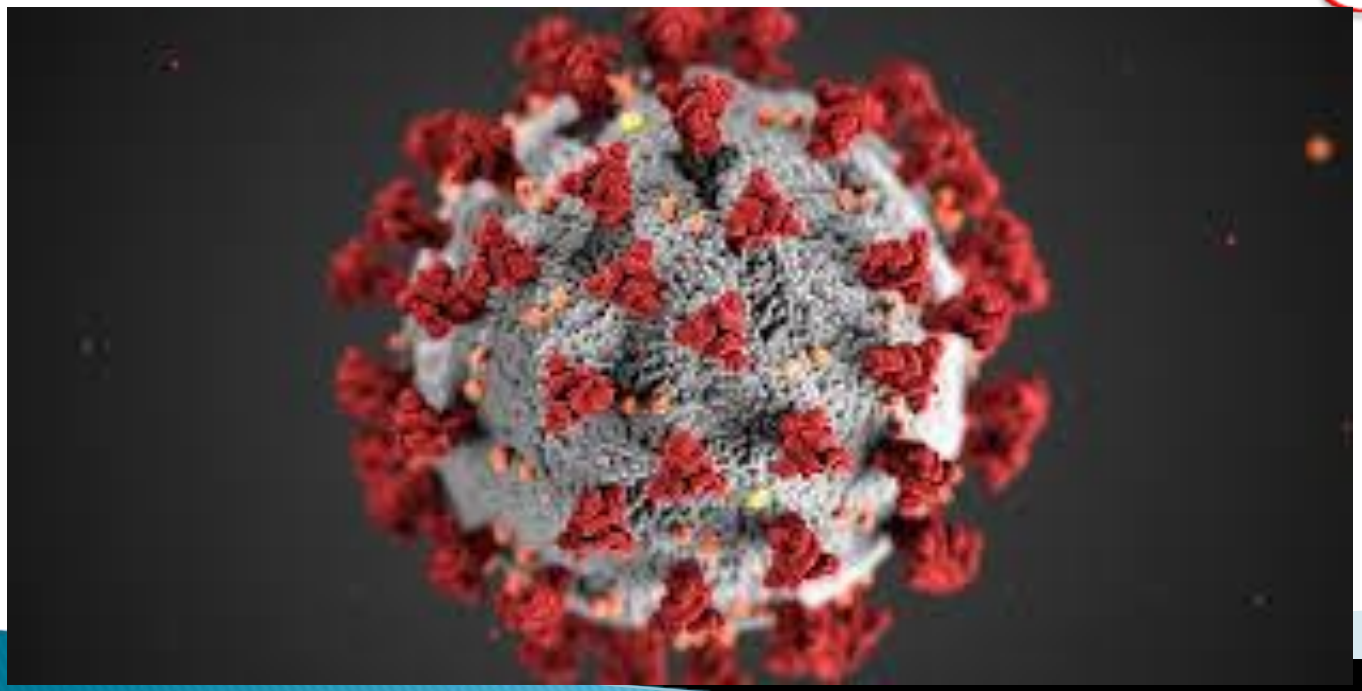
Antiviral drugs



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Virus : different from other microbes

- **Virus replication:**

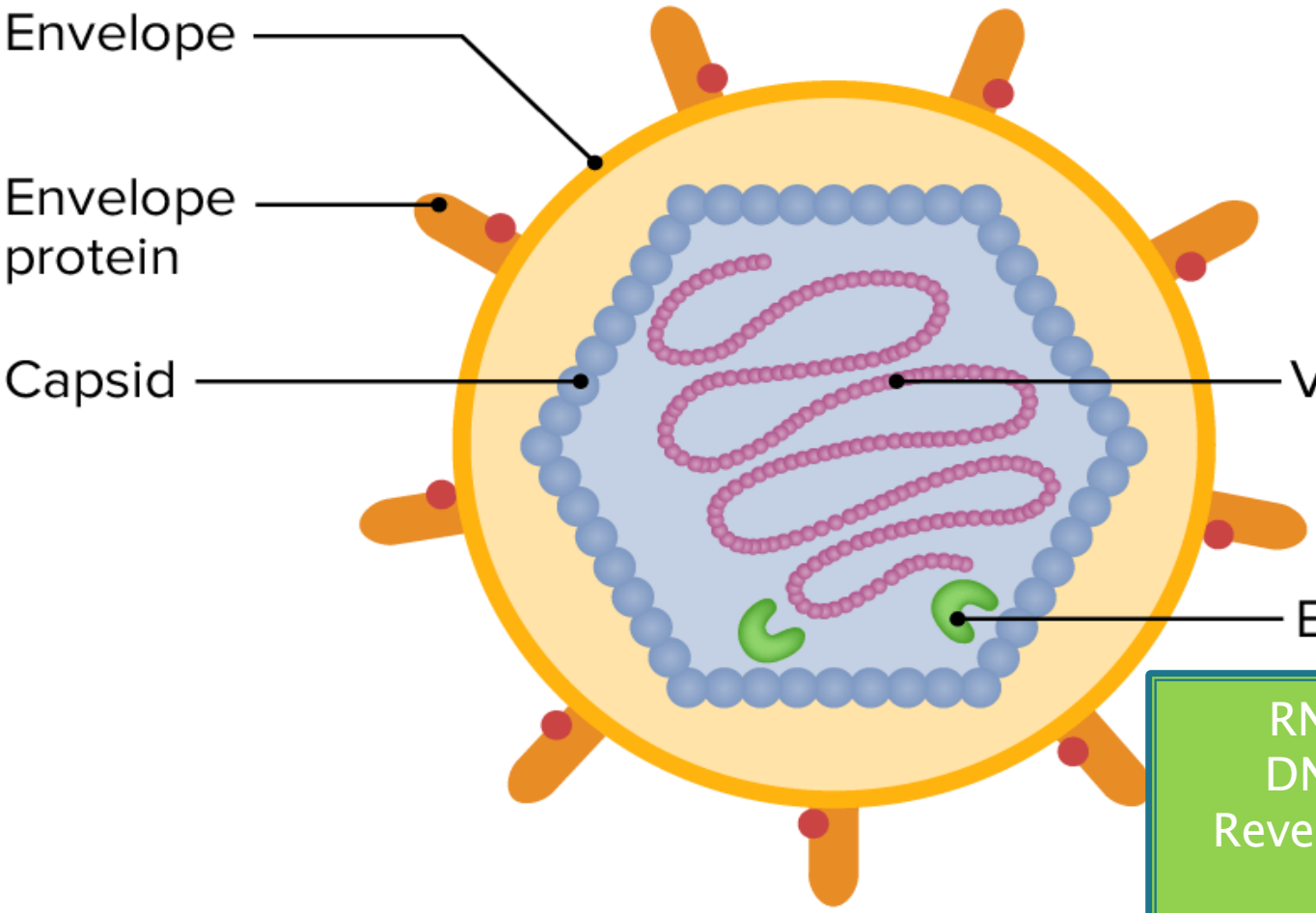
It has no metabolic machinery.

