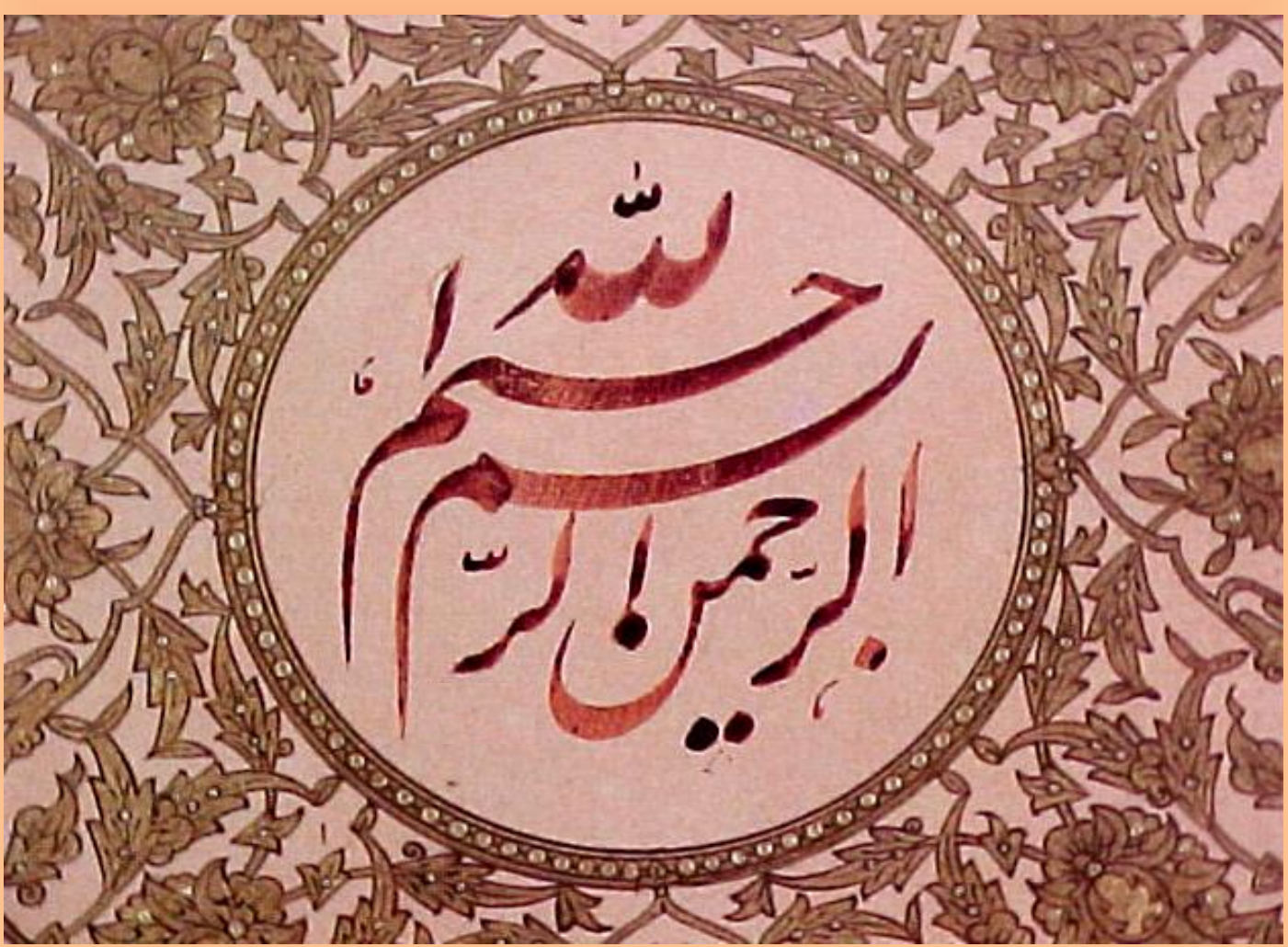
بسم الله الرحمن الرحيم

Antiviral drugs

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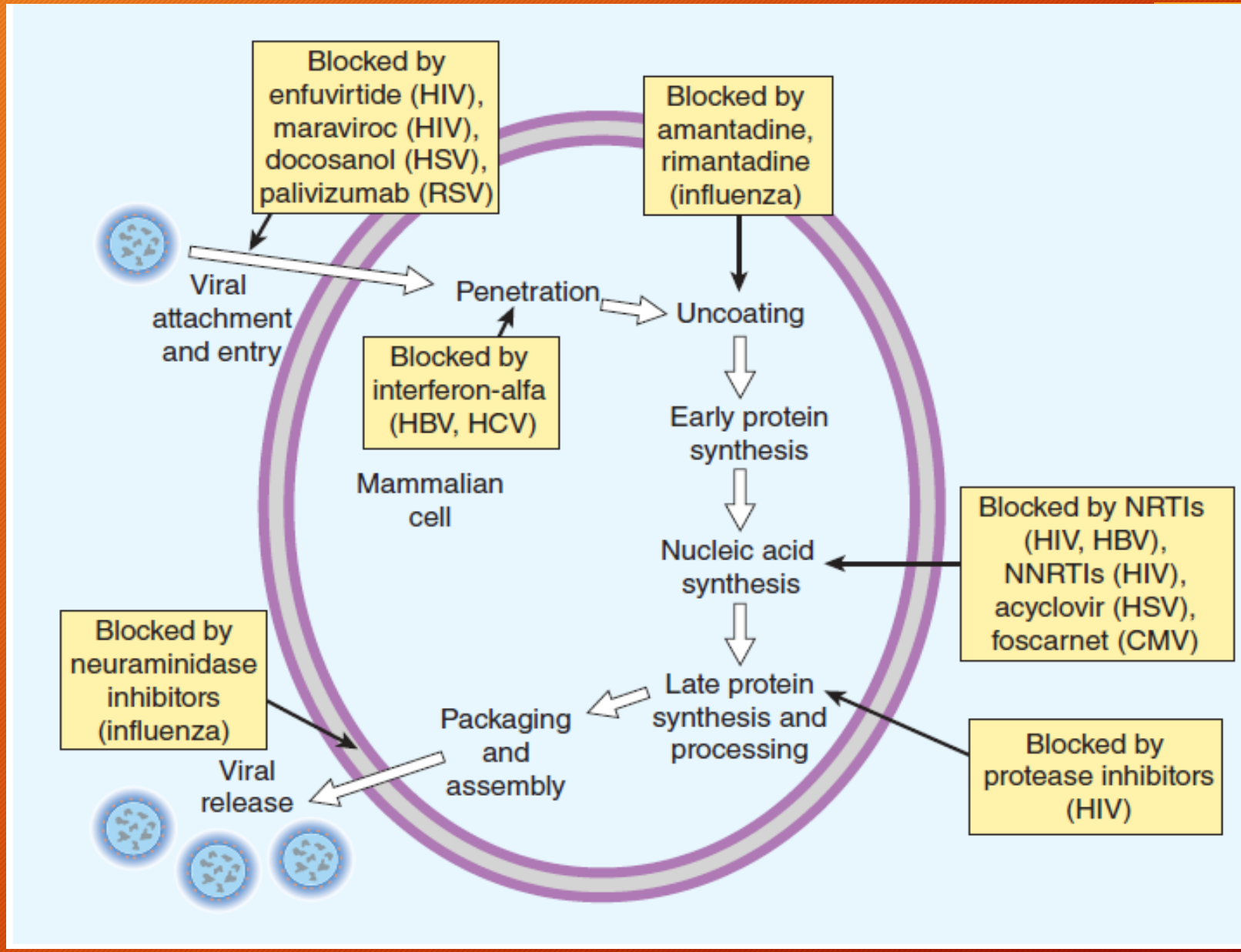
Viral infections

- Common causes of human disease.

- 60% of illnesses result from viruses.
- 15% of illnesses result from bacteria.

