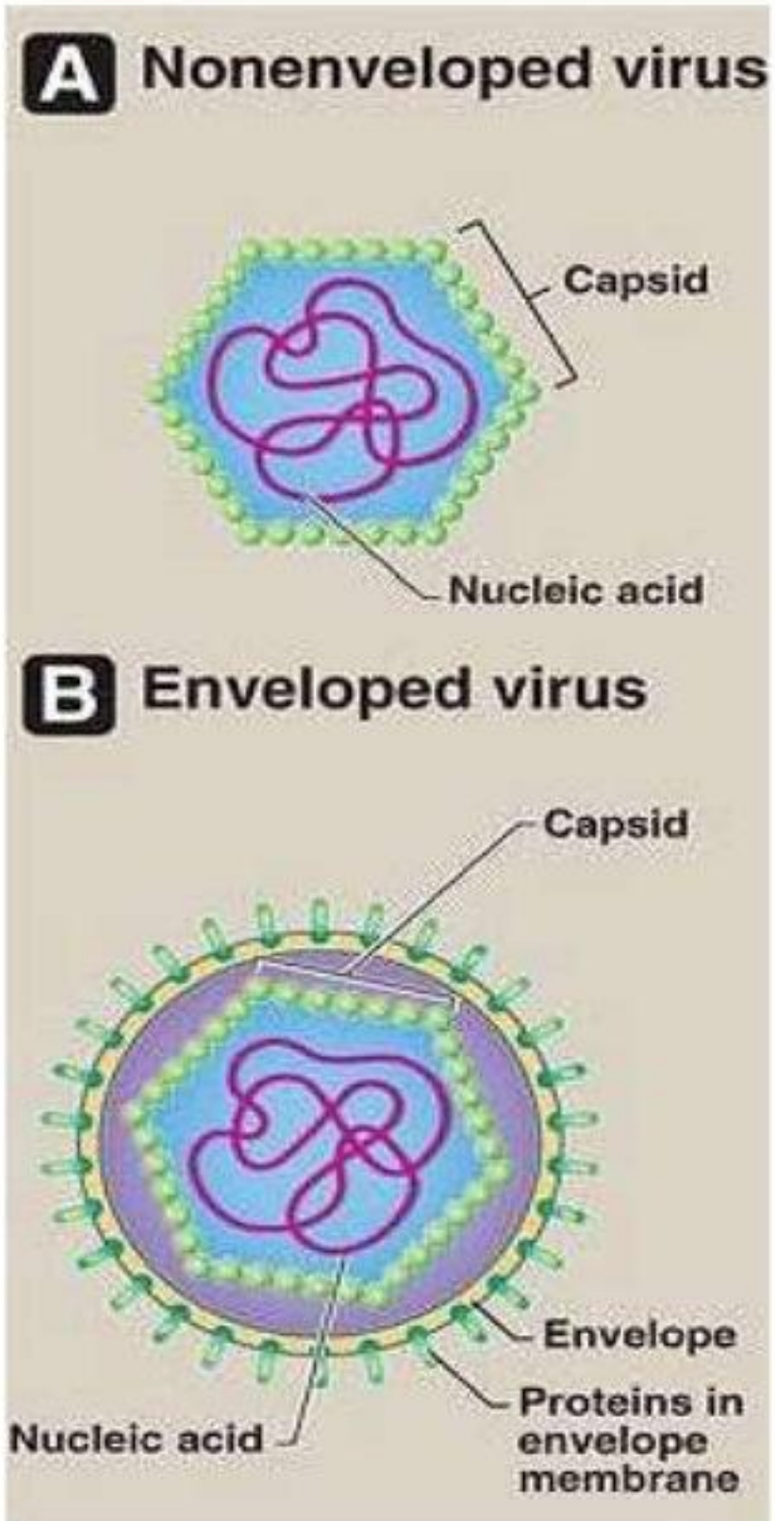
