Lecture 1

HIV & AIDS

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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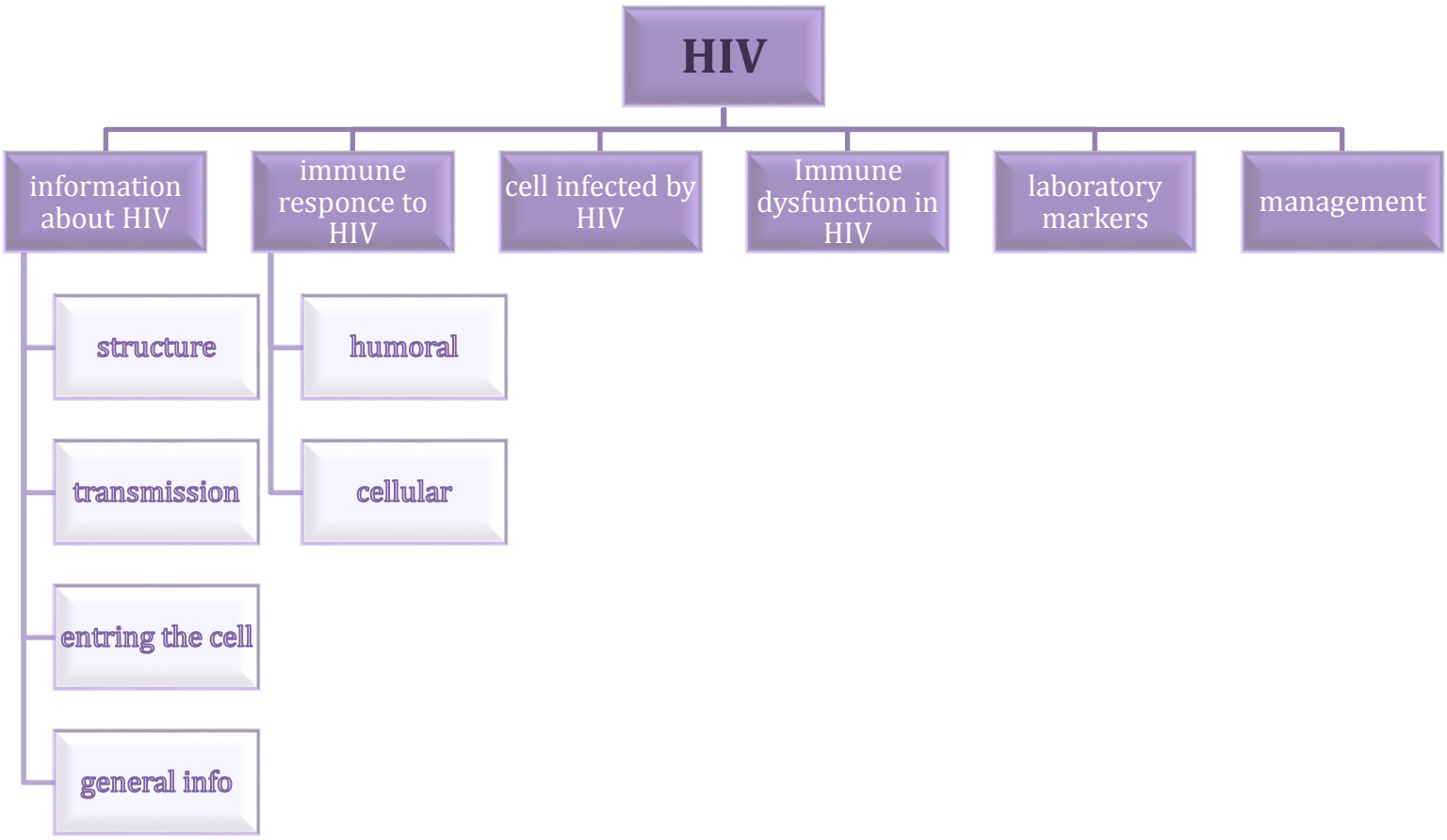
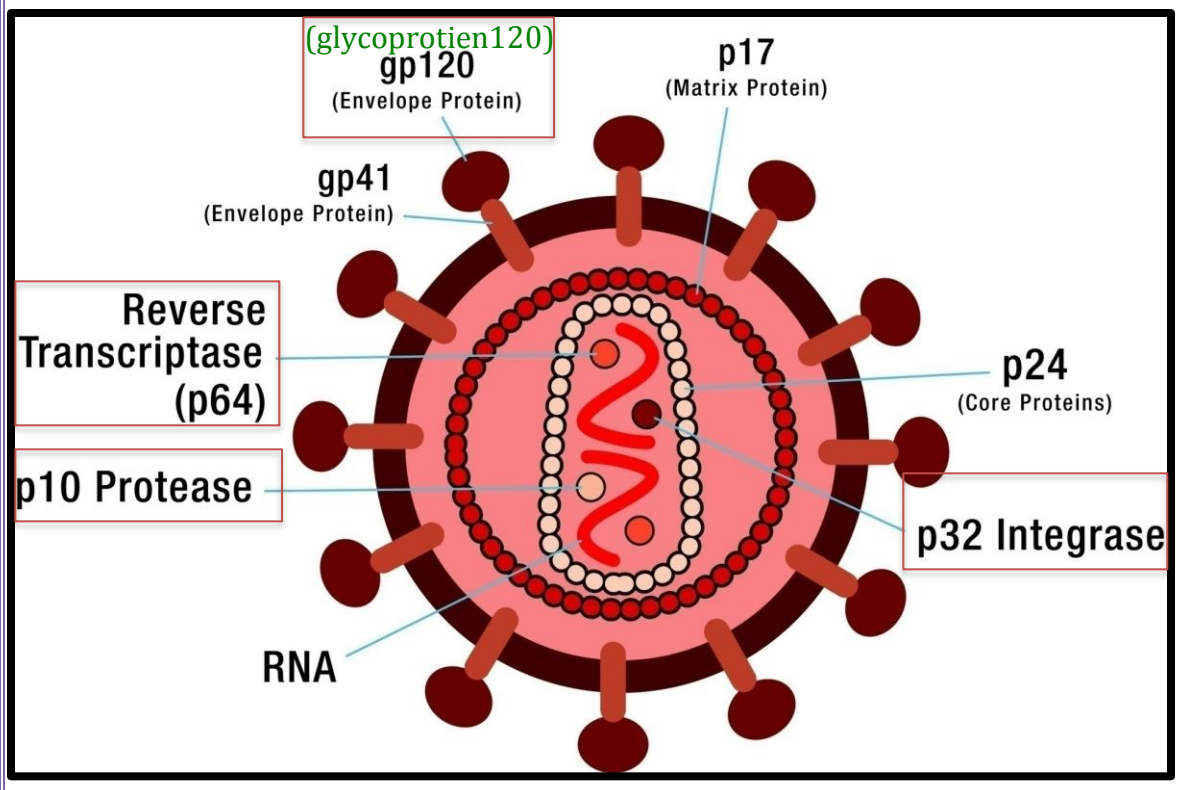

