Antiviral drugs

Prepared by

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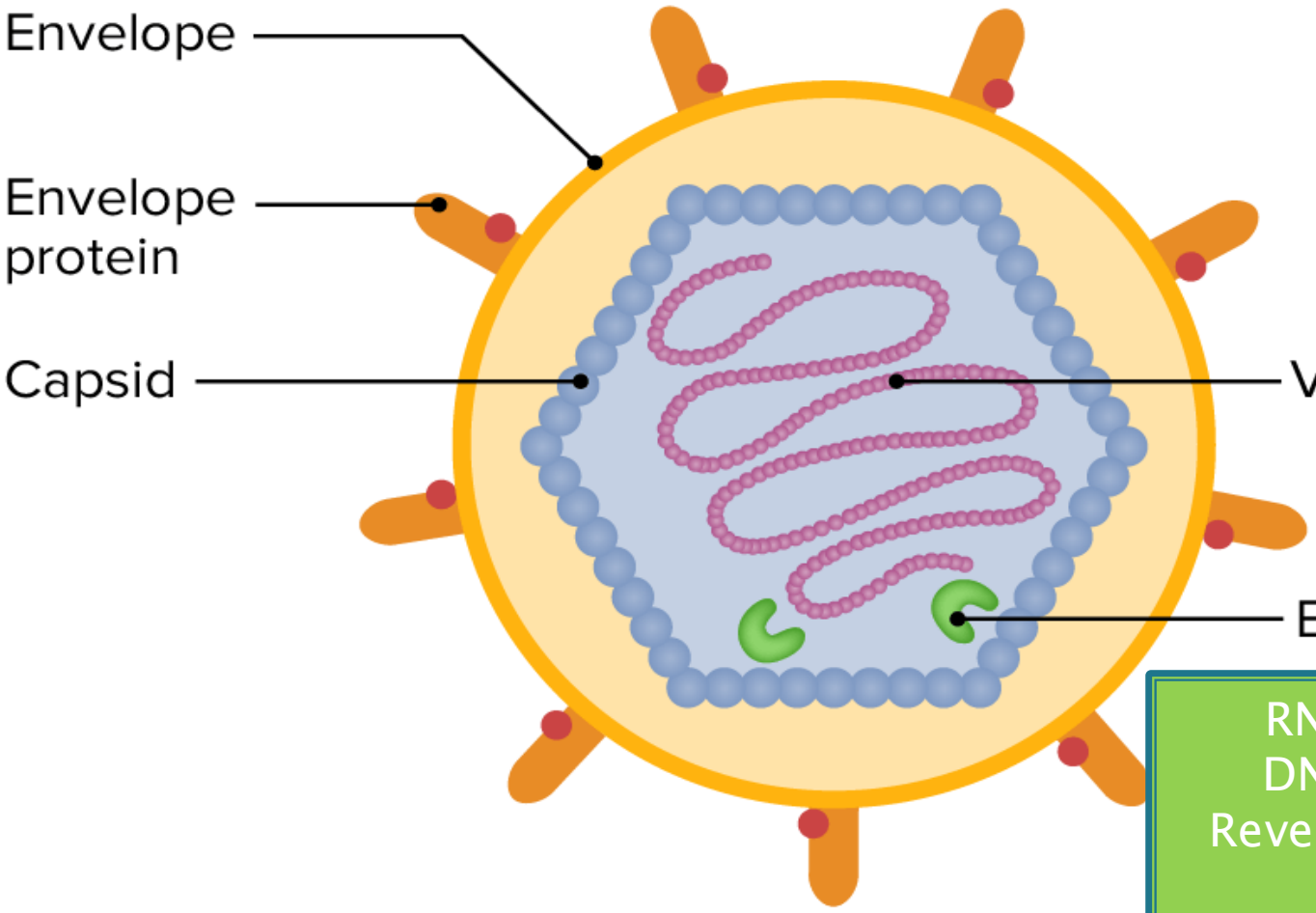
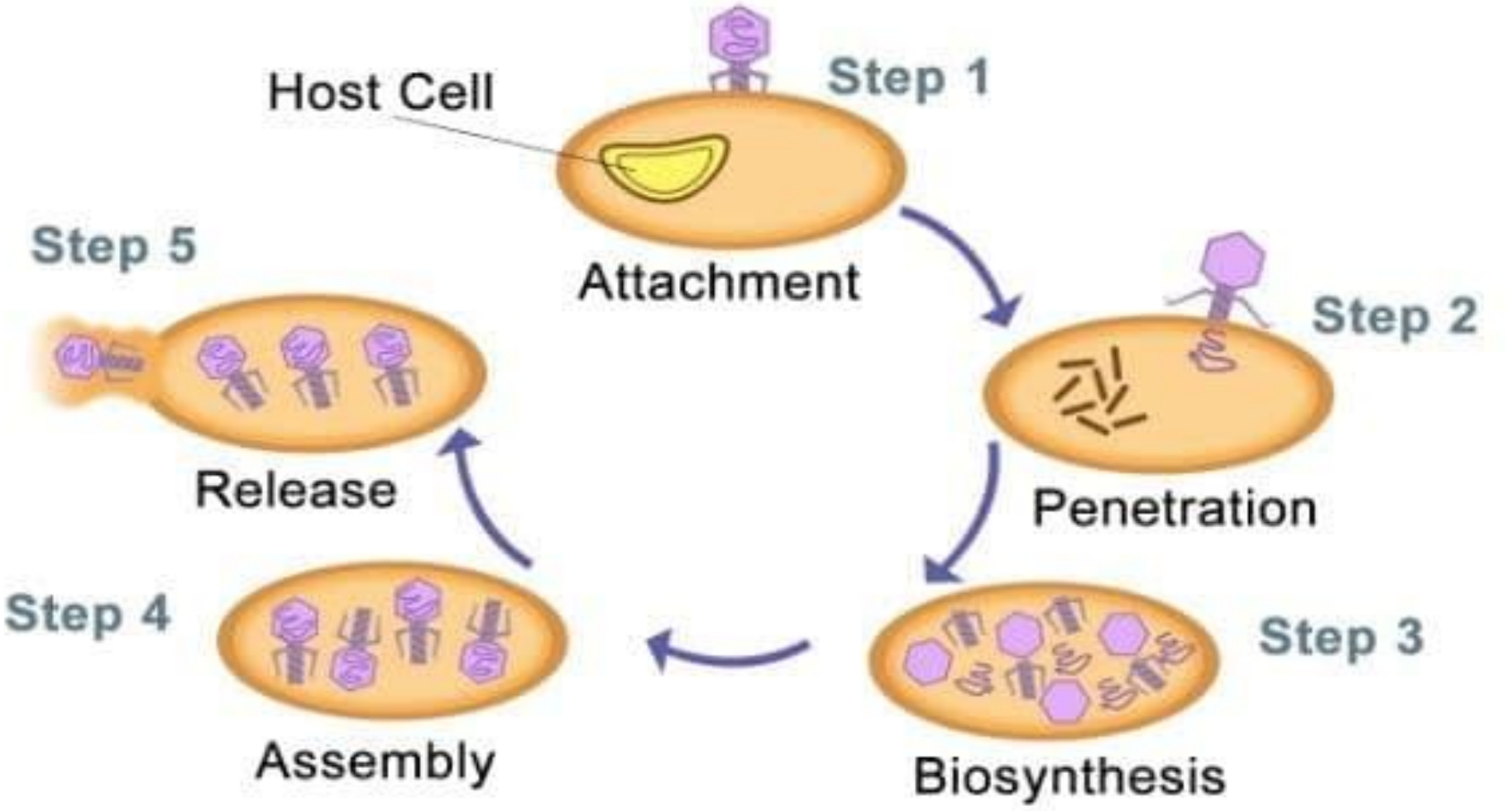
Virus structures