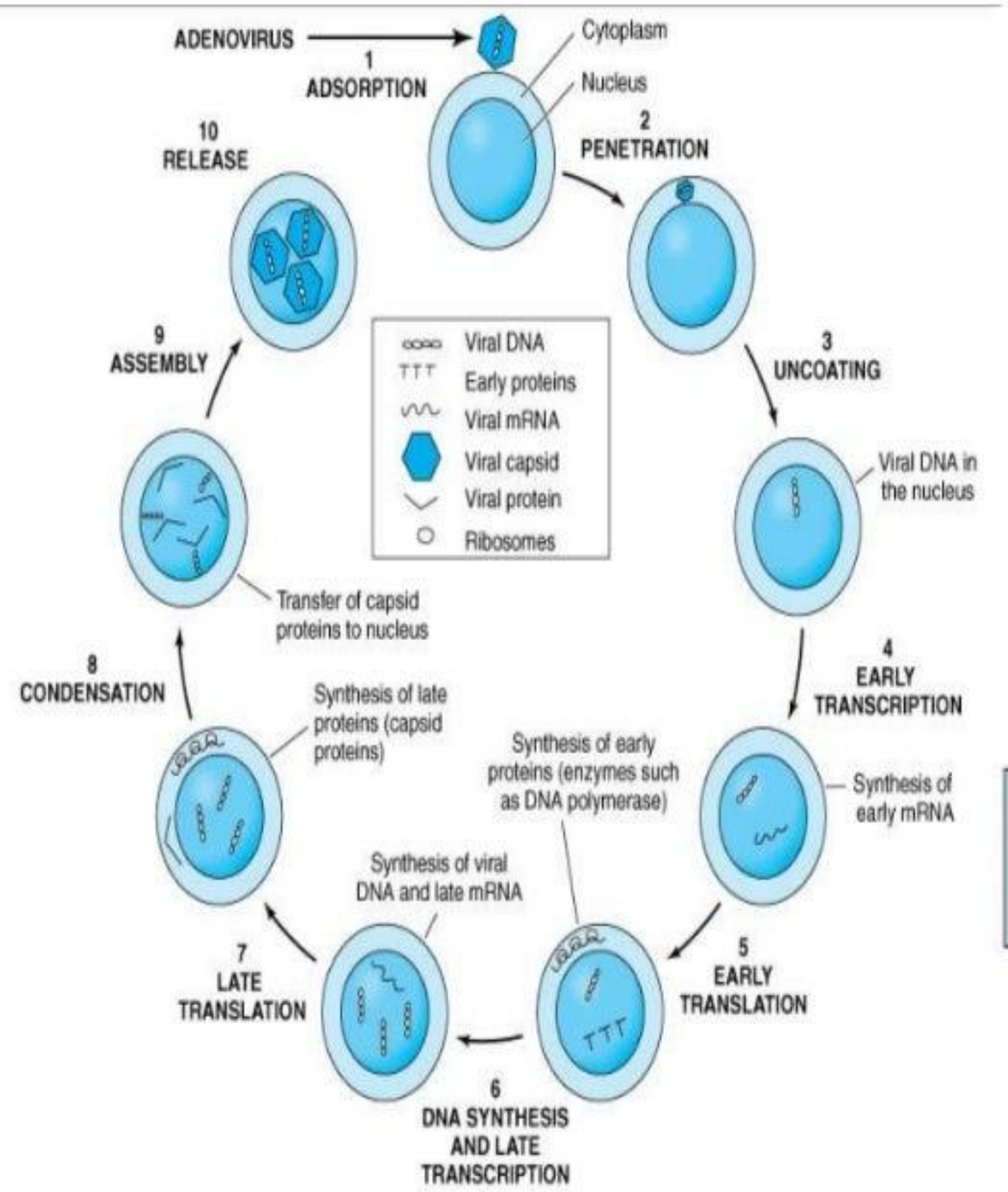
Antiviral drugs

