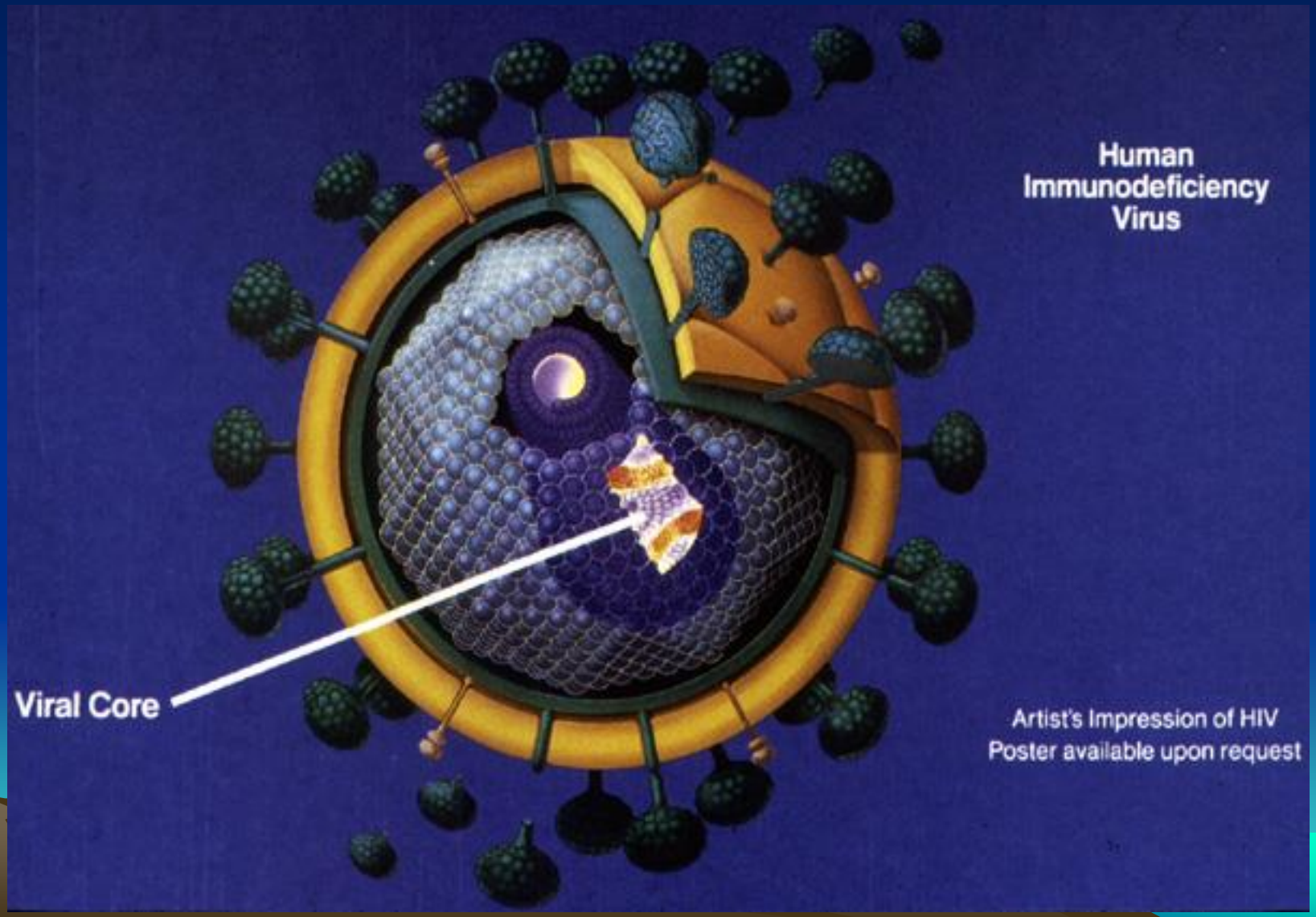
Antivirals (Antiviral drugs)



Antivirals (Antiviral drugs)

1- Viruses are obligate intracellular parasites.

2- They differ from other infectious agents in:

-Size, chemical structure.

