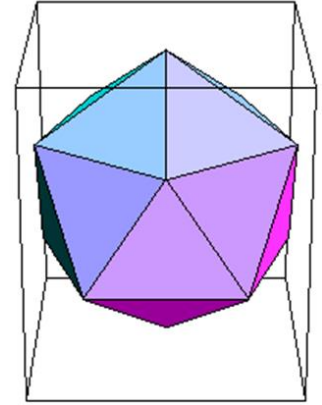




Antiviral Drugs

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Viruses

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

must grow inside host & use its metabolic machinery. (unlike bacteria)

Viruses are obligate intracellular parasites; with no, or little, metabolic machinery of their own.

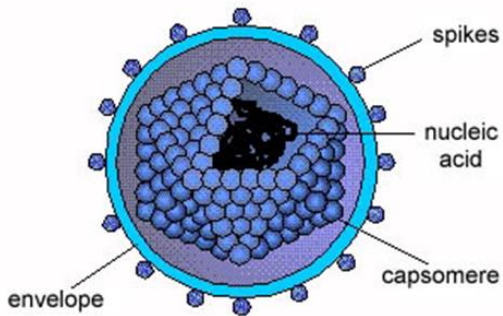
Their replication depends primarily on synthetic processes of the host cell.

They have to utilize the biochemistry of the host cell to succeed and grow (this is what makes selective antiviral therapy so difficult).

Deaths

- WWI: 20 million.
- Influenza 1918: 50 million.
- WWII: 80 million.

Virus Structure



Animal Virus Structure

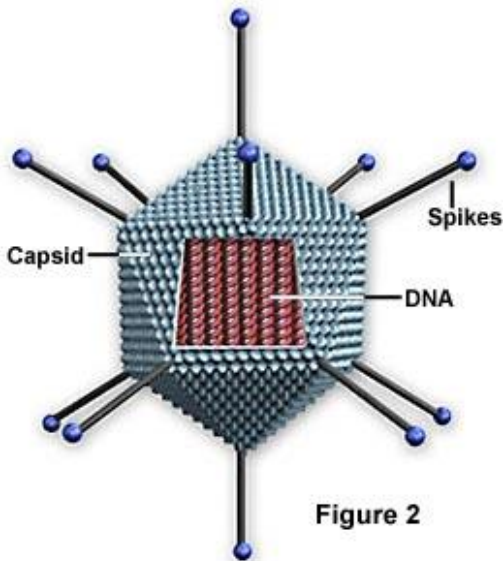
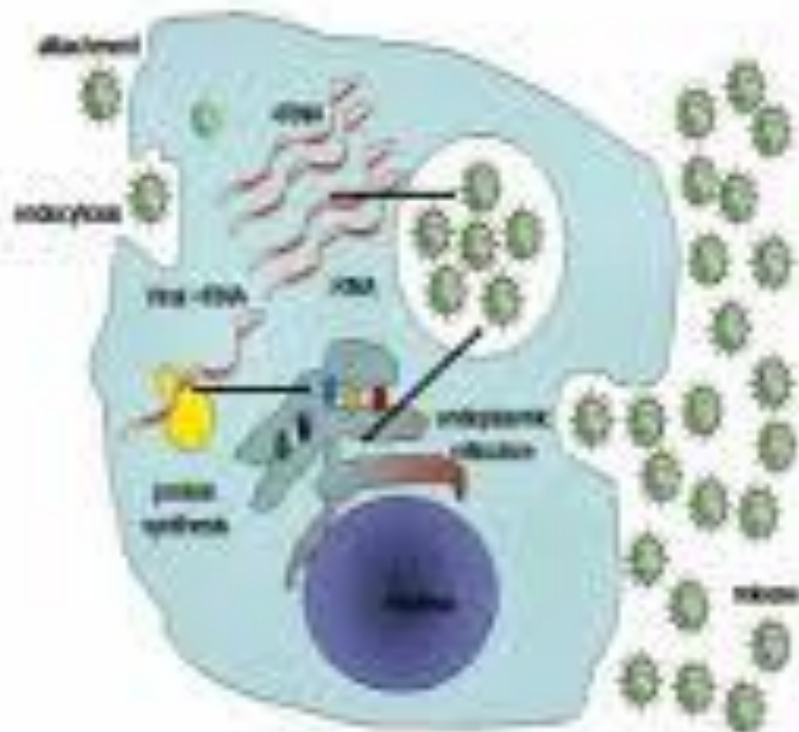