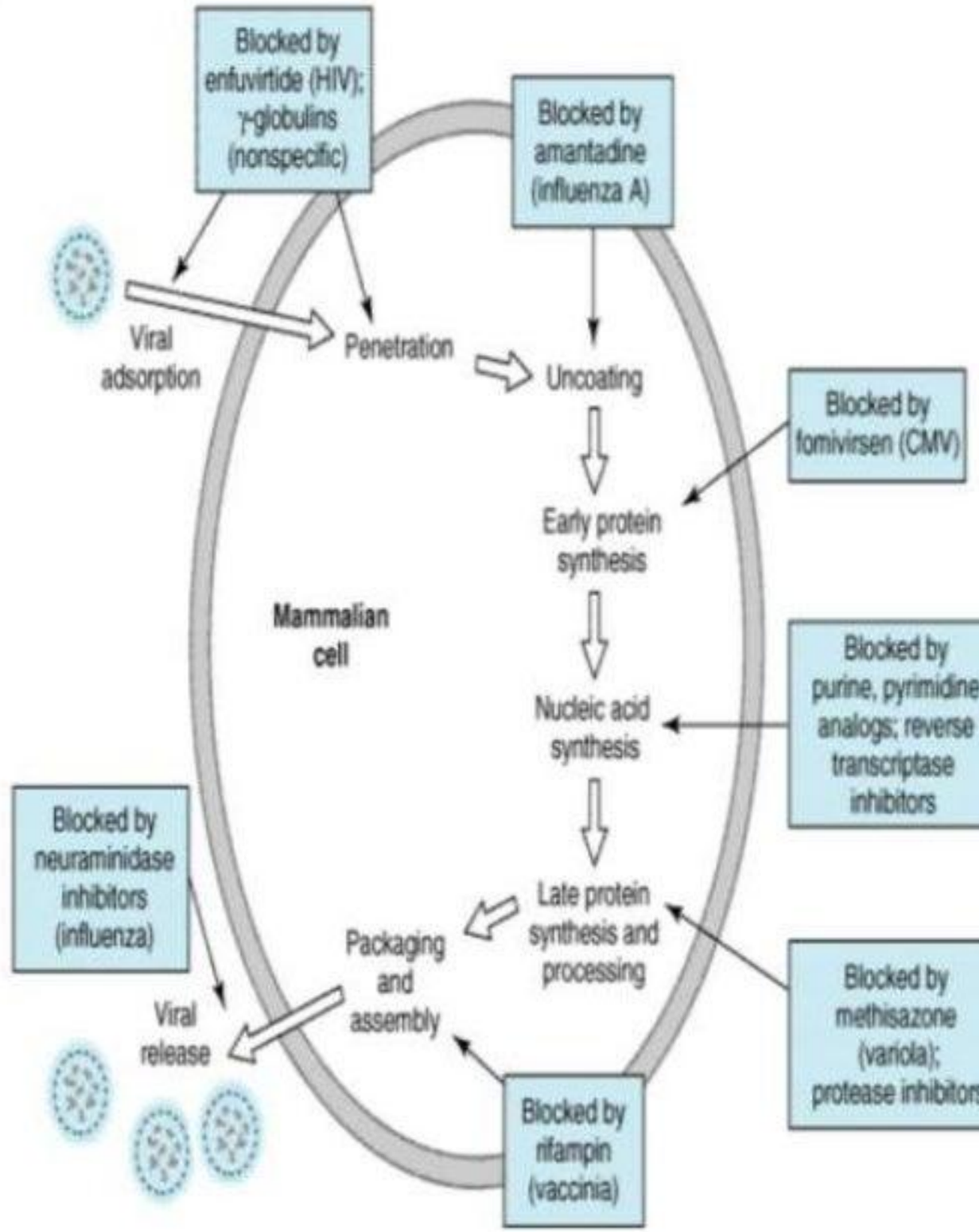
Virus-Introduction

- Viruses are obligate intracellular parasites
- Their replication depends primarily on synthetic processes of the host cell
- Effective antiviral agents inhibit virus-specific replicative events or preferentially inhibit virus-directed rather than host cell-directed nucleic acid or protein synthesis



Viral replication and sites of antiviral drug action





Classification of Antiviral Drugs

CLASSES	DRUGS
1. Anti-Herpes virus	Idoxuridine, Trifluridine Acyclovir, Valacyclovir, Famciclovir Ganciclovir, Valganciclovir Cidofovir Foscarnet Fomivirsen
2. Anti-influenza virus	Amantadine, Rimantadine Oseltamivir, Zanamivir
3. Anti-Hepatitis virus/Nonselective antiviral drugs	
a. Primarily for Hepatitis B	Lamivudine, Adefovir dipivoxil, Tenofovir
b. Primarily for Hepatitis C	Ribavirin, Interferon α

CLASSES	DRUGS
4. Anti-retrovirus	
a. Nucleoside reverse transcriptase inhibitors (NRTIs)	Zidovudine (AZT), Didanosine, Stavudine Lamivudine, Abacavir, Emtricitabine Tenofovir (Nt RTI)
b. Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	Nevirapine, Efavirenz, Delavirdine
c. Protease inhibitors	Ritonavir, Atazanavir, Indinavir, Nelfinavir Saquinavir, Amprenavir, Lopinavir
d. Entry (Fusion) inhibitor	Enfuvirtide
e. CCR5 receptor inhibitor	Maraviroc
f. Integrase inhibitor	Raltegravir