HIV
information about HIV
immune responce to HIV
cell infected by HIV
Immune dysfunction in HIV
laboratory markers
management
structure
transmission
entring the cell
general info
humoral
cellular

❖Structure of HIV cell



We need to Know only about gp120 &p64

- Envelope protein(gp120):

  Is essential to let HIV attach to CD4 & chemokine receptors.

- Reverse transcriptase (p64): is responsible to convert RNA to DNA inside the cell.

❖Transmission of HIV (mode of infection)

HIV transmit by 4 ways:

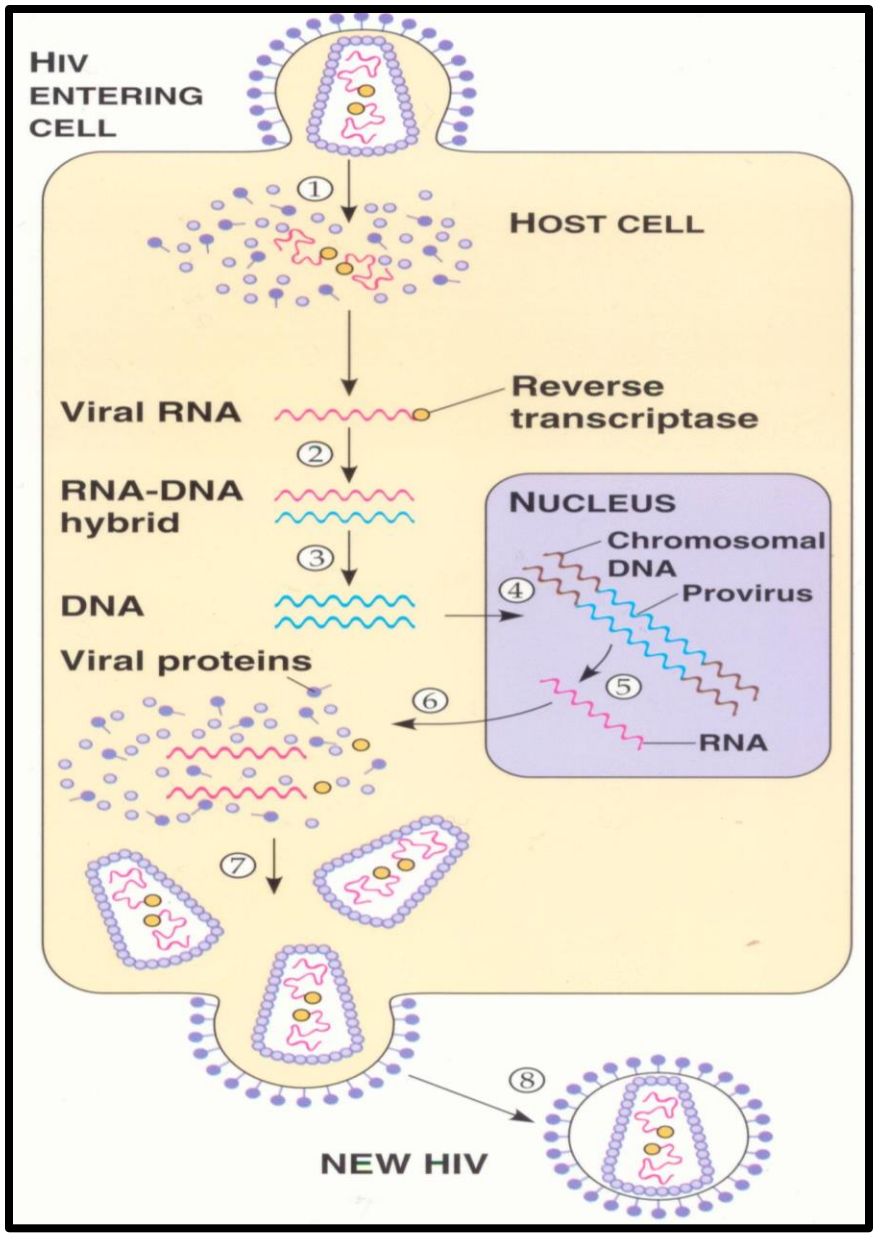
