Anti-viral Drugs

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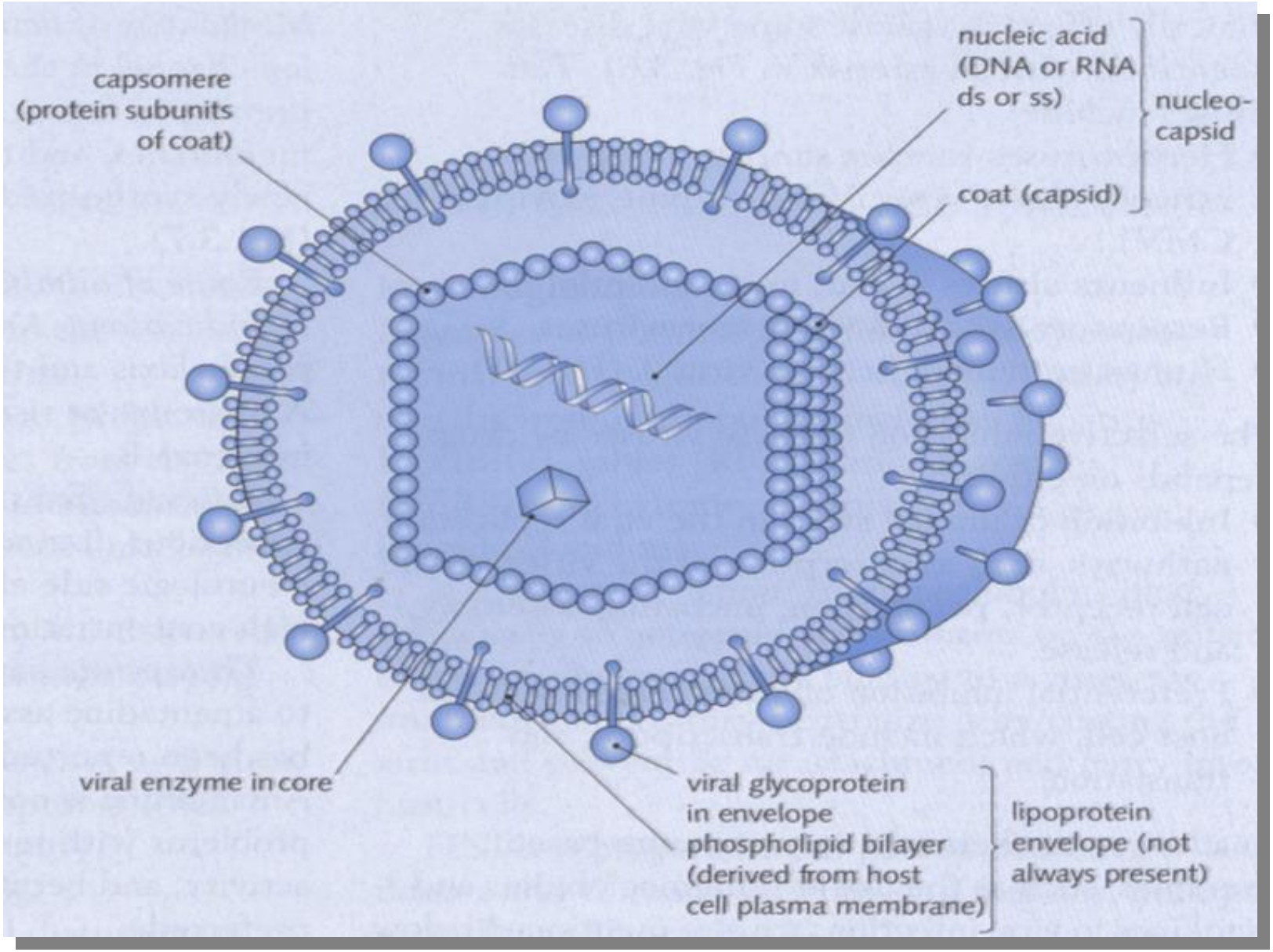
Viruses

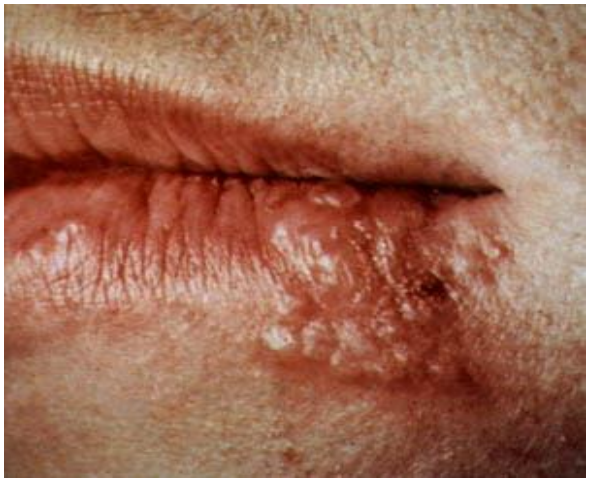
- Viruses are obligate intracellular parasites that lack independent metabolism and can only replicate within the host cells they enter and infect.
- A virus particle, or virion, consists essentially of DNA or RNA enclosed in a protein coat (capsid)
- In addition, certain viruses may possess a lipoprotein envelope and replicative enzymes.
- Viral nucleic acids may be single stranded (ss) or double stranded (ds)
- Additionally by the time a viral infection becomes detectable clinically the viral replication process tends to be very far advanced making chemotherapeutic intervention difficult.
- All current antiviral agents are virustatic rather than virucidal therefore they rely upon host immunocompetence for a complete clinical cure.