1. Anti-Herpes Virus
Acyclovir

❖ **Mechanism of action:**

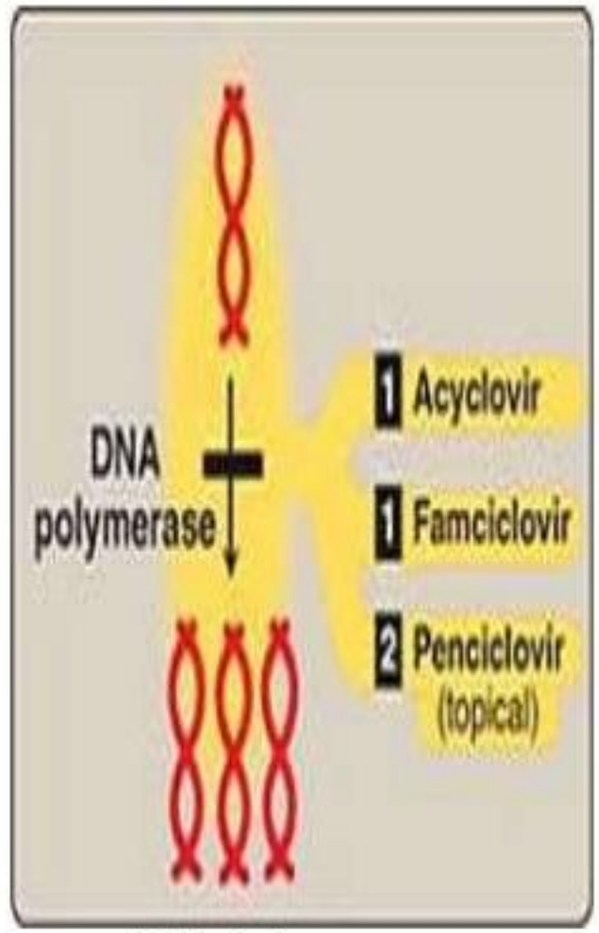
Acyclovir

↓ Herpes virus specific thymidine kinase

Acyclovir monophosphate

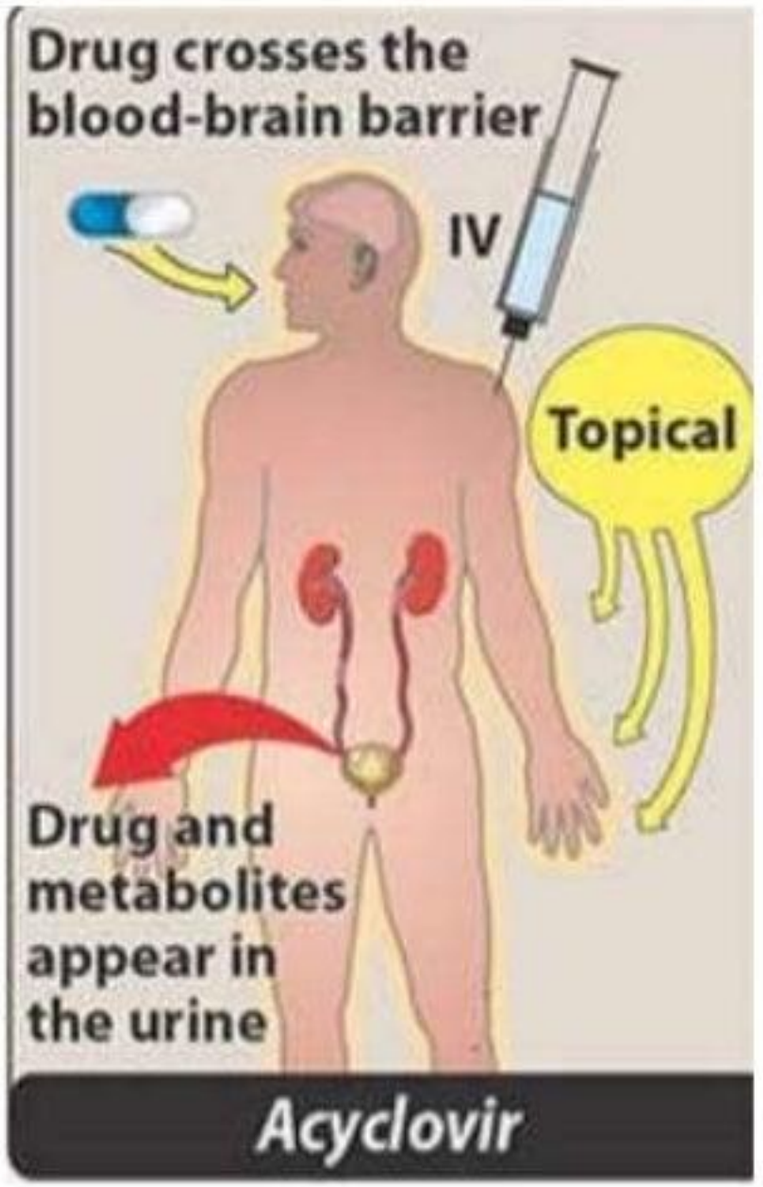
↓ Cellular kinases

Acyclovir triphosphate → Inhibits herpes virus DNA polymerase competitively



Gets incorporated in viral DNA and stops lengthening of DNA strand; the terminated DNA inhibits DNA-polymerase irreversibly

Acyclovir



❖ **Pharmacokinetics:**

- About 20% of an oral dose of acyclovir is absorbed
- Less plasma protein bound
- Primarily excreted unchanged in urine both by glomerular filtration and tubular secretion
- It accumulates in patients with renal failure
- Its plasma half life is 2-3 hours

Acyclovir

❖ Uses:

- Genital Herpes simplex
  Primary disease
  Recurrent disease
- Mucocutaneous H. simplex
- H. simplex encephalitis (type-1 virus)
- H. simplex keratitis
- Herpes zoster
- Chickenpox

❖ Adverse effects:

- Topical: stinging and burning sensation after each application
- Oral: Headache, nausea, malaise and some CNS effects
- Intravenous: Rashes, sweating, emesis, and fall in BP(in few)
- Dose dependent decrease in GFR (in renal failure)

Valacyclovir

- An ester prodrug of acyclovir
- Improved oral bioavailability due to active transport by peptide transporters in the intestine
- Drug of choice in herpes zoster
- High-dose can cause gastrointestinal problems and thrombotic thrombocytopenia purpura in patients with AIDS

FAMCICLOVIR

- An ester prodrug of penciclovir
- Used as an alternative to acyclovir for genital or orolabial herpes and herpes zoster
- Side effects are headache, nausea, loose motions, itching, rashes and mental confusion

Ganciclovir

