

Anti-viral drugs

- Viruses have no cell wall and made up of nucleic acid components
- Viruses containing envelope – antigenic in nature
- **Viruses are obligate intracellular parasite**
- They do not have a metabolic machinery of their own – uses host enzymes

Anti-viral drugs

- Certain viruses multiply in the cytoplasm but others do in the nucleus
- Most multiplication take place before diagnosis is made

Anti-Viral drugs

- 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 agents *inhibits active replication* so the viral growth resumes after drug removal.

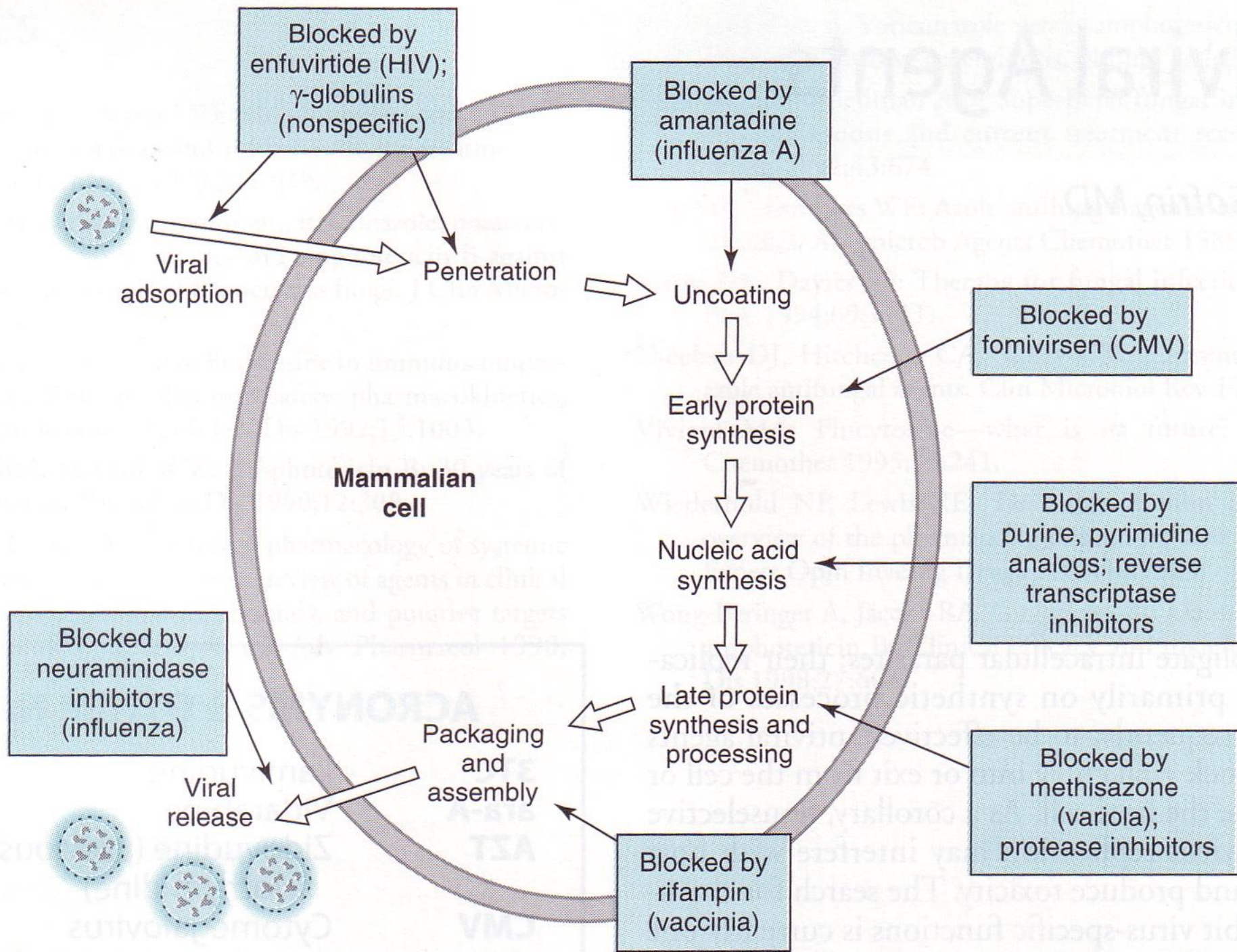
Anti-viral drugs

- 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 conc. at the site of infection within the infected cells