1. Sexual transmission at genital or colonic mucosa
2. Blood transfusion
3. Mother to infant
4. Accidental occupational exposure (like in surgery or in the lab)

Feature of HIV:

- It attacks the immune system and its main target is CD4+ T cell.
- HIV is a virus that can't live outside the cell.(intracellular).
- The Difference between HIV and AIDS is that "Patient with AIDS, has clinical sign and symptoms with severe illness (opportunistic) & AIDS is the last stage of HIV infection.

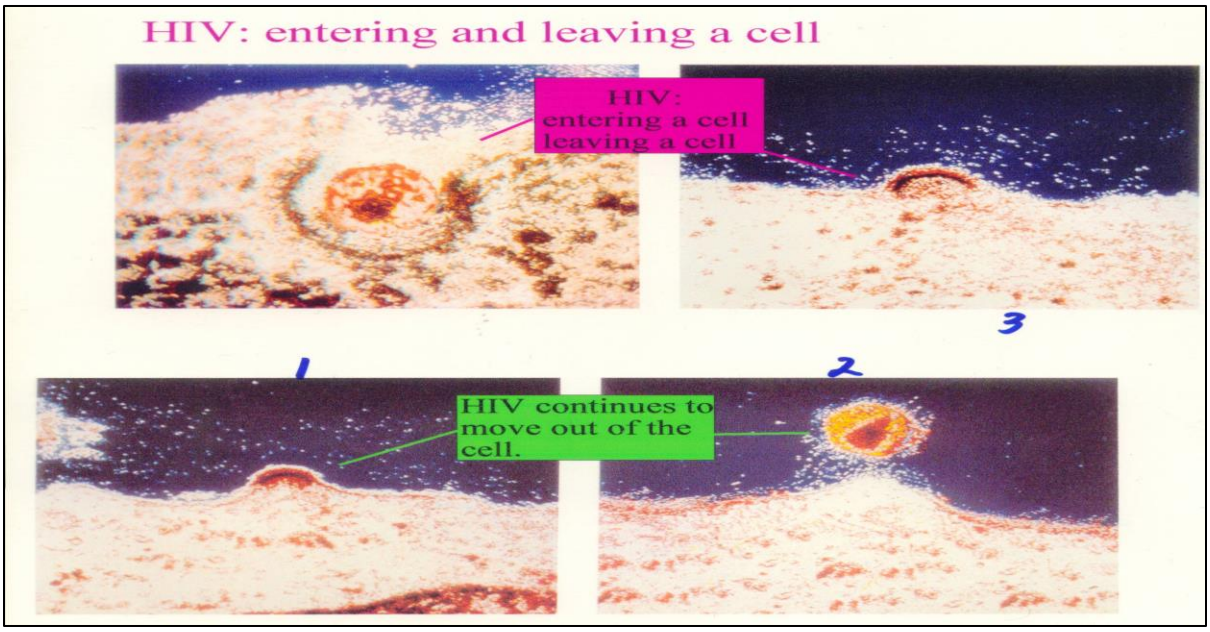
❖How HIV Enters Cells:

