

Topic- Secondary Immunodeficiency disease

Course- M.Sc Microbiology

Semester- M.Sc 2nd Semester

Paper- Immunology (202)

Unit-IV Topic-1

INTRODUCTION

- Secondary immunodeficiency, or acquired immunodeficiency, is the loss of immune function and results from exposure to various agents.
- The most common secondary immunodeficiency is **acquired immunodeficiency syndrome**, or **AIDS**, which results from infection with the human immunodeficiency virus 1 (HIV-1).
- AIDS patients, like other individuals with severe immunodeficiency, are at risk of infection with so-called opportunistic agents.
- **Acquired hypogammaglobulinemia**- The major symptom includes recurrent infection, manifests itself in young adults. The patients generally have very low but detectable levels of total immunoglobulin.

- T-cell numbers and function may be normal, but there are some cases with T-cell defects and these may grow more severe as the disease progresses.
- Treatment- Immunoglobulin therapy. T
- There is no evidence for genetic transmission of this disease. Mothers with acquired hypogammaglobulinemia deliver normal infants. However, at birth the infants will be deficient in circulating immunoglobulin, because the deficiency in maternal circulation is reflected in the infant.
- **Agent-induced immunodeficiency-** it results from exposure to any of a number of chemical and biological agents that induce an immunodeficient state.
- Example—Drugs which are used to combat autoimmune diseases such as rheumatoid arthritis or lupus erythematosus.

- Corticosteroids, which are commonly used for autoimmune disorders, interfere with the immune response in order to relieve disease symptoms.
- cyclosporin A (immunosuppressive drug), which is used at the time of transplantation in order to blunt the attack of the immune system on transplanted organs.

Acquired Immunodeficiency Syndrome (AIDS) /HIV-1

- HIV-1 causes, acquired immunodeficiency syndrome (AIDS) was first reported in the United States in 1981 in Los Angeles, New York, and San Francisco.
- In 1982 public health officials began to use the term "acquired immunodeficiency syndrome," or AIDS, to describe the occurrences of opportunistic infections, Kaposi's sarcoma (a kind of cancer), and *Pneumocystis jirovecii* pneumonia in previously healthy people.
- In 1983, scientists discovered the virus that causes AIDS. The virus was at first named HTLV-III/LAV (human T-cell lymphotropic virus-type III/ lymphadenopathy-associated virus) by an international scientific committee. This name was later changed to HIV (human immunodeficiency virus).

Transmission of AIDS

Common means of transmission include homosexual and heterosexual intercourse, receipt of infected blood or blood products, and passage from mothers to infants.

- Exposure to infected blood accounts for the high incidence of AIDS among intravenous drug users who normally share hypodermic needles.
- Infants born to mothers who are infected with HIV-1 are at high risk of infection.
- Possible vehicles of passage from mother to infant include blood transferred in the birth process and milk in the nursing period.
- Transmission from an infected to an uninfected individual is most likely by transmission of HIV-infected cells—in particular, macrophages, dendritic cells, and lymphocytes. Infection is greatly enhanced by the presence of other sexually transmitted diseases (STDs).

A Retrovirus, HIV-1, Is the Causative Agent of AIDS

- The causative agent was discovered and characterized by efforts in the laboratories of Luc Montagnier in Paris and Robert Gallo in Bethesda.
- It cause by retrovirus. Retroviruses carry their genetic information in the form of RNA. When the virus enters a cell, the RNA is reverse transcribed to DNA by a virally encoded enzyme, reverse transcriptase (RT).
- Which is called a **provirus**, is integrated into the cell genome.
- and is replicated along with the cell DNA. When the provirus is expressed to form new virions, the cell lyses. Alternatively, the provirus may remain latent in the cell until some regulatory signal starts the expression process.

