!! JAY AMBE !!

5. ANTI VIRAL DRUG

PREPARED BY

DR. NAITIK D. TRIVEDI,

M. PHARM, PH. D

LECTURER AT GOVERNMENT AIDED,

A. R. COLLEGE OF PHARMACY & G. H. PATEL INSTITUTE OF PHARMACY, VALLABH VIDYANAGAR, ANAND, GUJARAT

Mobile: +91 - 9924567864

E-mail: mastermindnaitik@gmail.com

&

DR. UPAMA N. TRIVEDI,

M. PHARM, PH. D

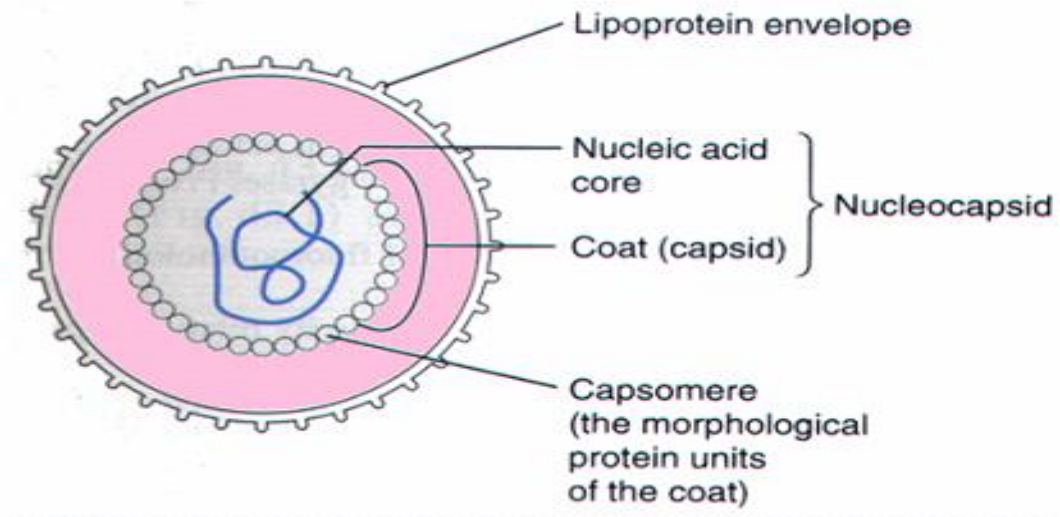
ASSOCIATE PROFESSOR & HoD (Pharm.D),

INDUBHAI PATEL COLLEGE OF PHARMACY AND RESEARCH CENTRE, DHARMAJ, GUJARAT

E-mail: ups.aasthu@gmail.com

VIRUS:

Virus are the smallest infective agents, consisting essentially of nucleic acid (either RNA or DNA) enclosed in a protein coat or capsid.



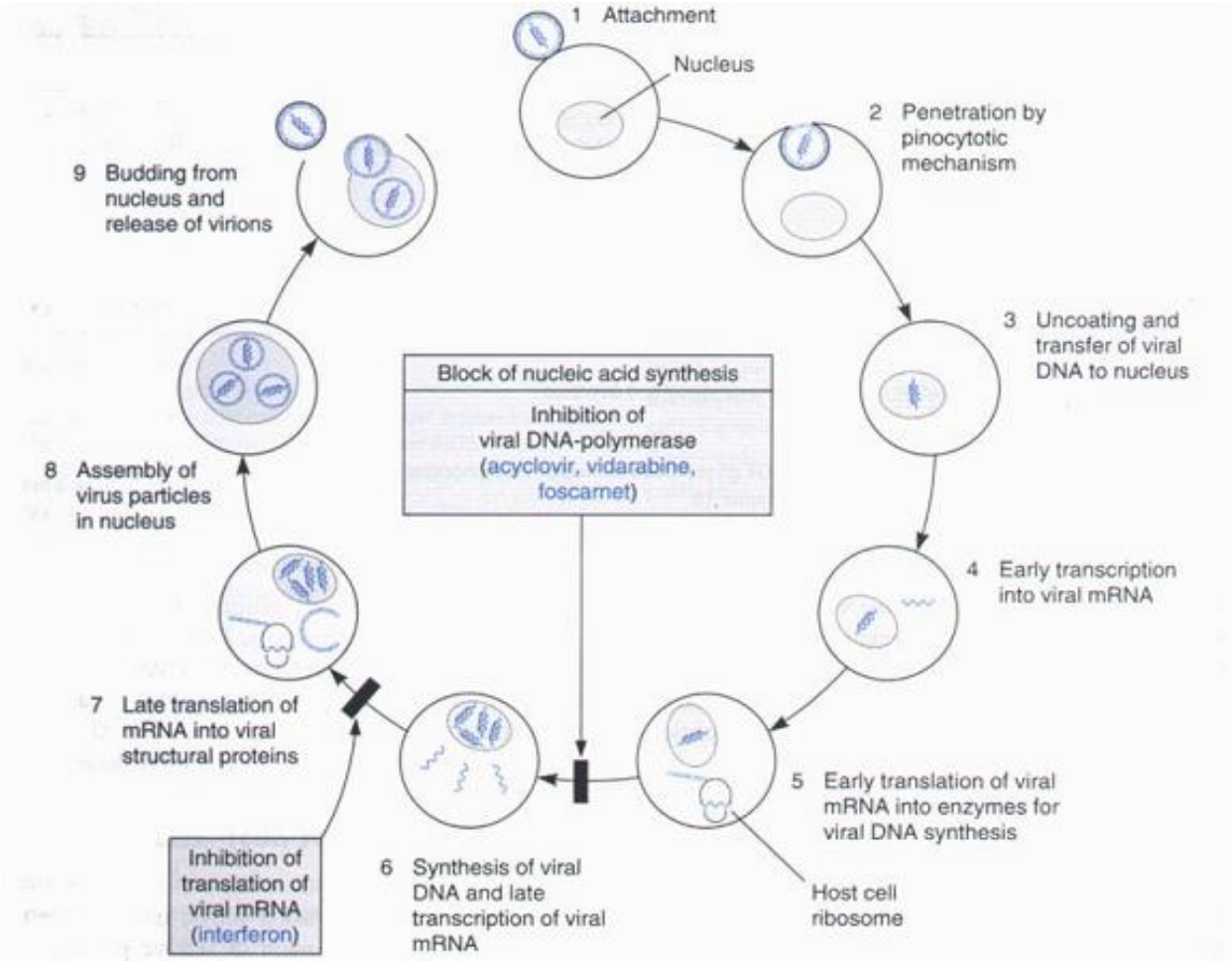
Some important examples of viruses and the diseases they cause are as follows:

DNA VIRUSES:

- Pox Viruses (smallpox)
- Herpes viruses (chickenpox, herpes etc)
- Adenoviruses (sore throat, conjunctivitis)
- Hepadnaviruses (serum hepatitis)
- Papillomaviruses (warts)

RNA VIRUSES:

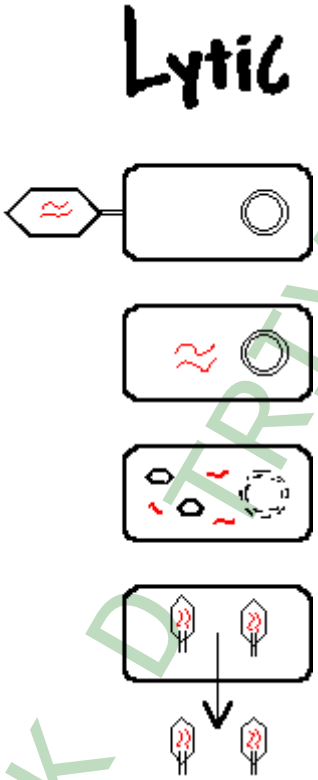
- Orthomyxoviruses (influenza)
- Paramyxoviruses (measles, mumps)
- Rhabdoviruses (rabies)
- Picornaviruses (colds, meningitis, poliomyelitis)
- Retroviruses (AIDS, T-cell leukemia)
- Arenaviruses (meningitis, Lassa fever)
- Arboviruses (arthropod-borne encephalitis, yellow fever)

