recovery of acute infection.
- When the CD4 count falls below 200, patients develop opportunistic infections

Laboratory Markers of HIV Infection

1-Viral load	Marker of HIV replication rate
2-CD4 count	Marker of immunologic damage

Diagnosis:

- Antibody test, ELISA, this is done first “routine test”
- Western blot, for confirmation
- HIV RNA viral load (done by PCR, the PCR looks directly for HIV.

The test is called HIV RNA viral load, but when asked how is it done, by PCR)

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

1-Reverse transcriptase inhibitors

2-Protease inhibitors

3-Fusion inhibitors

The antiviral therapy does not kill HIV or cure AIDS, it slows the replication of HIV so that the immune system can recover and confront other infections

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.

MCQs

1- HIV infected person called AIDS when the CD4 count is less than:

a) 400 b) 100 c) 200 d) 50

2-Which one of these cells infected by HIV in the colon?

a) macrophage b)lymphocytes c) langerhans d) chromaffin cells

3- the live span of an HIV version in the plasma is :

a)24 h b) 12h c) 6h d) 2h

4- the most sensitive test for HIV is:

a) ELISA b)PCR c) western blot d)antibody test

5- all elements of immune system are affected.

a)true b) false

6-apoptosis is a direct mechanism of CD4 Dysfunction.

a)true b) false

1-c
2-d
3-c
4-b
5-a
6-b

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