Figure 2

- **The Envelope:** Hybrid combination of cell lipids and virus proteins which permits attachment by the spikes.
- **The Capsid:** A protein shell of capsomer subunits.
- **Nucleic Acids:** DNA or RNA enclosed within the capsid used to replicate viruses within the host cell.

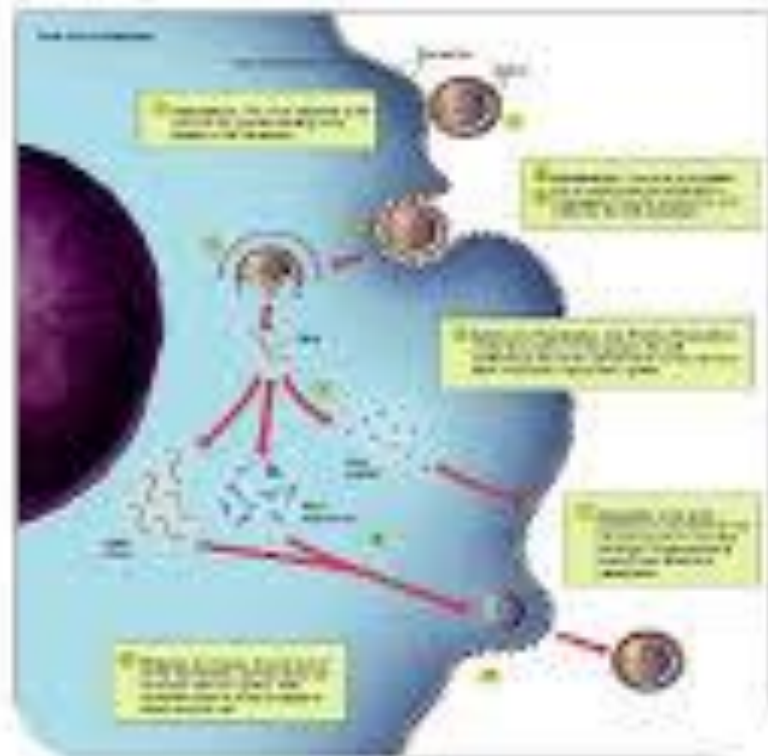
STEPS IN VIRAL REPLICATION

1. Attachment & adsorption
2. Penetration
3. Uncoating
4. Early viral mRNA synthesis
5. Early viral protein synthesis

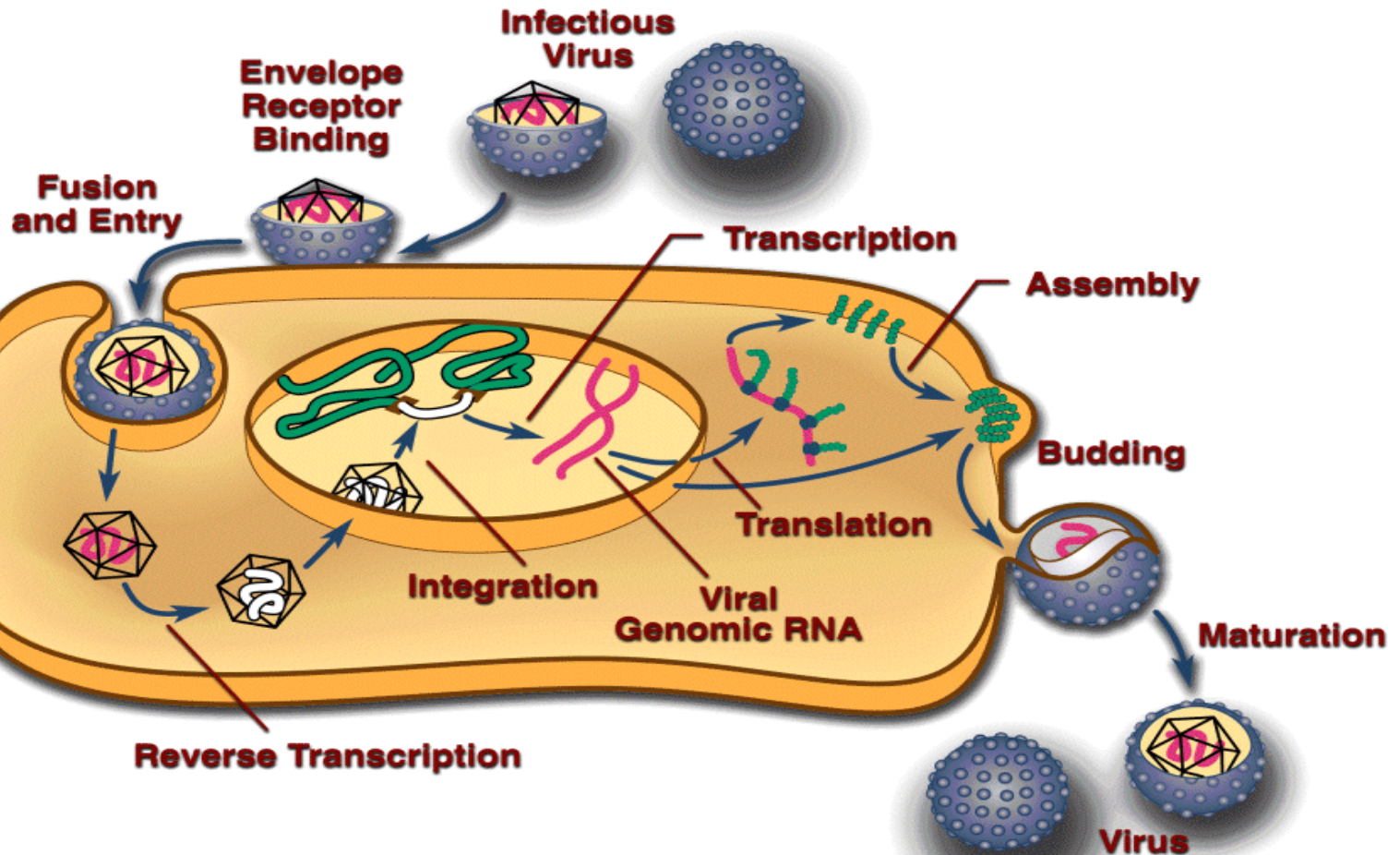


STEPS IN VIRAL REPLICATION

6. Viral genome replication
7. Late viral mRNA synthesis
8. Late viral protein synthesis
9. Assembly
10. Release → *could be by blood.*



Viral Replication



Patterns of Viral Infection

Acute infection:

- Complete viral clearance mediated by immune response
- E.g. Influenza, Rubella. → in pregnancy its dangerous, can cause congenital heart abnormality.
vaccine available ← gives life-long immunity after infection

Latent infection:

- Acute infection but followed by virus persistence in non-infectious form.
- Periodic reactivation of infection with viral shedding
- E.g. Chickenpox, Herpes simplex → can cause حزام ناري (neuve endings)

Chronic infection (progressive or persistent):

- Acute infection followed by lack of viral clearance
- Virus continuously shed or present in tissues
- e.g. HIV, Hepatitis C

DNA Viruses

he only said that
we have DNA &
RNA viruses.
(mesh mawdoo3na)