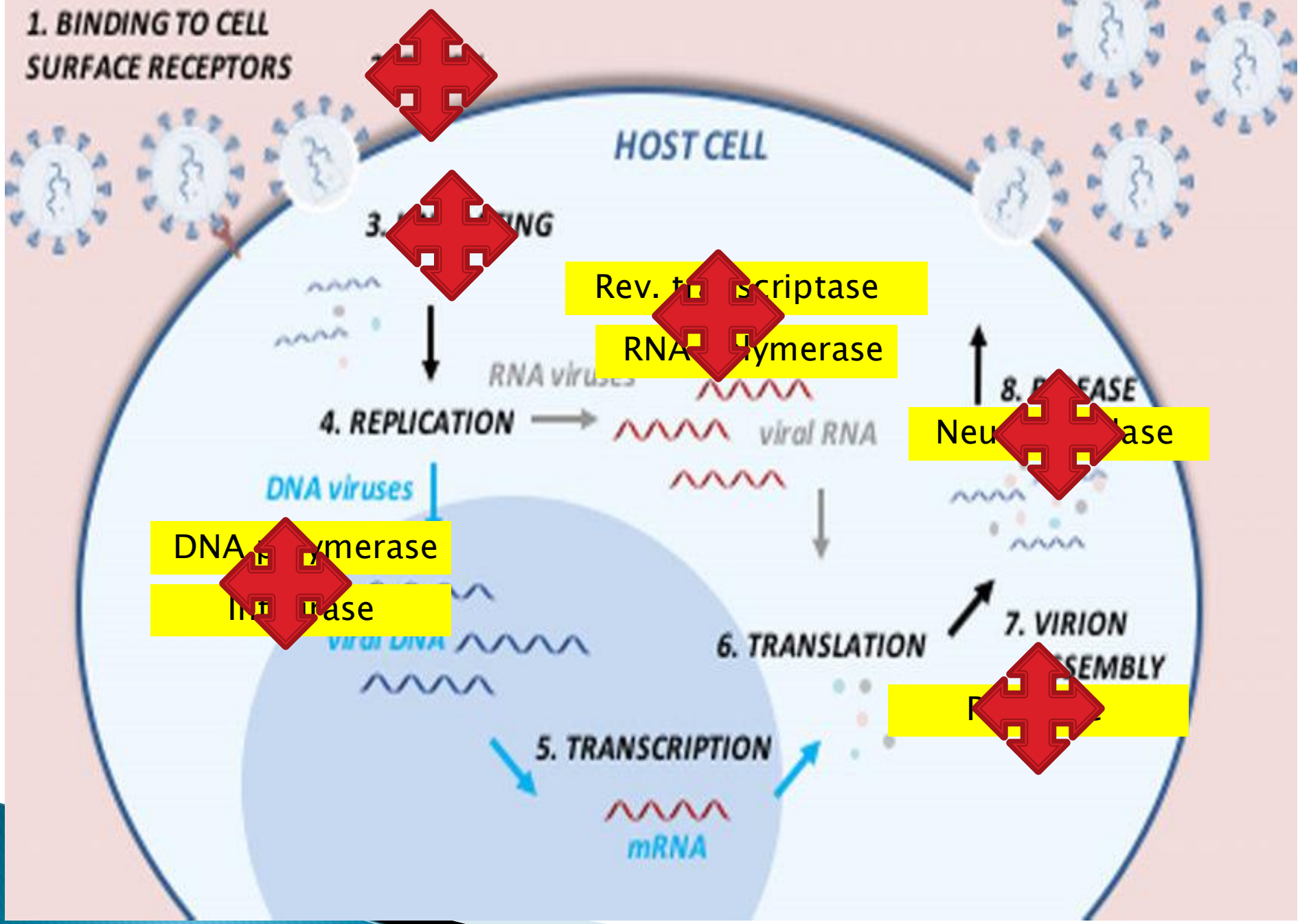


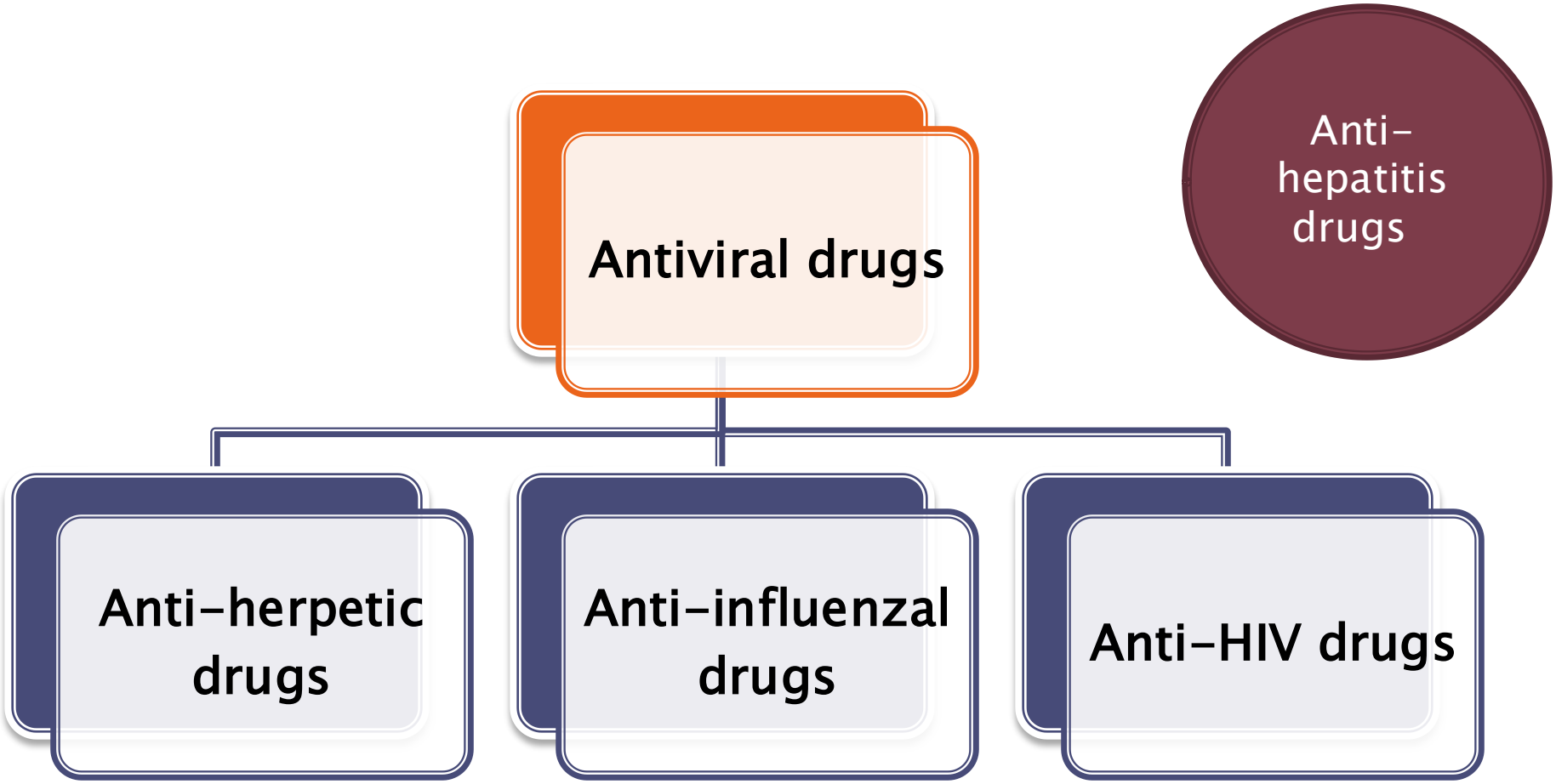
RNA OR DNA GENOME

RNA polymerase
DNA polymerase
Reverse transcriptase
Integrase
Protease
Neuraminidase

Steps of virus replication




1. BINDING TO CELL SURFACE RECEPTORS
HOST CELL
Rev. t scriptase
RNA ymerase
RNA viruses
4. REPLICATION
viral RNA
8. EASE
Neu ase
DNA viruses
DNA ymerase
ase
6. TRANSLATION
7. VIRION
SEMBLY
5. TRANSCRIPTION
mRNA