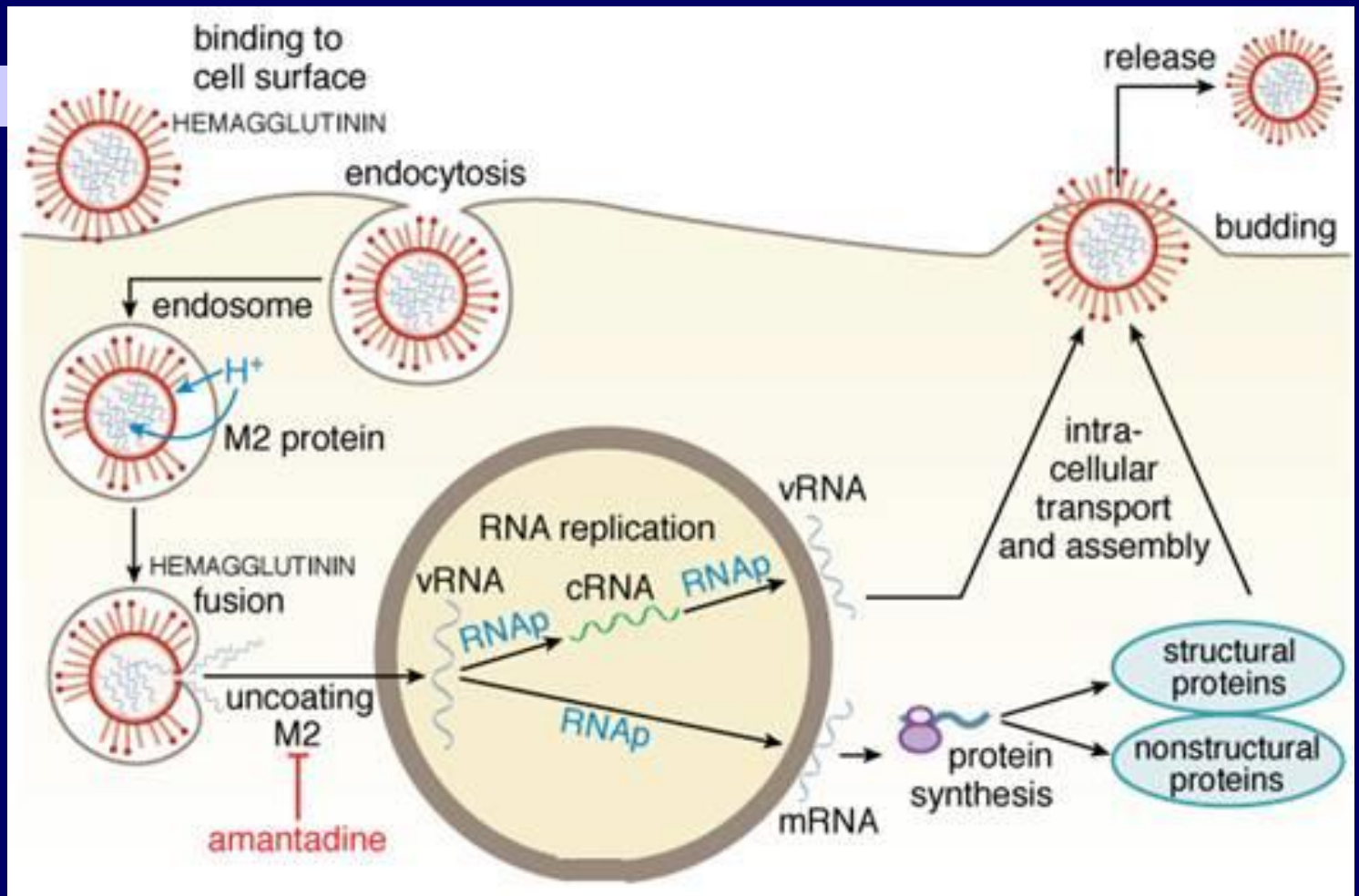
Anti-viral drugs

Stages of viral replication

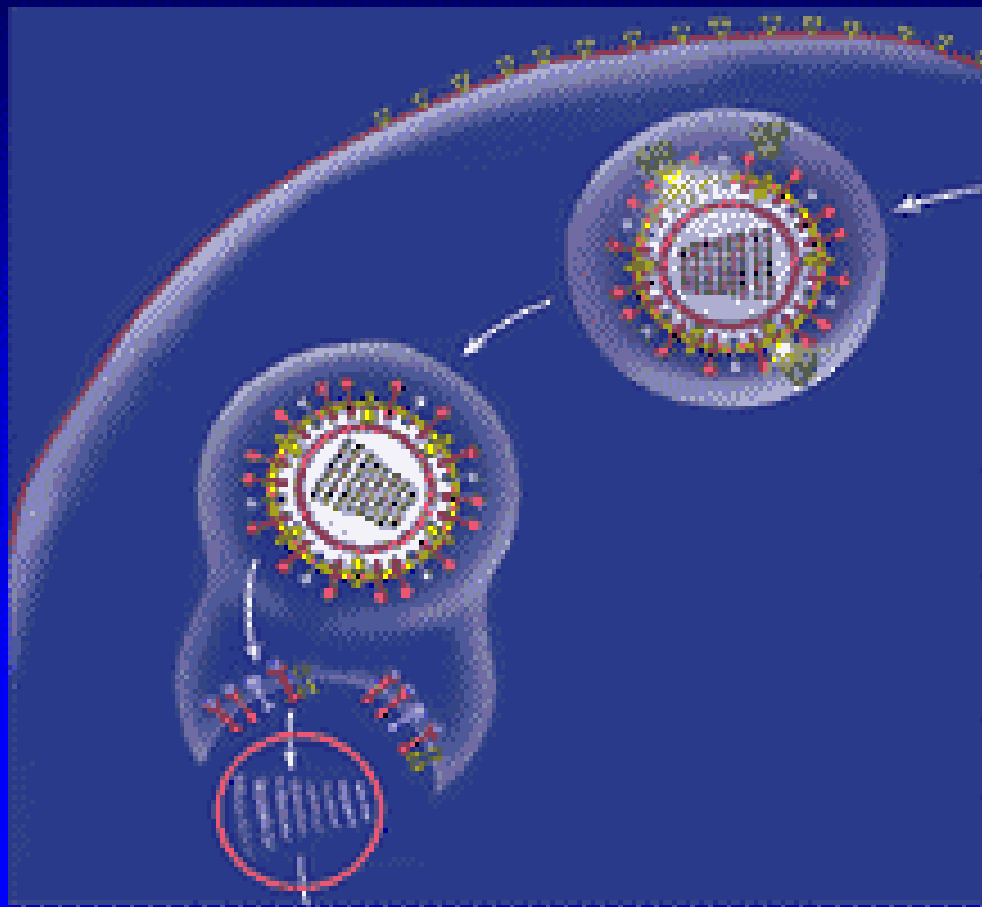
- Cell entry – attachment
- penetration
- Uncoating
- Transcription of viral genome
- Translation
- Assembly of virion components
- Release



Amantadine mechanism of action:



Amantadine and Rimantadine: Mechanism of Action



- Blocks M2 protein channel (type A only)
- Disrupts hydrogen transport, viral uncoating in host cell and therefore viral RNA transcription

Anti-viral drugs

Anti-herpes virus agents

- Acyclovir / Valacyclovir
- Famciclovir / Penciclovir
- Ganciclovir / Cidofovir
- Foscarnet
- Trifluridine / Idoxuridine / Vidarabine

Anti-viral drugs

Acyclovir & Congeners :

- **Valacyclovir** is a prodrug of Acyclovir with better bioavailability.
- Famciclovir is hydrolyzed to Penciclovir and has greatest bioavailability.
- Penciclovir is used only topically whereas Famciclovir can be administered orally.

Anti-Viral drugs

PHARMACOLOGY OF ACYCLOVIR AND CONGENERS

- Acyclovir, Valacyclovir, Ganciclovir, Famciclovir, Penciclovir all are guanine nucleoside analogs.