- An analogue of acyclovir
- Active against all herpes viruses- *H. simplex*, *H. zoster,* EBV and CMV
- Its active metabolite attains higher concentration inside CMV cells (plasma $t_{1/2}$ >24 hrs)

❖ **Adverse effects:**

- Systemic toxicity is high (bone marrow toxicity, rash, fever, vomiting, neuropsychiatric disturbances)
- Note: Used only for prophylaxis and treatment of severe CMV infections in immunocompromised patients

Cidofovir

❖ **Mechanism of action:**

- It inhibits viral DNA synthesis. Its phosphorylation is not dependent on viral enzymes (viral phosphokinase) and is converted to the active diphosphate by cellular enzymes.
- Cidofovir diphosphate does not preferentially accumulate in virus infected cells, but remains intracellularly for long periods to inhibit viral DNA polymerase

❖ **Pharmacokinetics:**

- Available in intravenous, intravitreal (injection into the eye's vitreous humor between the lens and the retina), and topical administration

Cidofovir

❖ **Uses:**

- CMV-induced retinitis in patients with AIDS

❖ **Adverse effects:**

- Dose related kidney damage
- Neutropenia, metabolic acidosis, uveitis and ocular hypotony also occur
- **Note:** Probenecid must be coadministered with cidofovir to reduce the risk of nephrotoxicity, but probenecid itself causes rash, headache, fever, and nausea

❖ **Contraindications:**

- Patients with preexisting renal impairment
- Patients taking concurrent nephrotoxic drugs, including NSAIDS

Foscarnet

- It is not a purine or pyrimidine analog; phosphonoformate pyrophosphate derivative and does not require activation by viral (or human) kinases
- CMV retinitis in immunocompromised hosts
- Acyclovir-resistant HSV and herpes zoster infections