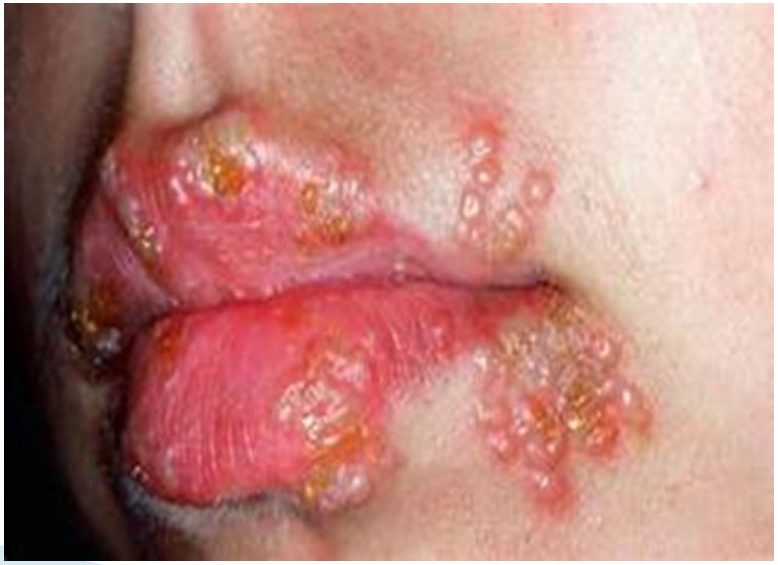

Antiviral drugs
Anti-herpetic drugs
Anti-influenzal drugs
Anti-HIV drugs
Anti-hepatitis drugs

-Anti-herpetic drugs (DNA VIRUS)

1-Acyclovir, famciclovir, valacyclovir

2-Ganciclovir, Valganciclovir

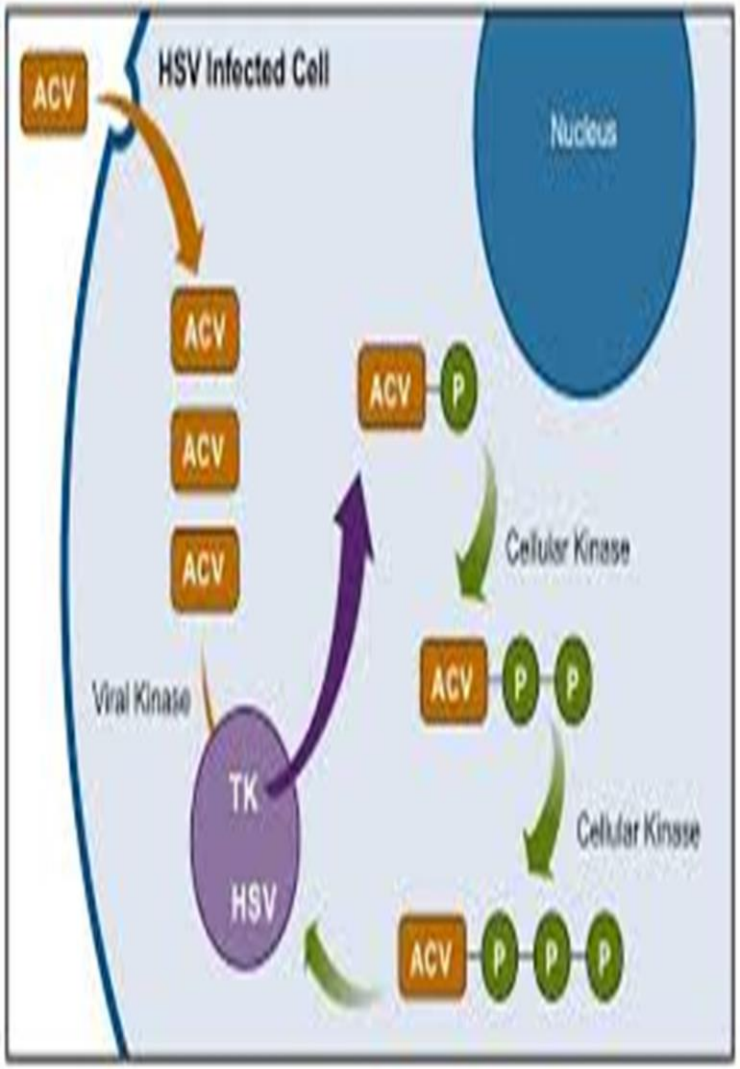
3-Foscarnet



1-Acyclovir- famciclovir- valacyclovir

Activation **Guanosine analogs**

- Mono-phosphorylated by HSV/VZV thymidine kinase (TK) (not phosphorylated in uninfected cells → few adverse effects).
- They are further activated by host-cell kinases to the triphosphates



Mechanism of action

- Triphosphates are substrates for viral **DNA polymerase** → incorporated into the DNA molecule → chain terminations