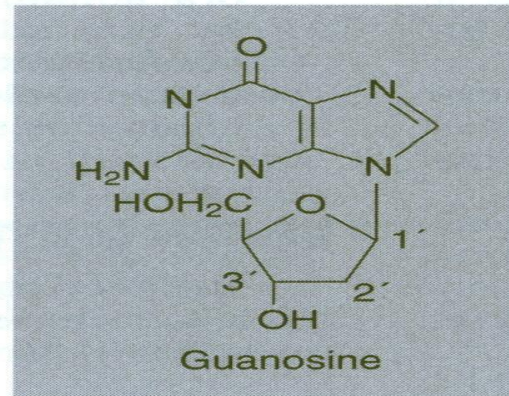
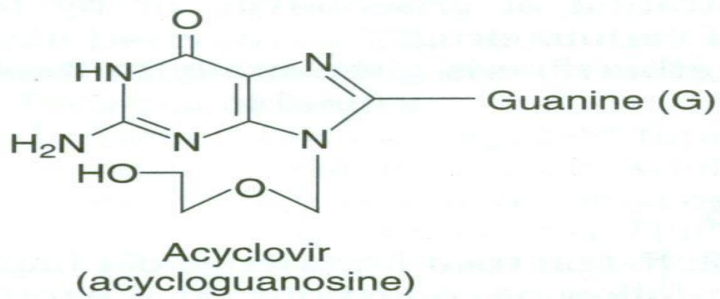
Anti-viral drugs

Mechanism of action of Acyclovir and congeners :

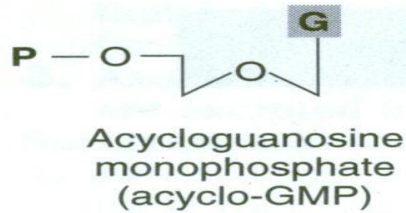
- All drugs are phosphorylated by a viral thymidine-kinase, then metabolized by host cell kinases to nucleotide analogs.
- The analog inhibits **viral DNA-polymerase**
- Only actively replicating viruses are inhibited

Mechanism: (Easy One)

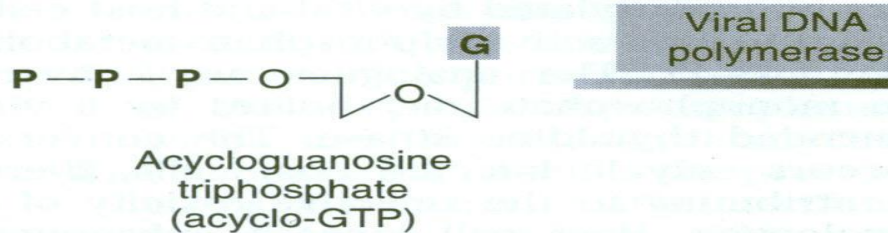
- Three phosphorylation steps for activation.
 - First converted to the monophosphate derivative by the *virus-specified* thymidine kinase; (selective activation)
 - Then to the di- and triphosphate compounds by *host's* cellular enzymes.
- Acyclovir triphosphate inhibits viral DNA synthesis by two mechanisms:
 - Competitive inhibition of deoxyGTP for the viral DNA polymerase, with binding to the DNA template as an irreversible complex;
 - Incorporation into the viral DNA → chain termination