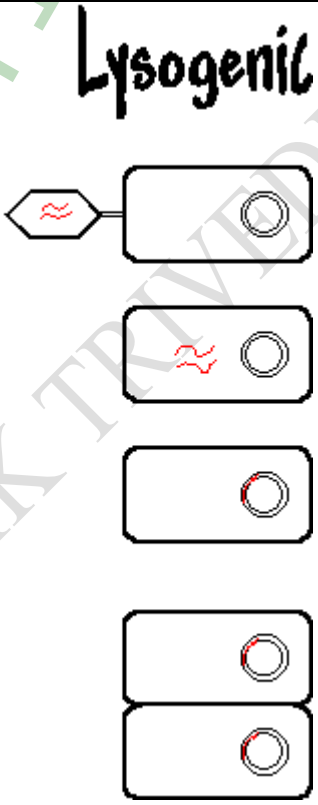


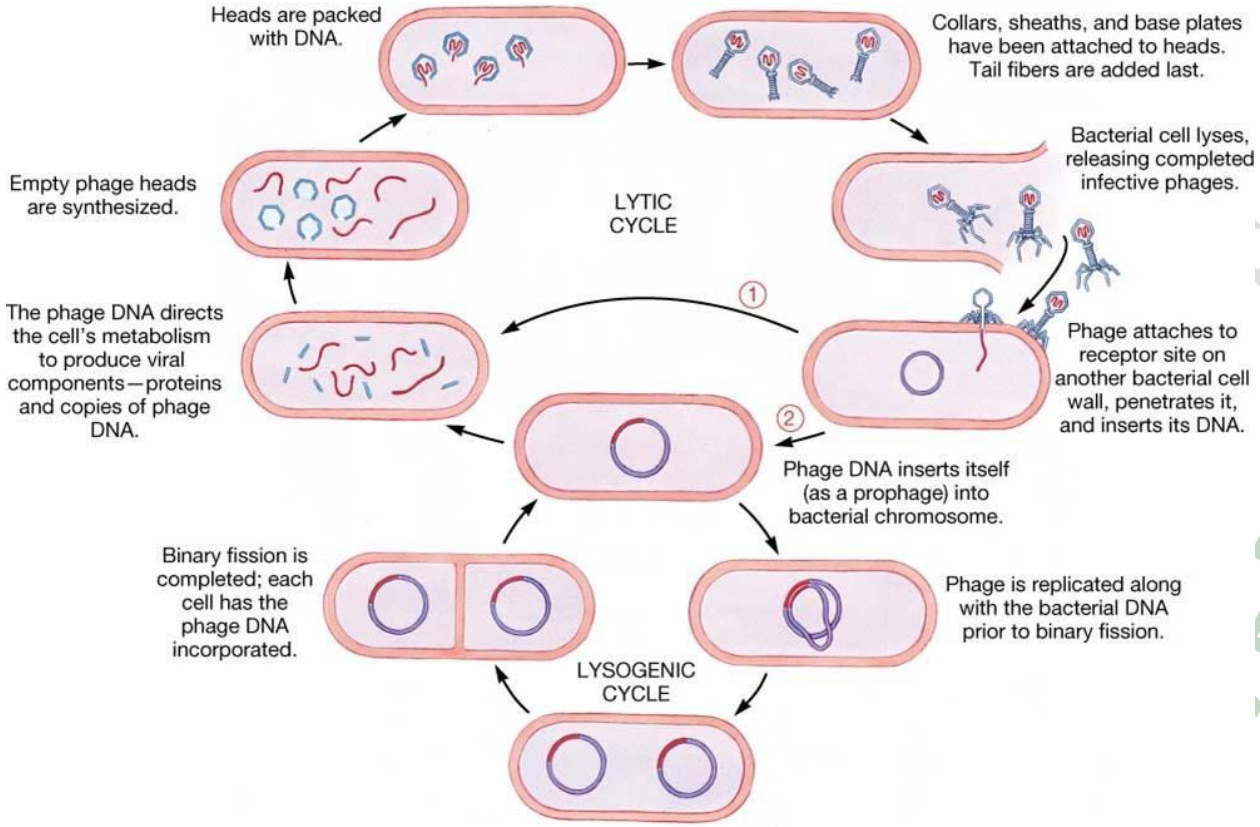
LIFE CYCLE OF VIRUSES:

Lytic versus **lysogenic** life cycles:

- In the **lytic stage**, many viral particles are made and copies are sent back into the environment.
- A virus is found in this phase when conditions are favorable, i.e. when bacteria is "growing like crazy"
- In the **lysogenic phase** there is no pathology. Under certain conditions the lysogenic lifestyle can switch to a lytic lifestyle.
- A virus is found at this stage under harsh conditions.

	The virus attaches to bacteria (host) The virus inserts its DNA into the bacteria The virus takes over the cell's machinery The virus reproduces itself and self-assembles. The host cell is destroyed

	*The virus is a **prophage** at this stage.* The virus binds to bacteria (host) The virus inserts its DNA into the bacteria The viral DNA gets incorporated into the cell's chromosome Viral DNA is replicated along with chromosomal material



CLASSIFICATION OF ANTIVIRAL DRUGS:

1. According to stages of viral replication:

A. Inhibition of free extracellular viruses:

Eg.: Gammaglobulins

B. Inhibition of penetration of viruses into the cells:

Eg.: Amanthadine, Disoxaril, Rimantidine

C. Inhibition of intracellular viral synthesis:

I. Inhibition of transcription of the viral genome:

a. DNA polymerase inhibitors:

Eg.: Aciclovir, Famciclovir, Ganciclovir, Ribavirin, Forscarnet

b. Reverse transcriptase inhibitors:

Eg.: Zidovudine, Didanosine, Zalcitabine

II. Post-translation event inhibitors:

Eg.: Protease inhibitors: Saquinavir, Ritonavir, Indinavir, Nelfinavir.