- gp120 envelope protein binds to CD4 molecule
  - CD4 found on T-cells macrophages, and microglial cells(the APCs in CNS)
  - Binding to CD4 is not sufficient for entry. (at least tow parts needed for entry)
- gp120 env protein binds to co-receptor
  - Chemokine receptors:
  - CCR5 and CXCR4 receptors (if there is any mutation in one of the Receptors the interaction will not take place).
- Binding of virus to cell surface results in <u>fusion of viral envelope with cell membrane</u>
- Viral core is released into cell cytoplasm



1. HIV (retrovirus*) enters cell
2. Reverse Transcriptase makes DNA copy of RNA
3. Viral DNA forms provirus with host DNA
4. Viral DNA makes mRNA
5. mRNA makes HIV proteins
6. HIV proteins become HIV capsid
7. mRNA is collected inside of HIV capsid forming new HIV
8. New HIV leaves cell and wraps itself in host membrane (envelope).

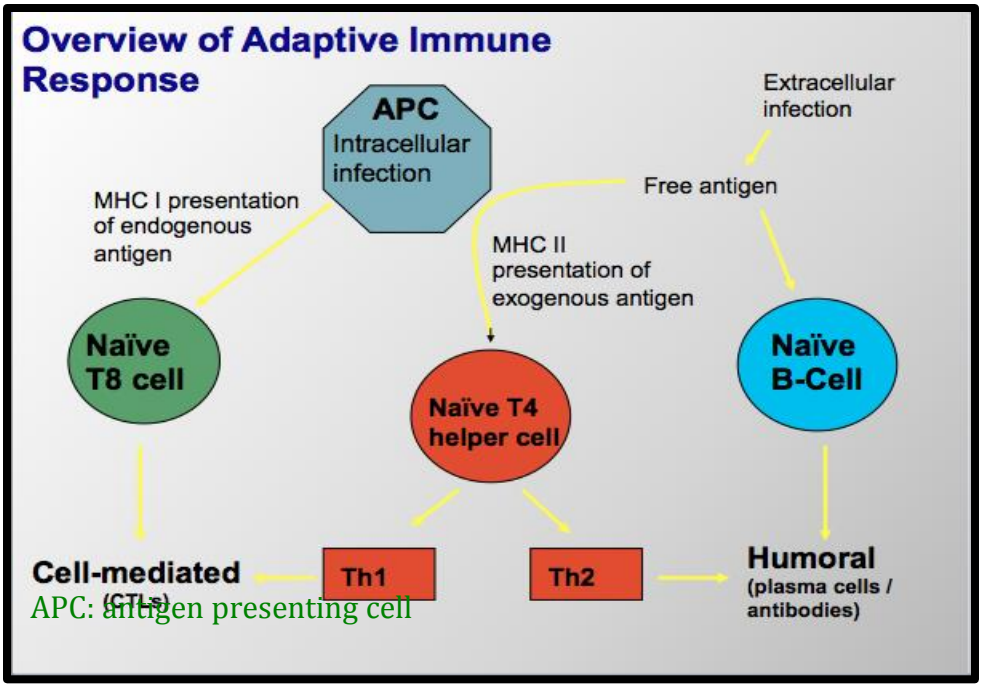
*Retrovirus: it has the reverse transcriptase, which convert viral RNA to DNA



❖Viral-host Dynamics (general info)

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

*Memory cells are imp to maintain a normal healthy state, and these cells remember all the Antigens that we've been exposed to. And when the HIV stays in those cells, they can't function properly.