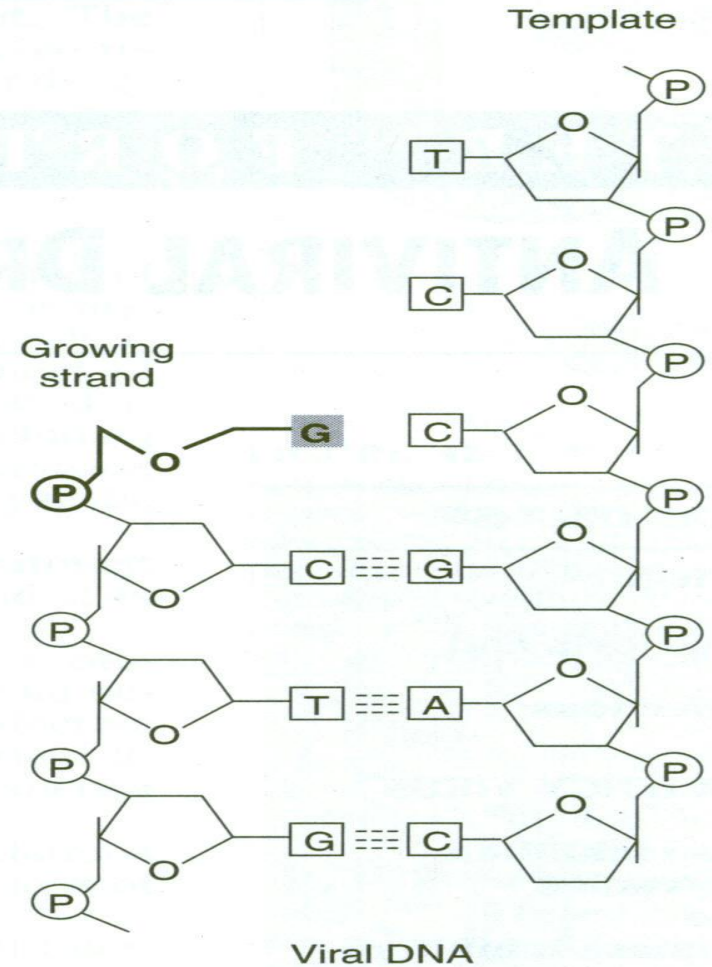
Viral kinase



Host cell kinase



Viral DNA polymerase



Anti-viral drugs

- Acyclovir is thus selectively activated in cells infected with herpes virus.
- Uninfected cells do not phosphorylate acyclovir.

Anti-Viral drugs

Antiviral spectrum :

- Acyclovir: HSV-1, HSV-2, VZV, Shingles.
- Ganciclovir / Cidofovir : CMV
- Famciclovir : Herpes genitalis and shingles
- Foscarnet : HSV, VZV, CMV, HIV
- Penciclovir : Herpes labialis
- Trifluridine : Herpetic keratoconjunctivitis

Anti-Viral drugs

Pharmacokinetics of Acyclovir :

- Oral bioavailability \sim 20-30%
- Distribution in all body tissues including CNS
- Renal excretion: $> 80\%$
- Half lives: 2-5 hours
- Administration: Topical, Oral , IV

Anti-viral drugs

Adverse effects of Acyclovir / Ganciclovir

- Nausea, vomiting and diarrhea
- Nephrotoxicity - crystalluria, haematuria, renal insufficiency
- Myelosuppression – Neutropenia and thrombocytopenia – Ganciclovir

Anti-viral drugs

Therapeutic uses :

Acyclovir is the drug of choice for:

- HSV Genital infections
- HSV encephalitis
- HSV infections in immunocompromised patient

Ganciclovir is the drug of choice for:

- CMV retinitis in immunocompromised patient
- Prevention of CMV disease in transplant patients

Anti-viral drugs

Cidofovir :

- It is approved for the treatment of **CMV retinitis in immunocompromised patients**
- It is a nucleotide analog of cytosine – no phosphorylation required.
- It inhibits viral DNA synthesis
- Available for IV, Intravitreal inj, topical
- Nephrotoxicity is a major disadvantage.

Anti-viral drugs

PHARMACOLOGY OF VIDARABINE

- Vidarabine is a nucleoside analog.
(adenosine)

Antiviral spectrum of Vidarabine :

HSV-1, HSV-2 and VZV.

Its use is limited to HSV keratitis only

Anti-viral drugs

Vidarabine

- The drug is converted to its triphosphate analog which inhibits viral DNA-polymerase.
- Oral bioavailability $\sim 2\%$
- Administration: **Ophthalmic ointment**
- **Used in HSV keratoconjunctivitis in immunocompromised patient.**
- **Anemia and SIADH are adverse effects.**

Anti-viral drugs

PHARMACOLOGY OF TRIFLURIDINE

- Trifluridine is a Pyrimidine nucleoside analogs - inhibits viral DNA synthesis.