Virus structure

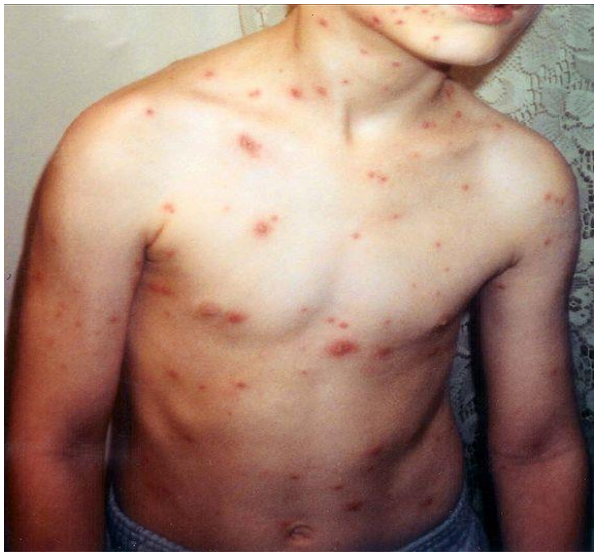


Viruses Types

- Herpesviruses (herpes simplex virus, HSV; varicella zoster virus, VZV; cytomegalovirus, CMV).

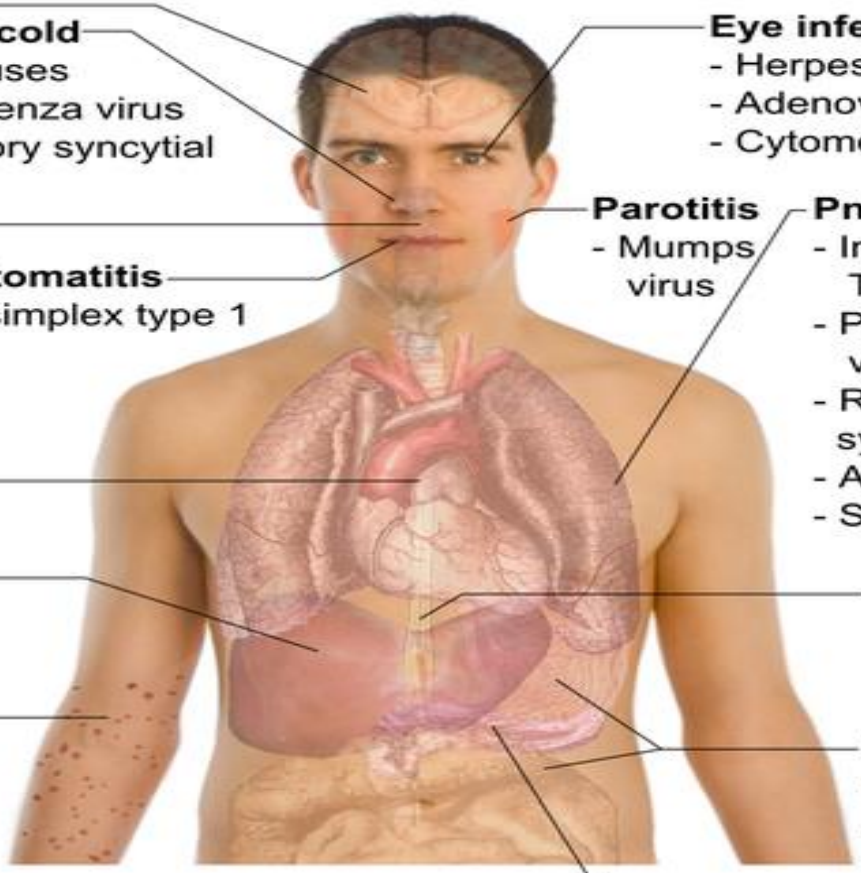


- Influenza viruses A and, more recently, B.
- Respiratory syncytial virus, arenaviruses.



- Human immunodeficiency virus 1 (HIV-1).

Overview of Viral infections



Encephalitis/ meningitis
- JC virus
- Measles
- LCM virus
- Arbovirus
- Rabies

Common cold
- Rhinoviruses
- Parainfluenza virus
- Respiratory syncytial virus

Eye infections
- Herpes simplex virus
- Adenovirus
- Cytomegalovirus

Parotitis
- Mumps virus

Pneumonia
- Influenza virus, Types A and B
- Parainfluenza virus
- Respiratory syncytial virus
- Adenovirus
- SARS coronavirus