APC: antigen presenting cell

- ❖ If the infection is intracellular this means that the viral Ag binds to MHC1 then the CD8 cells will become activated and start killing and destroying.
- ❖ If the infection extracellular this means that the Ag binds to MHC2 then they will activate CD4 cells which will lead to activation of T1/T2 helper cells and B cells.B cells will lead to formation of AB

❖General Principles of Viral-host Interactions

➢ Host: mounts HIV-specific immune responses

- Cellular (cell-mediated) - most important
- Humoral (antibody-mediated)

➢ Virus: subverts[1] the immune system

- Infects CD4 cells that control normal immune responses
- Integrates into host DNA
- High rate of mutation (No vaccination) "the mutation makes it hard to target the virus for vaccination".
- Hides in tissue not readily accessible to immune system

(and it is dangerous if the virus is in the CNS or bone marrow, cause we can't expose them to the optimal amount of the drug "even in toxic doses").

Subvert1: HIV will make the immune system either not see it, or attacks elsewhere. (misdirection of the immune system)

❖Immune system Responses to HIV:

The Immune system response to the HIV infection by 2 ways:

1. *Humoral Immune Responses*
2. *Cellular Immune Response*

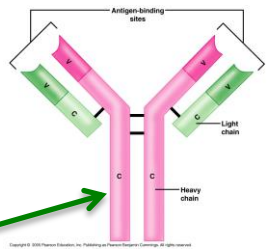
1st/ Humoral Immune responses to HIV:

⦿ Neutralization

- Antibodies bind to surface of virus to prevent attachment to target cell(No binding).

⦿ Antibody-dependent cell-mediated cytotoxicity (ADCC)

- Fc portion of antibody binds to Natural Killer(NK) cell
- Stimulates NK cell to destroy infected cell



FC portion

2nd/ Cellular Immune responses to HIV:

⦿ 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
- 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

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

Most important are macrophages because HIV hides & live inside them for a long time, so the virus can survive for a longer time. The reason why the virus stays longer in macrophages is because macrophages contain vesicles and inside these vesicles the virus will replicate and survive.

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 → recurrent infection
- Susceptibility to opportunistic infections

What normally happens is when we are exposed to foreign Ag our body can form Ab against them. But in case if HIV the immunity is lost and there is no response to infections

Mechanisms of CD4 Depletion and Dysfunction

1. **Direct** (physical presence of the virus and it's infecting the cell)
   - Elimination of HIV-infected cells by virus-specific immune responses
   - Loss of plasma membrane integrity because of viral budding

2. **Indirect**
   - Syncytium formation
   - Apoptosis
   - Autoimmunity

Syncytium formation is fusion of cells that are highly unstable and die quickly:

- Observed in HIV infection, most commonly in the brain
- Uninfected cells may then bind to infected cells due to viral gp 120
- 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 (important for growth of lymphocyte), IL-12(control of production of IFN-gamma)
  - 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 (inflammation of the spinal cord or of the bone marrow), polyneuritis
- **Surge in viral RNA** copies to >1 million → detected by PCR
- **Fall in CD4** count to 300-400
- **Recovery in 7-14 days**

Seroconversion → Development of antibodies in blood serum as a result of infection or immunization