- Adenoviruses (flu, conjunctivitis)
- Hepadnaviruses (hepatitis B)
- Herpesviruses (cytomegalovirus, chickenpox, Shingles, Varicella-zoster, Herpes simplex)
- Papillomaviruses (warts)
- Poxviruses (Smallpox)

RNA Viruses

- Arboviruses (tick-borne encephalitis, yellow fever)
- Arenaviruses (Lassa fever, meningitis)
- Orthomyxoviruses (influenza)
- Paramyxoviruses (measles, mumps)
- Picornaviruses (polio, meningitis, colds)
- Rhabdoviruses (rabies)
- Rubella virus (German measles)
- Retroviruses (AIDS)

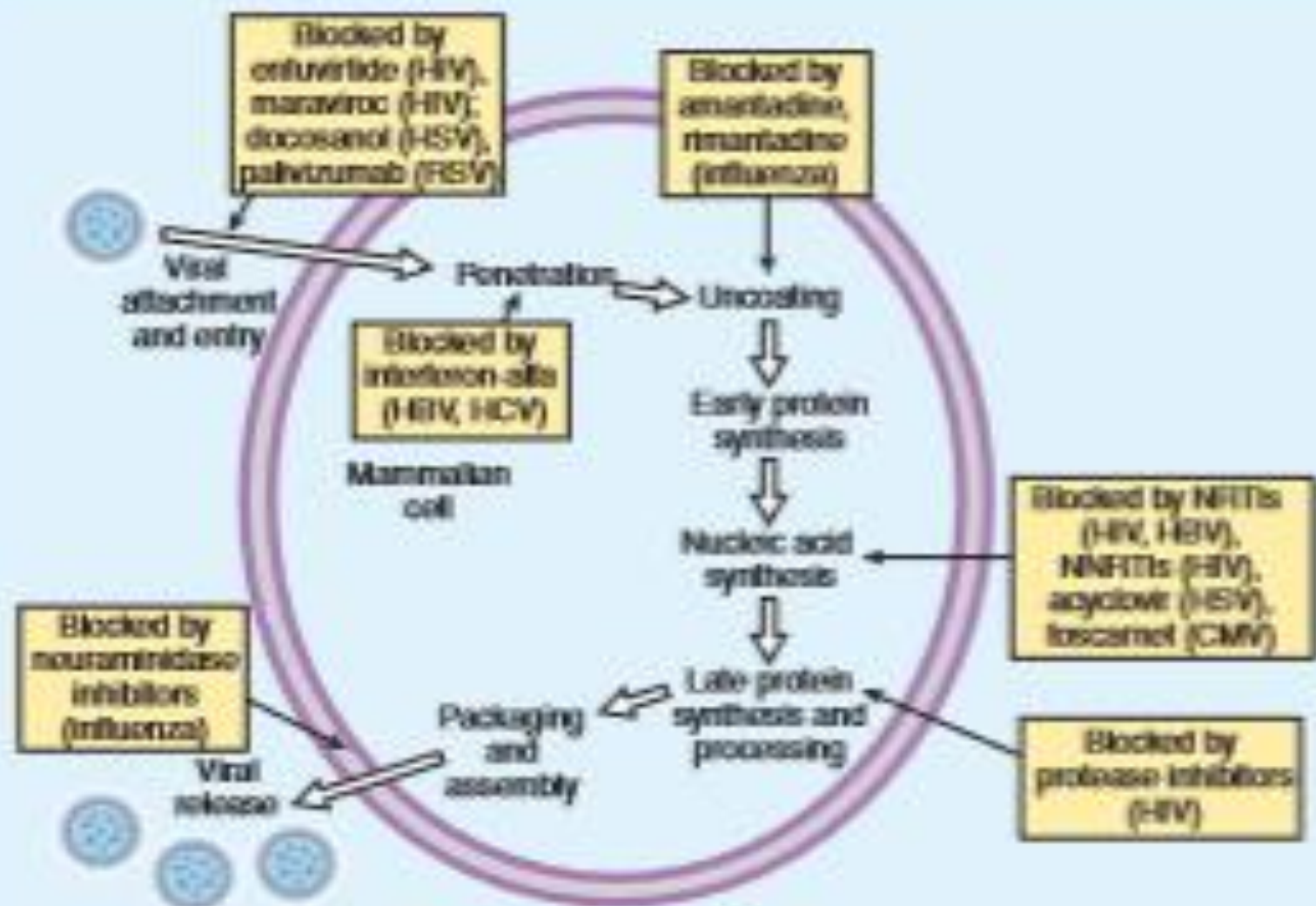
Antiviral Drugs

Current antiviral therapy can control these viruses:

- Cytomegalovirus (CMV)
- Hepatitis viruses
- Herpes viruses
- Human immunodeficiency virus (HIV)
- Influenza viruses (the “flu”) → *only if epidemic risk, not sporadic flu.*
- Respiratory syncytial virus (RSV)

Features of Antiviral Drugs

- ☐ Able to enter the infected cells.
- ☐ Interfere with viral nucleic acid synthesis and/or regulation.
- ☐ Some drugs interfere with ability of virus to bind to cells.
- ☐ Some drugs stimulate the immune system. *(indirect effect on like interferons infections)*
- ☐ Best responses to antiviral drugs are in patients with a competent immune system which works synergistically with the drug to eliminate or suppress viral activity
we should consider immunity system of patient before giving any type of drug especially bactericidal.



Treatment of Herpesviruses

Varicella-zoster,

Herpes simplex

Cytomegalovirus

Nucleoside Analogs

- **Result in “False” DNA building blocks or nucleosides**(a nucleoside consists of a nucleobase and the sugar deoxyribose).
- This abnormal nucleoside undergoes bio-activation by attachment of three phosphate residues
- **Acyclovir.**
- **Valacyclovir**(a pro-drug with better availability).
- **Famciclovir.**
- **Penciclovir.**