It depend on host cell to replicate.

It must attach to specific host cell to penetrate.

It uses host cell energy to synthesize virus protein and nucleic acid materials(DNA or RNA)

Virus structures



RNA OR DNA GENOME

RNA polymerase
DNA polymerase
Reverse transcriptase
Integrase
Protease
Neuraminidase

بسم الله الرحمن الرحيم

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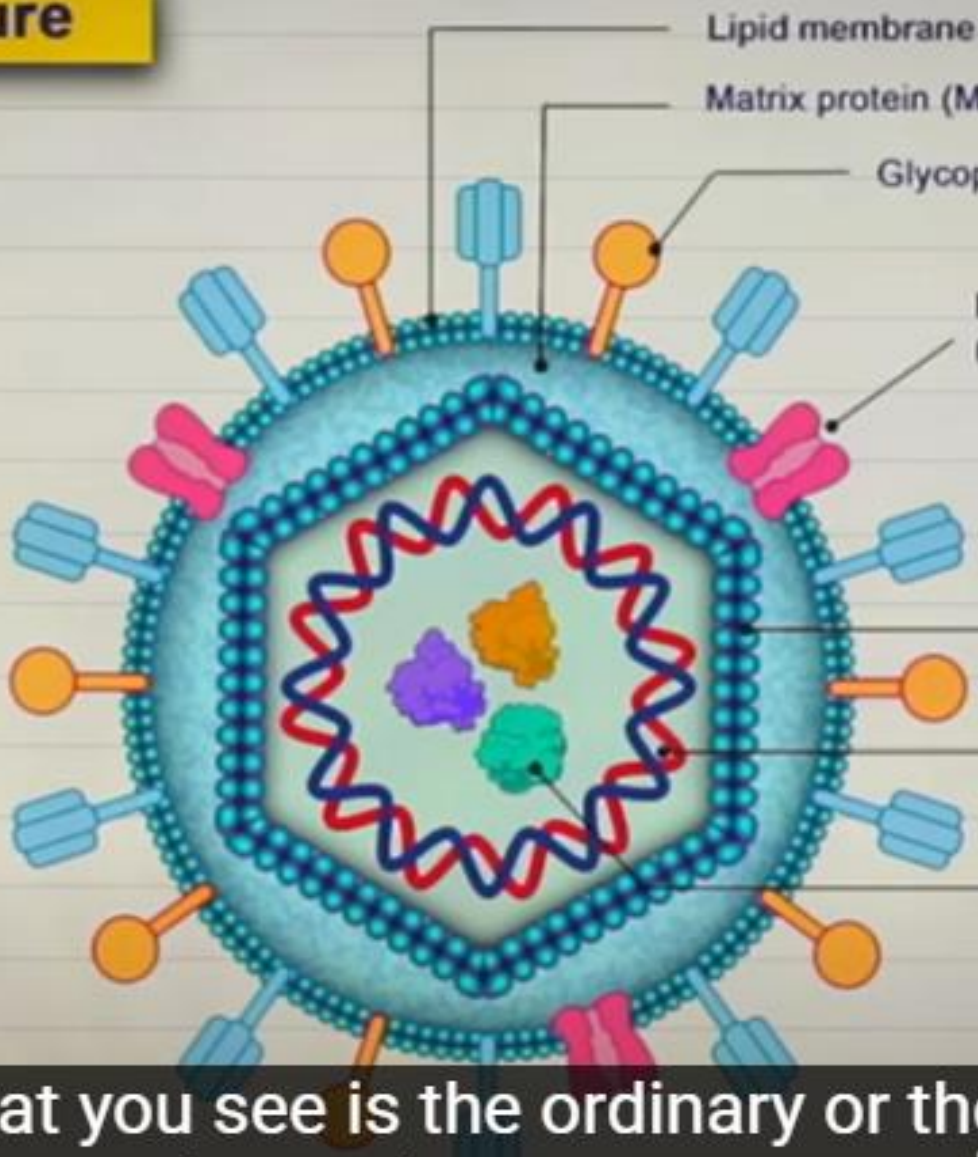
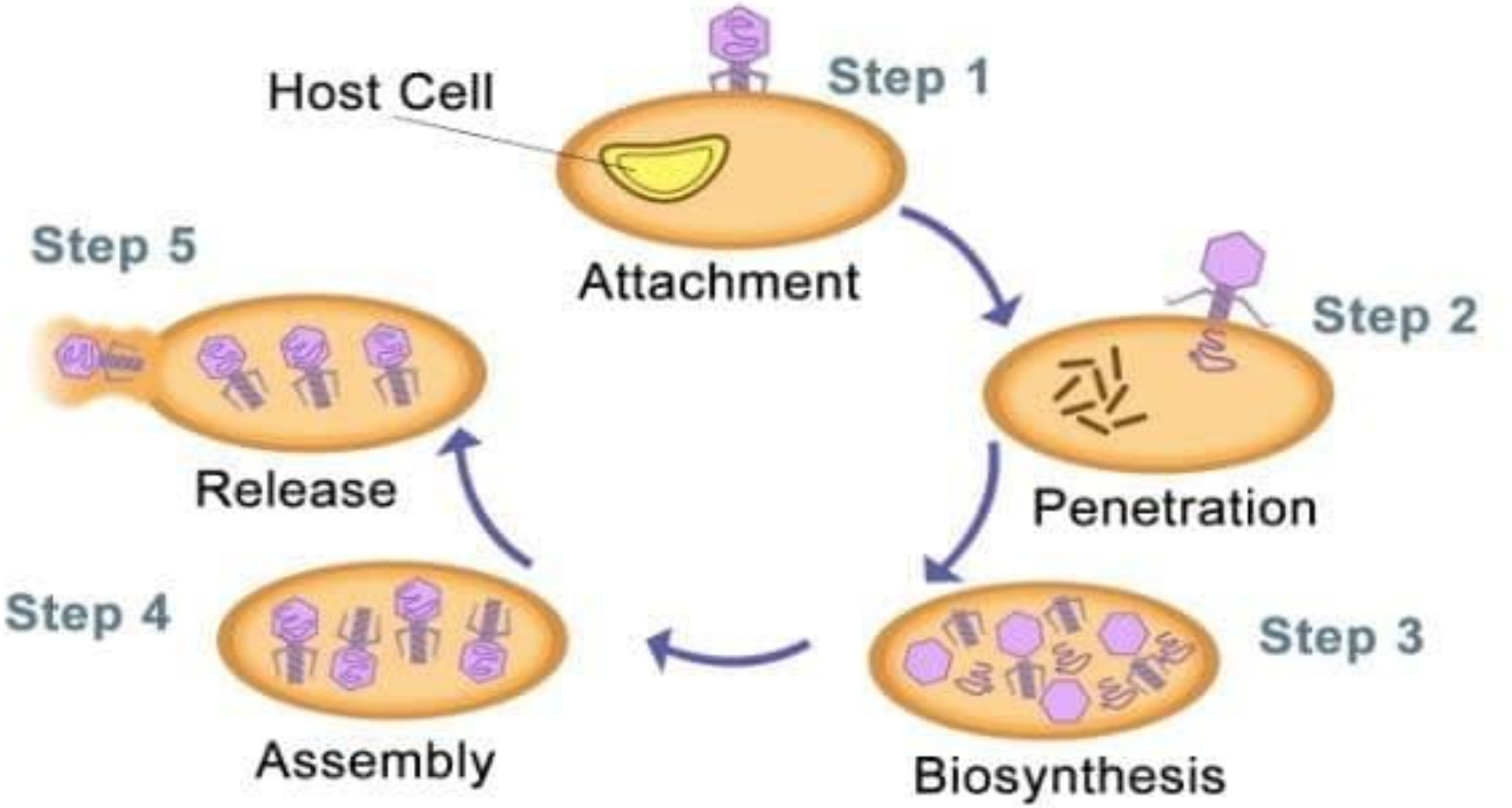
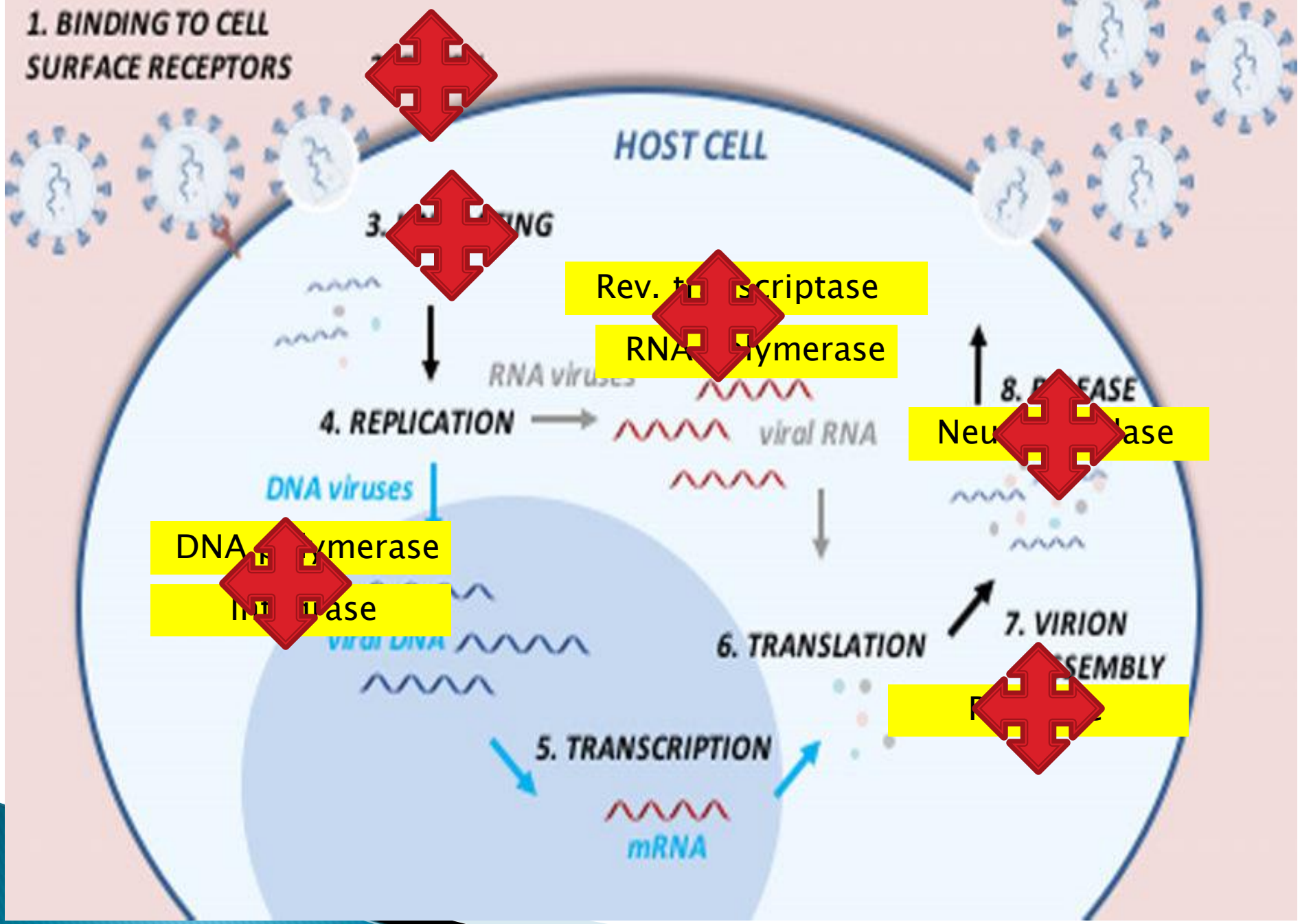


