LECTURE- 8 *lect. Dr. Ahmed Yaseen Abed*

Human Immune Deficiency virus

Human immunodeficiency virus (HIV) Is a retrovirus that causes human AIDS. Many retroviruses infect vertebrates, One genus of retrovirus, Lentivirus, includes the subspecies **HIV-1** and **HIV-2**, which cause **AIDS**.
Family: **Retroviridae**
Genus: **Lentivirus**
Species: Human Immunodeficiency Virus (HIV)
●HIV infects mainly CD4+ T cells, macrophages, and dendritic cells which express the surface receptor CD4.
●Destroying CD4+ T cells leads to opportunistic infection.
● Acquired immunodeficiency syndrome (AIDS) is the end stage of the disease that is associated with CD4+ T cell depletion, multiple or recurrent opportunistic infections, and unusual cancer (Kaposi sarcoma).

●HIV patient is **different from** an AIDS patient. AIDS is an **end stage of HIV** virus.

Two types of HIV

A- HIV-1: has 9 subtypes it is responsible for most cases of acquired immunodeficiency syndrome (AIDS)
HIV-1: most common cause of AIDS which :-
• Causes HIV infection worldwide.
• Highly virulent.
• Highly susceptible to mutations.
B- HIV-2: has 5 subtype it is less commonly and less virulent AIDS was first describe as disease in 1981 and the virus was isolated by end of 1983
• HIV-2 Causes the infection in specific regions e.g. **West Africa**, **Mozambique**.
• Relatively less virulent so less pathogenic .
• Relatively less susceptible to mutations.

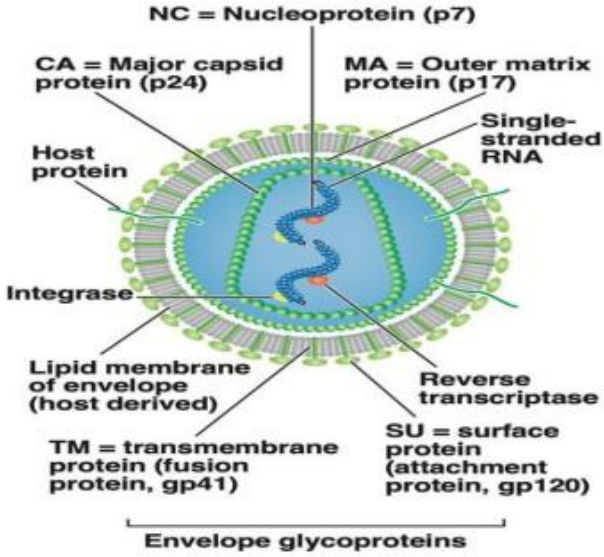


Figure: Structure of the human immunodeficiency virus.

Biological structure of HIV

➢ Envelope: the virus is surrounding by bilayer lipid envelope that covered by projected spikes (glycoprotein: gp41, gp120) which may act as attachment sites (HIV undergoes from high rate of antigenic variation in envelope glycoproteins).

The symmetry of HIV is Icosahedral (**20 sided**).

➢ Capsid proteins: consist of several proteins as capsid protein (**p24**) and matrix protein (p17)

➢ Core protein: contain many enzymes as reverse transcriptase (**R tase**) integrase

Enveloped virus and Virion consist of :-

1- Glycoprotein envelope (gp120, gp41).

2- Matrix layer (p17).

3- Capsid (p24).

4- Two copies of ss-RNA.

