ANTIVIRAL AGENTS

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OBJECTIVE

Know the various types of antiviral drugs in use, their pharmacokinetics, mechanism of action and the possible adverse effects.

INTRODUCTION

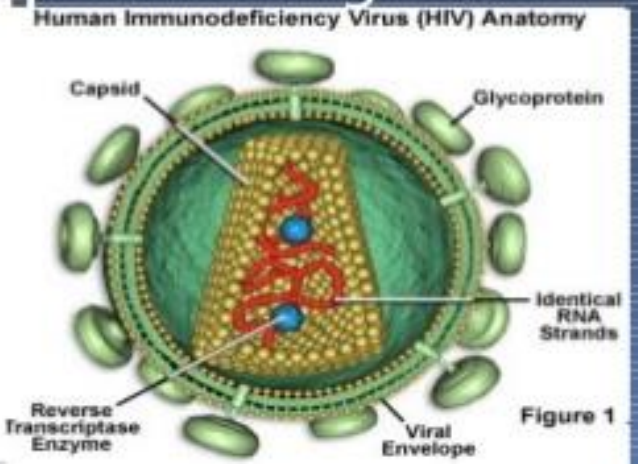
Viruses are obligate intracellular parasites.

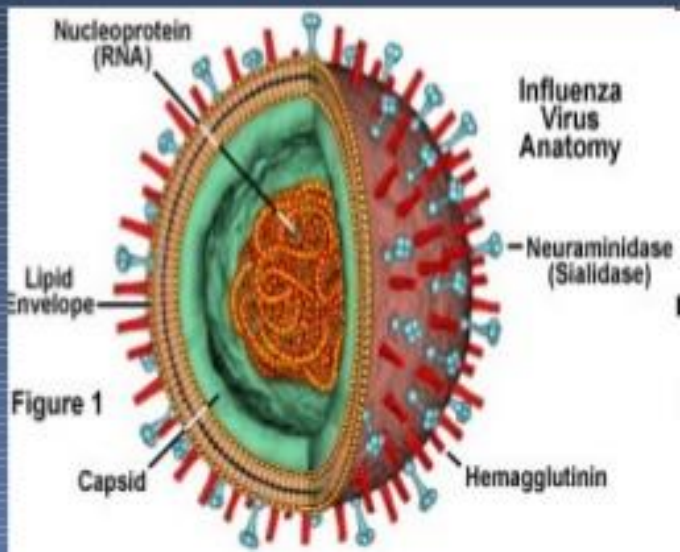
Their replication depends primarily on the host's synthetic processes.

Therefore to be effective, antiviral agents must either block the virus' entry into the host cell, their exit from the host cell or be active inside host cell.

Viruses, what are they?

- Viruses do not fit the pattern for a living organism
- Viruses are all parasites of the living
- They cannot make anything on their own, they use the cell's materials to build themselves
- Rogue DNA segment