- Their lack of enzymes that have function in energy metabolism.

- Their lack of protein synthesis metabolism

- They multiply only within the cells of the host.

3- They are either RNA or DNA viruses.

4- The nucleic acid is surrounded by a protein coat covered by an outer envelope that contains lipoprotein.

5- Antivirals are most active when viruses are replicating.

6- The earlier treatment as possible will give a good results.

Targets for Anti-viral therapy

1- Viral attachment to cell and fusion (**fusion inhibitors**).

2- Protein translation in infected cells (**interferon**).

3- Protein processing (**specific protease inhibitors**)

4- DNA synthetic enzymes (reverse transcriptase inhibitors, DNA polymerase inhibitors).

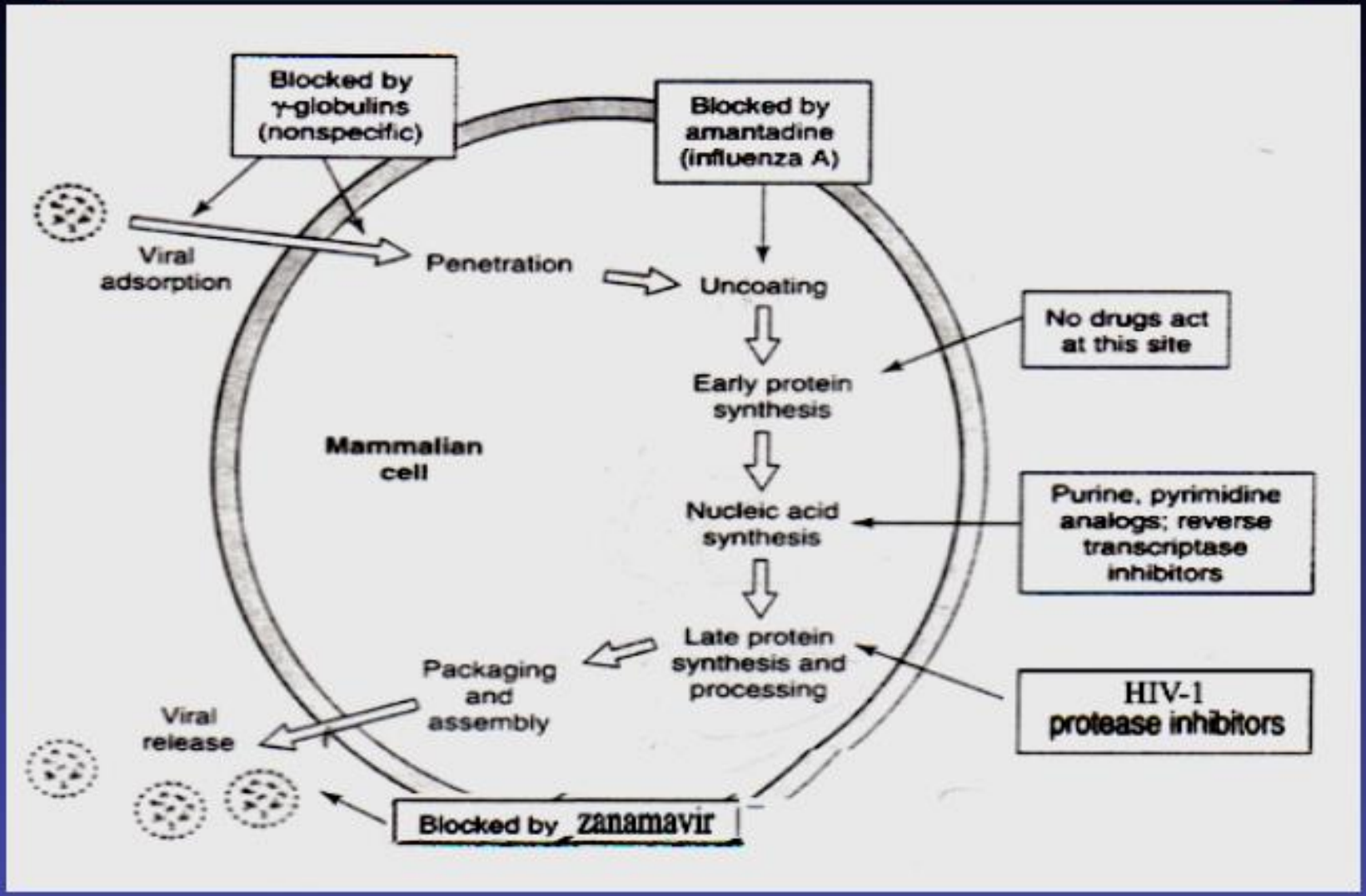
5- DNA integrase.