Pharyngitis
- Adenovirus
- Epstein-Barr virus
- Cytomegalovirus

Gingivostomatitis
- Herpes simplex type 1

Cardiovascular
- Coxsackie B virus

Hepatitis
- Hepatitis virus types A, B, C, D, E

Myelitis
- Poliovirus
- HTLV-I

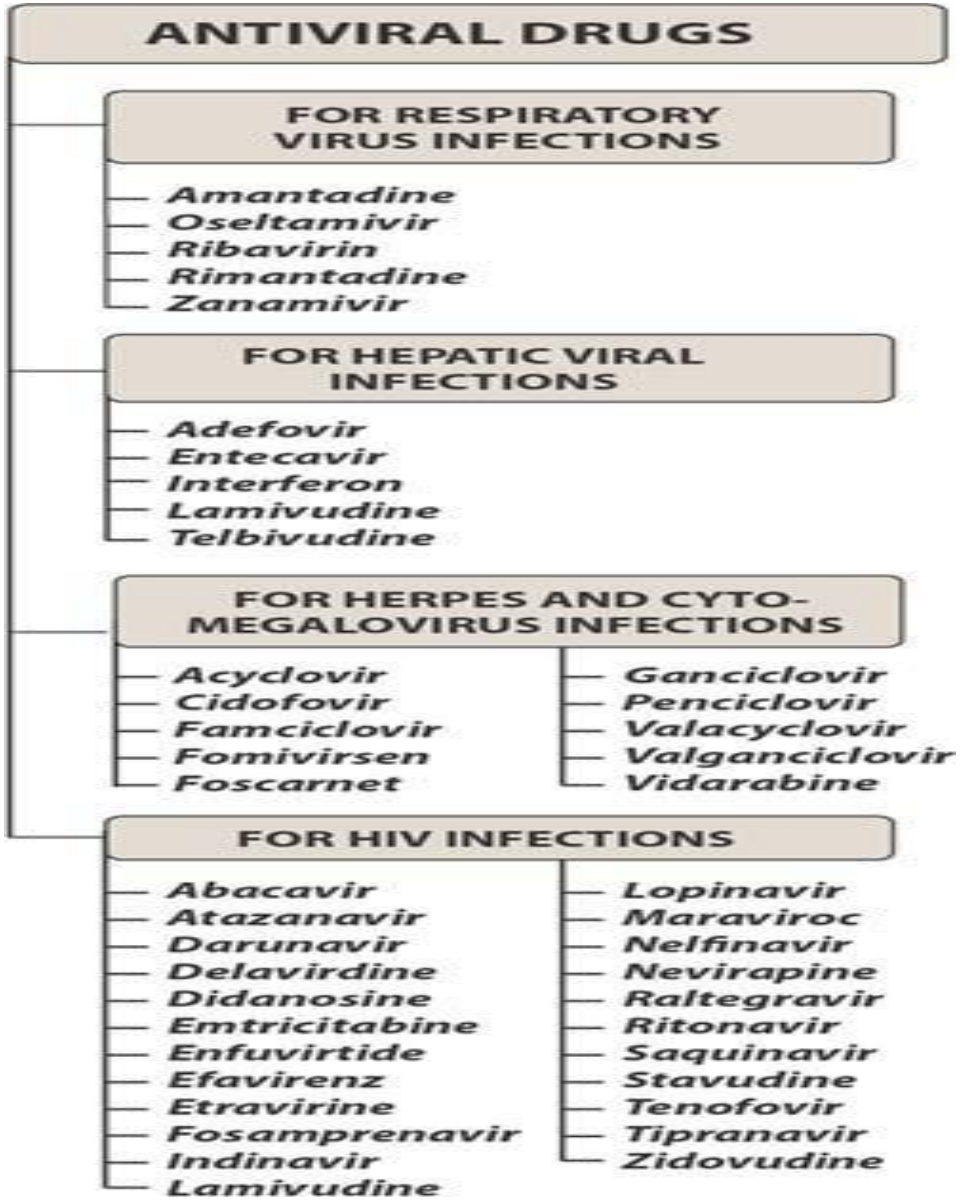
Skin infections
- Varicella zoster virus
- Human herpesvirus 6
- Smallpox
- Molluscum contagiosum
- Human papillomavirus
- Parvovirus B19
- Rubella
- Measles
- Coxsackie A virus

Gastroenteritis
- Adenovirus
- Rotavirus
- Norovirus
- Astrovirus
- Coronavirus

Sexually transmitted diseases
- Herpes simplex type 2
- Human papillomavirus
- HIV

Pancreatitis
- Coxsackie B virus

Anti-virals


ANTIVIRAL DRUGS
FOR RESPIRATORY VIRUS INFECTIONS
Amantadine
Oseltamivir
Ribavirin
Rimantadine
Zanamivir
FOR HEPATIC VIRAL INFECTIONS
Adefovir
Entecavir
Interferon
Lamivudine
Telbivudine
FOR HERPES AND CYTO-MEGALOVIRUS INFECTIONS
Acyclovir
Cidofovir
Famciclovir
Fomivirsen
Foscarnet
Ganciclovir
Penciclovir
Valacyclovir
Valganciclovir
Vidarabine
FOR HIV INFECTIONS
Abacavir
Atazanavir
Darunavir
Delavirdine
Didanosine
Emtricitabine
Enfuvirtide
Efavirenz
Etravirine
Fosamprenavir
Indinavir
Lamivudine
Lopinavir
Maraviroc
Nelfinavir
Nevirapine
Raltegravir
Ritonavir
Saquinavir
Stavudine
Tenofovir
Tipranavir
Zidovudine

A. Against respiratory viruses :

a. Amantadine: inhibits viral un-coating; **used for prevention or for early treatment of influenza A2.**

- It is effective orally; eliminated by kidney, so avoided in renal failure (RF). Also avoid in epilepsy since it increases brain excitability and can cause seizures. **It also has another independent action in being useful in Parkinsonism.**
- **Rimantadine** is similar but is largely eliminated by liver, and to a lesser extent by kidney