Antiviral spectrum Trifluridine :

- HSV-1, HSV-2 and VZV.
- Use is limited to Topical - Ocular HSV Keratitis

Anti-viral drugs

PHARMACOLOGY OF FOSCARNET

- Foscarnet is an inorganic pyrophosphate analog
- It directly inhibits viral DNA and RNA - polymerase and viral inverse transcriptase (it does not require phosphorylation for antiviral activity)

Anti-viral drugs

Foscarnet

- HSV-1, HSV-2, VZV, CMV and HIV.
- Oral bioavailability ~ 10-20%
- Distribution to all tissues including CNS
- Administration: IV

Anti-viral drugs

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)

Anti-viral drugs

Therapeutic uses of Foscarnet

- *It is an alternative drug for*
- HSV infections (acyclovir resistant / immunocompromised patient)
- CMV retinitis (ganciclovir resistant / immunocompromised patient)

Anti-viral drugs

Respiratory viral infections

Influenza –

- Amantadine / Rimantadine
- Oseltamivir / Zanamavir
(*Neuraminidase inhibitors*)

RSV bronchiolitis –

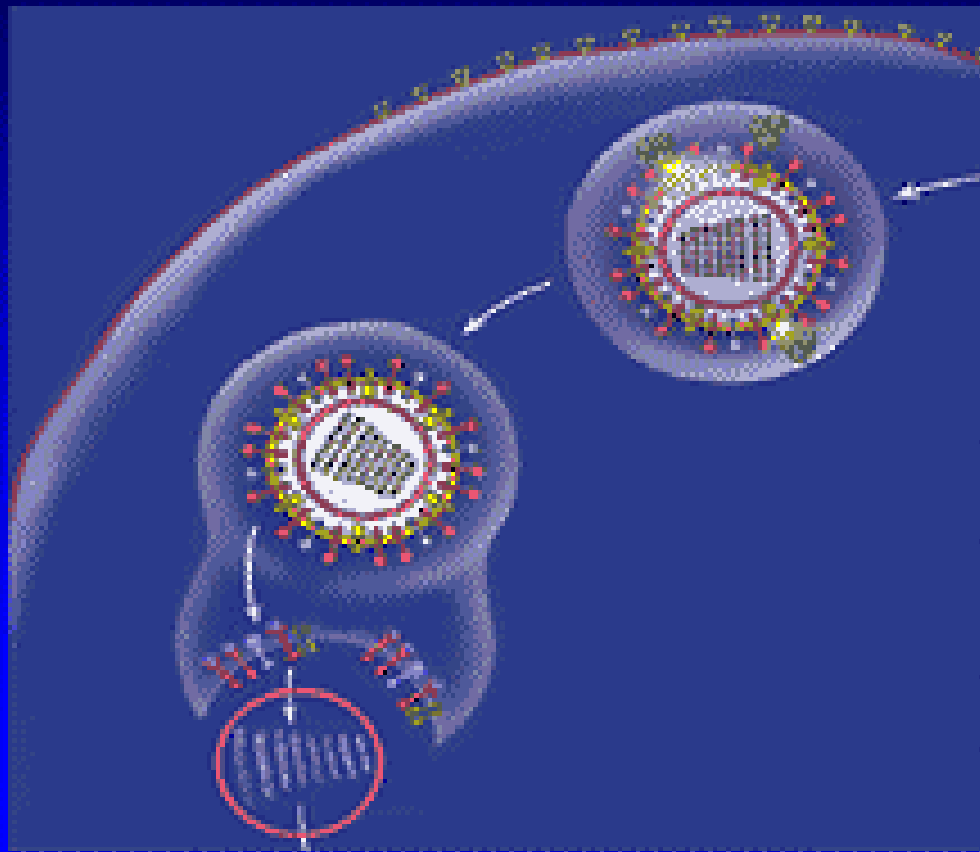
- Ribavirin

Anti-viral drugs

Amantadine and Rimantadine : Influenza

- Prevention & Treatment of influenza A
- **Inhibition of viral uncoating** by inhibiting the viral membrane protein M2
- Influenza A virus
- Amantadine has anti-parkinsonian effects.