- Upper respiratory tract infections:
  - Common cold
  - Influenza

One of the most common reasons for visits to a doctor


Blocked by enfuvirtide (HIV), maraviroc (HIV), docosanol (HSV), palivizumab (RSV)
Blocked by amantadine, rimantadine (influenza)
Viral attachment and entry
Penetration
Uncoating
Blocked by interferon-alfa (HBV, HCV)
Early protein synthesis
Mammalian cell
Nucleic acid synthesis
Blocked by NRTIs (HIV, HBV), NNRTIs (HIV), acyclovir (HSV), foscarnet (CMV)
Blocked by neuraminidase inhibitors (influenza)
Late protein synthesis and processing
Packaging and assembly
Viral release
Blocked by protease inhibitors (HIV)

Important Antiviral Drugs

Virus	Primary Drugs	Alternative or Adjunctive Drugs
CMV	Ganciclovir, valganciclovir	Cidofovir, foscarnet, fomivirsen
HSV, VZV	Acyclovir[a]	Cidofovir, foscarnet, vidarabine
HBV	IFN-α, lamivudine	Adefovir dipivoxil, entecavir, lamivudine, telbivudine
HCV	IFN-α, sofosbuvir	Ribavirin
Influenza A	Oseltamivir	Amantadine, rimantadine, zanamivir
Influenza B	Oseltamivir	Zanamivir

[a]Anti-HSV drugs similar to acyclovir include famciclovir, penciclovir, and valacyclovir; IFN-α, interferon-α.