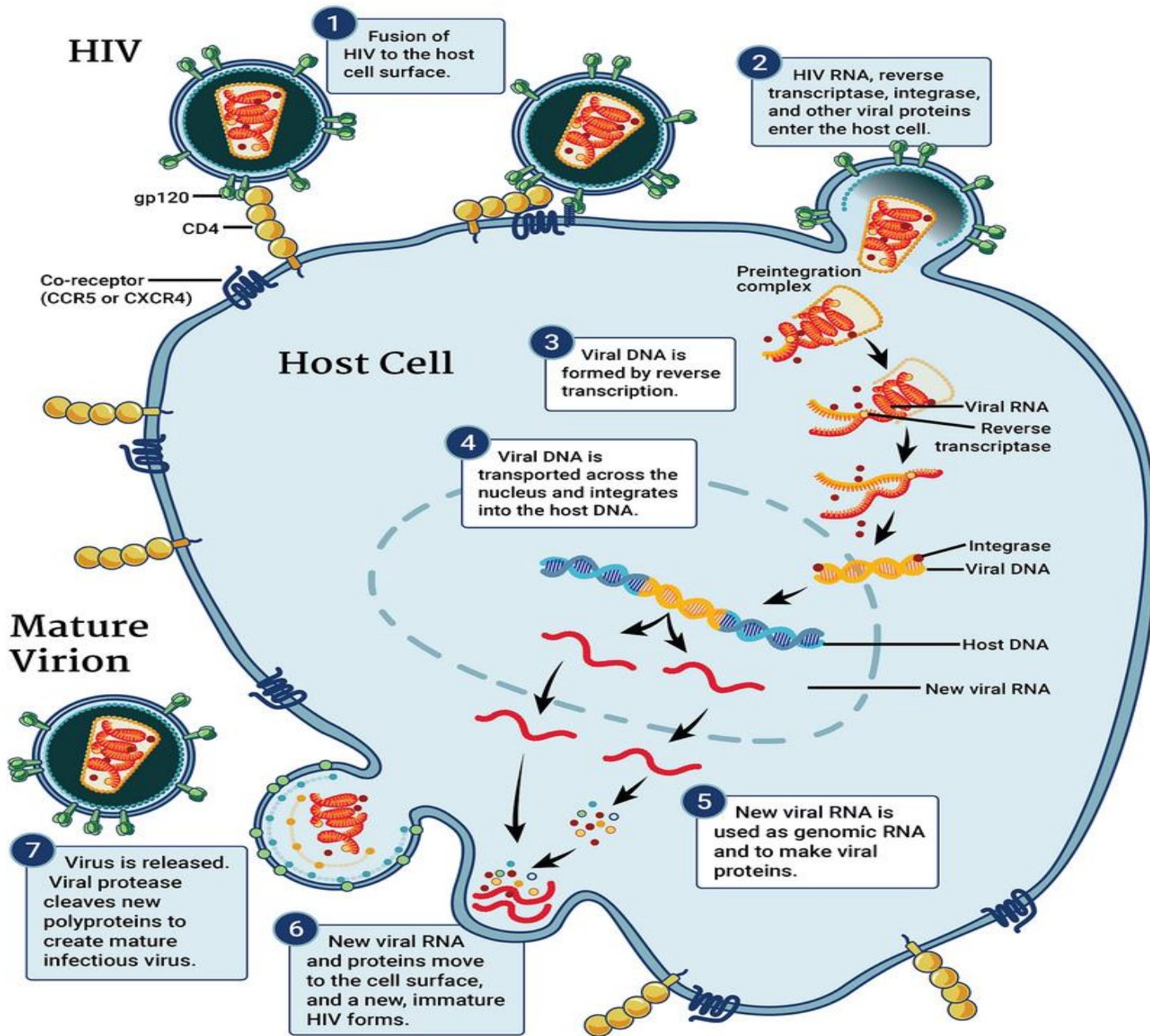
HIV-1 Replication Cycle

- The AIDS virus can infect human T cells in culture, replicating itself and in many cases causing the lysis of the cell host.
- **Steps -**
 1. Viral attachment to host cell (T cell with CD4 antigen)- This is mainly due to a high-affinity interaction between a coat (envelope or env) protein of HIV-1 and cell-surface CD4. Certain HIV strains will infect monocytes and other cells that have CD4 on their surface.
 2. Entry
 - The infection of a T cell, is assisted by the Tcell co-receptor CXCR4 (fusin named in initial report).
 - (An analogous receptor called CCR5 functions for the monocyte or macrophage).
 3. The RNA genome of the virus is reverse transcribed
 4. A cDNA copy (provirus) integrates into the host genome

5. The integrated provirus is transcribed viral RNA messages spliced and translated into proteins.
6. Complete new copy of the RNA genome synthesized and form new viral particles.
7. The gag proteins of the virus are cleaved by the viral protease into the forms that make up the nuclear capsid in a mature infectious viral particle.

Strains of HIV-

- 1. T-tropic strains-** CXCR4 serve as co-receptors for HIV-1 on T cells
- 2. M-tropic strains** - CCR5 serve as co-receptors for HIV-1 on macrophages.