Amantadine and Rimantadine: Mechanism of Action



- Blocks M2 protein channel (type A only)
- Disrupts hydrogen transport, viral uncoating in host cell and therefore viral RNA transcription

Anti-viral drugs

Pharmacokinetics of Amantadine

- Oral bioavailability \sim 50-90%
- Amantadine cross extensively BBB whereas Rimantadine does not cross extensively .
- Administration: Oral

Anti-viral drugs

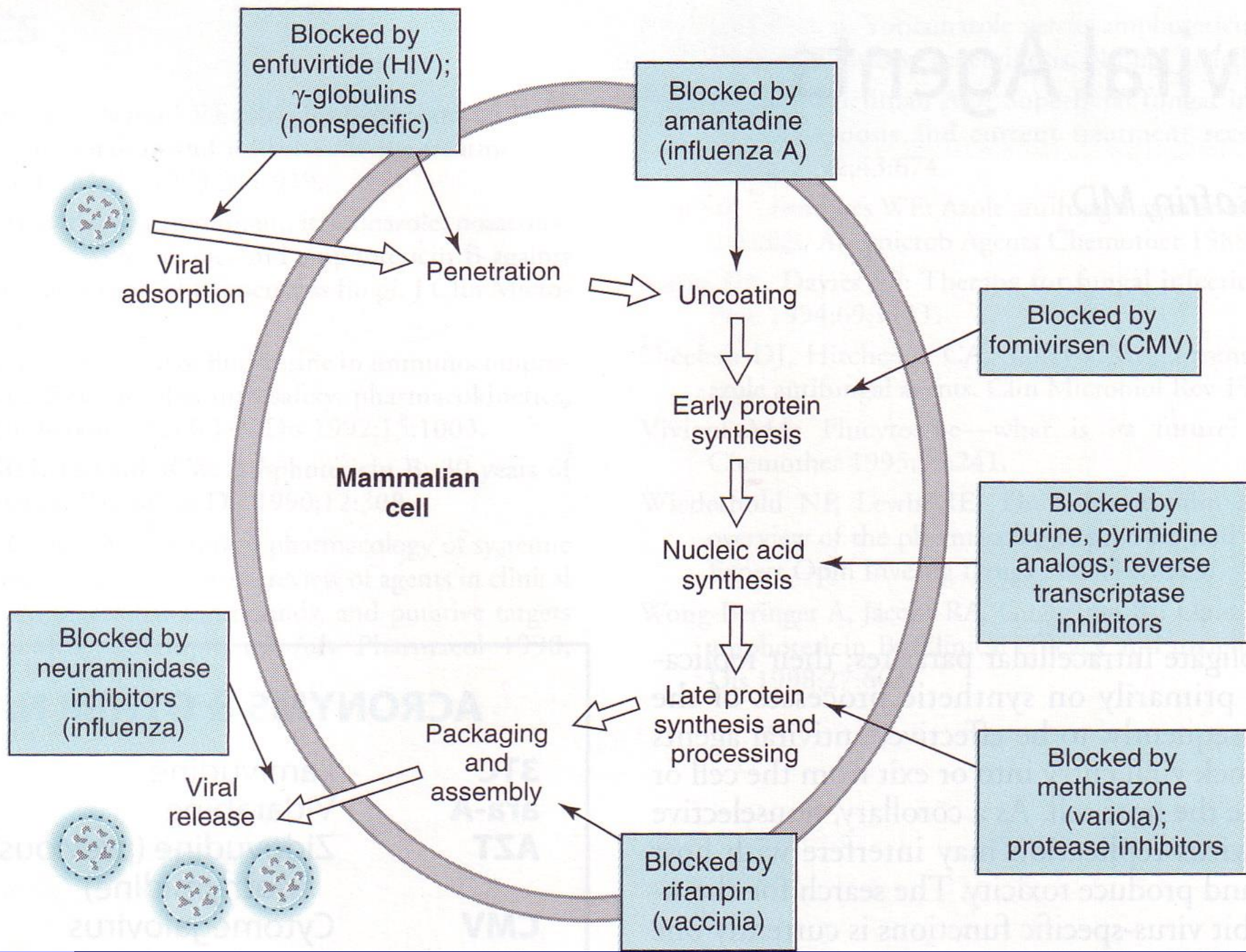
Neuraminidase inhibitors : Influenza Oseltamivir / Zanamavir

- **Influenza** contains an enzyme *neuraminidase* which is essential for the replication of the virus.
- ***Neuraminidase inhibitors*** prevent the release of new virions and their spread from cell to cell.