What you see is the ordinary or the classic form of humans' viruses

Steps of virus replication

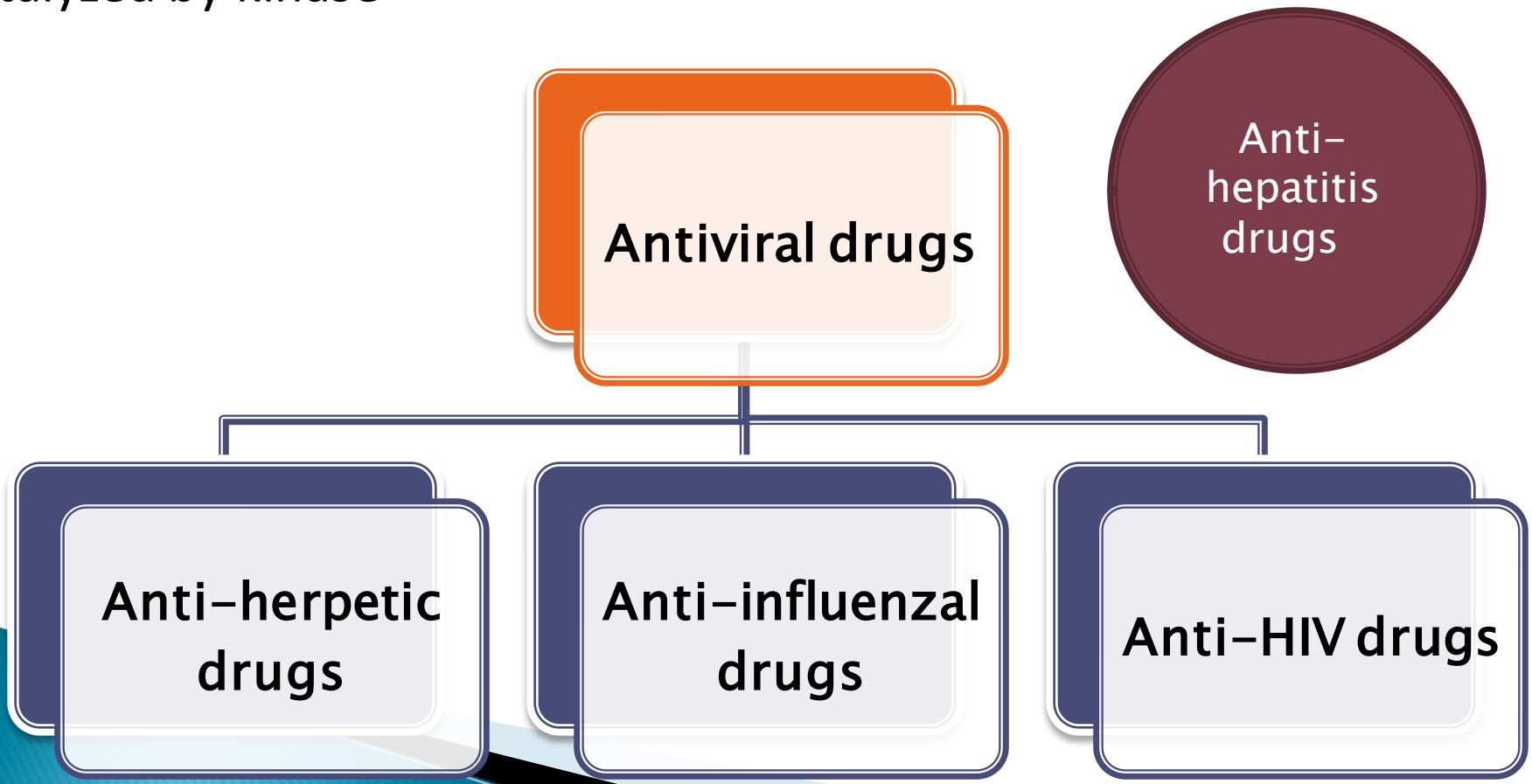



1. BINDING TO CELL
SURFACE RECEPTORS
HOST CELL
Rev. t scriptase
RNA ymerase
RNA viruses
4. REPLICATION
viral RNA
8. EASE
Neu ase
DNA viruses
DNA ymerase
ase
6. TRANSLATION
7. VIRION
SEMBLY
5. TRANSCRIPTION
mRNA

•Many antiviral drugs are antimetabolites that resemble the structure of naturally occurring purine and pyrimidine bases or their nucleoside forms.

•Antimetabolites are usually prodrugs requiring metabolic activation by host cell or viral enzymes.

•Commonly, such activation involves phosphorylation reactions catalyzed by kinase

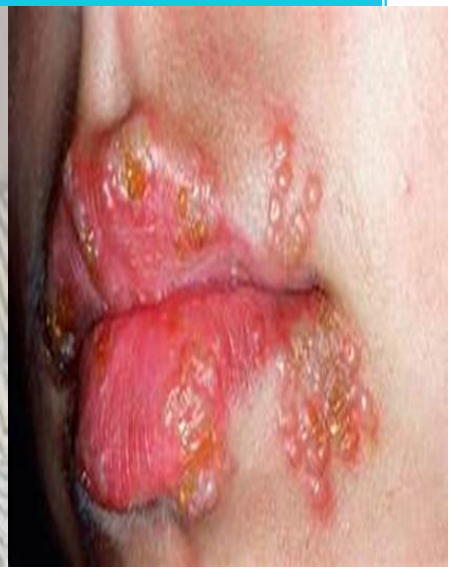


➢ Anti-herpetic drugs (DNA VIRUS)