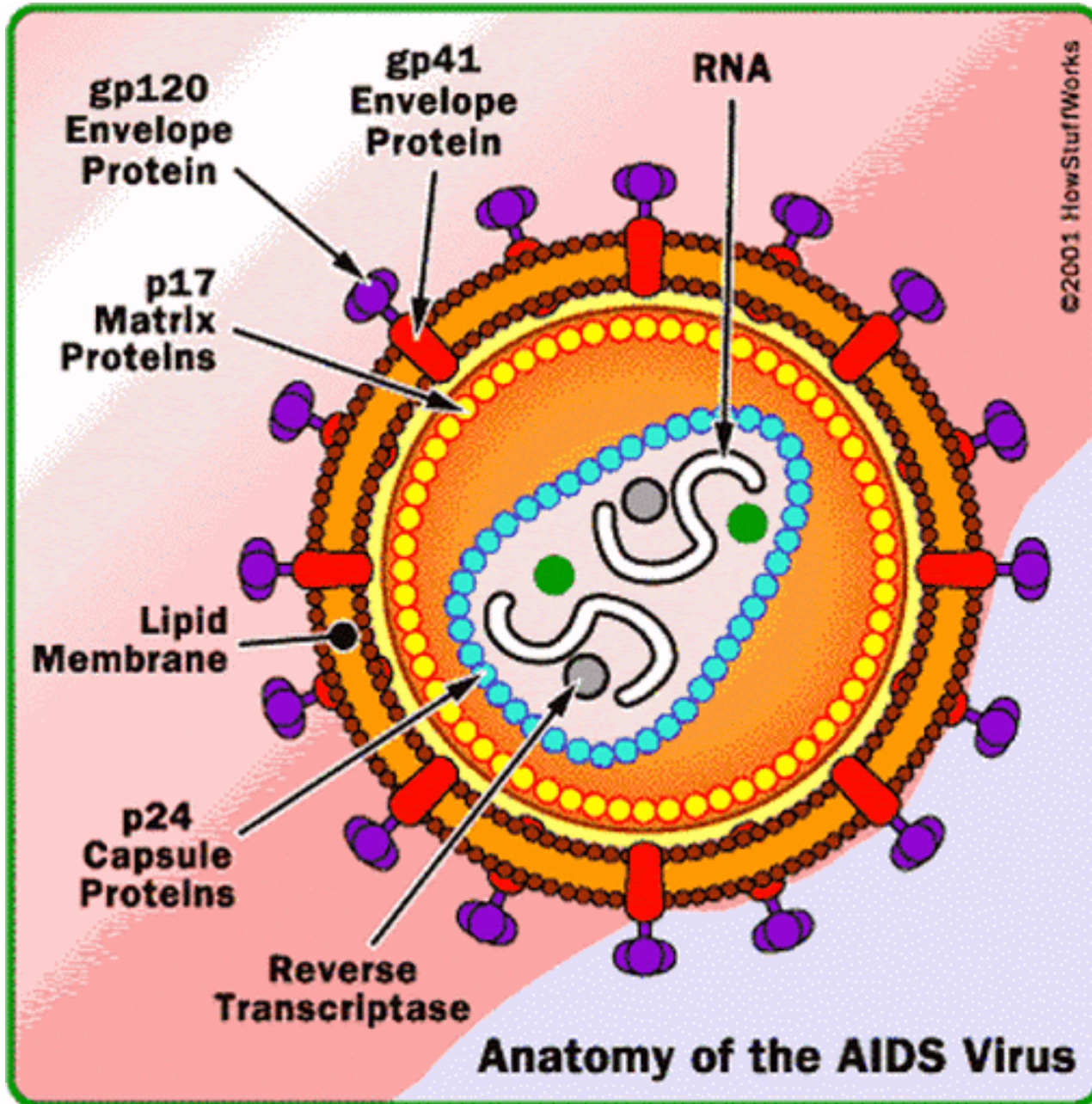


Replication Cycle of HIV Virus

Role of cytokines and chemokines in virus replication

- It was known from *in-vitro* studies that certain chemokines had a negative effect on virus replication while certain pro-inflammatory cytokines had a positive effect.
- Both of the HIV co-receptors, CCR5 and CXCR4, function as receptors for chemokines. Because the receptors cannot bind simultaneously to HIV-1 and to their chemokine ligand, there is competition for the receptor between the virus and the normal ligand, and the chemokine can block viral entry into the host cell.
- Whereas the chemokines compete with HIV for usage of the coreceptor and thus inhibit viral entry, the pro-inflammatory cytokines induce greater expression of the chemokine receptors on the cell surface, making the cells more susceptible to viral entry.

- **Syncytia formation-** HIV-1 infection of T cells with certain strains of virus leads to the formation of giant cells or syncytia.
- Syncytia or multinucleated giant-cell formation is one of the major cytopathic effects induced by human immunodeficiency virus (HIV) infection.
- Cell fusion results from the strong interaction of CD4 molecules on the surface of the uninfected T cells and gp120, an external envelope glycoprotein of HIV on the infected T cells.
- **Sign and symptoms-** The symptoms of HIV vary depending on the stage of infection. Symptoms includes fever, Swollen glands, Sore throat, Night sweats, Muscle aches, Headache, Extreme tiredness, Rash.