6- Immune system (effective vaccines, restore immune surveillance).

Viral Replication: General Scheme

- Adsorption to and penetration of susceptible cells
- Synthesis of early, nonstructural proteins
- Synthesis of RNA or DNA
- Synthesis of late, structural proteins
- Assembly of viral particles and their release from cell

Viral replication cycle: General Scheme



Classification:

I- Drugs that directly impair virus replication:

Acyclovir:

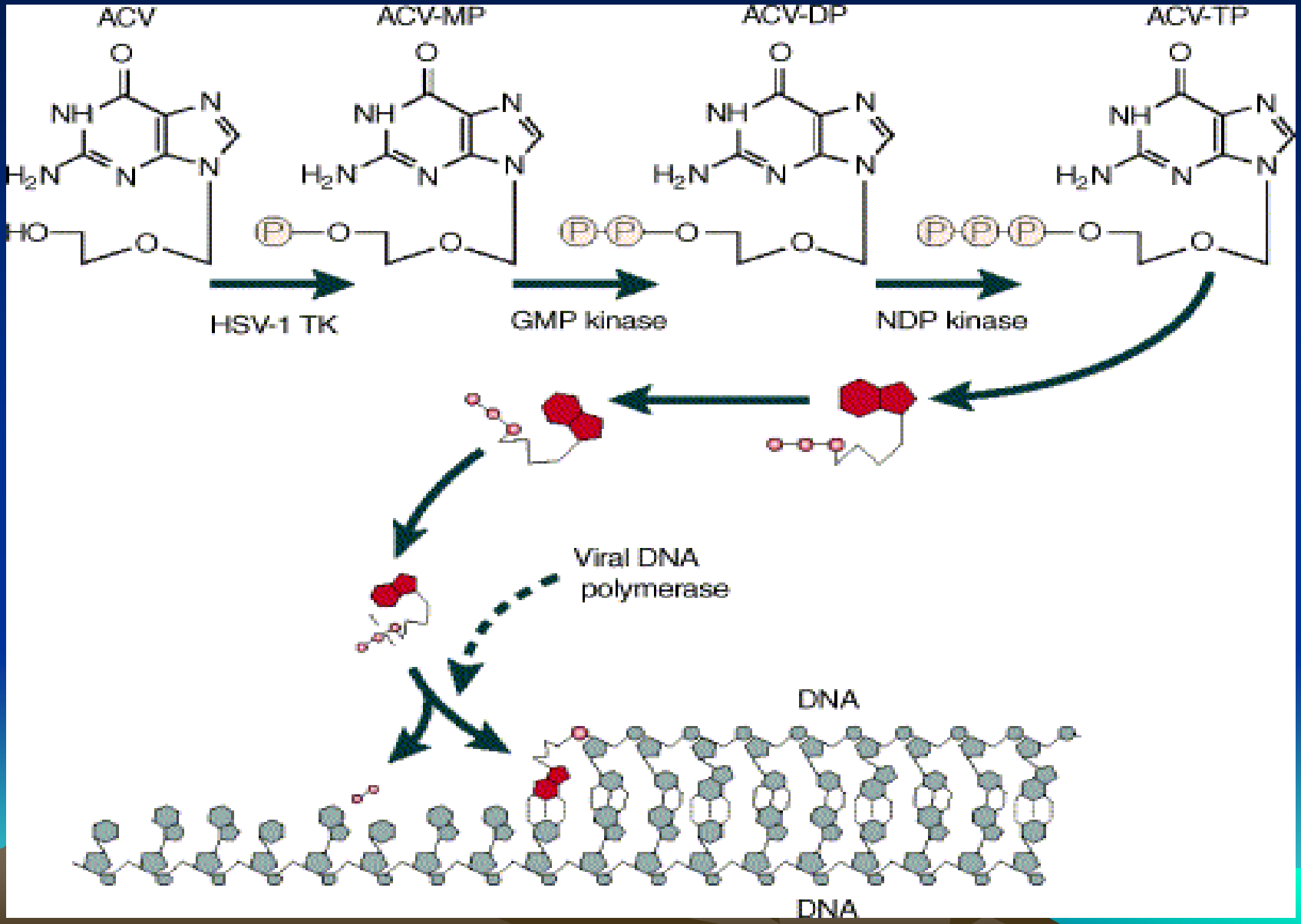
It is a synthetic purine nucleoside analog (**Deoxyguanosine**).