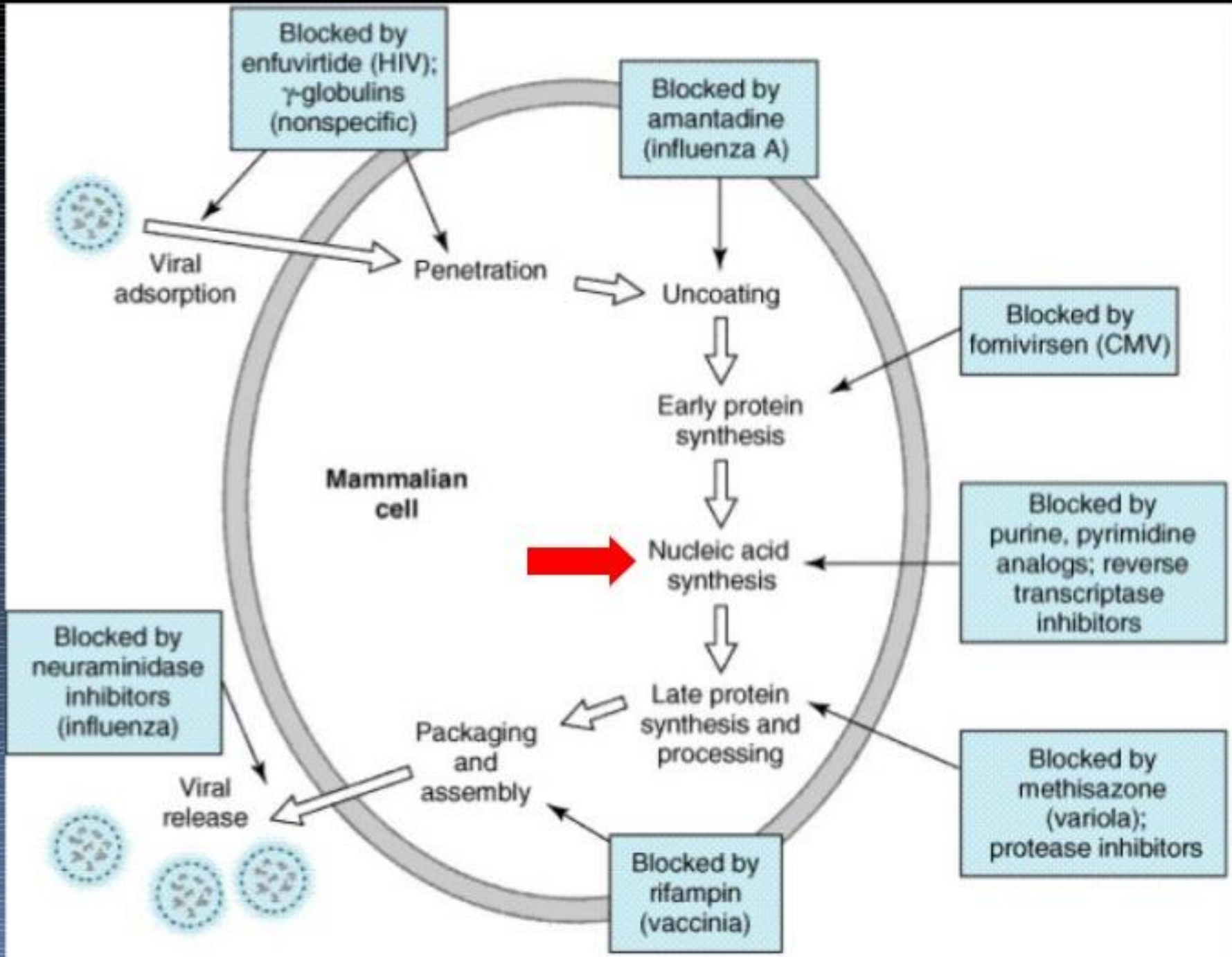




Viral replication consists of these steps:

- Attachment to host cell
- Entry through cell membrane
- Uncoating of viral nucleic acid
- Synthesis of early regulatory proteins i.e nucleic acid polymerases
- Synthesis of RNA or DNA
- Synthesis of late structural proteins
- Assembly/maturation of viral particles
- Release from the cell

Antiviral agents can potentially target any of these processes.


Blocked by enfuvirtide (HIV); γ-globulins (nonspecific)
Blocked by amantadine (influenza A)
Viral adsorption
Penetration
Uncoating
Blocked by fomivirsen (CMV)
Early protein synthesis
Mammalian cell
Nucleic acid synthesis
Blocked by purine, pyrimidine analogs; reverse transcriptase inhibitors
Blocked by neuraminidase inhibitors (influenza)
Late protein synthesis and processing
Packaging and assembly
Blocked by methisazone (variola); protease inhibitors
Viral release
Blocked by rifampin (vaccinia)

Some Viral Diseases

DNA-based viruses	Resultant disease
Herpes simplex types 1, 2	herpes (skin); encephalitis (brain)
Varicella zoster	chickenpox (children)
Herpes zoster	shingles (adult)
Human papillomavirus	warts (plantar, genital), cancer
Epstein-Barr virus	Mononucleosis ("mono"); Burkitt's lymphoma; nasopharyngeal carcinoma
Poxvirus	smallpox; chickenpox

RNA-based viruses	Resultant disease
HIV-1, HIV-2	HIV; AIDS
Rhinovirus	respiratory/GI infections ("common cold")
Hepatitis A, B, C viruses	Hepatitis
Influenza A, B, C viruses	Influenza A, B, C