III. Inhibition of early protein synthesis:

Eg.: Guanidine, Hydroxybenzylbenz-imidazole

IV. Inhibition of nucleic acid synthesis:

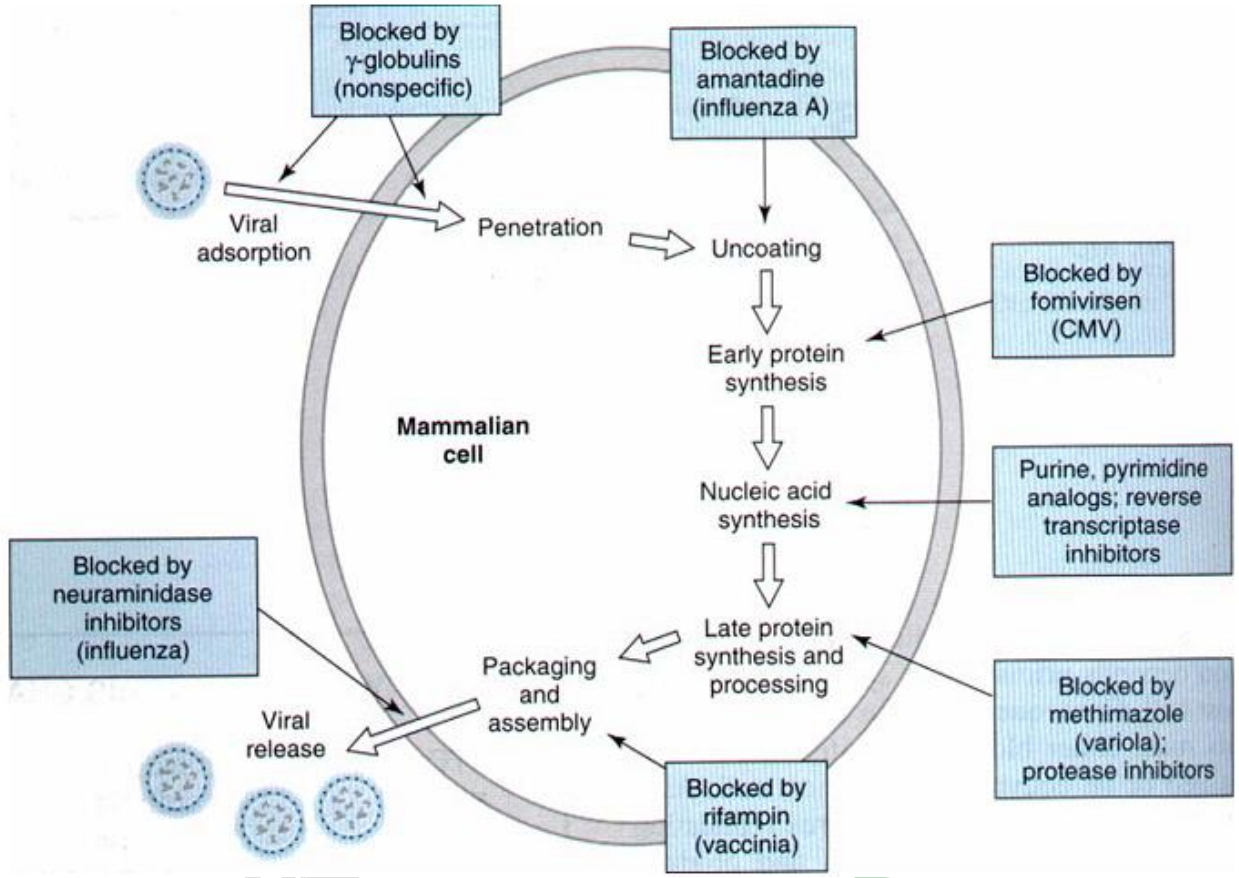
Eg.: Rebavirin, Idoxouridine, Cytarabin, Vidarabin, Trifluridin, Forscarnet, Acyclovir,Zidovudine, Ganciclovir etc.

D. Inhibition of assembly:

Eg.: Methesazone

E. Miscellaneous agent:

Eg.: Interferon



2. According to viral specific action:

A. Anti-herpes virus agents

Eg.: Acyclovir, Valacyclovir, Famciclovir, Penciclovir, Ganciclovir, Cidofovir, Foscarnet Trifluridine, Idoxuridine , Vidarabine

B. Anti-influenza viruses:

Eg.: Amantadine, Rimantadine, Oseltamivir, Zanamivir

C. Anti-retroviruses:

I. Nucleoside reverse transcriptase inhibitors:

Eg.: Zidovudine, Stavudine, Didanosine, Zalcitabine, Lumivudine, Abacavir

II. Non nucleoside reverse transcriptase inhibitors:

Eg.: Nevirapine, Efavirenz, Delavirdine

III. Protease inhibitors:

Eg.: Saquinavir, Indinavir, Ritonavir, Nelfinavir, Amprenavir, Lopinavir

D. Non selective anti-viral agents:

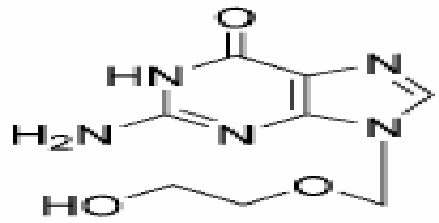
Eg.: Ribavirin, lamivudine, Fomiversen, Imiquimod, Interferon – α etc.