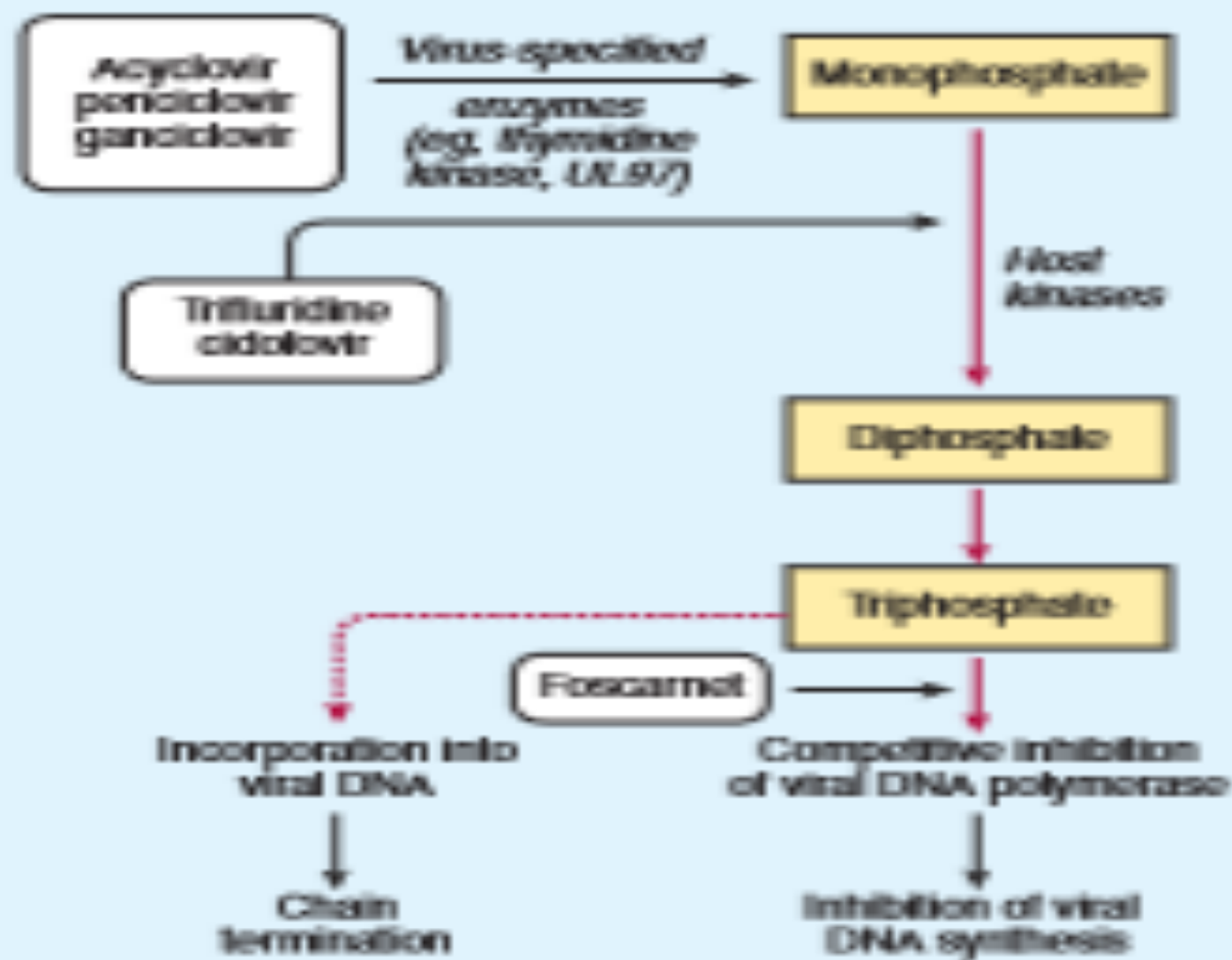


FIGURE 49–3 Mechanism of action of antihelopes agents.

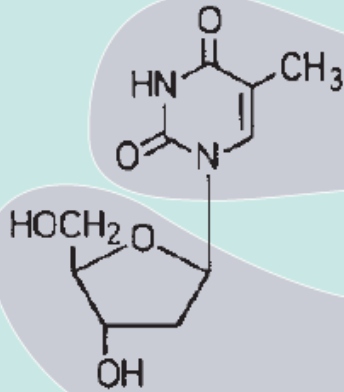
Antimetabolites = incorrect DNA building blocks

Correct:

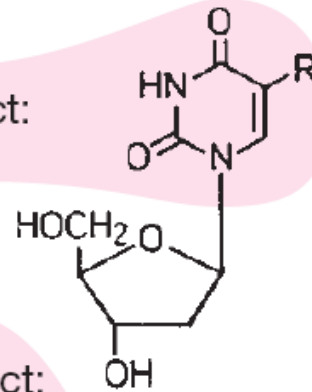
Thymidine

Thymine

Desoxyribose



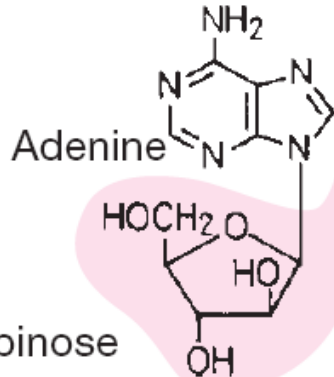
Incorrect:



R: - I Idoxuridine
- CF₃ Trifluridine
- C₂H₅ Edoxudine

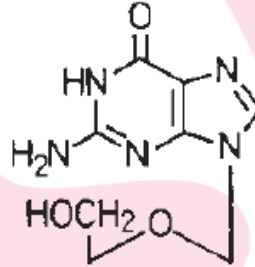
Insertion into
DNA instead
of thymidine

Vidarabine

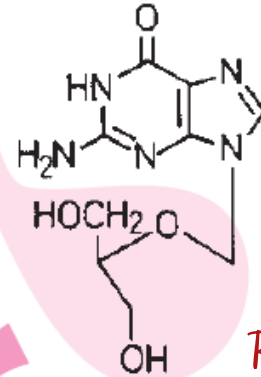


Arabinose

Acyclovir



Ganciclovir



Guanine

Inhibition of viral DNA polymerase

should be
phosphorylated
by 3 phosphate
groups

Acyclovir

- A virally coded thymidine kinase (specific to *H.simplex* and varicella-zoster virus) performs the initial phosphorylation step; the remaining two phosphate residues are attached by cellular kinases.
- Acyclovir triphosphate inhibits viral DNA polymerase resulting in chain termination.
- Selectively activated by the viral kinase for initial phosphorylation and accumulates only in infected cells.
- It is rapidly broken down in cells, is orally active and is relatively non-toxic systemically.
- Diffuses readily into most tissues.
- Available for oral, IV, and topical administration.
 ↳ encephalitis

Acyclovir

A Guanine analogue with activity against Herpes viruses.



1. Selectively inhibits viral DNA polymerase.
2. Incorporated into DNA and terminates synthesis

Resistance:

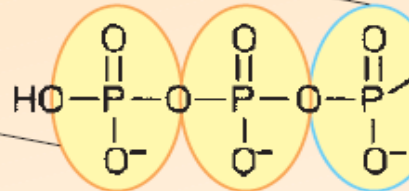
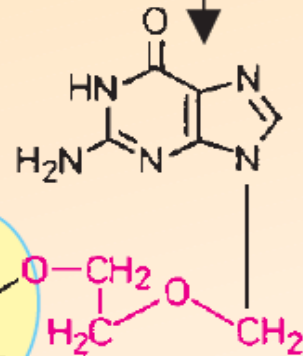
1. ↓ activity of thymidine kinase
2. Altered DNA polymerase