ANTIHERPES DRUGS

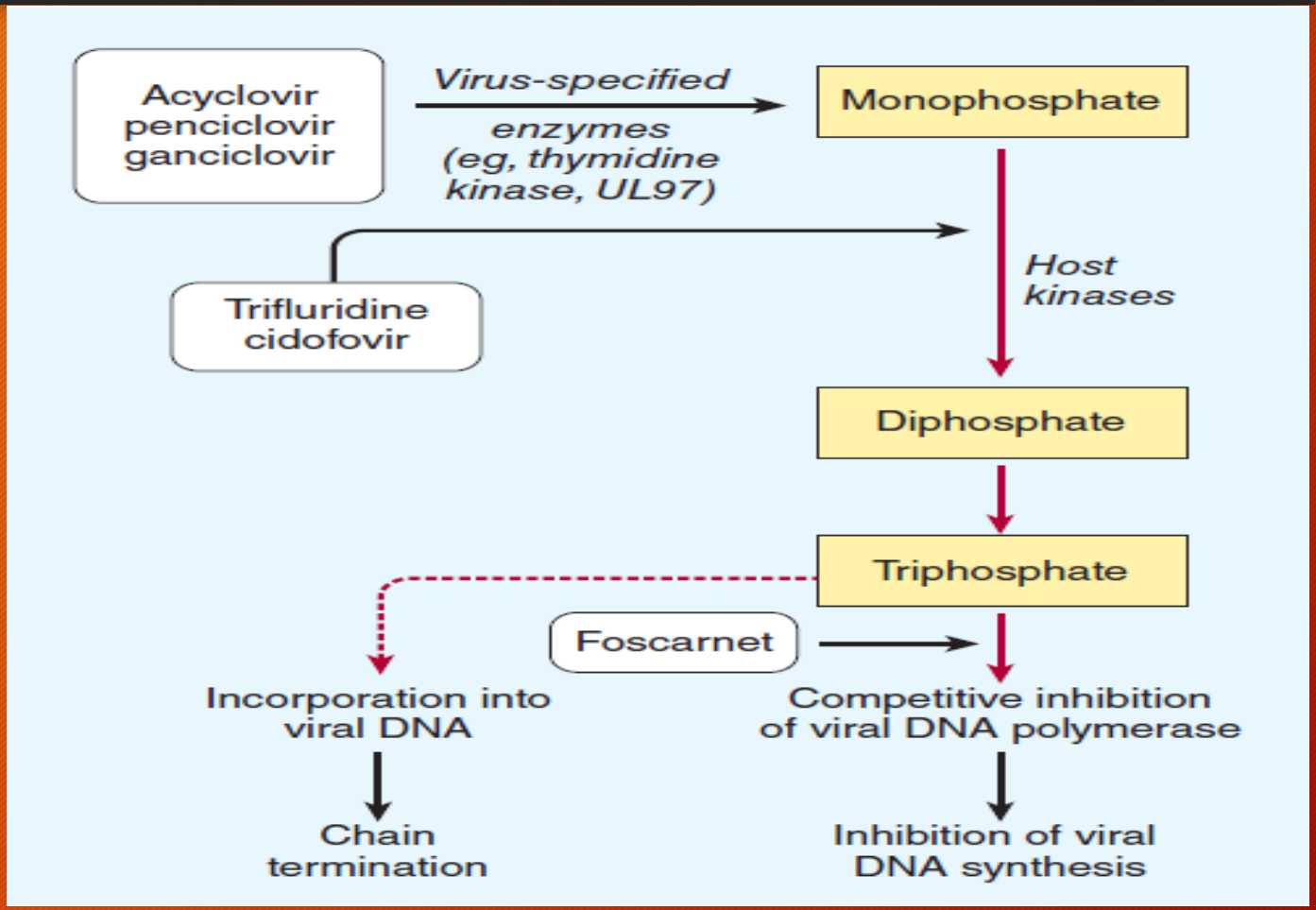
- **Aciclovir**

Powder for injection 250 , 500 mg
Tablet 200 , 400 , 800 mg
Ophtalmic ointment 3%
Topical cream 5%

- **Ganciclovir**

Powder for injection 500 mg

ANTIHERPES DRUGS



ANTIHERPES DRUGS

- Acyclovir$(PO_4)_3$ competitively inhibits:
- ***viral DNA polymerases*** → much further
- ***cellular DNA polymerases*** → much lesser

- **Acyclovir:**
- ***irreversible DNA polymerase inhibitor***

ANTIHERPES DRUGS

- Oral bioavailability → 10-30%
- Percutaneous absorption → low
- Distribution → wide (body fluids, CSF)
- Salivary concentrations → low
- Mean half-life:
  - Adult → 2.5 hours (1.5-6 h)
  - Neonates → 4 hours
  - Anuric patients → 20 hours (dose adjust is nedded)

Adverse effects

- **Oral acyclovir:**
  - **Nausea, diarrhea**
  - **Rash, headache**
  - **Renal insufficiency**
  - **Neurotoxicity**
  - **Neutropenia (in neonates)**

Adverse effects

- **I.V. acyclovir:**
  - **Renal insufficiency** (5%)
  - **CNS side effects** (1-4%)

Topical acyclovir

Topical cream 5%
Eye ointment 3%

↓

HSV (Herpes simplex virus)

Type 1 (herpes labialis)

Oral acyclovir (tab. 200, 400, 800 mg)

HSV (Herpes simplex virus)

Type 1 (herpes labialis = orolabial herpes)
Type 2 (herpes genitalis) 1st episode & recurrent
Mucocutaneous herpes in the immunocompromised

VZV (Varicella-zoster virus)

Varicella → Chicken pox
Herpes zoster → Shingles

Anti-CMV drugs

- Ganciclovir
- Valganciclovir

Anti-CMV drugs (Ganciclovir)

- Mechanisms :inhibits DNA polymerases of CMV
- Pharmacokinetics:it is usually given as IV, and penetrates well into tissues (CNS, EYE), bioavailability less than 10%, can also be used orally.

Valganciclovir is a prodrug of ganciclovir, has high oral bioavailability, can be used in CMV retinitis