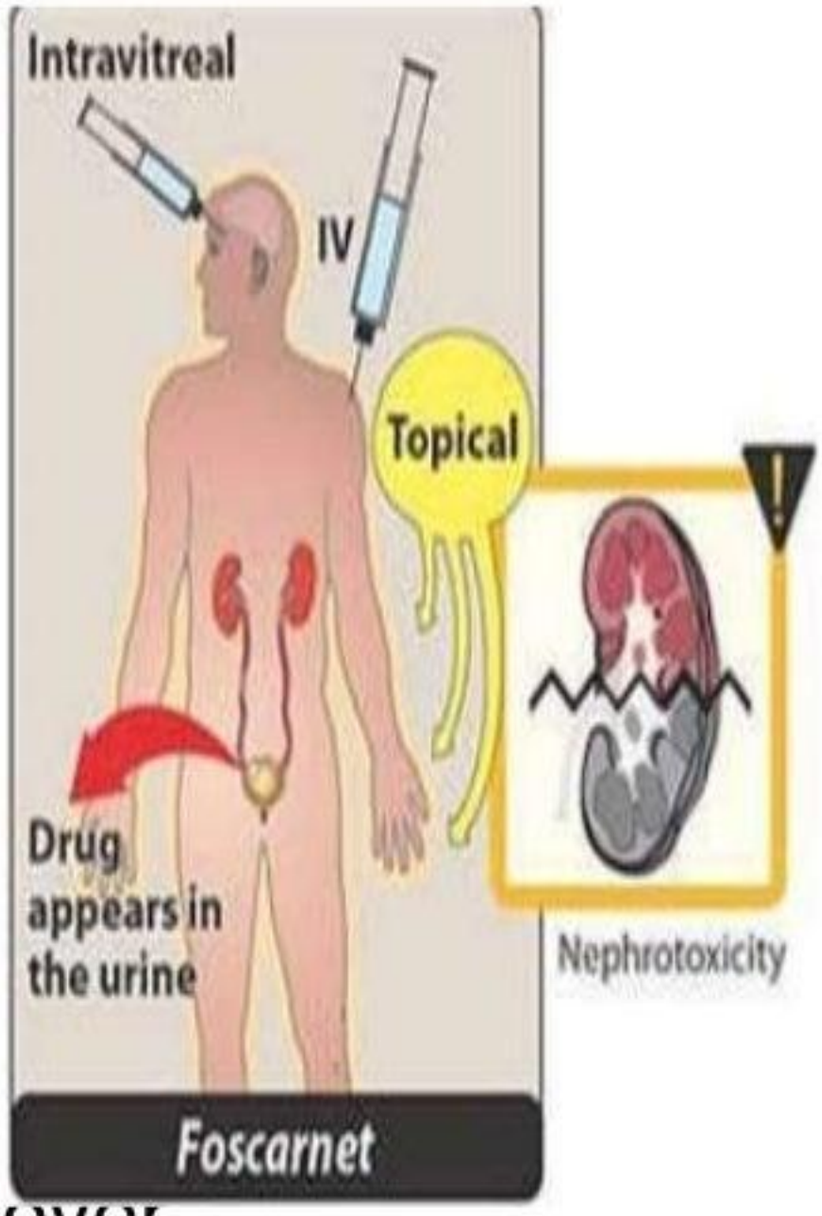
❖ **Mechanism of action:**

➢ It reversibly inhibits viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis

Foscarnet

❖ **Pharmacokinetics:**

- Poorly absorbed orally; intravenously
- Must also be given frequently to avoid relapse when plasma levels fall
- It is dispersed throughout the body; >10% enters the bone matrix
- Excreted into the urine



❖ **Adverse effects:**

- Nephrotoxicity, anemia, nausea, and fever
- Hypocalcemia and hypomagnesemia
- Hypokalemia, hypo- and hyperphosphatemia
- Seizures and arrhythmias

