Virology

Lec (1)

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Teaching Objectives:

1. To list general characteristic of human immunodeficiency virus
2. To distinguish between different subfamily.
3. To recognize the mechanism of entry and replication

Retroviridea: The most important is Human immunodeficiency virus (HIV) cause (AIDS). Classification of retroviridea into subfamilies.

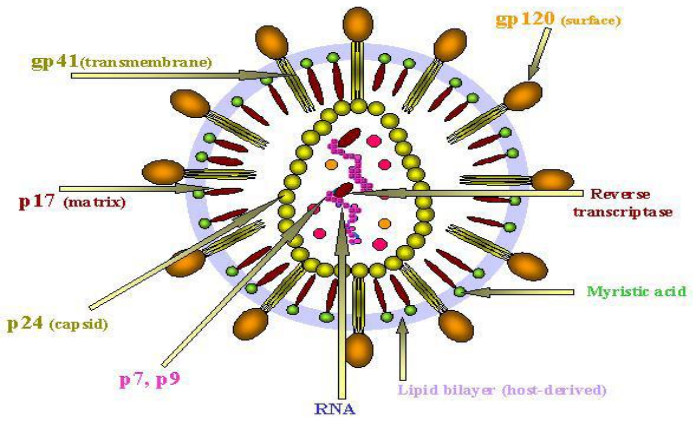
Subfamily	Disease produced	Infects
Oncovirinae -Human T cell Lymphotropic Virus-1 (HTLV-1) -Human T cell Lymphotropic Virus-2 (HTLV-2)	 - Adult T-cell leukemia (lymphoma) -Hairy cell leukemia	 Human Human
Spumaviriae	In apparent persistent infection	Primate and animals
Lentivirinae - HIV-1 - HIV-2 - Simian immunodeficiency virus (SIV-1)	 -Immunodefficency - Less pathogeneic -Animal association	 - Human - Human and Primate -Monkey

Lentivirinae

Human immunodeficiency virus (HIV) is the primary etiologic agent of acquired immunodeficiency syndrome (AIDS). The illness was first described in 1981 when center of disease control had report cases of immunodeficiency, and the virus was isolated in 1983. Both HIV-1 and HIV-2 cause AIDS, but **HIV-1** is found worldwide, whereas **HIV-2** is found primarily in West Africa.

The important properties of lentiviruses:

-Virion: spherical, 80-100 nm, cylindrical core. Genome: two molecules of ssRNA, positive sense, linear



Human immunodeficiency has nine genes, three **structural genes or typical genes** such as env, gag, and pol. In addition to 6 regulatory genes, from these genes two **required for replication** like tat and rev, while the other genes which called **accessory genes** such as nef, vif, vpr, and vpu are important in disease pathogenesis.

Internal structural proteins

1- Env (Envelope): cleaved by cellular protease into

-Surface glycoprotein Gp120 (protrude outside the lipid bilayer and it is important for attachment to the cell surface receptor CD4).

-Transmembrane (TM) Gp41 embedded in the lipid bilayer, function fusion the cell

2-gag (Group specific Ag): cleaved by viral protease into 3 Ags:

-Matrix protein (P17)

-Core protein (P24)

-Nucleocapsid protein (p7)

3-Pol (Polymerase protein): cleaved by viral protease into

A - Reverse transcriptase (RT enzyme **or** RNA dependent DNA polymerase **or** p66) transcribes RNA genome into DNA. And act as bifunctional enzyme. It also has ribonuclease H activity. Rribonuclease H degrades RNA when it is in the form of an RNA-DNA hybrid molecule.

B - Protease (cleaves precursor polypeptides)

C - Integrase enzyme (IN or P32) the function is integrate the viral genome in the host cell chromosome.

Six regulatory genes

1- Transactivating protein (**tat):** activation of transcription of viral genes.

2- Regulator of expression of virion protein **(rev):** controls transport the passage of late mRNA from the nucleus into the cytoplasm.