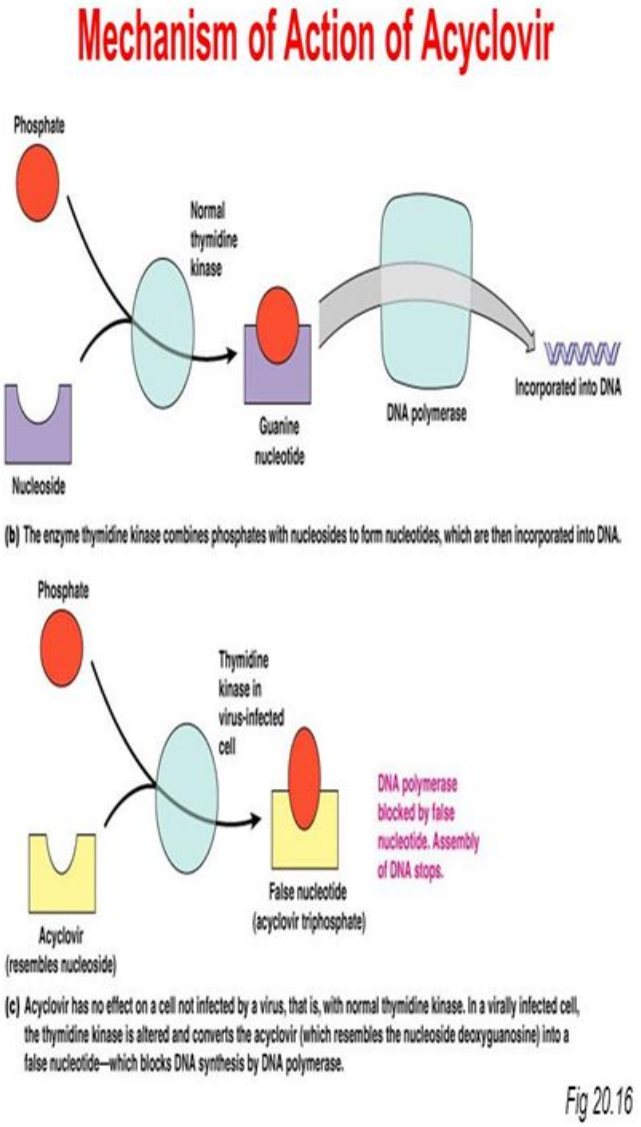


Fig 20.16

- **Clinical uses:**
  - ✓ Treatment of herpes simplex (1,2) and varicella zoster virus infections **(drug of choice)**
  - ✓ Prophylaxis in immunocompromised patients
- **Toxicity**
  - ✓ Crystalluria & nephropathy so Maintain good hydration

Notes

- ❖ No role in post-herpetic neuralgia
- ❖ Valacyclovir is a prodrug of acyclovir (oral=IV acyclovir)
- ❖ For herpes zoster, use famciclovir

2-Ganciclovir

Activation: Monophosphorylated by CMV kinase → effective against CMV.

Mechanism of action: Like acyclovir.

Clinical uses:

- ✓ Treatment & prophylaxis of **cytomegalic virus infection** (especially immuno-compromized patients).

Toxicity:

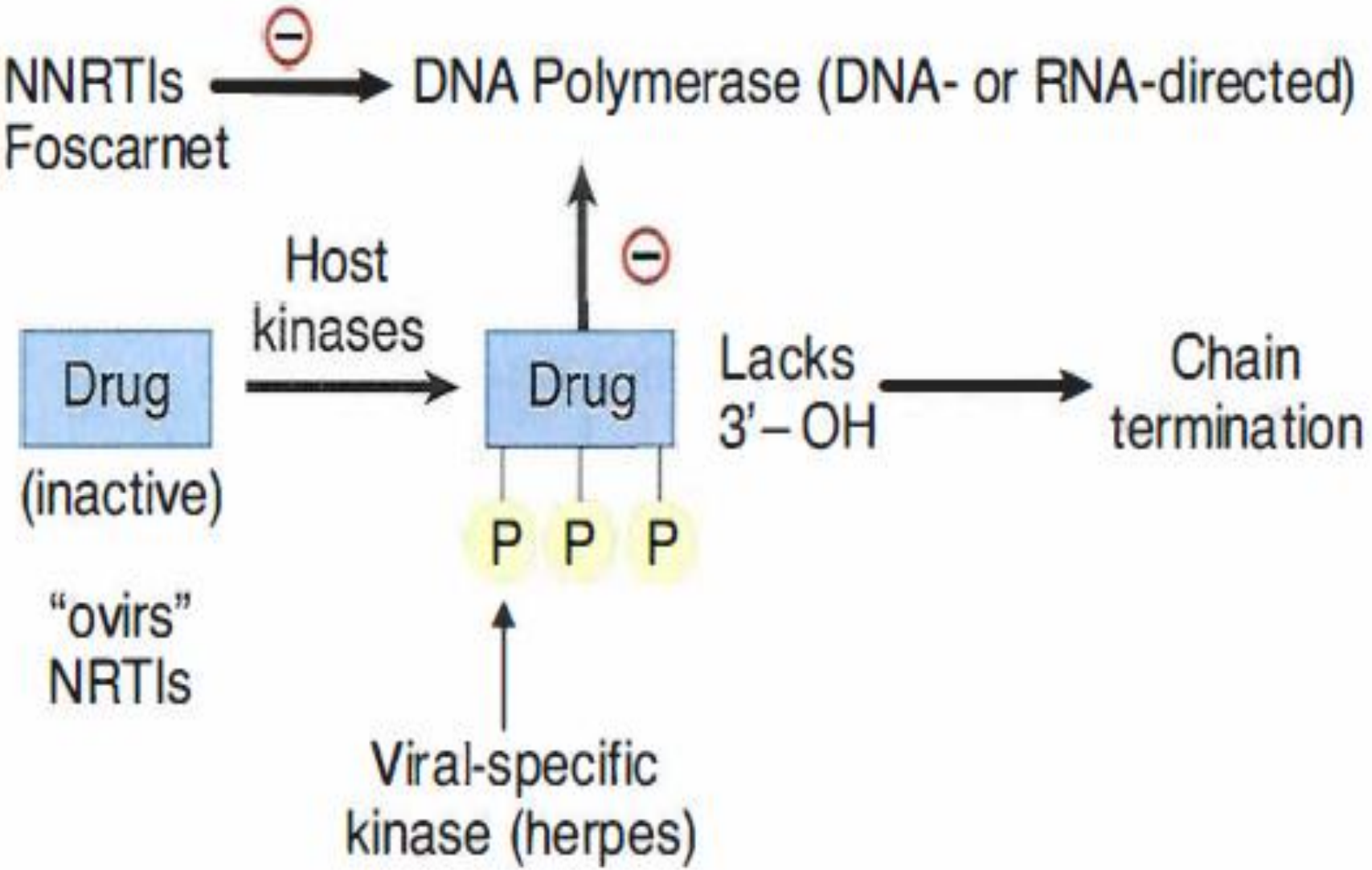
- Myelo-suppression (Leucopenia, thrombocytopenia).
- Nephropathy