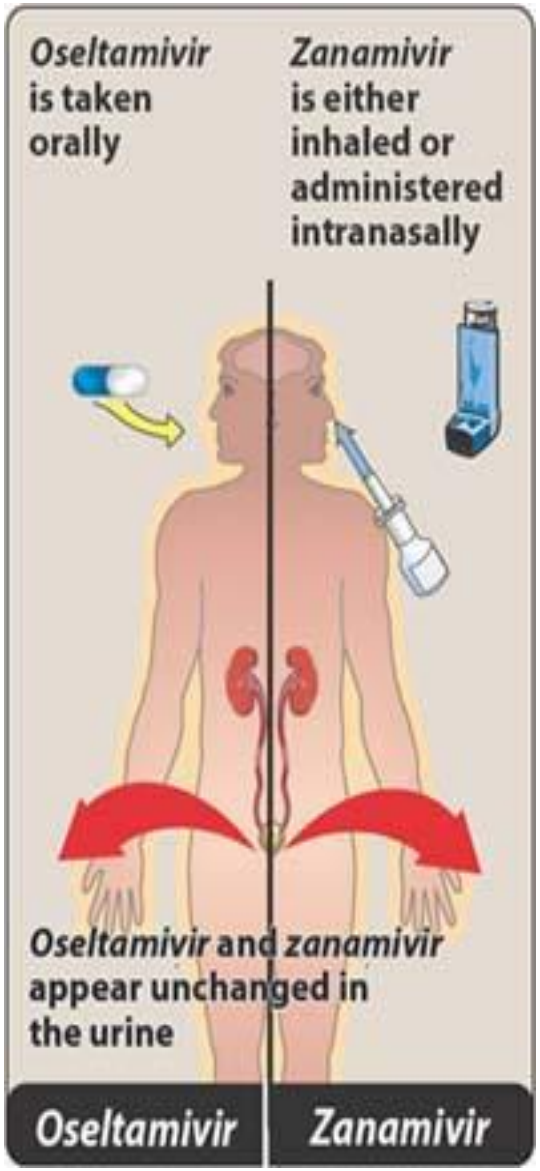
b. Neuraminidase inhibitors : inhibit release of new viral progeny which occurs by budding, and may also block viral entry into host cells.

1. Oseltamivir (Tamiflue): given orally; it is a prodrug, being activated by liver or gut.

- It is used in prevention and early treatment of influenza A or B, or virulent H5N1 virus of avian influenza. It is eliminated from body by kidney in urine

- **SEs** include nausea and vomiting

2. Zanamivir (Relenza): given by inhalation for prevention & early treatment of influenza A or B. It may cause bronchospasm. Avoid in asthma.



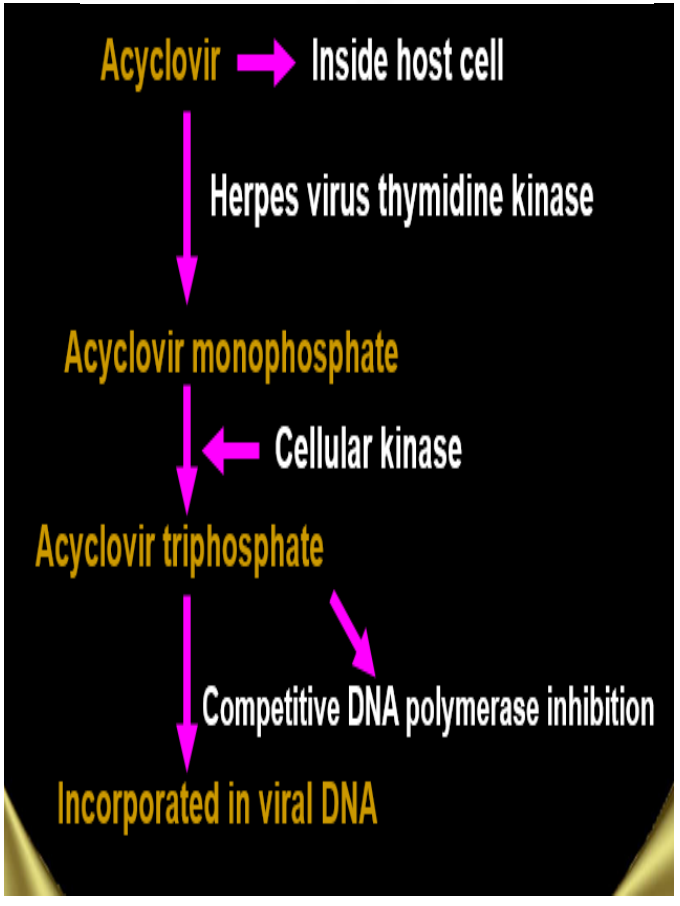
c. Ribavirin:

- **It decreases viral mRNA synthesis. Effective against many RNA and DNA viruses.**
- It is useful by inhalation **for Respiratory Syncytial Virus infection** in infants which cause acute bronchiolitis that has high mortality.
- It is also used oral **with subctaneous IFN-αlpha-2b for chronic hepatitis C;** they must be used together to be effective.
- It is eliminated by kidney in urine, so avoided in RF.
- **Side effects** include fatigue, rash, nausea, and hemolytic anemia. It is avoided during pregnancy since it is **teratogenic** in animals

B. Against herpes viruses :

a. Against herpes simplex & varicella-zoster virus

1. Acyclovir : Converted inside viral infected cells into acyclo-guanosine monophosphate by viral thymidine kinase which has much more affinity (x 1000) for it than host kinase. Thus it is concentrated in virally infected cells much more than in un-infected cells. Then it is converted by host kinase into triphosphate form which is incorporated into DNA & competitively inhibits viral DNA polymerase in viral DNA synthesis & cause premature termination of proviral DNA chain.