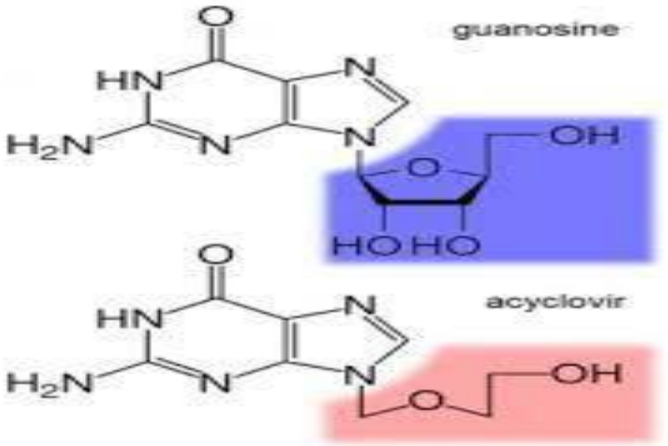
1-Acyclovir, famciclovir, valacyclovir

2-Ganciclovir, Valganciclovir

3-Foscarnet



1-Acyclovir- famciclovir- valacyclovir

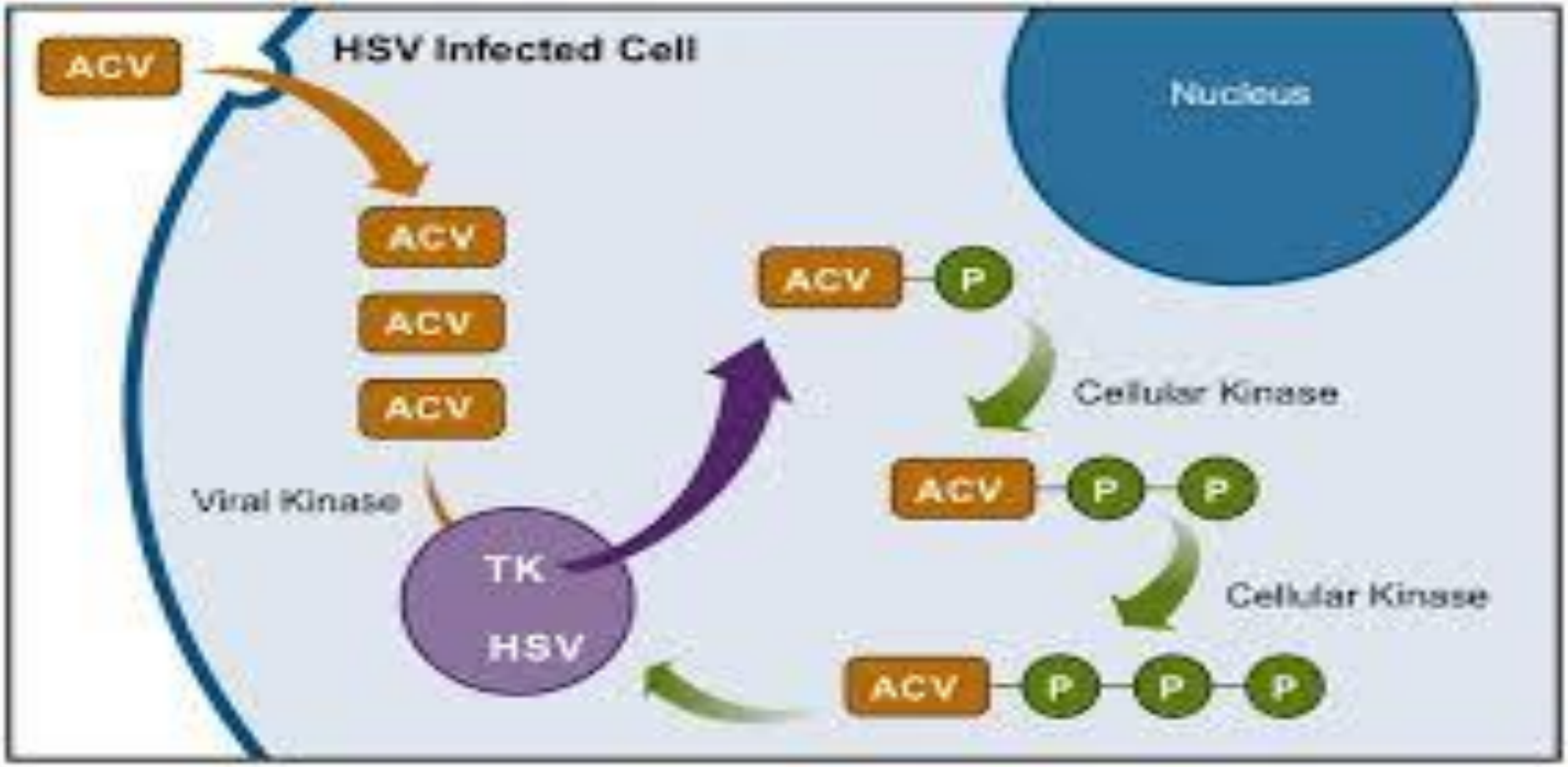


Activation:

- **Guanosine analogs**.
- Mono-phosphorylated by

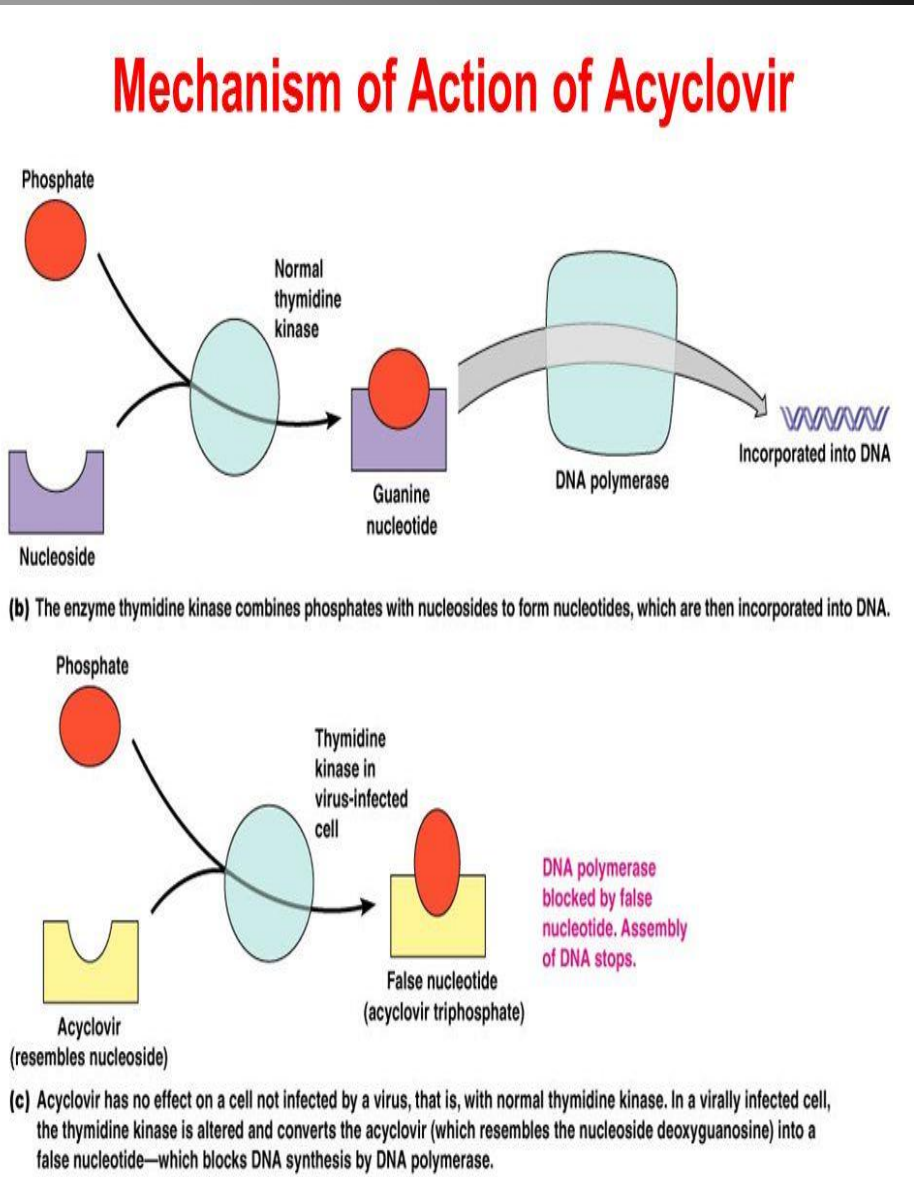
HSV/VZV thymidine kinase (TK) (not phosphorylated in uninfected cells → few adverse effects).

- 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



Clinical uses:

- ✓ Treatment of herpes simplex and varicella zoster virus infections
- ✓ Prophylaxis in immuno-compromized 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)

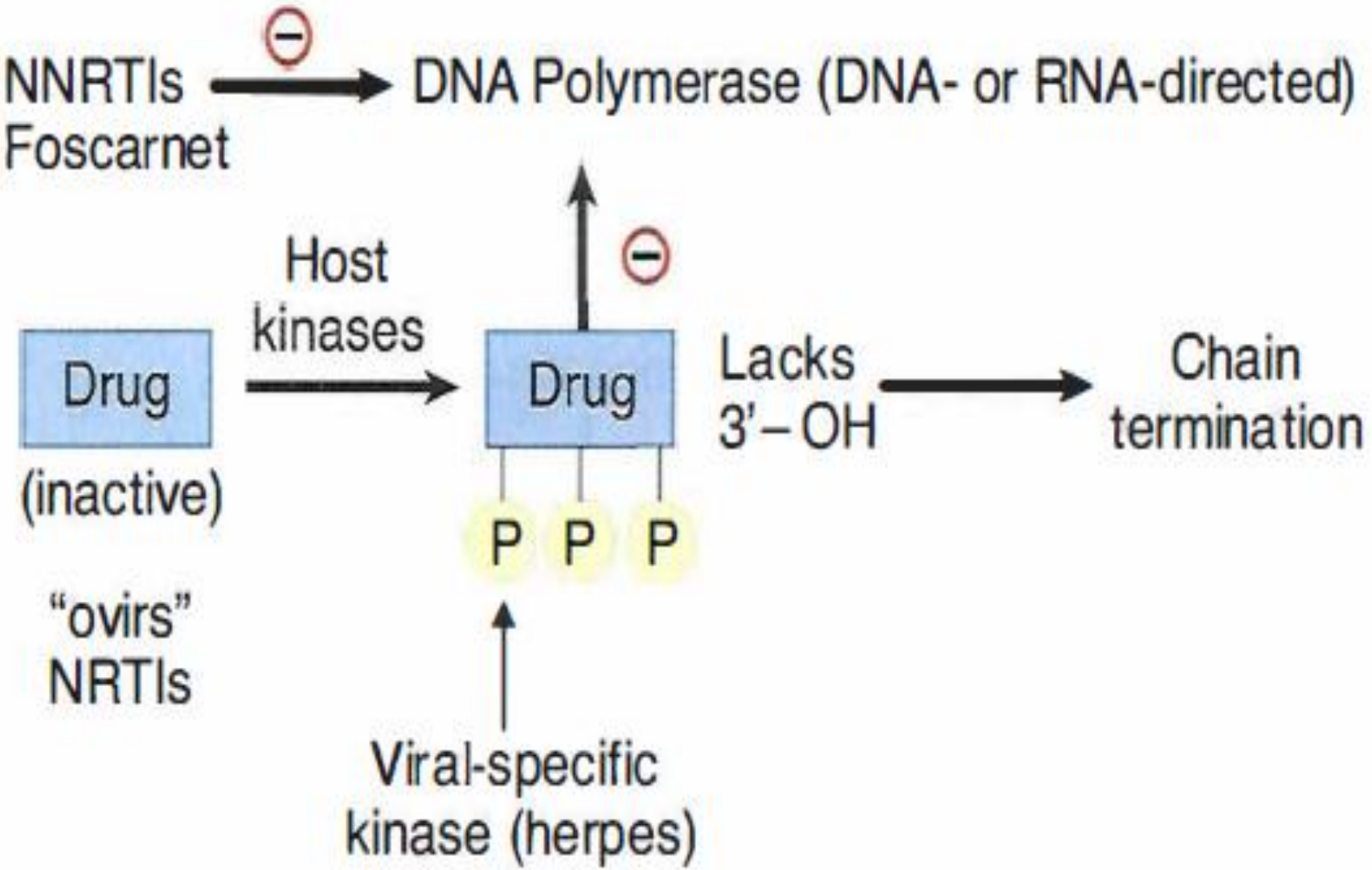
3-Foscarnet

- ✓ 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

1-Amantadine & Rimantadine

- **Mechanism of action:**
  - ✓ Block attachment, penetration, and uncoating of influenza A virus
- **Clinical uses:**
  - ❖ Influenza 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