Notes:

- ❖ **Valganciclovir** is a prodrug with **better bioavailability** (oral replacement for IV ganciclovir)

3-Foscarnet

- ✓ Doesn't require activation by viral or human kinases
- **Mechanism of action:**
  - ✓ Inhibition(-) of Viral DNA polymerase
  - ✓ (-) RNA polymerase
  - ✓ (-) HIV reverse transcriptase
- **Clinical uses:**
  - ✓ Ganciclovir-resistant **CMV infection**
  - ✓ Acyclovir-resistant **HSV infection**
- **Toxicity:**
  - ✓ Nephrotoxicity
  - ✓ Electrolyte disturbances that may cause seizures (hypocalcemia & hypomagnesemia)



Common Mechanism for "ovirs" and NRTIs

Anti influenza
(RNA VIRAL)

- Amantadine & rimantadine
- Oseltamivir & Zanamivir
- Baloxavir & marboxil

1-Amantadine & Rimantadine

- **Mechanism of action:**
  - ✓ Block attachment (M2 proton channel blocker) , penetration, and uncoating of influenza A virus
- **Clinical uses:**
  - ❖ Influenza A prophylaxis (no longer useful due to high resistance).
  - ❖ Adjuvant anti-Parkinsonian effect (with rapid tolerance).
- **Toxicity:**
  - ✓ Nervousness, Insomnia, Seizures with overdose, and Atropine-like action

2-Oseltamivir & Zanamivir

- **Mechanism of action:**

inhibit neuraminidases of influenza A & B ➔ viral clumping ➔ prevents new viral particles from being released in the body.

- **Clinical uses:**
  - Prevention & treatment of influenza A & B (48h)

Side effects:

Oseltamivir: nausea, vomiting, headache

Zanamivir: bronchospasm (avoid in asthma/COPD)

Neuropsychiatric effects (rare, esp. children)