Mechanism of action:

- Generally, it is Phosphorylated by viral thymidine kinase (TK) →converted to triphosphate form → inhibiting Herpes virus DNA synthesis by interfering with viral DNA polymerase enzyme activity and → inhibiting DNA replication due to lack of 3' –OH group.

NB: Acyclovir is activated by the viral thymidine kinase (TK) enzyme to monophosphate. Then, host enzymes convert the mono-phosphate to di- and tri-phosphates.

Mechanism of action of Acyclovir



Spectrum of activity:

It has activity against Herpes simplex virus [HSV-2 (genital), HSV encephalitis] and Varicella-Zoster.

NB: Not effective against cytomegalovirus (CMV) infections because CMV thymidine kinase (TK) does not activate acyclovir.

Uses:

1- It is used either orally (20% bioavailability) or locally (ointment) for treatment of primary Herpes simplex infections.

2- Intravenously for treatment of serious infections.

Resistance to acyclovir:

1- Mutations in viral TK gene: alter affinity for drug or just completely inactivate the gene

2- Viral DNA polymerase mutations: reduce recognition of phosphorylated drug as substrate for DNA synthesis

Idoxuridine:

1- It is a thymidine analog phosphorylated to triphosphate within the cells.

2- Its use is restricted to topical administration (solution or ointment) against Herpes simplex keratitis because of its toxicity.

Mechanism of action:

Idoxuridine, which closely resembles thymidine, inhibits thymidylic phosphorylase and specific DNA polymerases, which are necessary for the incorporation of thymidine into viral DNA. Idoxuridine is incorporated in place of thymidine into viral DNA, resulting in faulty DNA and the inability to infect or destroy tissue or to reproduce.

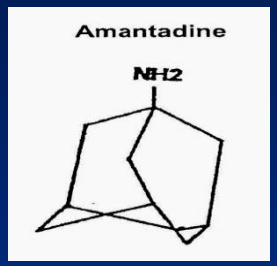
Clinical uses:

1- Idoxuridine is indicated in the treatment of keratitis caused by herpes simplex virus (HSV) and [vaccinia virus] .

2- Idoxuridine is used in the treatment of keratoconjunctivitis caused by herpes simplex virus (HSV).

Amantadine:

It is a tricyclic amine (a cyclic compound with an amino function group)



Mechanism of action:

- It blocks either assembly of Influenza A virus or the release of viral nucleic acid in the host cell (interfere with uncoating).

Pharmacokinetics:

- It is well absorbed orally not metabolized , excreted through kidney

Uses:

It is used for prophylaxis during Influenza A virus epidemics.

It is useful in shorting the duration of symptoms.

Mechanism of Action: The mechanism by which Amantadine exerts its antiviral activity is not clearly understood. It appears to mainly prevent the release of infectious viral nucleic acid into the host cell by interfering with the function of the transmembrane domain of the viral M2 protein. In certain cases, Amantadine is also known to prevent virus assembly during virus replication. It does not appear to interfere with the immunogenicity of inactivated influenza A virus vaccine.

Antiviral Activity: Amantadine inhibits the replication of influenza A virus isolates from each of the subtypes, i.e., H1N1, H2N2 and H3N2. It has very little or no activity against influenza B virus isolates

- Ribavirin:

- It is a synthetic purine nucleoside analog.