ACYCLOVIR:

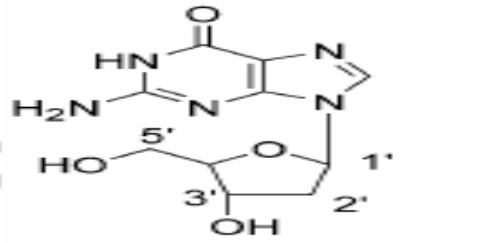
- A widely used antiviral with main implications in the treatment of herpes
- Seen as a "new age" in antiviral therapy, Gertrude Elion, its creator, was given the Nobel prize for medicine in 1988
- It is a nucleoside analogue and prevents viral replication in infected cells
- Extremely selective and low in toxicity

Structure:

- Purine Mimic
- Similarity to 2`-deoxyguanosine: lack of 3` hydroxyl



acyclovir



2'-deoxyguanosine

Mechanism of action:

Acyclovir

↓ Herpes virus specific thymidine kinase

Acyclovir Monophosphate

↓ Cellular kinases

Acyclovir triphosphate

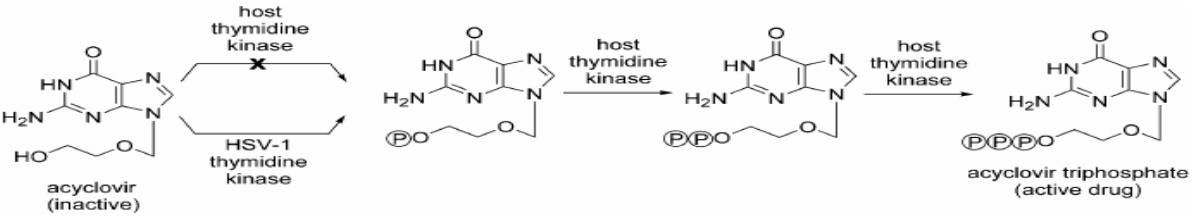
↙ ↘

Inhibits herpes virus and Polymerase competitively strands.

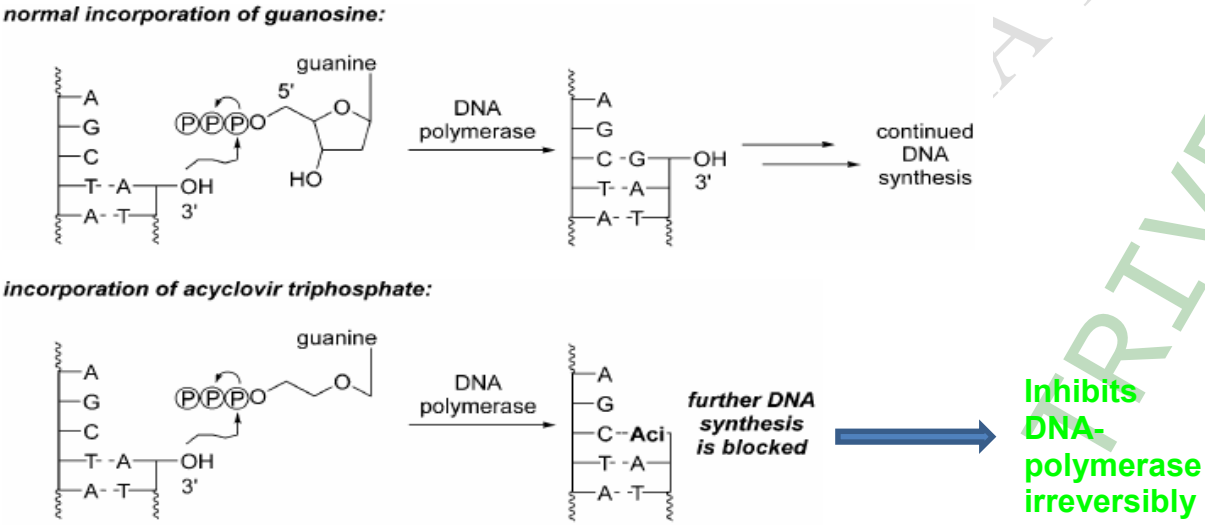
DNA Gets incorporated in viral DNA stops lengthening of DNA

The terminated DNA Inhibits DNA-polymerase irreversibly

Step 1: Activation:



Step 2: Incorporation into growing DNA chain:



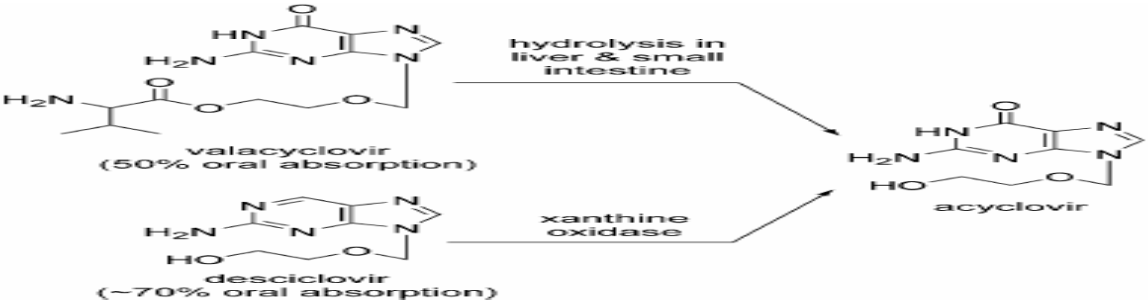
Antiviral spectrum:

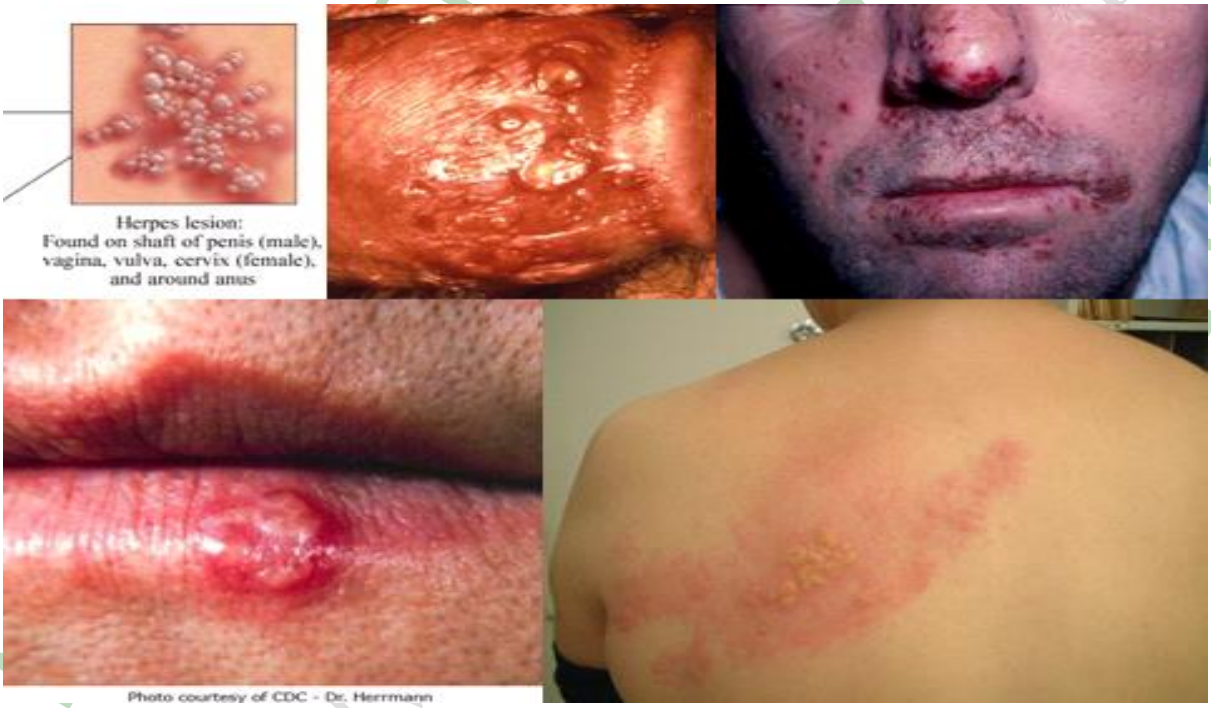
- **Effective against the following:**
  1. Herpes simplex virus type I (HSV-1)
  2. Herpes simplex virus type II (HSV-2)
  3. Varicella zoster virus (VZV)
  4. Epstein-Barr virus (EBV)
  5. Cytomegalovirus (CMV) -- least activity

Pharmacokinetics:

- Poor oral absorption and is only 15 - 20% (lipophilic) and unaffected by food
- Good CSF penetration
- Excreted unchanged in urine – glomerular filtration and active tubular secretion (peritoneal and hemodyalysis)
- Half-life: 2-3 Hrs only
- Good corneal penetration
- Bioavailability can be improved by design of suitable prodrugs

- Valaciclovir – ester prodrug of acyclovir
- Famciclovir: ester prodrug of gunine analogue





Therapeutic Uses:

1. Genital Herpes simplex: HSV -II
   - Primary disease: Ointment – Oral - IV
   - Recurrent disease: Oral – IV (5 mg/kg q8 hrly)

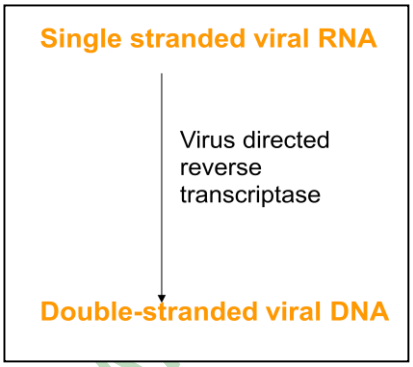
     (Suppressive oral therapy 400 mg BD)
2. Mucocutaneous H. simplex: Type - I
   - Acyclvir cream
   - Oral or IV in immunocompromized patients
3. H. simplex encephalitis: type – 1
   - 10 to 20 mg/kg/8hr X 10 days
4. H. simplex keratitis
5. H. zoster

6. Chicken pox

- **Resistance:**
  - Resistance to acyclovir can develop in HSV or VZV through alteration in either the viral thymidine kinase or the DNA polymerase
  - Immunocompromised hosts
  - foscarnet, cidofovir, and trifluridine (acyclovir resistant strain)
- **ADRs:**
  - Oral: Nausea, diarrhea, and headache
  - IV: Rashes, sweating and emesis and fall in BP
  - Reversible renal dysfunction due to crystalline nephropathy
  - Neurologic toxicity (eg, tremors, delirium, seizures)
  - No Teratogenicity
  - 10 years therapy