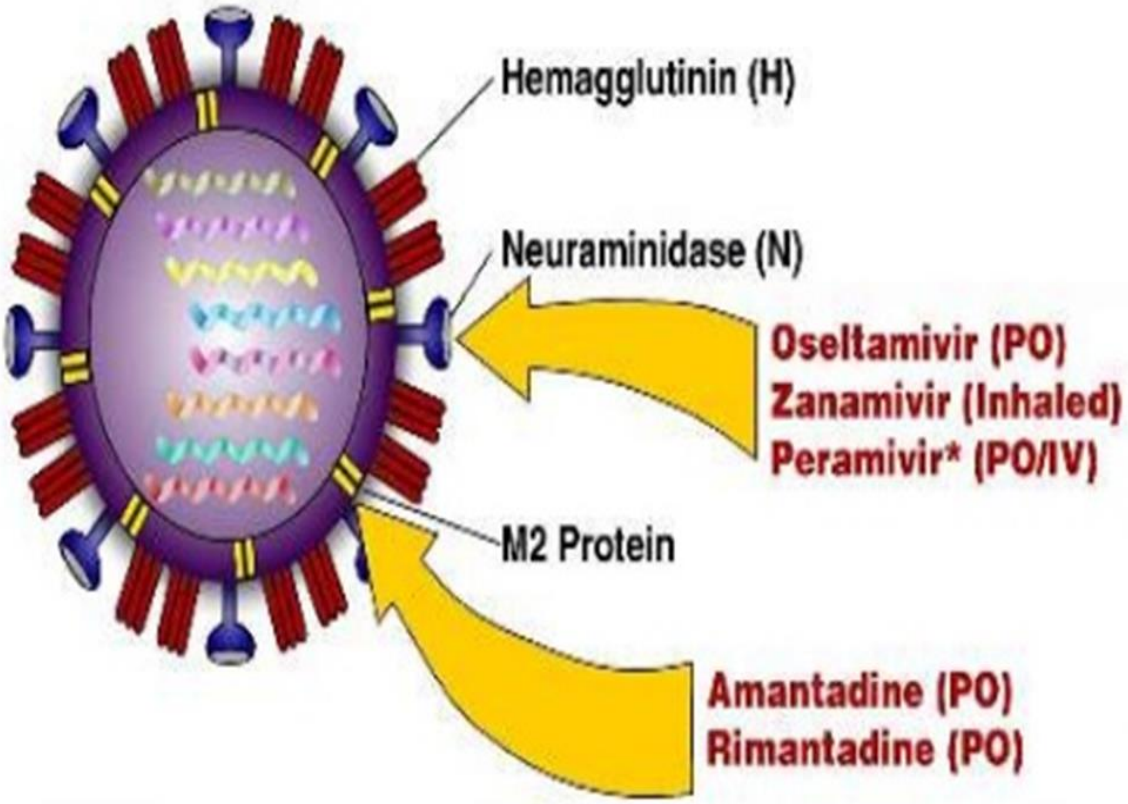
2-Oseltamivir & Zanamivir

- **Mechanism of action:**

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

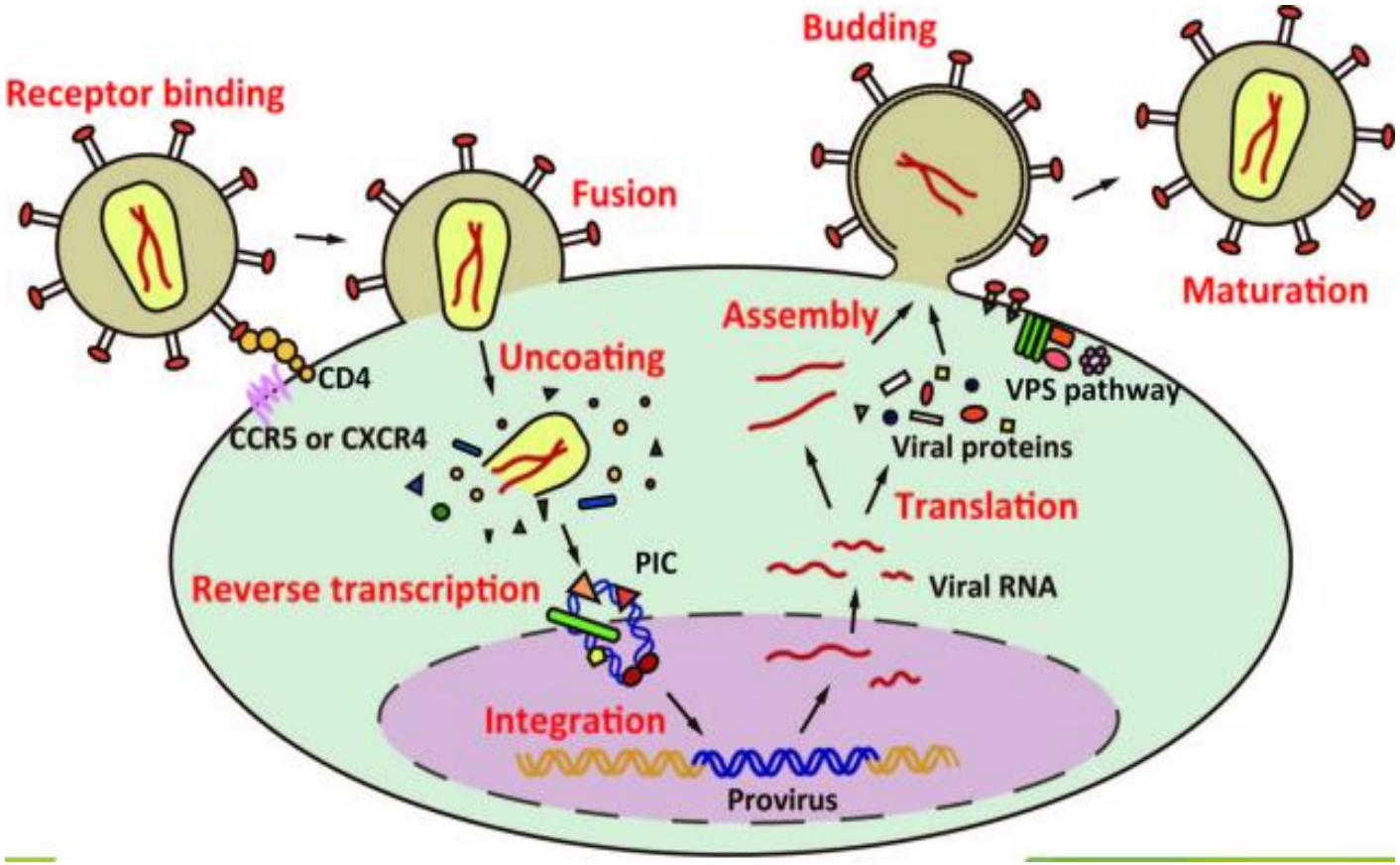
- **Clinical uses:**
  - Prevention & treatment of influenza A & B

