Antiviral drugs

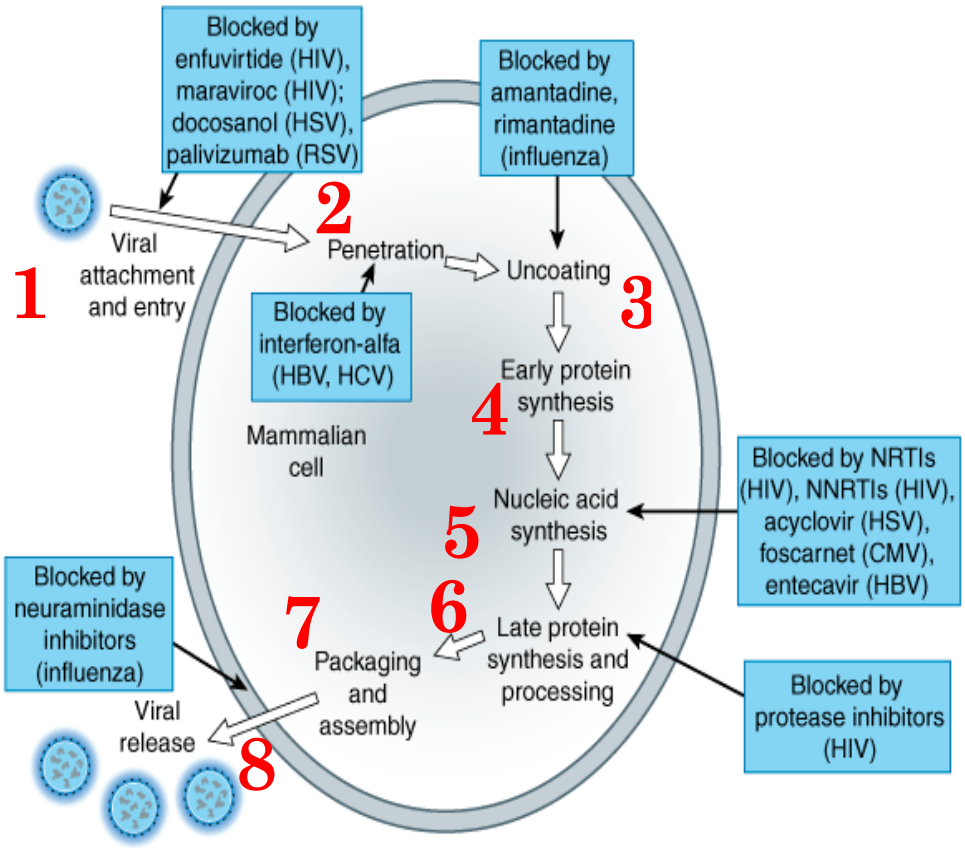
Virus particles (virions) consist of following parts:

1- Nucleic acid core: DNA or RNA

2- Often, contain virus-specific enzymes

3- Surrounded by protein: "capsid"

4- Sometimes an outer lipid "envelope"



- Many viruses infect a specific host cell.
- Many viral infections are self-limiting and require no medical treatment—ex. Rhinoviruses that cause common cold.
- Common viral infections such as the influenza, mumps, or chicken pox are usually overcome by the body's immune system.
- Other viruses cause serious and even fatal disease & require aggressive therapy—ex. HIV that causes AIDS.

- Many antiviral drugs are Purine or Pyrimidine analogs.
- Many antiviral drugs are Prodrugs. They must be phosphorylated by viral or cellular enzymes in order to become active.
- Anti-viral drugs inhibit active replication so the viral growth resumes after drug removal.
- Current anti-viral agents do not eliminate non-replicating or latent virus.
- Effective host immune response remains essential for the recovery from the viral infection.
- Clinical efficacy depends on achieving inhibitory concentration at the site of infection within the infected cells.

1-Anti-herpes virus drugs:

Acyclovir / Valacyclovir / Famciclovir / Penciclovir/ Ganciclovir / Cidofovir / Foscarnet / Trifluridine and Vidarabine.

-Valacyclovir is a prodrug of Acyclovir with better bioavailability.

-Famciclovir hydrolyzed to Penciclovir and has greatest bioavailability.

-Penciclovir used only topically whereas Famciclovir can be administered orally.

Mechanism of action of Acyclovir and congeners:

Acyclovir derivatives phosphorylated by a viral thymidine-kinase, and then metabolized by host cell kinases to nucleotide analogs. The analog inhibits viral DNA-polymerase; only actively replicating viruses are inhibited .Acyclovir thus selectively activated in cells infected with herpes virus. Uninfected cells do not phosphorylate acyclovir.

Antiviral spectrum :

- Acyclovir: HSV-1, HSV-2, VZV(varicella zostor virus) .
- Acyclovir Administration: Topical, Oral , IV.
- **Ganciclovir** / Cidofovir : CMV (cytomegalovirus)
- **Famciclovir** : Herpes genitalis and shingles
- **Foscarnet** : HSV, VZV, CMV, HIV (human immunodeficiency virus).
- **Penciclovir** : Herpes labialis
- **Trifluridine** : Herpetic keratoconjunctivitis.