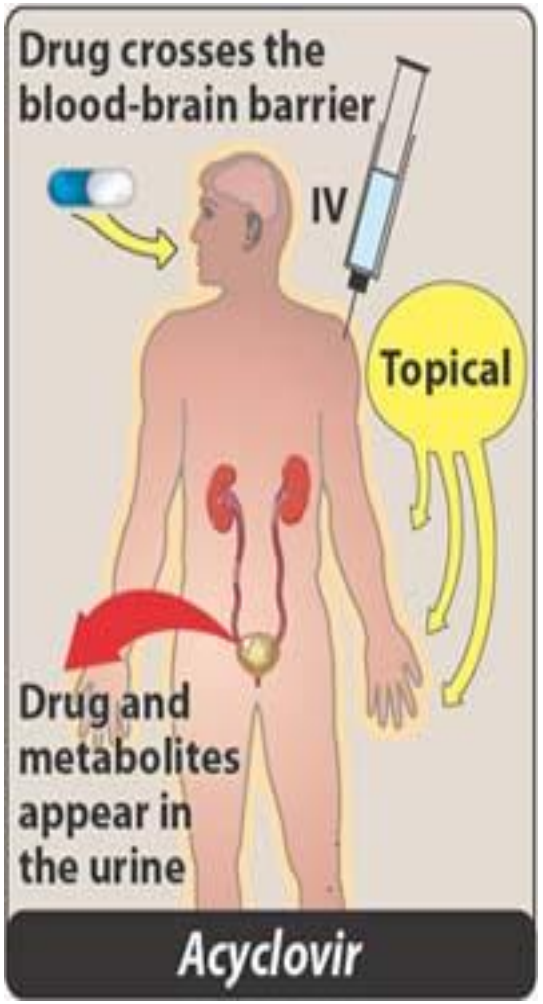
- **Topically** , it is used as ointment for herpetic keratitis and as cream for oral & genital herpes simplex.

- **Oral tablets** are used (x 4/d) for primary treatment & to prevent recurrence of genital & oral herpes & also used for treating herpes zoster; about 20% absorbed from gut.

- **IV** for severe herpes simplex or varicella- zoster infection in immuno-suppressed patients & for cases of herpetic encephalitis.

- It is eliminated by kidney (Filtration & tubular secretion). safe in pregnancy (not teratogenic or embryotoxic) .

- ***S.Es :*** they include : G.I (nausea, diarrhea), CNS (headache, occasionally neurotoxicity in large doses), Renal crystal precipitation & damage can occur with IV use (can be avoided by giving large amounts of IV fluids).



2. Valacyclovir:

- **given** Oral ; it is better absorbed from intestine than acyclovir, and so is more bioavailable (about 60%) ; it is converted by first pass liver metabolism into acyclovir.

3. Famciclovir and Penciclovir: given Oral;

- **Famciclovir is converted to penciclovir in liver.**

- **Penciclovir** acts similar to acyclovir to inhibit viral DNA synthesis . It is used for **genital or oral herpes.**

- **Famciclovir** is used for **herpes zoster.**

4. Others For herpetic keratitis :

a. Idoxuridine : Eye drops, ointments ; it is incorporated into DNA instead of thymidine, so decrease viral DNA synthesis. ***S.Es include*** stinging sensation and Allergy

b. Vidarabine (adenine arabinoside) : 3% ointment

c. Trifluridine (trifluorothymidine) : 1% eye drops

- Both drugs decrease viral DNA synthesis.

b. Against cytomegala virus (CMV) :

1. **Ganciclovir : Like acyclovir, it is** converted inside host cell into active triphosphate form . **Used IV for CMV retinitis. May be given by intra-vitreous injection or as ocular implant; orally it is about 6-9% absorbed from gut; may cause neutropenia, anemia, & thrombocytopenia (due to BM depression)**

2. Foscarnet : this is non-nucleoside derivative; it is **useful IV for ganciclovir-resistant CMV and for acyclovir-resistant herpes zoster**. It is eliminated by kidney.

- **SEs** are renal toxicity, CNS (hallucination, seizures), hypocalcemia.

3. **Cidofovir:** must be phosphorylated inside host cells into active diphosphate form; it is used IV for CMV retinitis; longer intra-cellular t½ than ganciclovir; nephrotoxic (reduced by probenecid).

4. **Fomiversen**: bind to viral mRNA to inhibit protein synthesis & virus growth; given by **intravitreous injection** for resistant cases; slowly eliminated from retina; systemic anti-CMV therapy also needed; toxicity is iritis, vitritis, rise in IOP.

C. Against HIV (in AIDS patients)

1. Nucleoside Reverse Transcriptase Inhibitors [NRTIs]:

- **Agents must be converted to triphosphate form by host enzymes to become active**. It inhibits reverse transcriptase (RT) competitively, & causes premature termination of proviral DNA chain.

a. Zidovudine (Azidothymidine): It is a synthetic analogue of thymidine. **Most commonly used**; oral dose is 200 mg tid, or 300 mg bid. It is eliminated by liver & kidney. CSF level is about 60% of plasma.

- **S.Es:** Neutropenia, anemia and sometimes thrombocytopenia due to bone marrow depression (additive to ganciclovir), CNS, Myopathy, G.I.(common) hepatomegaly with cholestasis and lactic acidosis.

b. Didanosine: synthetic analogue of adenosine

- **S.Es**: peripheral neuropathy & pancreatitis.