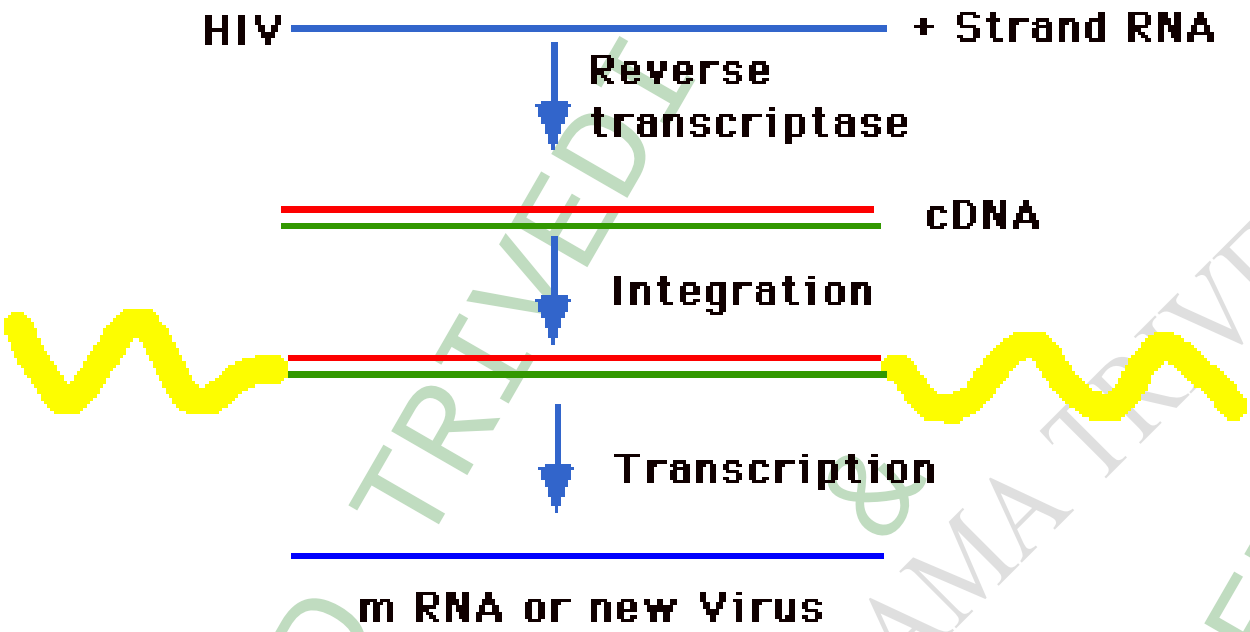
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIS):

- Drugs used against retrovirus – HIV
- Useful in prolonging and improving quality of life
- Do not cure the infection
  - Zidovudine (AZT)
  - Abacavir (ABC)
  - Lamivudine (3TC)
  - Didanosine (ddI)
  - Zalcitabine (ddC)
  - Stavudine (d4T)



Mechanism of action:

- When HIV infects a cell, reverse transcriptase copies the viral single stranded RNA genome into a double-stranded viral DNA
- The viral DNA is then integrated into the host chromosomal DNA
- Then, host cellular processes start transcribing viral RNA and mRNA to reproduce the virus
- Regulatory and structural proteins are produced under the direction of viral mRNA
- Zidovudine inhibits viral reverse transcriptase (RNA dependent DNA polymerase)
- Zidovudine prevents infection of new cell by HIV, but not effective on already infected host chromosomes



- **Resistance:**
  - Point mutation altering reverse transcriptase enzyme
- **Kinetics:**
  - Bioavailability – 60-80%.
  - t1/2 – 1 hour, intracellular half-life of the active triphosphate is 3 hours.
  - Conc. in CSF – 65% of that in plasma, crosses placenta and excreted in milk
  - Metabolism – Most of the drug is metabolized to inactive glucuronide in the liver, only 20% of the active form is excreted in the urine
- **Unwanted effects:**
  - Blood dyscrasias – Anaemia and Neutropenia
  - G.I disturbances – Nausea, vomiting, abdominal pain
  - Myopathy, Paraesthesia, Myalgia
  - Skin rash, Insomnia, Fever, Headaches, Abnormalities of liver function
- **Drug Interaction:**
  - Paracetamol – AZT toxicity and azoles – inhibits AZT metabolism
- **Uses:**
  - HIV infection in combination with other drugs – minimum 2 other (3TC and NVP)

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI):

Eg: Nevirapine (NVP), Efavirenz (EFZ), Delavirdine (DLV)

Mechanism of action:

- Direct inhibitor of reverse transcriptase without intracellular phosphorylation
- NNRTIs bind to the Reverse transcriptase near the catalytic site and cause its denaturation
- More potent on HIV-1 than Zidovudine but not HIV-2
- Cross resistance among themselves but not with others