Morphology of HIV Virus

Therapeutic Agents Inhibit Retrovirus Replication

Two types of antiviral agents most commonly used-

1. Drugs that interfere with the reverse transcription of viral RNA to cDNA-- zidovudine, or AZT (azidothymidine). The introduction of AZT, a nucleoside analog, into the growing cDNA chain of the retrovirus causes termination of the chain (but chance to develop mutant strains)
- The administered AZT is used not only by the HIV-1 reverse transcriptase but also by human DNA polymerase. The incorporation of AZT into the DNA of host cells kills them (Precursors of red blood cells thus anemia is side effects)
 - A different approach to blocking reverse transcription employs drugs such as Nevirapine, which inhibit the action of the reverse transcriptase enzyme.

2. Agent that block the step at which precursor proteins are cleaved into the units needed for construction of a new mature virion.
 - This step requires the action of a specific viral protease, which can be inhibited by chemical agents; this precludes the formation of infectious viral particles.
 - Current treatment for AIDS is a combination therapy, using regimens designated HAART (highly active anti-retroviral therapy) that includes combination the use of two nucleoside analogs and one protease inhibitor.
 - The use of immune modulators, such as recombinant IL-2, in conjunction with HAART is being examined as a strategy to help reconstitute the immune system and restore normal immune function.