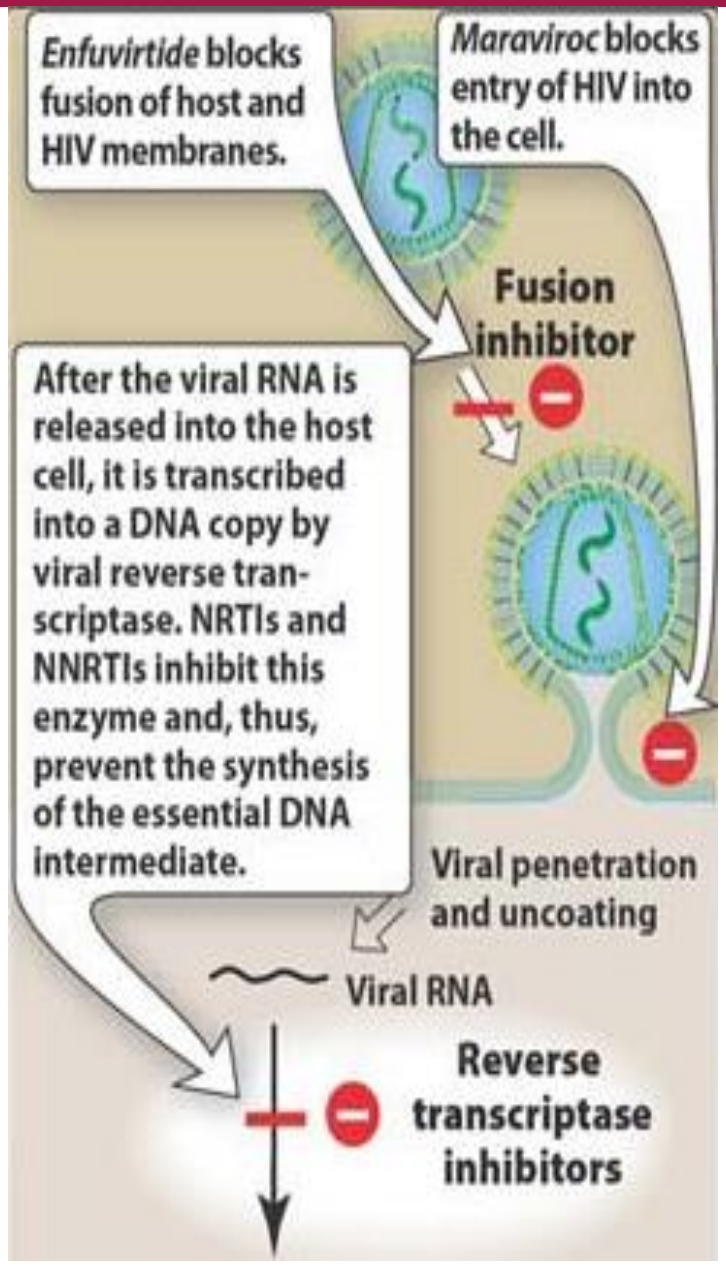
c. Zalcitabine: Cytidine analogue. long acting. Used commonly with zidovudine.

- **S.Es**: peripheral neuropathy, rarely pancreatitis .

d. Emtricitabine: cytidine analogue; approved for HIV

e. Stavudine: thymidine analogue; its intracellular phosphorylation is reduced by zidovudine; so avoid combined use; excreted by kidney; short t½ .

- **S.Es** is peripheral neuropathy (avoid use with neurotoxic anti-HIV drugs e.g. zalcitabine or didanosine).



f. Lamivudine: also cytidine analogue; long acting & least toxic. Best additive to zidovudine or stavudine & is best given in combination. Less dose in RF.

- **Also useful against hepatitis B** virus and can be given with or without interferon IFN-alpha 2b; alternative is oral **adefovir or tenofovir .**