➢ **Kinetics:**

- Administered Orally.
- Plasma half-life – 20 min.
- Conc. in CSF – 45% of that in plasma.
- Metabolism – Metabolized in the liver and metabolite is excreted in the urine (CYP3A4)
- Nevirapine can prevent mother-to-baby transmission of HIV if given to the parturient mother and the neonate

➢ **Unwanted effects:**

- Skin rash(17%)
- Fever
- Headaches
- Lethargy.
- If not monitored carefully: Stevens-Johnson syndrome or Toxic epidermal necrolysis.
- Fulminant hepatitis (occasionally)

➢ **Dose: 200 mg/day**

RETROVIRAL PROTEASE INHIBITORS (PIS):

Eg.: Saquinavir (SQV), Nelfinavir (NFV), Indinavir (IDV), Ritonavir (RTV), Lopinavir and Amprenavir (AMP)

Mechanism of action:

- In last stage of HIV growth cycle viral polyproteins are formed and then become immature budding particles

- Protease is responsible for cleaving these precursor molecules to produce the final structural proteins of the mature virion core
- PIs bind to these proteins and inhibit formation of structural proteins
- All given orally
- CSF levels – negligible with Saquinavir & highest with Indinavir (76% of plasma conc.)
- They are used in combination with Reverse transcriptase inhibitors
- ADRs: CYP3A4 isoenzyme
- G.I disturbances
- Metabolic abnormalities, e.g. insulin resistance, High blood sugar & Hyperlipidaemia
- Altered distribution of fat (some fat wasting, some fat accumulation)
- ↑ conc. of liver enzymes with Ritonavir & Indinavir
- Parasthesias around the mouth, in hands & feet with Ritonavir & Amprenavir
- Renal stones (with Indinavir)
- Stevens-Johnson syndrome (with Amprenavir)

SAQUINAVIR (SQV):

- Oral formulation hard gel capsules – poor bioavailability (4%)
- Replaced in clinical use by a soft gel capsule formulation
- Administered after fatty meal
- Large volume of distribution but is 98% protein-bound
- The elimination half-life is 12 hours
- Excreted primarily in faeces
- High first pass metabolism
- ADRs include GIT disturbances – nausea, diarrhoea, abdominal discomfort and dyspepsia

HIV TREATMENT:

HAART (Highly Active Antiretroviral Therapy)

- Aggressive therapy aimed at supressing plasma viral load
- Combination treatment is essential
- Combination treatment → HAART

2 NRTIs + 1 NNRTI (Z+L+Efavirenz) OR

2 NRTIs + 1 or 2 Protease inhibitors (Z+L+lopinavir)

WHO Recommendations for a First Line Regimen in Adults and Adolescents:

Drugs to be taken	Use in Women of Childbearing age or who are Pregnant?	Available as FDC?
d4T+3TC+NVP	Yes	Yes
ZDV+3TC+NVP	Yes	Yes
d4T+3TC+EFZ	No	No
ZDV+3TC+EFZ	No	No

ANTI-INFLUENZA DRUGS:

Eg.: Amantadine, Oseltamivir, Peramivir, Rimantadine, Zanamivir

- Tricyclic amine unrelated to any nucleic acid precursor

Amantadine - Approved by FDA in 1976 to treat influenza A (not influenza B)

- Mechanism:
  - Inhibits the un-coating of the viral genome
  - Specifically targets a protein called M2 (an ion channel)
  - Inactive against influenza B, which lacks M2
- Pharmacokinetics:
  - Well absorbed orally; crosses BBB
  - 90% excreted unchanged ; no reports of metabolic products
- Side effects:
  - Low toxicity at therapeutic levels; some CNS side effects (scary hallucinations
- Doses: 100 mg BD or 200 mg OD

Osetalmivir (Tamiflu), Zanamivir:

- Broad spectrum – Influenza A, B and avian influenza
- Oseltamivir is a prodrug that is activated in the gut and liver to O. carboxylate
- MOA: Neuraminidase inhibitor (important for viral replication and release)
- Not further metabolized and excreted in kidney
- Half life: 6-8 Hrs
- ADRs: Nausea and vomiting
- Used in both prophylaxis and treatment
- Dose: 75 mg BD for 5 days

Interferone α:

- **Interferon has broad spectrum anti-viral activity (DNA viruses):**
  - herpes simplex 1 and 2; herpes zoster
  - human papillomavirus (genital warts)
- **(RNA viruses):**
  - Influenza, chronic hepatitis, common cold
  - Breast cancer. lung cancer
  - Karposi's sarcoma (cancer associated with AIDS)
- **Pharmacokinetics:**
  - Not orally bioavailable
  - Topically routes: intramuscular, subcutaneous, topical (nasal spray)
- **Mechanism of action:**
  - Binds to cell surface receptors
  - Induces expression of translation inhibitory protein (TIP)
  - TIP binds to ribosome, inhibits host expression of viral proteins
- Available as vials for injection
- ADRs: Flue like symptoms, neurotoxicity, myelosuppression etc