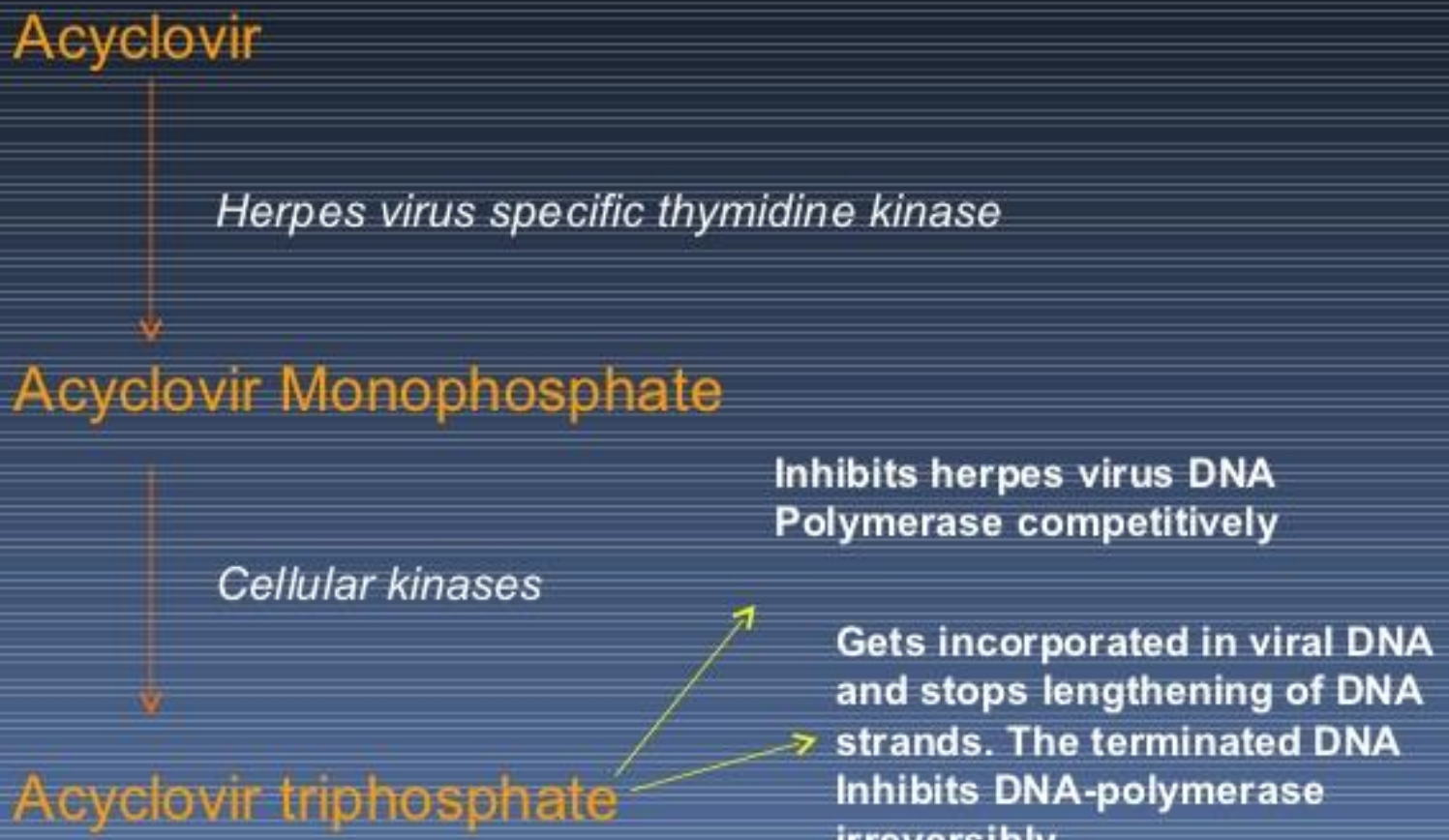
ACYCLOVIR

It is an acyclic guanosine derivative.

Mechanism of action

- Acyclovir requires three phosphorylation steps for activation.
- It is converted first to the monophosphate derivative by the virus-specified thymidine kinase, and then to Di- and Triphosphate compounds by host cell enzymes.
- Because it requires viral kinase for initial phosphorylation, acyclovir is selectively activated and therefore the active metabolites accumulate only in infected cells.
- Acyclovir inhibits viral DNA synthesis by chain termination following incooperation.

Acyclovir – MOA (Summary)



Pharmacokinetics

Acyclovir bioavailability is approximately 20% after administration of a standard (200 mg) dose orally, and may be dose dependent.

The mean elimination *t*1/2 of **acyclovir** is three hours and it crosses the blood–brain barrier producing a CSF concentration that is approximately 50% of that in plasma.

Clearance is largely renal and includes an element of tubular secretion; renal impairment requires dose/schedule adjustment.

Acyclovir – 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

Contraindications

Acyclovir is relatively contraindicated in pregnancy as it is an analogue of guanosine and so potentially teratogenic in the first trimester.