3- Baloxavir and marboxil

• Cap-dependent endonuclease inhibitors

Mechanism of Action

•Inhibits viral **RNA polymerase (PA subunit)**

Block cap snatching from host mRNA

Spectrum

•Influenza A & B

Advantages

•Oral Single-dose therapy

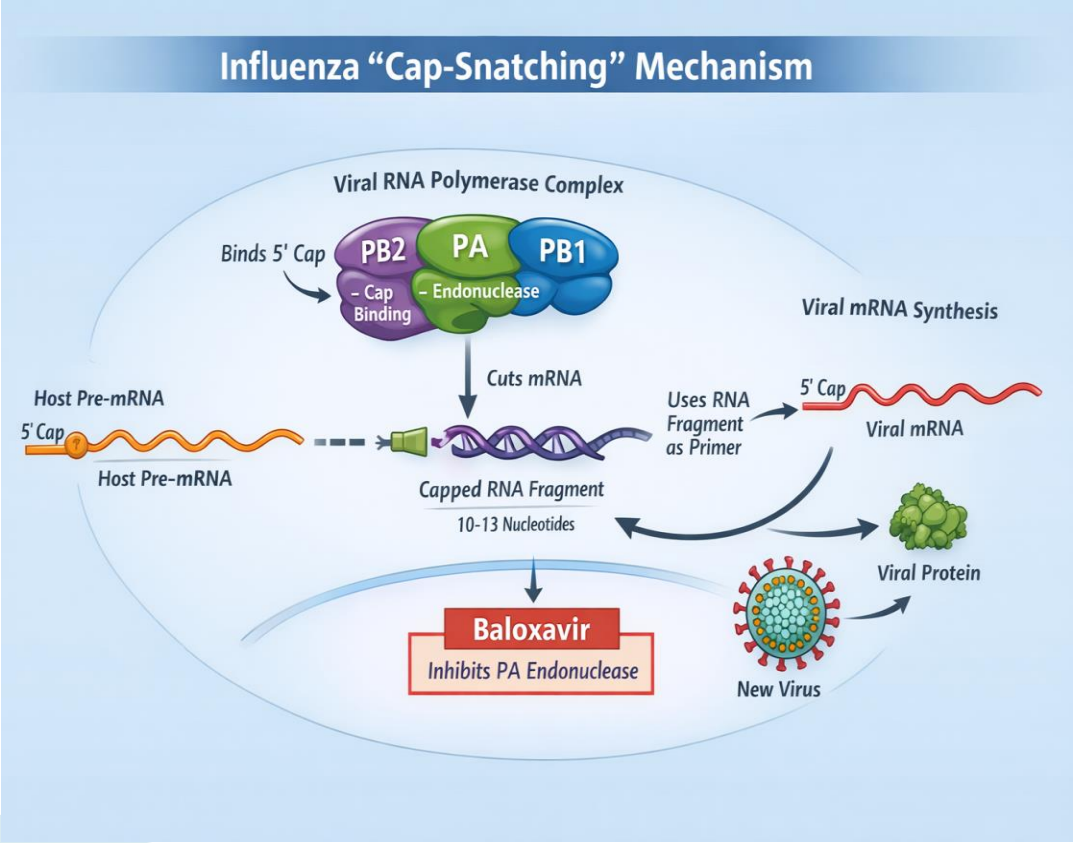
•Rapid viral load reduction

Adverse Effects

•Diarrhea

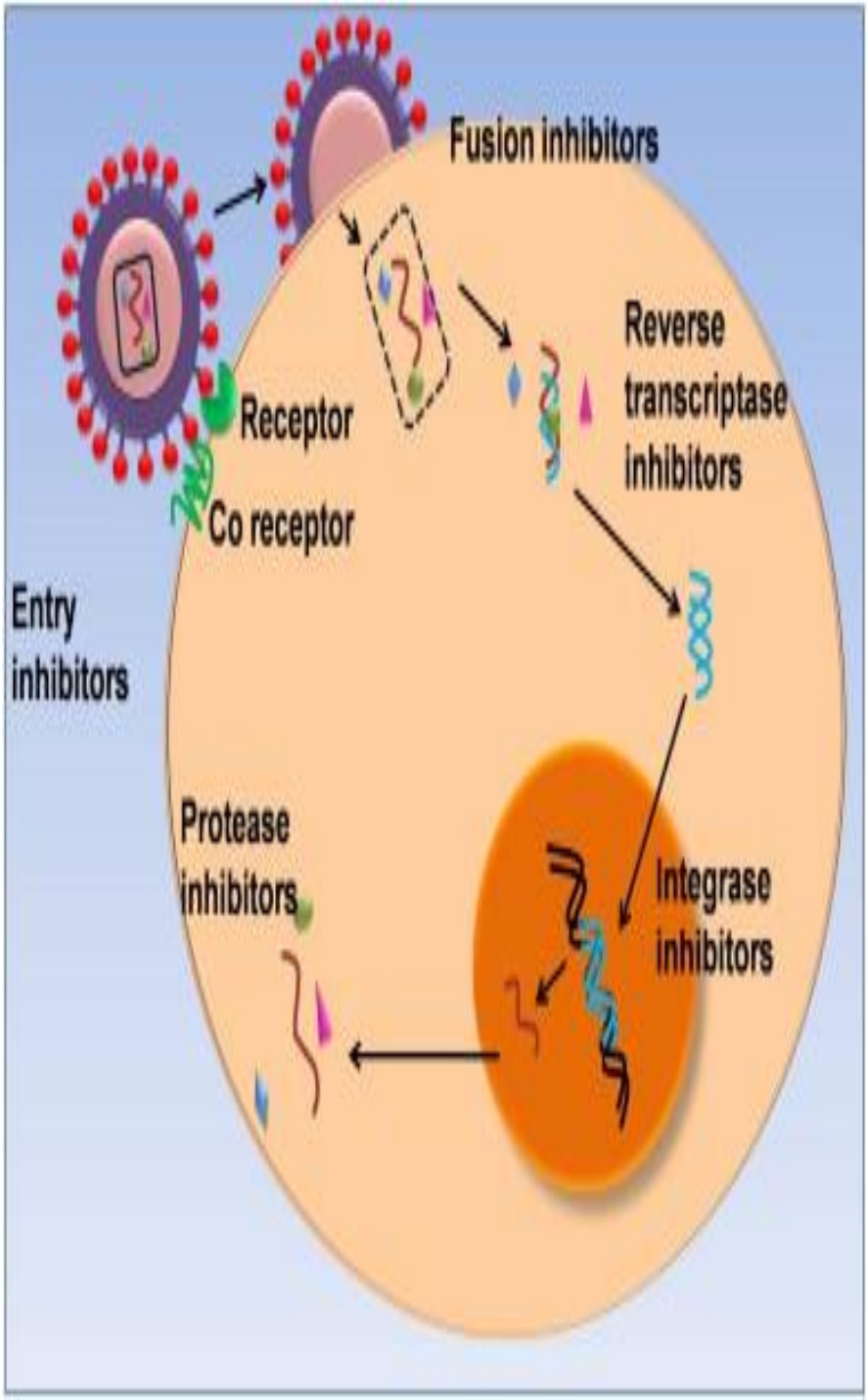
•Nausea

•Headache



Anti-HIV drugs

- Fusion inhibitors
- Reverse transcriptase inhibitors (NRTIs).
- *Protease inhibitors (PIs).*
- *Integrase inhibitors*



- Highly active antiretroviral therapy **(HAART)** is often initiated on the time of diagnosis.
- Strongest indication is for patients with AIDS-defining illness, **low CD4+** (< 500 cells/mm3), or **high viral load.**
- **Regimen** consists of **3 drugs** (to prevent resistence):

_ 2 NRTIs and 1 of the following (NNRTIs, protease inhibitors, or integrase inhibitors).

Nucleoside reverse transcriptase inhibitors (NRTIs):

- 1- Zidovudine. 2-Lamivudine.
- 3- Tenofovire 4- Didanosine

Mechanism of action:

- Phosphorylated by host kinases (except tenofovire).
- Competitive inhibition of reverse transcriptase and is incorporated into viral DNA, leading to chain termination.

Clinical use:

Main component of HAART.

Zidovudine

Is used for general prophylaxis and for prevention of vertical transmission in pregnancy.

Toxicity:

- *Bone marrow depression (can be reversed by granulocyte colony stimulating factor [G-CSF] and erythropoietin).*
- *Peripheral neuropathy and myopathy.*
- *Lactic acidosis.*

Non-nucleoside reverse transcriptase inhibitors (NNRTIs).

- ***Efavirenz, Etravirin.***
- ***Mechanism:***

• Bind to and inhibit reverse transcriptase, inhibiting DNA synthesis.

• No need for phosphorylation

• Not competitive (binds to a site other than the site of NRTIs).

- ***Toxicity:***

- Rash & hepatotoxicity (common with all members).

-Efavirenz causes vivid dreams and is contraindicated with pregnancy.

Protease inhibitors (PIs).