Infected cell:
herpes simplex
or varicella-zoster

Viral
thymidine
kinase

Cellular kinases

Acyclovir



Active metabolite

Viral DNA template

Base

Base

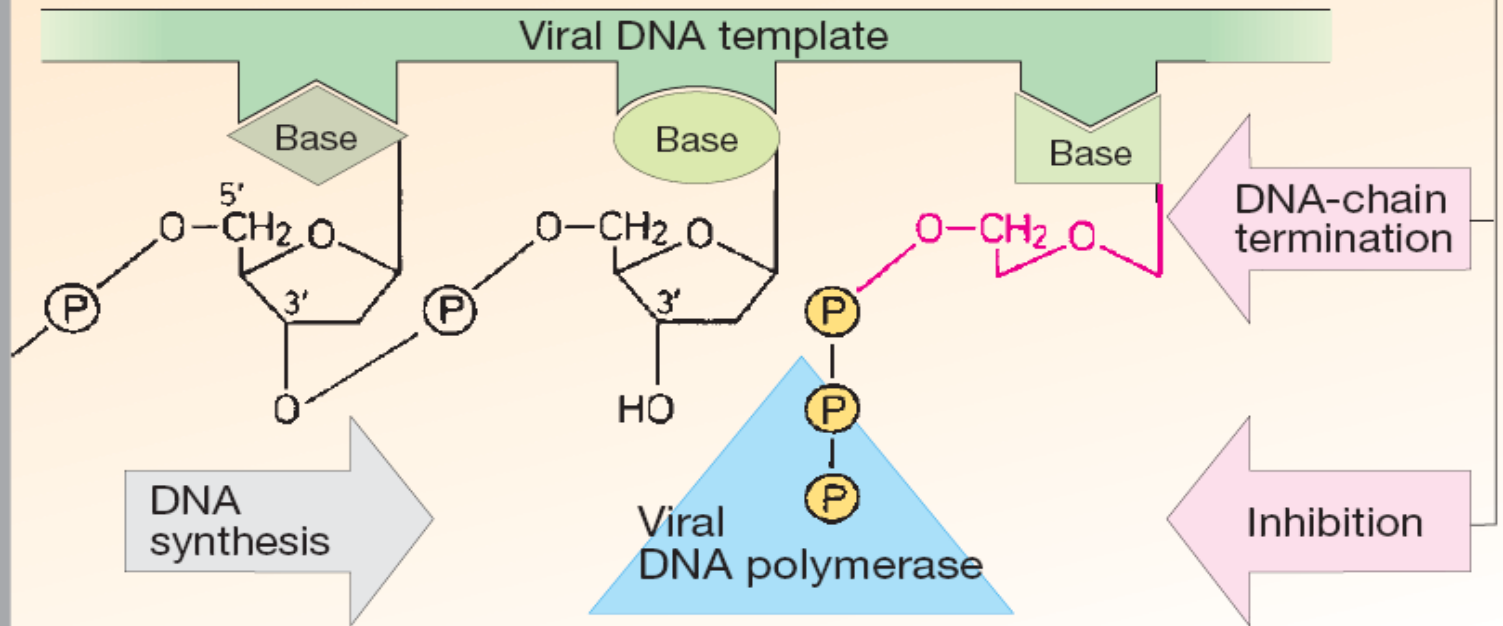
Base

DNA-chain
termination

DNA
synthesis

Viral
DNA polymerase

Inhibition



Uses of Acyclovir

- Herpes simplex infections (genital herpes, and herpes encephalitis). Shortens the duration of symptoms. (doesn't really kill the virus)
- Chickenpox in immuno-compromised patients.
no vaccine available ↪ usually self-limited. gives life-long immunity after infection.
- Prophylactically, to prevent reactivation of latent viruses in patients immunosuppressed with drugs or radiotherapy.
reduces immunity
- Prophylactically, in frequent recurrences of genital herpes.
↪ usually in females. it can be transmitted to child through birth canal during delivery.

Adverse Effects of Acyclovir

- Nausea, vomiting, diarrhea and headache.
- Renal insufficiency and neurotoxicity when given I.V.
- Not teratogenic, used to suppress active genital herpes in pregnant women.

Vidarabine

more toxic
than acyclovir

- Selectively inhibits virally induced DNA polymerase more than the endogenous enzyme.
- Vidarabine is a chain terminator and is active against herpes simplex, varicella zoster, and vaccinia.
- Use is limited to topical treatment of severe herpes simplex infection.
↳ not given orally / IV
- Before the introduction of acyclovir, it was used in the treatment of herpes simplex encephalitis
- Used in treatment of immunocompromised patients with herpetic and vaccinia keratitis and in keratoconjunctivitis.
cornea affected

Ganciclovir

- Same mechanism of action of Acyclovir, requires activation by triphosphorylation before inhibiting viral DNA polymerase causing termination of viral DNA elongation.
- Active against all Herpes viruses including CMV (100 times than acyclovir)
- Low oral bioavailability so, usually given I.V.
- Gel formulation is available for herpetic keratitis.

Ganciclovir

- Most common adverse effects: **bone marrow** suppression (leukopenia 40%, thrombocytopenia 20%), and **CNS effects** (headache, behavioral, psychosis, coma, convulsions).
- 1/3rd of patients have to stop treatment because of adverse effects.
- Drug of choice for CMV infections: retinitis, pneumonia, colitis.

Foscarnet

- An inorganic pyrophosphate analog which inhibits herpes virus DNA polymerase, RNA polymerase, and HIV reverse transcriptase directly without requiring activation by phosphorylation.
- Active IV against Herpes (I, II, Varicella , CMV), including those resistant to Acyclovir and Ganciclovir.
- **Nephrotoxicity** (25%) is the most common side effect
- Uses: CMV (retinitis and other CMV infections), Herpes simplex, and HIV.