Mechanism of action:

-It acts by inhibiting enzyme needed for synthesis of guanine nucleotides.

- It inhibits viral RNA polymerase enzyme by competing for substrate sites.

- It interferes with the formation of messenger RNA.

NB: It is converted intracellularly to **5'-triphosphate derivative** which inhibits viral RNA polymerase

Spectrum of activity and uses:

It is effective against several DNA and RNA viruses including Herpes simplex, Influenza A and B.

-

Pharmacokinetics: Administered both orally and I.V

Clinical uses:

1- Ribavirin is currently used in combination with interferon-alpha to treat: **Hepatitis C virus infection.**

2- Ribavirin is used as a monotherapy to treat:

Severe cases of respiratory syncytial virus infection (usually as an aerosol.) and Lassa fever virus infection.

Adverse effects:

It causes haemolytic anaemia

Zidovudine:

-It is a nucleoside analog reverse-transcriptase inhibitor (NRTI), a type of antiretroviral drug used for the successful treatment of HIV/AIDS infectiousness.

-It is a therapeutic analog of thymidine.

- It is well absorbed orally from GIT.

- It is rapidly excreted unchanged in the urine.

- It must be converted to phosphorylated product .

- It is indicated for serious manifestation of human immunodeficiency virus in patients with acquired immunodeficiency syndrome

2- Drugs that modulate the host immune system:

Interferons:

-They are naturally occurring glycoprotein that can be produced by any mammalian cell, including lymphocytes and fibroblasts when the cells are stimulated in the inflammatory process.

Interferons are glycoproteins that come in 3 varieties:

- α (made in leukocytes):

-β (made in fibroblasts):

They induced by viral infection, IL1, IL2, TNF

-γ (made in T cells): activated T cells produce gama interferon to modulate the immune response.

Mechanism of action:

They inhibit the synthesis of protein and DNA resulting in:

1- Blocking the ability of viral replication.

2- Suppressing cell proliferation

3- Immunomodulating effect by increasing phagocytosis by macrophages.

Preparation and uses:

- There are two available products:

1- Interferon alpha 2 a

2- Interferon alpha 2 b

- They are given I.M or S.C for treatment of AIDS, Hairy cell leukemia , genital warts

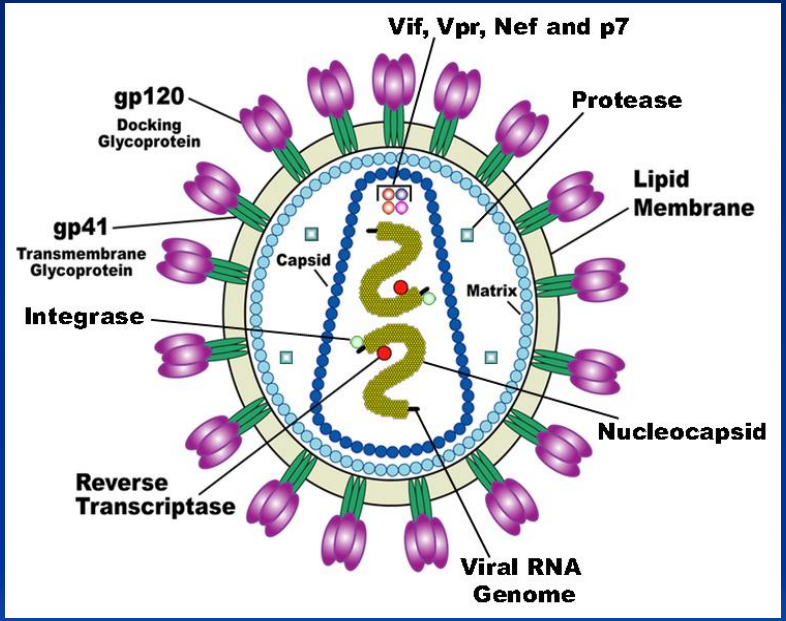
-Also, they are used to restrict the viral hepatitis and Herpes keratoconjunctivitis.

Adverse effects:

1- Bone marrow suppression

2- Increased liver enzymes.

3- Abortifacient in primates.



Structure of HIV/AIDS