Adverse effects of Acyclovir / Ganciclovir :

1. Nausea, vomiting and diarrhea
2. Nephrotoxicity - crystalluria, haematuria, renal insufficiency
3. Myelosuppression.
4. Neutropenia and thrombocytopenia – Ganciclovir.

Foscarnet:

M.O.A: It directly inhibits viral DNA and RNA -polymerase and viral inverse transcriptase (it does not require phosphorylation for antiviral activity). Selectively inhibits the pyrophosphate binding site on viral DNA polymerases at concentrations that do not affect human DNA polymerases.

-Foscarnet antiviral medication used to treat herpes viruses, including drug-resistant cytomegalovirus (CMV) and herpes simplex viruses types 1 and 2.

-Distribution to all tissues including CNS

-Administration: IV

Adverse effects of Foscarnet

- Hypocalcemia and hypomagnesemia (due to chelation of the drug with divalent cations) are common.
- Neurotoxicity (headache, hallucinations , seizures)
- Nephrotoxicity (acute tubular nephrosis, interstitial nephritis)

Therapeutic uses of Foscarnet :

It is an alternative drug for

HSV1,2 infections (acyclovir resistant / immunocompromised patient).

CMV retinitis (ganciclovir resistant / immunocompromised patient).

2- Respiratory viral infection drugs

A. Influenza (Oseltamivir / Zanamavir (Neuraminidase inhibitors)

(Amantadine / Rimantadine)

B. RSV bronchiolitis (respiratory syncytial virus) (Ribavirin)

Oseltamivir: Marketed under the trade name **Tamiflu**, is an antiviral drug, which may slow the spread of influenza (flu) virus between cells in the body by stopping the virus forming.

Chemically cutting ties with its host cell. The drug is taken orally in capsules or as a suspension. It is used to treat influenza A virus and influenza B virus. Oseltamivir is a prodrug, a (relatively) inactive chemical, which is converted into its active form by metabolic process after it is taken into the body. **It was the first orally active neuraminidase inhibitor commercially developed.**

Zanamivir: Is a neuraminidase inhibitor used in the treatment and prophylaxis of influenza caused by influenza A virus and influenza B virus.

Amantadine and Rimantadine :

Prevention & Treatment of influenza A

Inhibition of viral uncoating by inhibiting the viral membrane protein M2.

Ribavirin : Oral, IV, Inhalational in RSV.

It is a guanosine (ribonucleic) analog, used to stop viral RNA synthesis and viral mRNA capping, thus, it is a nucleoside inhibitor. Antiviral spectrum: DNA and RNA viruses are susceptible, including influenza, parainfluenza viruses, RSV, Lassa virus (Lassa hemorrhagic fever LHF)

Ribavirin is an alternative drug for:

Influenza, parainfluenza, measles virus infection in immunocompromised patients and hepatitis C in combination with interferons.

- Adverse effects: Anemia and jaundice are. Not advised in pregnancy.

- Therapeutic uses Ribavirin: Ribavirin is the drug of choice for **RSV** bronchiolitis and pneumonia in hospitalized children (given by aerosol)

3-Hepatic Viral infection drugs

1. **Interferons.**
2. **Lamivudine** – hepatitis B virus(HBV).
3. **Entecavir** – HBV– lamivudine resistance strains.
4. **Ribavirin** – Hepatitis C (with interferons).

Interferons:

Interferons (IFNs) are natural proteins produced by the cells of the immune systems in response to challenges by foreign agents, such as viruses, bacteria, parasites and tumor cells.

-Antiviral, immune modulating and anti-proliferative actions.

- Administered Intralesionally, S.C, and I.V.

Three classes of interferons – α, β, γ .

- α and β interferons are produced by all the cells in response to viral infections.
- γ interferons are produced only by T lymphocyte and NK cells in response to cytokines – immune regulating effects
- γ has less anti-viral activity compared to α and β interferons.

Mechanism of action of Interferons:

Induction of the following enzymes:

1) A protein kinase, which inhibits protein synthesis.

2) an oligo-adenylate synthase which leads to degradation of viral mRNA.

3) A phosphodiesterase which inhibit t-RNA.

The action of these enzymes leads to an inhibition of translation.

Antiviral spectrum : Interferon α

-Includes HBV, HCV and HPV (Human papilloma virus).

- Anti-proliferative actions may inhibit the growth of certain cancers like Kaposi sarcoma and hairy cell leukemia.

Therapeutic uses of Interferons

1-Chronic hepatitis B and C (complete disappearance is seen in 30%).

2-HZV infection in cancer patients (to prevent the dissemination of the infection).

3-CMV infections in renal transplant patients.

4-Condylomata acuminata (given by intralesional injection).

5-Hairy cell leukemia (in combination with zidovudine)

6-AIDS related Kaposi's sarcoma

Adverse effects of Interferons

1. Acute flu-like syndrome (fever, headache)
2. Bone marrow suppression (granulocytopenia, thrombocytopenia)
3. Neurotoxicity (confusion, seizures)
4. Cardiotoxicity - arrhythmia
5. Impairment of fertility.