2. Non-Nucleoside RTIs (NNRTIs)

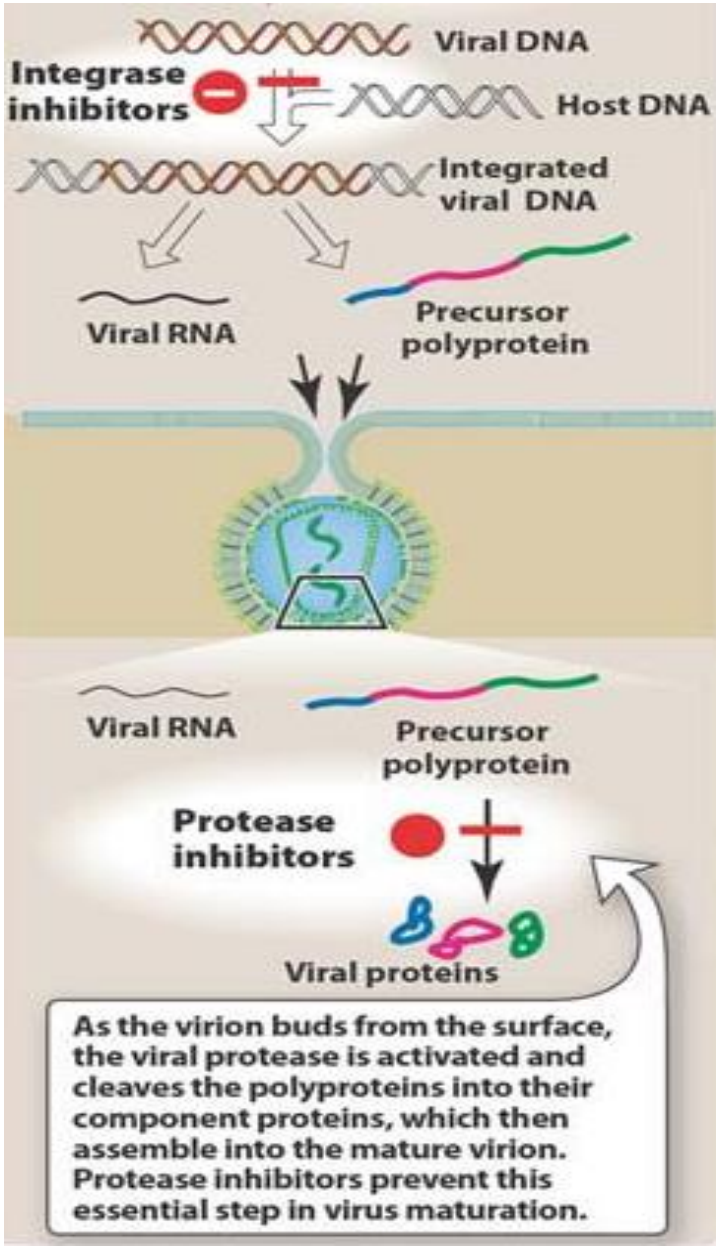
- **Nevirapine , Delaviradine, Efavirenz**
  - **Don't require intracellular phosphorylation. Directly inhibit viral RT of HIV.**
  - **Less S.Es :** Maculopapular rash in 10-20%

- Liver toxicity in ~ 5% with Nevirapine

3. Protease inhibitors (PIs) :

- Inhibits viral protease that converts large viral polyproteins into smaller polyproteins for virions.
- **Indinavir**, **Ritonavir, Saquinavir, Nelfinavir**

- **S.Es :**
  - G.I. : most common ;
  - Renal stones: with indinavir in 3-5%.
  - Liver toxicity : with ritonavir and saquinavir in ~5%.

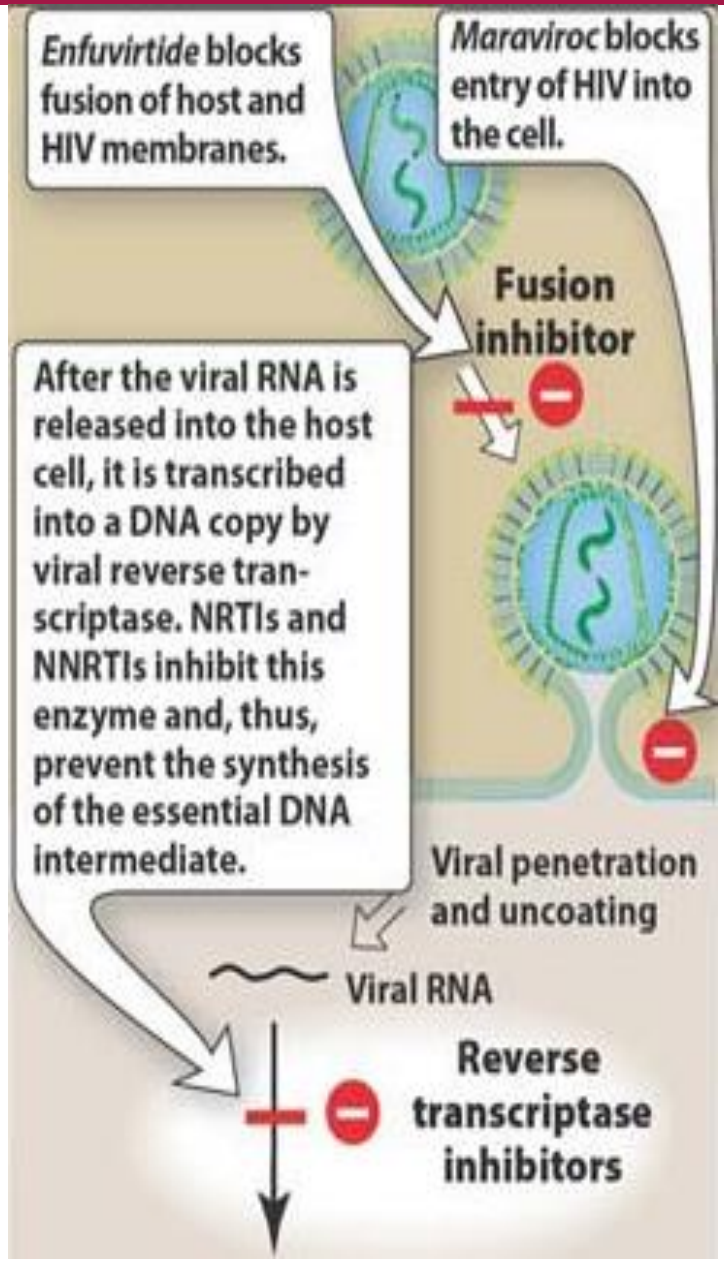


Note : Best results in HIV infection treatment are obtained with combination of 4 drugs : 2 NRTIs + 1 NNRTI + 1 protease inhibitor.