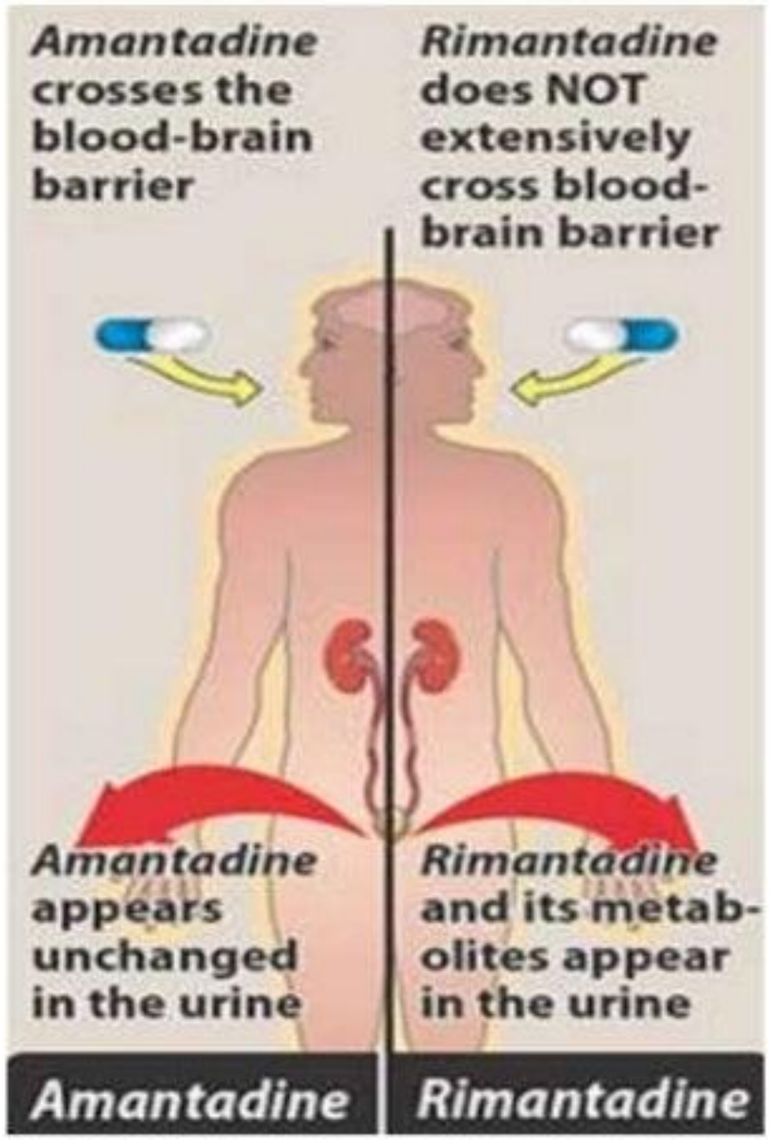
2. Anti-influenza virus
Amantadine

- Its antiviral activity is strain specific = inhibits replication of influenza A virus but not influenza B

❖ **Mechanism of action:**

- ➢ It acts at uncoating as well as viral assembly in viral replication
- ➢ Blocks the viral membrane matrix protein, M2, which functions as a channel for hydrogen ion
- ➢ This channel is required for the fusion of the viral membrane with the cell membrane that ultimately forms the endosome (during internalization of the virus by endocytosis)

Amantadine



❖ **Pharmacokinetics:**

- Well absorbed orally and excreted unchanged in urine over 2-3 days

❖ **Adverse effects:**

- Nausea, anorexia, insomnia, dizziness, nightmares, lack of mental concentration
- Hallucinations (rarely)
- Ankle edema (local vasoconstriction)

Amantadine

❖ **Uses:**

- Prophylaxis of influenza A2 during an epidemic or seasonal influenza (~ 2 months)
- Treatment of influenzal (A2) illness

➢ Reduction in fever, congestion, cough and quicker recovery

➢ Parkinsonism

❖ **Contraindications:**

- Epilepsy and other CNS disease; gastric ulcer, pregnancy

Rimantadine

- Methyl derivative of amantadine
- More potent, longer acting ($t_{1/2}$ 30 hours) and better tolerated
- Side effects is lower
- Oral bioavailability is higher and it is largely metabolized by hydroxylation followed by glucuronide conjugation
- Metabolites are excreted in urine

Oseltamivir

- Influenza A (amantadine sensitive as well as resistant), H5N1 (bird flu), nH1N1 (swine flu) strains and influenza B
- An ester prodrug; rapidly and nearly completely hydrolysed during absorption in intestine and by liver to the active form oseltamivir carboxylate (an oral bioavailability of ~ 80%)
- Active metabolite is excreted unchanged by the kidney
- t½ of 6–10 hours

Oseltamivir

❖ **Mechanism of action:**

➢ Neuraminidase enzyme ✕ **Oseltamivir**

↓

Release of progeny virions from the infected cell

↓

Spread of the virus in the body

❖ **Uses:**

- Prophylaxis and treatment of influenza A, swine flu, bird flu and influenza B