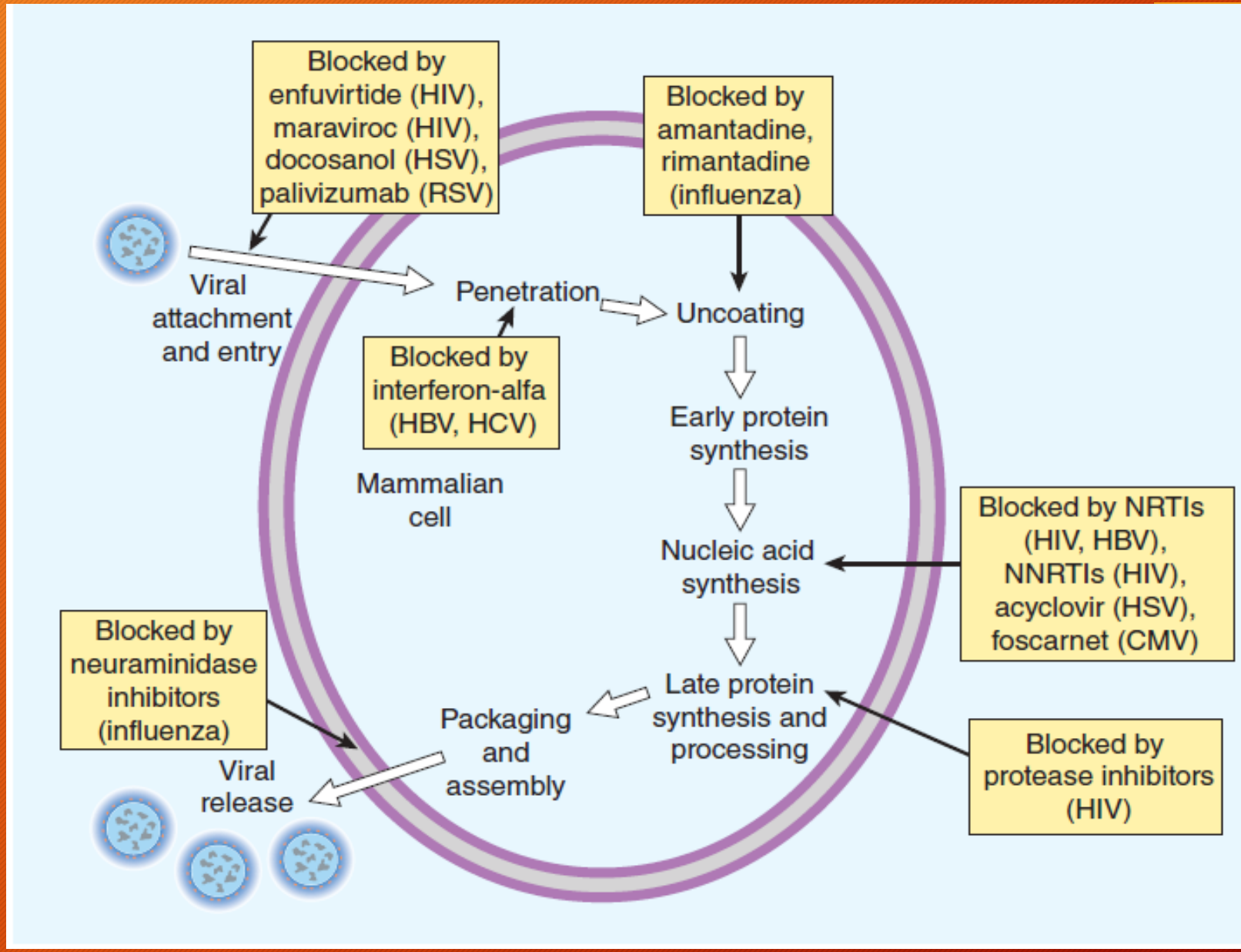
Anti-CMV drugs (Ganciclovir)

- Clinical uses and toxicity:

used for the prophylaxis and treatment of CMV retinitis and other CMV infections. Systemic toxic effects include leukopenia, thrombocytopenia, mucositis, hepatic dysfunction, and seizures. The drug may cause severe neutropenia when used with zidovudine

ANTI-INFLUENZA AGENTS

- **Amantadine**
- **Rimantadine**
- **Oseltamivir**
- **Zanamivir**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Amantadine