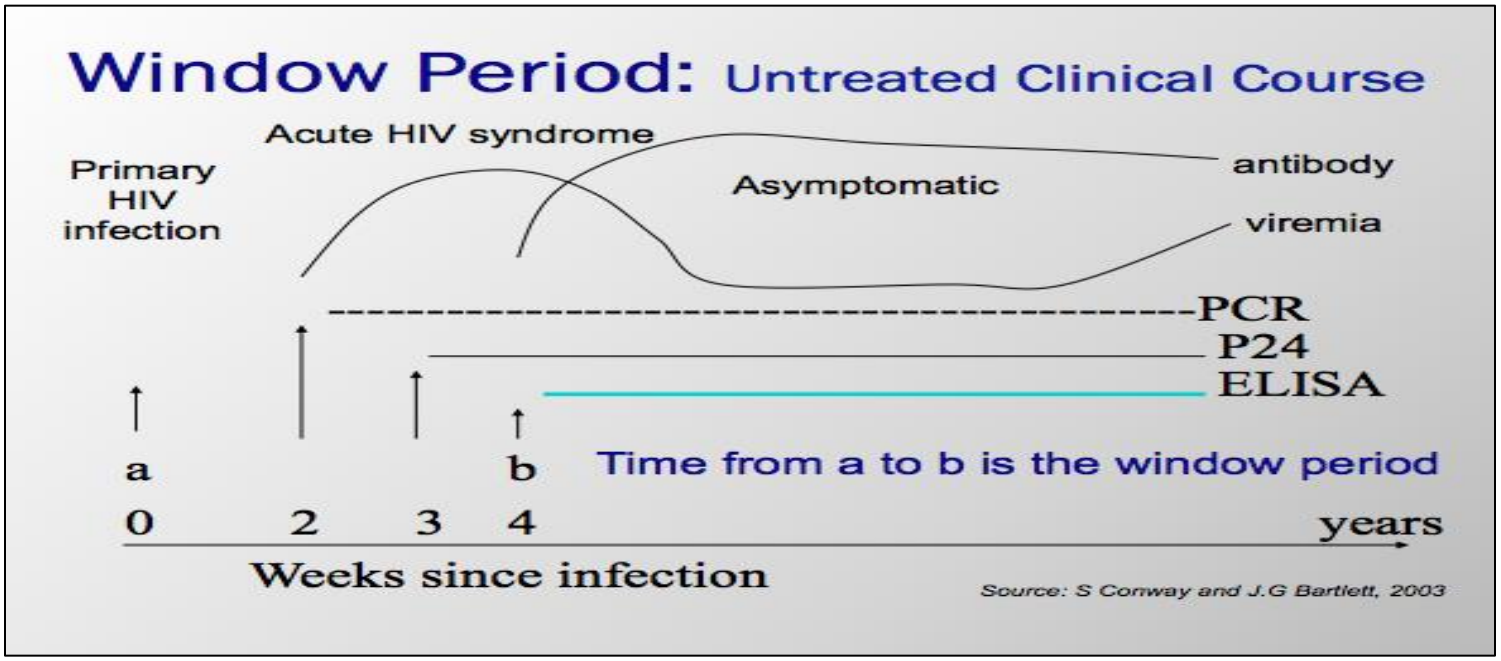
- Median **8 weeks** after infection.
- Level of viral load post sero-conversion correlates with risk of progression of disease.
- **Asymptomatic Phase.**
- Remain well with no evidence of HIV disease except for generalized lymphadenopathy.
- **Fall of CD4 count by about 50-150 cells per year.**

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.

Window Period



Untreated Clinical Course (0 = time of infection, after 2 weeks the RNA may be detected via **PCR**, after 3 weeks the viral proteins may be detected via **western blot test**, by 4 weeks the disease may be detected by **ELISA**.)

Normally PCR is not used because, its expensive and time consuming. The only one of the 3 that is done on a routine basis is ELISA (used for detecting the Ab) **but ELISA is only effective after about 1 month of infection**, Which means that till the 4th week the blood contains HIV but undetected. **(Time between week 1 to 4 is called the window period.)** The time that the virus can NOT be detected

Laboratory Markers of HIV Infection

- Viral load

  Marker of HIV replication rate

- CD4 count (Flow cytometry)

  Marker of immunologic damage

  If the ratio of CD4 to CD8 is less than one , there is infection

Diagnosis

- Antibody test by ELISA
- Western blot detect proteins
- HIV RNA viral load detected 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

None of them stops the virus , they just extend the life of HIV pateint

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 ; Remember; in your practice if you see a pt. who has got candida infection in the oral cavity; think about HIV for your diagnostic investigation.

Q1/ which one of the following tests is used to diagnose HIV RNA viral load:

A) RIBA.
B) ELISA.
C) PCR.
D) Western blot test.

Q2/ What usually human immunodeficiency virus (HIV) affects?

A) Neutrophil.
B) CD4.
C) Macrophages.
D) B+C.

Q3/ which one of the following is not way of transmission of HIV?

A) Blood transfusion
B) Mother to infant
C) Airborne
D) Accidental occupational exposure

Q4/ Which of the following is the first step of HIV enters the cell?

A) Reverse Transcriptase makes DNA copy of RNA
B) Gp120 bind to CD4 molecule
C) Gp41 bind to CD4 receptor
D) None

Q5/ Which of the following is true about cells infected by HIV?

A) Bone marrow: lymphocytes
B) Brain: dendritic cell
C) Colon: lymphocyte
D) Thymus: macrophages

Q.	A.
1	C
2	D
3	C
4	B
5	A

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