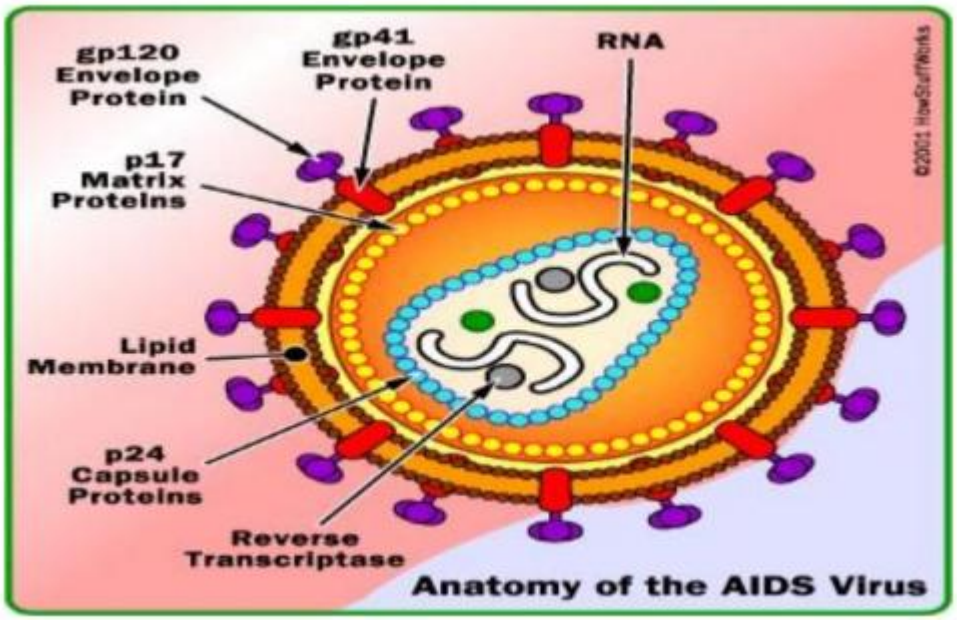
5- **Enzymes**: • Reverse transcriptase • Integrase, • Protease

6- Genome consists of two copies of (+) **ssRNA** (diploid).

➢ **The genome consists of 9 genes:**

3 structural genes (gag, pol, env) required for **the replication** of retroviruses

and 6 non-structural genes (tat, nef, rev, vif, vpr, vpu) regulate **viral expression** and are important in disease pathogenesis **in vivo.**



Viral Replication

Viral replication will be described into six steps:

1. Attachment to a specific cell surface receptor

Attachment is accomplished via the gp120 fragment of the env gene product on the HIV surface, which preferentially binds to a CD4 receptor molecule. Thus, the virus infects helper T cells, lymphocytes, monocytes, and dendritic cells, which contain this protein in their cell membranes.

2. Entry of virus into the cell: An additional coreceptor, a chemokine receptor (CCR5 and CXCR4 produced by lymphocytes and macrophages), is required for entry of the viral core into the cell. Binding to a coreceptor activates the viral gp41 gene product, triggering fusion between the viral envelope and the cell membrane.

3. Reverse transcription of viral RNA: After entering the host cell, HIV RNA is transcribed into DNA by reverse transcriptase—an RNAdirected DNA polymerase that enters host cells as part of the viral nucleocapsid.

4. Integration of the provirus into host cell DNA: Viral integrase cleaves the chromosomal DNA and covalently inserts the provirus, the integrated provirus thus becomes a stable part of the cell genome.

5. Transcription and translation of integrated viral DNA sequences: With host cell activation, DNA is transcribed to **mRNA** and **viral genomic RNA**. Viral

mRNAs are translated to give viral enzymes and structural proteins.

6. Assembly and maturation of infectious progeny: As the virion buds from the surface, the viral protease is activated and cleaves the poly- proteins into their component proteins, which then assemble into the mature virion. The mature retrovirus acquires an envelope as it buds from the infected host cell.