- Best time for administrarion: 24 hours

Dose → 100 mg (1 capsule) daily → 5 days

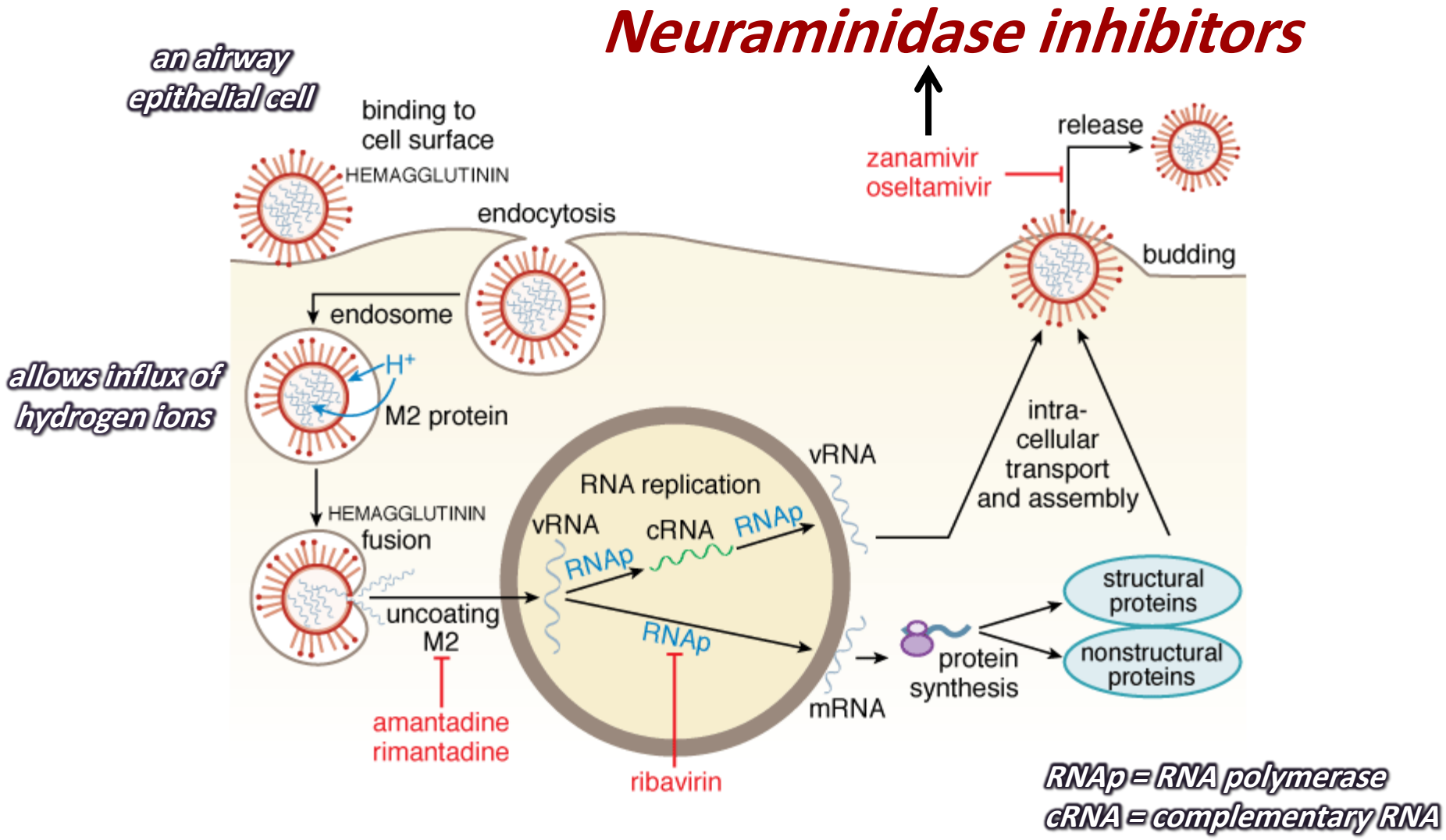
- Clinical efficacy → ↓ duration of disease (type A)
- Prophylaxis against infected individuals
- Other pharmacological effects:
- DA-receptor agonist, anticholinergic
- Rimantadine's activity is same as amantadine, but has a longer half-life and not dose adjust in renal failur
- Side effects → GI irritation, dizziness, ataxia, insomnia, seizure, anticholinergic effects

Anti-influenza agents

- **Zanamivir** (Relenza)

- **Oseltamivir** (Tamiflu)
  - It is a prodrug
  - Active metabolite: oseltamivir carboxylate

Neuraminidase → a viral surface enzyme
It is necessary for releasing the progeny virus



Anti-influenza agents

- **Zanamivir** (Relenza)

Inhaler 5 mg/Blister

- **Oseltamivir** (Tamiflu)

Capsule 30 , 45 , 75 mg
Powder for solution 60 mg/5ml

Best time for administration

within 48 hours after the onset of symptoms

Oseltamivir

Dose → 75 mg, twice daily → 5 days

Zanamivir

Dose → 10 mg, twice daily → 5 days

Oseltamivir, Zanamivir

- **Clinical efficacy:**
  - ↓ duration of disease (influenza A,B)
  - Prophylaxis against infected individuals

- **Side effects:**
  - headache, dizziness, insomnia
  - Nausea, vomiting, diarrhea, cramp, cough
  - **Zanamivir** → ***Respiratory depression***