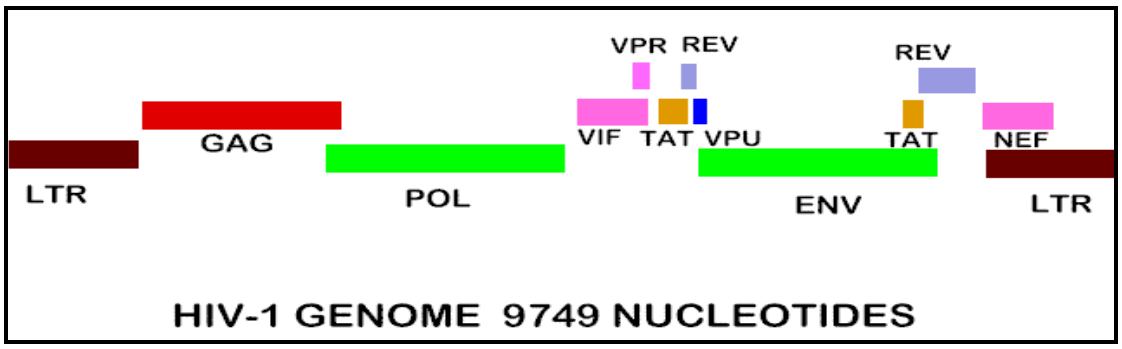
3- Negative regulatory factor **(nef**): repress the synthesis of Class I MHC protein, reducing the ability of cytotoxic T-cell to kill HIV infected cell.

4- Viral infectivity factor (**vif)**: enhances HIV infectivity by inhibiting the action of APOBEC3G an enzyme that causes hyper mutation in retroviral DNA (Apolipoprotein B RNA edited the enzyme considered as innate host defenses against HIV infection.

5- Viral protein R **(vpr**): transports viral core from cytoplasm into nucleus in non dividing cells.

6- Viral protein U **(vpu)**: enhances virion release from cell.

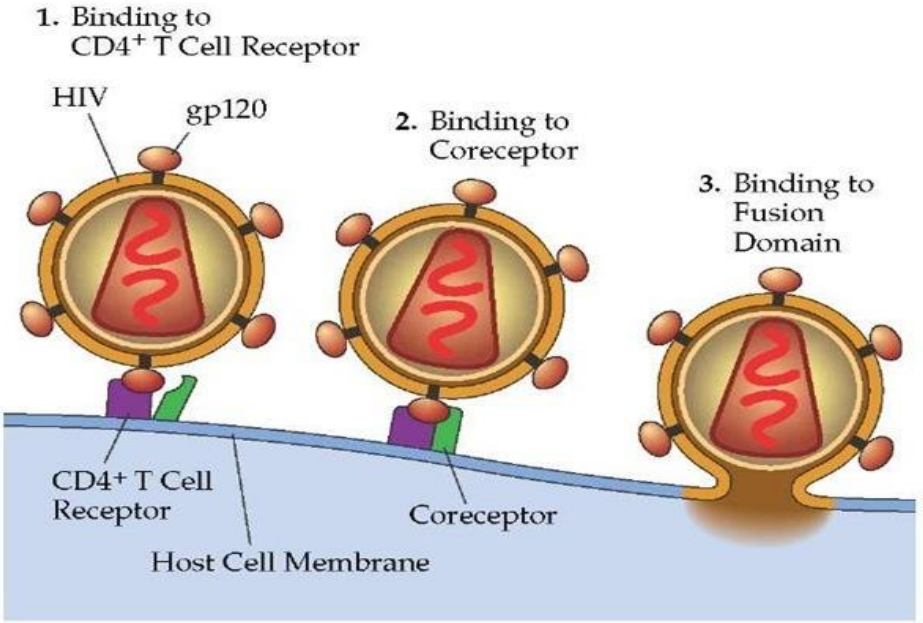
At both ends are long terminal repeats (LTR), which are transcription initiation sites. Within the 5' LTR is the binding site for the TAT protein, called the transactivation response element (TAR)



Virus receptor:

All primate lentiviruses use as receptor the CD4 molecule, which is expressed on T lymphocytes. In addition to CD4, a second receptor is necessary for HIV-1 to gain entry to the cells. The Chemokine receptors (soluble factors with chemoattractant and cytosine properties) serve as a second receptor (The CCR5 is the co-receptor for M-tropic strains and CXCR4 for T-topic strains) found on the surface of macrophage and monocyte.