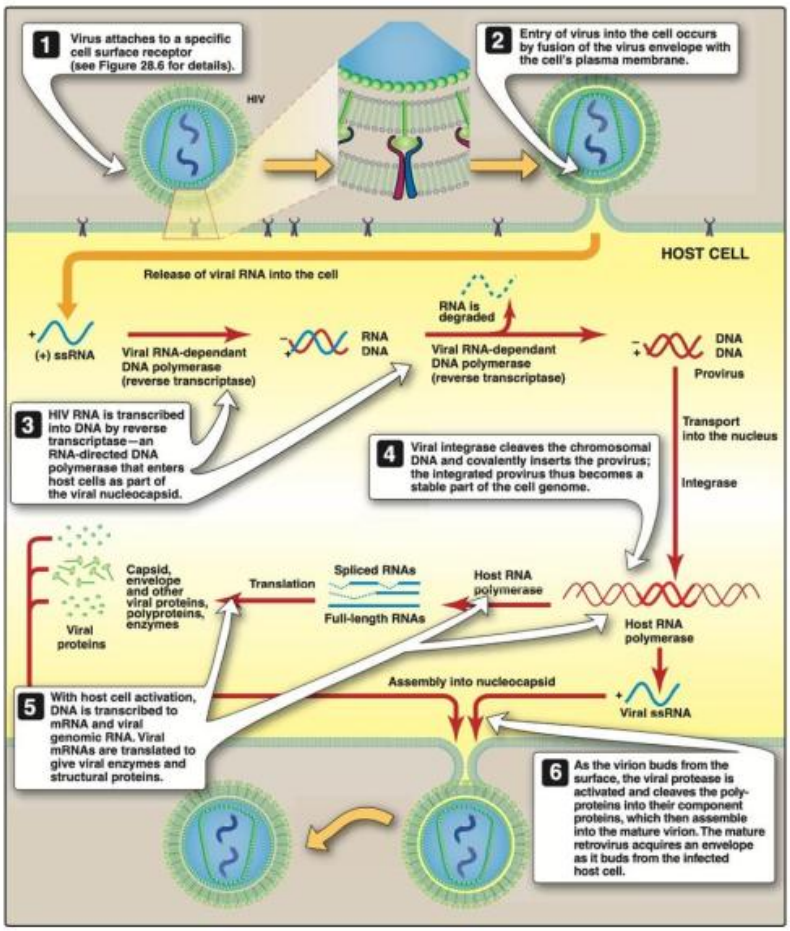


Figure: The human immunodeficiency virus (HIV) replication cycle. ssRNA = single strand RNA.

Virus receptors

The virus use CD4 molecule which is expressed on macrophages and T lymphocytes in addition to that HIV required a co receptor which is CCR5 a co receptor for the macrophage strains of HIV-1, whereas CXCR4 is the co receptor for the lymphocyte strain of HIV-1. these co receptors are acting normally as a chemokines receptors on the cell, and required for fusion of the virus with the cell membrane . the virus first bind to CD4 and then to the co receptors. These interactions causes conformational changes in the viral envelope activating **gp41 fusion protein** and **triggering membrane cell fusion**. Individual who possess

homozygous deletions in these co receptors may be protected from infection by HIV-1.

Mod of transmesion

υ **Sexual contact** : HIV has high affinity to semen and vaginal secretion therefore the virus can be transmitted by anal or vaginal intercourse among homosexual and heterosexual individuals

υ **parenteral transmission** : it can be transmitted by blood transfusion or by needles or syringes such as intravascular drugs uses(IVDU)

υ **mother to child :** HIV can transmitted to neonate across placenta or during delivery or breast milk

υ **other methods** : for transmission of HIV fluids or body such as urine tear saliva Bacterial infections such as TB syphilis salmonella infection viral infection EBV CMV hepatitis and herpes simplex fungal infection as candida albicans (cause oral thrush) protozoa infection pneumocystis carinii (cause pneumonia).

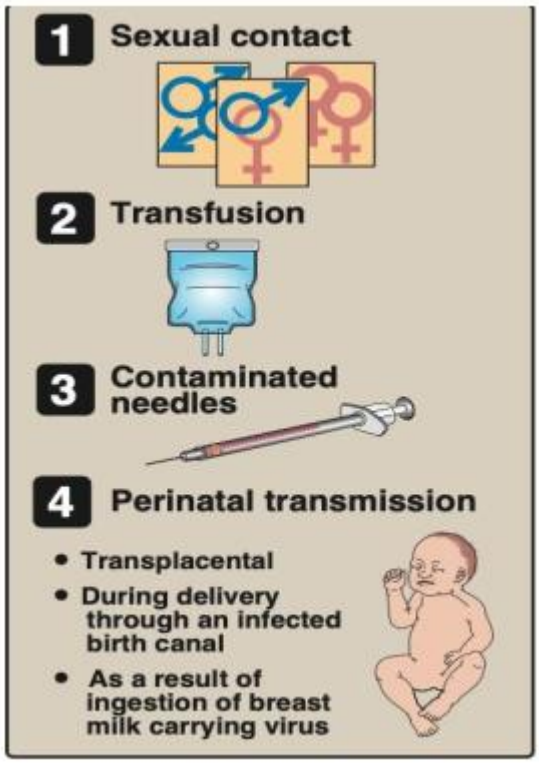


Figure: Common modes of transmission of HIV

Acute phase of HIV:

●Incubation period 2 weeks and lasts for about 12 weeks.
●Mostly asymptomatic, but in about 25-65% of the cases, patients may develop symptoms resemble infectious mononucleosis or Flu (fever, headache, anorexia, fatigue, lymphadenopathy, skin rash) which resolved in 2 weeks.
● Rapid viral replication (high viral load >106 copies/mL) .
● Gradual decrease in CD4+ T cell count.
● Blood markers in the acute stage:
● Normal to slightly decrease number of CD4+ T cells.