Contraindication

Oseltamivir

Should not be used in infants (< 1 year)

Zanamivir

Patients with asthma or COPD
Children < 7 years old

Anti-influenza drugs

- Amantadine

↓

Uncoating inhibitor
Influenza A

- Oseltamivir
- Zanamivir

↓

Neuraminidase inhibitor
Influenza A , B

AGENTS USED IN VIRAL HEPATITIS

- The agents available for use in the treatment of infections caused by HBV are suppressive rather than curative
- The primary goal of drugs used for infections caused by HCV is viral eradication
- The drugs available include interferon-α (IFN-α), lamivudine, adefovir dipivoxil, entacavir, telbivudine, tenofovir, ribavirin, and sofosbuvir

AGENTS USED IN VIRAL HEPATITIS

IFN-α

Mechanisms: IFN-α is a cytokine that acts to increase the formation of antiviral proteins. It activates a host cell ribonuclease that preferentially degrades viral mRNA. IFN-α also promotes formation of natural killer cells that destroy infected liver cells

Pharmacokinetics: it is used IV or SC, its elimination from kidney. It can be administered once a week

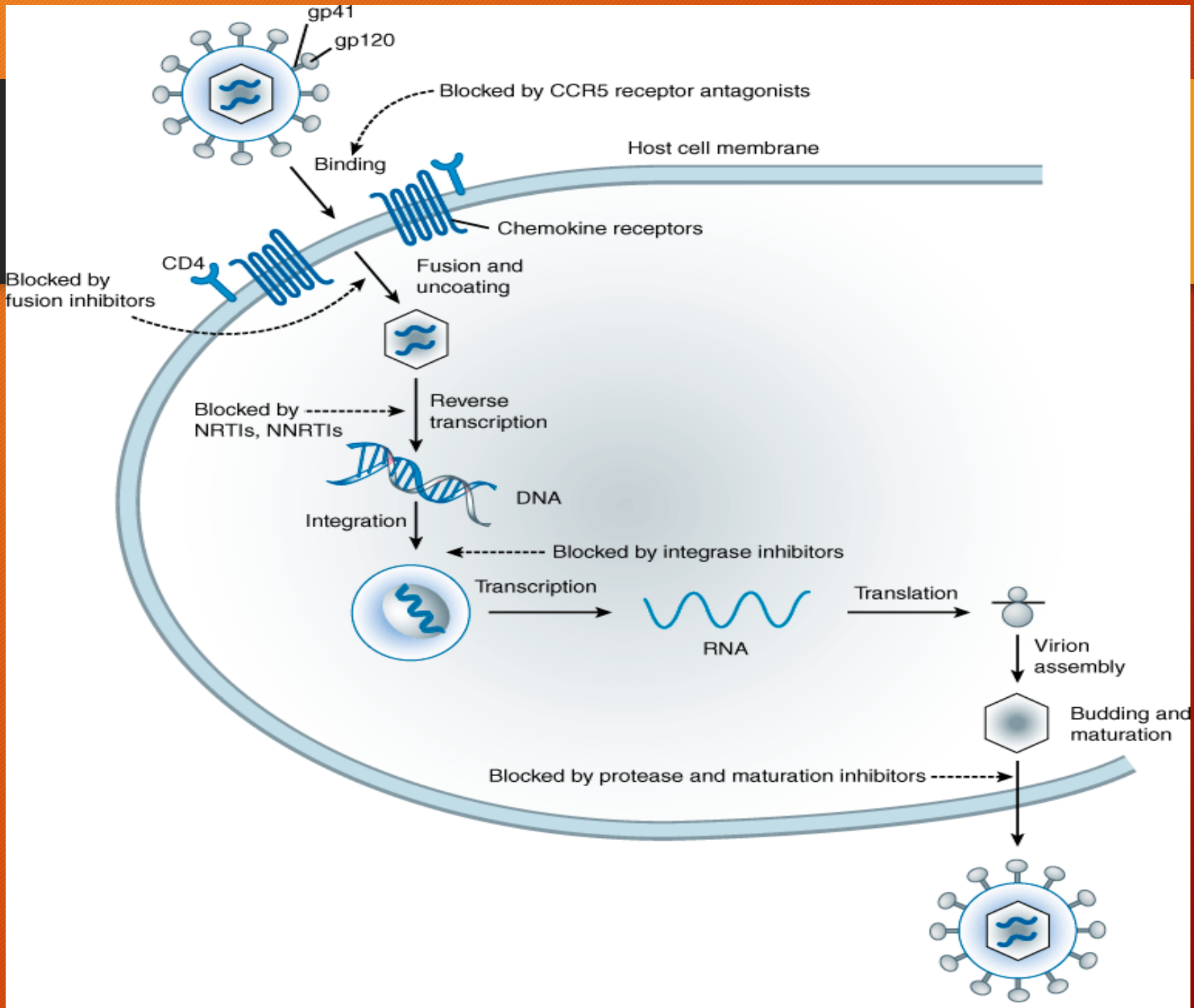
AGENTS USED IN VIRAL HEPATITIS

IFN-α

Clinical uses: Interferon-α is used in chronic HBV as an individual agent or in combination with other drugs. When used in combinations with ribavirin, the progression of acute HCV infection to chronic HCV is reduced. Pegylated IFN-α together with ribavirin is superior to standard forms of IFN-α in chronic HCV.
Toxicity:GI irritation, a flu-like syndrome, neutropenia, reversible hearing loss, thyroid dysfunction, mental confusion, and severe depression. No use in pregnancy.

Anti-HIV agents

- NRTIs
  - Nucleoside Reverse Transcriptase Inhibitors
- NNRTIs
  - Non-Nucleoside Reverse Transcriptase Inhibitors
- Protease inhibitors


gp41
gp120
Blocked by CCR5 receptor antagonists
Binding
Host cell membrane
Chemokine receptors
CD4
Blocked by
fusion inhibitors
Fusion and
uncoating
Blocked by
NRTIs, NNRTIs
Reverse
transcription
DNA