The virus first bind to the CD4 and then to the second receptor. These interactions cause conformational changes in the viral envelope, activating the gp41-fusion peptide and triggering membrane fusion.



Routes of transmission: HIV is transmitted by three main routes:

1- Blood transfusion and organ transplantation

Parenteral exposure to infected blood and blood products:

The most efficient mode of transmission, yield 90-100% infection rate depending on the level of viremia and CD4 T cell count at the time of donation. The risk of transmission following minor injuries or Needle stick is around 0.3%. The high-risk populations are multiple blood transfusions,

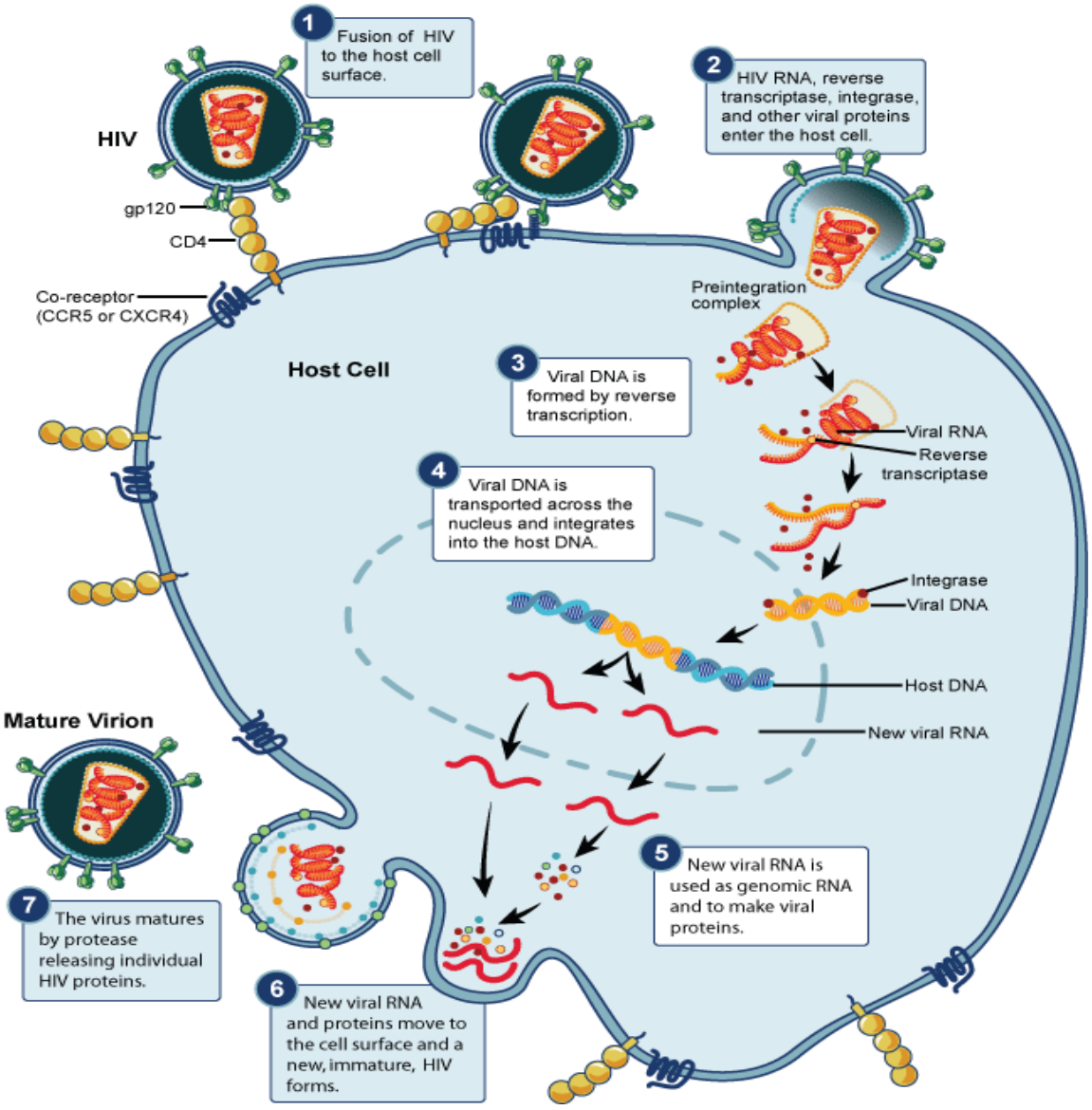
IDUs (60-70%), Prisoners, HCWs. However, screening of blood has dramatically reduced the rate of infection. Sharing of syringes, skin piercing instruments and related objects are important tools in HIV transmission.