Anti-viral drugs

Neuraminidase inhibitors : Influenza **Oseltamivir / Zanamavir**

- These are effective against both types of influenza A and B.
- Do not interfere with immune response to influenza A vaccine.
- Can be used for both prophylaxis and acute treatment.



Anti-viral drugs

Neuraminidase inhibitors : Influenza **Oseltamivir / Zanamavir**

- Oseltamivir is orally administered.
- Zanamavir is given intranasal.
- Risk of bronchospasm with zanamavir

Anti-viral drugs

PHARMACOLOGY OF RIBAVIRIN

- **Ribavirin** is a guanosine analog.
- *Inhibition of RNA polymerase*

Antiviral spectrum : DNA and RNA viruses are susceptible, including influenza, parainfluenza viruses, **RSV**, Lassa virus

Anti-viral drugs

Ribavirin : RSV

- Distribution in all body tissues, except CNS
- Administration : Oral, IV, Inhalational in RSV.
- Anemia and jaundice are adverse effects
- Not advised in pregnancy.

Anti-viral drugs

Therapeutic uses Ribavirin

Ribavirin is the drug of choice for:

- RSV bronchiolitis and pneumonia in hospitalized children (given by aerosol)
- Lassa fever

Ribavirin is an alternative drug for:

- Influenza, parainfluenza, measles virus infection in immunocompromised patients

Anti-viral drugs

Hepatic Viral infections :

- Interferons
- Lamivudine – cytosine analog – HBV
- Entecavir – guanosine analog – HBV – lamivudine resistance strains
- Ribavirin – Hepatitis C (with interferons)

Anti-viral drugs

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
- Three classes of interferons – α , β , γ

Anti-viral drugs

Interferons

- **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**

Anti-viral drugs

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**

Anti-viral drugs

Antiviral spectrum : Interferon α

- Includes HBV, HCV and HPV.
- Anti-proliferative actions may inhibit the growth of certain cancers - like Kaposi sarcoma and hairy cell leukemia.

Anti-viral drugs

Pharmacokinetics : Interferons

- Oral bioavailability: $< 1\%$
- Administered Intralesionally, S.C, and I.V
- Distribution in all body tissues, except CNS and eye.
- Half lives: 1-4 hours

Anti-viral drugs

Adverse effects of Interferons

- Acute flu-like syndrome (fever, headache)
- Bone marrow suppression (granulocytopenia, thrombocytopenia)
- Neurotoxicity (confusion, seizures)
- Cardiotoxicity - arrhythmia
- Impairment of fertility

Anti-viral drugs

Therapeutic uses Interferons

- Chronic hepatitis B and C (complete disappearance is seen in 30%).
- HZV infection in cancer patients (to prevent the dissemination of the infection)
- CMV infections in renal transplant patients
- Condylomata acuminata (given by intralesional injection). Complete clearance is seen ~ 50%.
- Hairy cell leukemia (in combination with zidovudine)
- AIDS related Kaposi's sarcoma

Virus	Diseases	Drug(s) of choice	Alternative drugs
FLU A	Influenza	Amantadine	Rimantadine
RSV	Pneumonia, bronchiolitis	Ribavirin (aerosol)	
HSV	Genital herpes	Acyclovir	Foscarnet
	Keratitis Conjunctivitis	Trifluridine	Idoxuridine Vidarabine
	Encephalitis	Acyclovir	
	Neonatal HSV infection	Acyclovir	Vidarabine
	Herpes infections in immuno-compromised host	Acyclovir	Foscarnet

VZV	In normal host	No therapy	
	In immunocompromised host, or during pregnancy	Acyclovir	Foscarnet
CMV	Retinitis	Ganciclovir	Foscarnet
HIV	AIDS HIV antibody positive with CD4 count < 500/mm ³	Zidovudine ± protease inhibitors	Didanosine, Stavudine
HBV HCV	Hepatitis B, C	Interferons	