Integration
Blocked by integrase inhibitors
Transcription
RNA
Translation
Virion
assembly
Budding and
maturation
Blocked by protease and maturation inhibitors

NRTIs

- Zidovudine (AZT)
- Didanosine (ddI)
- Lamivudine (3TC)
- Stavudine (d4T)
- Adefovir

NRTIs

- Each agent requires intracytoplasmic activation via phosphorylation by cellular enzymes to the triphosphate form.

- there is no cross-resistance between the NNRTIs and the NRTIs

Adverse effects of NRTIs

- All NRTIs may be associated with mitochondrial toxicity, probably owing to inhibition of mitochondrial DNA polymerase gamma.
- Less commonly, lactic acidosis with hepatic steatosis may occur, which can be fatal.

Adverse effects of NRTIs

- Myopathy
- Rapidly rising ALT/AST levels
- Progressive hepatomegaly
- Metabolic acidosis
- Pancreatitis

NNRTIs

- Nevirapine
- Efavirenz
- Delavirdine

Sever adverse effects
Drug-drug interaction

NNRTIs

- Bind directly to reverse transcriptase resulting in inhibition of RNA- and DNAdependent DNA polymerase activity.
- The binding site of NNRTIs is near to but distinct from that of NRTIs.

- Unlike the NRTI agents, NNRTIs:
  - Do not compete with nucleoside triphosphates
  - Do not require phosphorylation to be active.

Adverse effects of NNRTIs

- **GI intolerance**
- **Skin rash** (even Stevens-Johnson syndrome)
- **All NNRTI agents are substrates for CYP3A4 and can act as:**
- **inducers (nevirapine)**
- **inhibitors (delavirdine)**

Protease inhibitors

- Lopinavir
- Ritonavir
- Nelfinavir
- Indinavir

Protease inhibitors

- Lopinavir
- Ritonavir
- Nelfinavir
- Indinavir

Sever adverse effects
Drug-drug interaction

Adverse effects of PIs

- GI intolerance
- Bleeding
- Hyperglycemia
- Insulin resistance
- Hyperlipidemia
- Hepatitis
- Metabolic syndrome

Drugs of choice

- HSV , VZV ..... Aciclovir
- CMV ..... Ganciclovir
- HBV , HCV ..... INF α-2b
- HIV..... 2 NRTIs + 1 PI
- Influenza A ..... Amantadine
- Influenza A , B ... Oseltamivir