Adverse effects

These include:

1. a reversible rise in plasma urea and creatinine;
2. neurological disturbance;
3. rash;
4. nausea and vomiting;
5. hepatitis.

Drug interactions

Probenecid prolongs the half-life of **acyclovir** by 20% by inhibiting renal tubular secretion.

VALCYCLOVIR

It is a prodrug of acyclovir.

It is rapidly converted to acyclovir after oral administration by the intestinal and liver enzymes, resulting in serum levels that are three to five times greater than that achieved by oral acyclovir.

The indications are the same as those of acyclovir.

GANCYCLOVIR

Ganciclovir, a guanine analogue, is used to treat sight- or life-threatening CMV infections (e.g. retinitis, pneumonitis, colitis and oesophagitis) in immunocompromised hosts.

It also has potent activity against herpes viruses 1 and 2 and is used to treat **aciclovir**-resistant herpes.

A loading dose is administered intravenously followed by maintenance infusions. Oral **ganciclovir** is available for therapy despite its poor bioavailability and is only slightly less effective than intravenous therapy in CMV retinitis in AIDS patients. It is easier for the patients and less expensive.

Intravitreal **ganciclovir** implants are effective in treating CMV retinitis and are more effective at suppressing progression of disease than systemic **ganciclovir**.

Mechanism of action

Ganciclovir is metabolized intracellularly to its monophosphate in herpes-infected cells by the virally encoded thymidine kinase.

It undergoes further phosphorylation by host kinases to its triphosphate anabolite which competitively inhibits the CMV (or HSV) DNA polymerase. If it is incorporated into nascent viral DNA, it causes chain termination.

Ganciclovir is concentrated ten-fold in infected cells compared to uninfected cells.

Pharmacokinetics

Only 4–7.5% of an oral dose of **ganciclovir** is absorbed, yielding a **ganciclovir** bioavailability of 60%.

Ganciclovir has a mean elimination *t*1/2 of between two and five hours and is virtually totally excreted by the kidney.

Dose reduction is needed in renal failure.

Adverse effects

These include:

. neutropenia and bone marrow suppression (thrombocytopenia and less often anaemia); cell counts usually return to normal within two to five days of discontinuing the drug;

• temporary or possibly permanent inhibition of spermatogenesis or oogenesis;

• phlebitis and pain at intravenous infusion site;

• rashes and fever;

• gastro-intestinal upsets;

• transient increases in liver enzymes and serum creatinine

in underhydrated patients.

VALGANCYCLOVIR

It is a prodrug of gancyclovir.

It is well absorbed and rapidly metabolised in the intestines and liver to gancyclovir.

Its bioavailability when given orally is 60%.

Its indications, mechanism of action and adverse effects are the same as those of acyclovir

FOSCARNET

Foscarnet is a nucleotide analogue that acts as a noncompetitive inhibitor of viral DNA polymerase and inhibits the reverse transcriptase from several retroviruses.

It is inactive against eukaryotic DNA polymerases at concentrations that inhibit viral DNA replication.

Uses

Foscarnet is active against several important viruses, notably HIV-1 and all human herpes viruses, including **acyclovir** resistant herpes viruses and cytomegalovirus (CMV).

It is used to treat CMV infections (retinitis, pneumonitis, colitis and oesophagitis) and **acyclovir**-resistant herpes simplex virus (HSV) infections in immunocompetent and immunosuppressed hosts.

Foscarnet is given intravenously as loading dose followed by infusions. Dose reduction is required in patients with renal failure.

Adverse effects

These include the following:

- nephrotoxicity: minimized by adequate hydration and dose reduction if the serum creatinine rises; monitoring of renal function is mandatory;
- central nervous system effects include irritability, anxiety and fits;
- nausea, vomiting and headache;
- thrombophlebitis;
- hypocalcaemia and hypomagnesaemia;
- hypoglycemia

RIBAVIRIN

Ribavirin is active against a number of RNA and DNA (HSV-1and HSV-2, influenza) viruses.

It is used to treat hepatitis C(combined with **interferon**) or bronchiolitis secondary to respiratory syncytial virus infection in infants and children.

Administration for bronchiolitis is via aerosol inhalation.

Anti-Influenza Drugs

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
  - (also):
  - breast cancer; lung cancer;
  - Karposi's sarcoma (cancer associated with AIDS)
- Pharmacokinetics:
  - Not orally bioavailable
  - Topically routes: intramuscular, subcutaneous, topical (nasal spray)

Interferone

- 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

THANK YOU