- Atazanavir, Lopinavir, Ritonavir.
- Mechanism :
  - HIV-1 protease cleaves the polypeptide products of the viral mRNA into functional parts, which then allow the assembly and maturation of new viruses.
  - PIs act by *inhibiting* this enzyme.
- *Ritonavir* (enhancer): is usually combined with other PIs, increasing their activity by inhibiting CYP450.

- Toxicity:
  - Hyperglycemia (insulin resistance) &lipodystrophy.
  - Nausea & diarrhea.
  - Drug-drug interactions.

N.B. No bone marrow depression.

Integrase inhibitors.

- **Raltegravir and Elivtegravir**
- ***Mechanism :***

Inhibit the integration of the viral genome into the host cell's DNA.

First-line in the modern ART regimen

Adverse effects: insomnia, headache, rare myopathy

Fusion inhibitors:

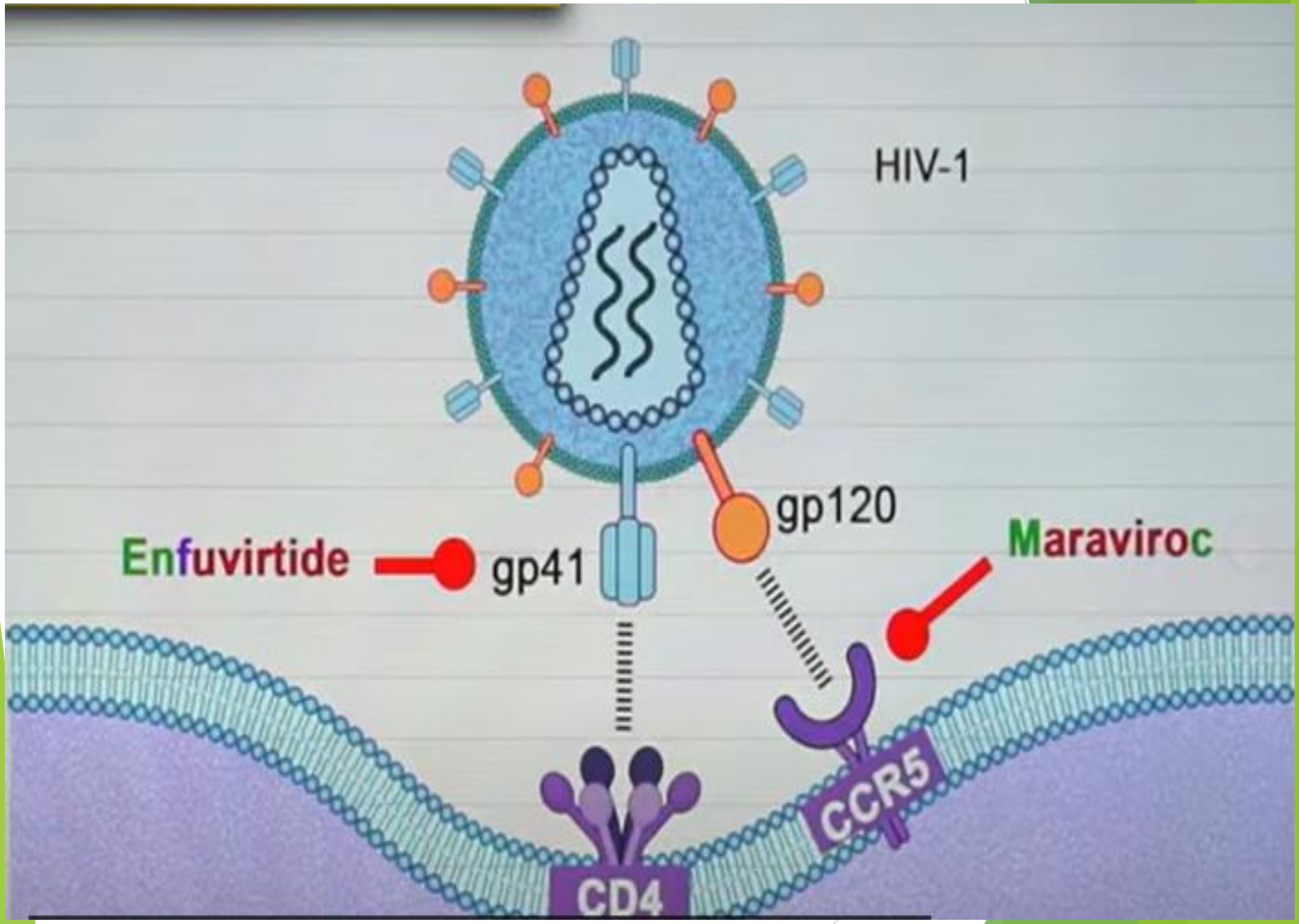
•Used in **resistant HIV strains**
•Enfuvirtide: subcutaneous injection
•Maraviroc: requires tropism testing (only CCR5-tropic virus)

Enfuvirtide

- **Mechanism of action:**
- It binds to the gp41 subunit of the viral envelope glycoprotein, preventing the fusion of the viral and cellular membranes.
- **Adverse effects:**
  1. Injection site reaction and hypersensitivity.
  2. Increased incidence of bacterial pneumonia

Maraviroc

- **Mechanism of action:**
- binds specifically and selectively to the membrane host protein CCR5, one of two chemokine receptors necessary for entry of HIV into CD4+ cells
- So, it inhibits binding and entry of the virus into immune cells
- **Adverse effects**:
- 1- Cough
- 2-Diarrhea
- 3-Muscle and joint pain


HIV-1
gp120
Enfuvirtide
gp41
Maraviroc
CCR5
CD4

Thank You!!!

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