2- Sexual contact: Is the most important route accounting for 75% of all HIV cases worldwide. However, the rate of transmission is variable (0.1-10%) and influenced by many factors, e.g. viral load and presence of ulcerative as result of infected with syphilis, cancroid and herpes genitals.

3-Perinatal transmission from infected mother to neonate also occurs either across the placenta, at birth or via breast-feeding. The transmission rate is variable (15-30%). Breast-feeding is a common route.

4-Other routes: Saliva and other body fluids.

Summary of replication cycle.



1- The initial step in the entry of HIV into the cell is the binding of the virion gp120 envelope protein to the CD4 protein on the cell surface. The virion gp120 protein then interacts with a second protein on the cell surface, one of the chemokine receptors. Chemokine receptors, such as CXCR4 and CCR5 proteins, are required for the entry of HIV into CD4-positive cells. The T-cell-tropic strains of HIV bind to CXCR4, whereas the macrophage-tropic strains bind to CCR5.

2- Next, the virion gp41 protein mediates fusion of the viral envelope with the cell membrane, and the virion enters the cell.

3- Uncoating occur in cytoplasm of cell, the RT-transcriptase transform the genome RNA into double-stranded DNA, which integrates into the host cell DNA. The viral DNA can integrate at different sites in the host cell DNA, and multiple copies of viral DNA can integrate. Integration is mediated by a virus-encoded endonuclease (integrase).

4- Viral mRNA is transcribed from the proviral DNA by host cell RNA polymerase and translated into several large polyproteins. The Gag and Pol polyproteins are cleaved by the viral-encoded protease, whereas the Env polyprotein is cleaved by a cellular protease. The Gag polyprotein is cleaved to form the main core protein (p24), the matrix protein (p17), and several smaller proteins. The Pol polyprotein is cleaved to form the reverse transcriptase, integrase, and protease.

5-The immature virion containing the precursor polyproteins forms in the cytoplasm, and cleavage by the viral protease occurs as the immature virion buds from the cell membrane. It is this cleavage process that results in the mature, infectious virion.

Pathogenesis of HIV.

1- HIV is first found in the blood 4–11 days after infection.

2- HIV infects helper T cells and kills them (Decrease in the number of CD4-positive helper T cells), resulting in **suppression of cell-mediated immunity**. This predisposes the host to various opportunistic infections and certain cancers such as Kaposi's sarcoma and lymphoma.

3- The death of HIV-infected cells is also the result of immunologic attack by cytotoxic CD8 lymphocytes. Effectiveness of the cytotoxic T cells may be limited by the ability of the viral Tat and Nef proteins to reduce class I MHC protein synthesis.

4- HIV also infects brain monocytes and macrophages, producing multinucleated giant cells and significant central nervous system symptoms. The fusion of HIV-infected cells in the brain and elsewhere mediated by gp41 is one of the main pathologic findings.