● Appearance of the viral RNA, and then the core antigen (p24 antigen) which indicate active viral replication.
● Appearance of two antibodies, Anti-envelop (Anti-gp120) & Anti-core (Anti-p24).
● The first choice marker for detection HIV in the acute phase is HIV RNA.

● Antibody tests may give false negative (no antibodies were detected despite the presence of HIV) results during the window period, an interval of three weeks to six months between the time of HIV infection and the production of measurable antibodies to HIV seroconversion.

Chronic phase of HIV:

Lasts for about 10 years in adults, and 5 years in children.
●Totally asymptomatic but the patients is still contagious.
●Relatively low viral load (500 cells/mm3).
●At the end of this stage, two syndromes appear:
1- Persistent generalized lymphadenopathy (PGL):
→Is defined as enlargement of lymph nodes for at least 1 cm in diameter in the absence of any illnesses or medications that known to cause PGL. → Clinical features: • In two or more lymph nodes out of the inguinal area. → Persists for at least 3 months.
2- AIDS-related complex (ARC):
►Is a group of clinical symptoms that come before AIDS and may include the following:
► Fever of unknown origin that persists > 1 month.
► Chronic diarrhea, persisting > 1 month.
►Weight loss > 10% of the original weight (slim disease).
►Fatigue, night sweating, and malaise.
►Neurological disease as myelopathy and peripheral neuropathy.
Blood markers in the chronic stage:
➢ Viral load (HIV RNA) increases gradually, and HIV core antigen (p24) may appear in blood.
➢ Anti-envelop (Anti-gp120) & Anti-core (Anti-p24) are positive.
➢ CD4+ T cell count gradually decreased .

AIDS phase

The end stage of the disease.
-Continuous viral replication (high viral load).
-Marked decrease in CD4+ T cell count < 200 cell/mm3.
-Defects in cellular immunity. Persistent or frequent multiple opportunistic infections.
-Unusual cancer (i.e. Kaposi sarcoma).

Blood markers in AIDS stage:

- High viral load (HIV RNA), and HIV core antigen (p24) appears in blood.
- Detection of both HIV RNA & the antigen p24 indicative of active viral replication.
- Anti-envelop (Anti-gp120) & Anti-core (Anti-p24) are positive.
- CD4+ T cell count decreased to very low levels (<200 cells/mm3).

Dignoses of HIV

1. Cell count of WBC for determination of T4/T8 ratio υ Isolation of virus by cell culture (in difficult)
2. serologic for detection of HIV an tibodies by ELISA radioimmune assay (RIA) and immunofluorescent test (IFT)
3. PCR has highly sensitivity and specificity to detect HIV genome in infected Cell.\

Control

1.prevention : safety sex practice
2. routine screening of donated blood for HIV
3. needles exchange program for IVDUS teeth brush razor …..etc should be not Used
4. avoidance pregnancy breast –feeding if infected mother

Treatment with antiviral therapy

υ Viral binding inhibitors such as CD4-lgG chimera
υ Rtase inhibitoors :azidothymidine (AZT) υ protein synthesis inhibitors ritonavir
υ Viral assembly inhibitors interferon –Alfa υ Gene therapy is developed now.
υ No vaccine available (because changes in antigenicity of HIV)

Questions

Q1: Define AIDS ?

Q2:- Answer True or false :-

1- HIV patient is different from an AIDS patient. AIDS is an end stage of HIV virus.

2- HIV belong to the lentiviridae .

Q3:- Multiple choice :-

1- Co receptor for the macrophage strains of HIV-1 is :-

a- CD4 b- CCR5 c- CD8 d- CXCR4

2- The 1st choice marker for detection HIV in the acute phase is :-

a- p24 antigen b- Anti p24 c- HIV RNA d- Anti-gp120

3- AIDS stage in HIV infection include :-

a- Normal CD4+ T cell count b- high CD4+ T cell count c- decrease CD4+ T cell count d- None of them.