- **Lipodystrophy :** due to interference with carbohydrate and lipid metabolism. occurs **with prolonged therapy in combinations.**
- Lipodystrophy syndrome: metabolic effects include fat redistribution, insulin resistance & dyslipidemia
- Fat redistribution after chronic use including loss of fat from extremities & its accumulation in abdomen & base of neck (buffalo hump**)**

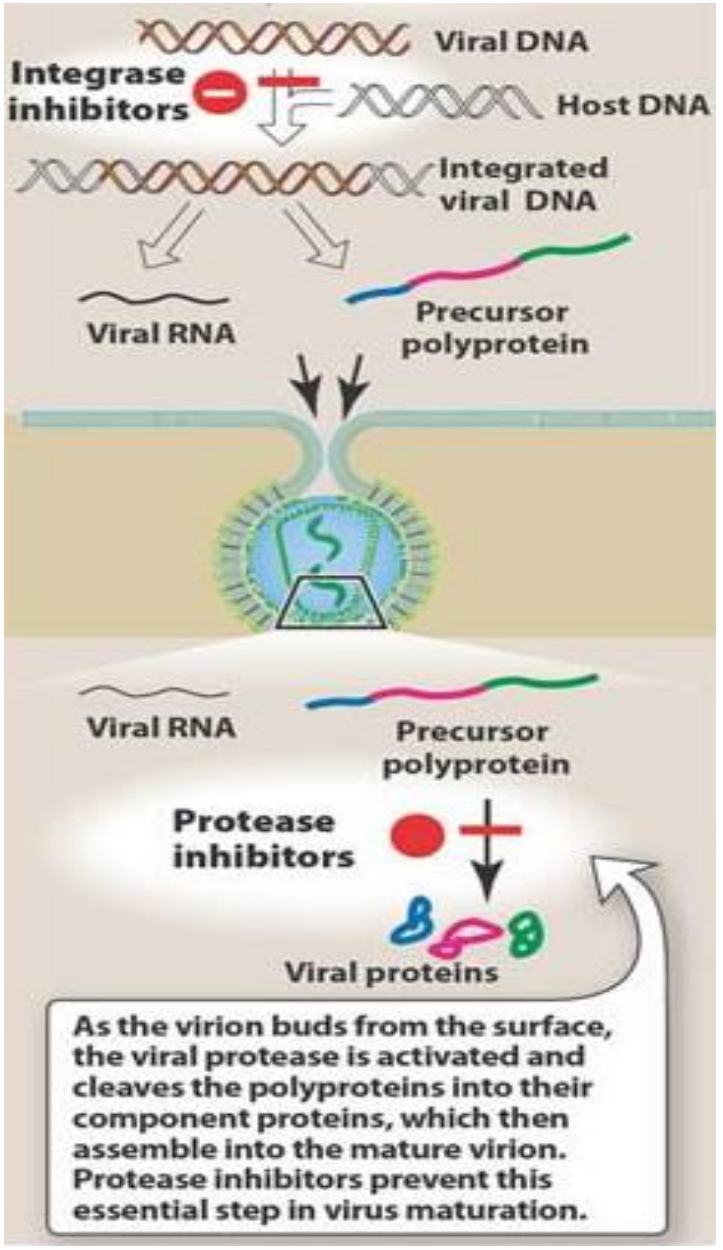
4. Fusion inhibitors

- **Enfuvirtide:** it binds to surface glycoprotein of HIV, preventing its attachment and penetration into host cells.
- It is used in combinations if resistance to other anti-HIV drugs develops .
- given **SC**;



5. Integrase Inhibitors

- **Raltegravir (RAL)**
- Raltegravir is the first of new class of antiretroviral drugs known as integrase inhibitors.
- Raltegravir specifically inhibits the final step in integration of stand transfer of the viral DNA into our own host cell DNA.



Antiviral drugs for hepatic viral infections:

a. Lamivudine:

b. Interferons IFNs:

- These **are protective glycoproteins that are produced by virally infected cells to make other normal cells resist viral infection.**

- IFN-*alpha* is produced by leukocytes, IFN-*beta* is produced by fibroblasts , and IFN-*gamma* is produced by lymphocytes.

- ***IFN-alpha* (2a, 2b) are prepared by DNA recombinant biotechnology.**

MOA :

a. stimulation of intracellular enzymes in virally infected cells which leads to inhibition of translation of viral mRNA by ribosomes; it may also inhibit formation of viral mRNA

b. stimulate cellular immune defences against virus, and **also against some cancers.**

- **IFN-a (2b, or 2a) is used <u>SC or IM against</u> :** hepatitis B or C virus infections, Kaposi"s sarcoma, severe herpes zoster, and intra-lesional injection into viral genital warts.

Interferon-α	*Interferon-β*	*Interferon-γ*
Chronic hepatitis B and C	Relapsing-remitting multiple sclerosis	Chronic granulo-matous disease
Genital warts caused by papilloma-virus		
Leukemia, hairy-cell Leukemia, chronic myelogenous		
Kaposi's sarcoma		

- **IFN-a (2b):** is also used in some cancers e.g. chronic myeloid leukemia, hairy cell leukemia, malignant melanoma, & metastatic renal cell cancer.

- **S.Es:**

- **Flue-like illness** : this occurs within few hours of administration; it is a **common reaction**
- **CNS** : **causing fatigue and depression. Severe anorexia** occurs , leading to weight loss
- **CVS** : hypotension and cardiac arrhythmias may occur
- **Bone marrow depression** may occur leading to neutropenia or thrombocytopenia.

Thank you