Antiviral Therapies for Influenza

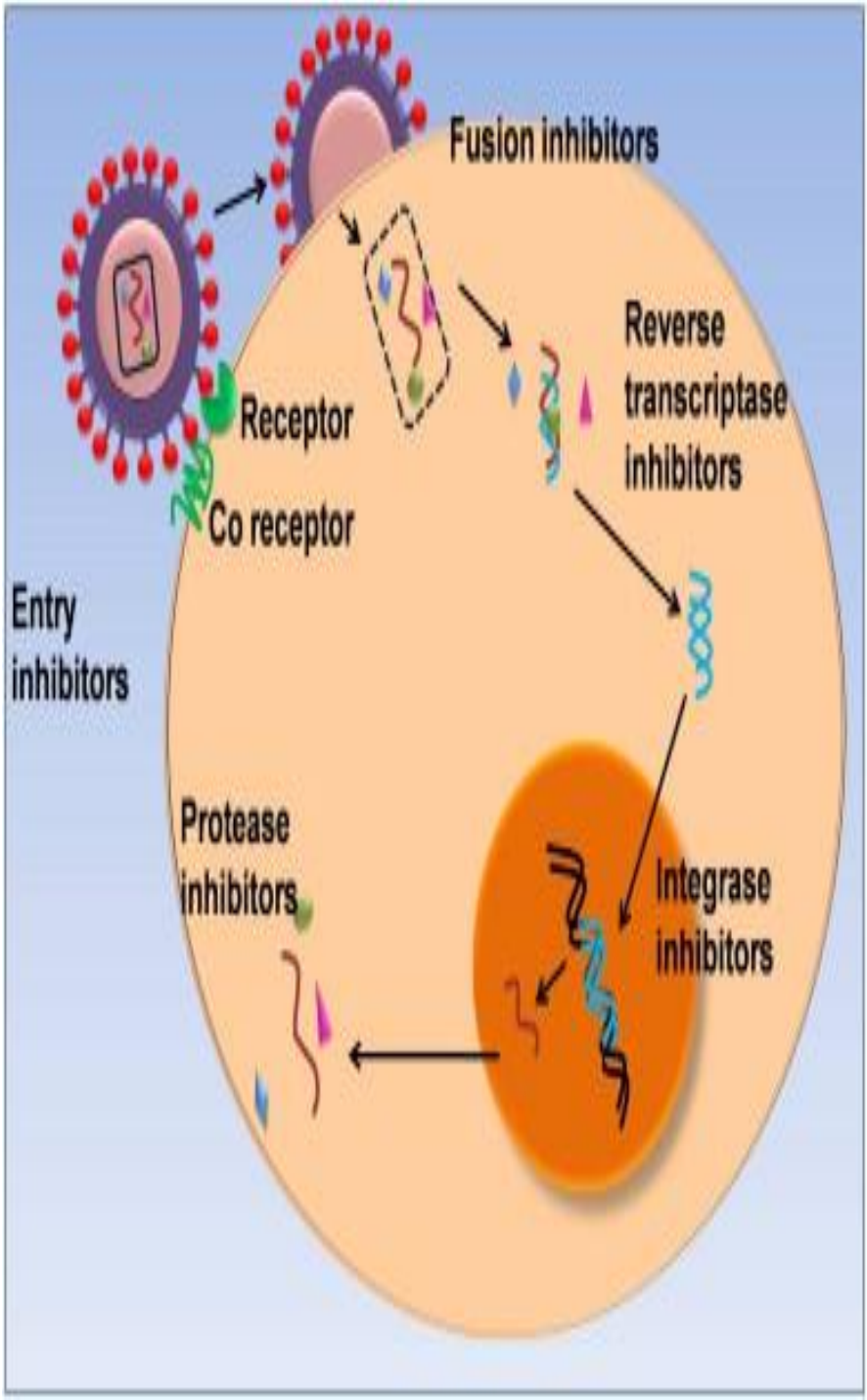


*Investigational

Anti-HIV


Budding
Receptor binding
Fusion
Maturation
Assembly
Uncoating
CD4
CCR5 or CXCR4
VPS pathway
Viral proteins
Translation
PIC
Reverse transcription
Viral RNA
Integration
Provirus

- 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 tenofovir).
- Cause competitive inhibition of reverse transcriptase and chain termination of DNA.

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 (bind to a site other than 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 then, assembly & maturation of new viruses.
  - PIs act by ***inhibiting*** this enzyme.
- ***Ritonavir*** is usually combined with other PIs and increases their activity by inhibiting CYP450.

- Toxicity:

- Hyperglycemia (insulin resistence) &lipodystrophy.
- Nausea & diarrhea.
- Drug-drug interactions.

N.B. No bone marrow depression.

Integrase inhibitors.

- **Raltegravir and Elivtegravir**

- ***Mechanism :***

Inhibit integration of viral genome in host cell DNA.

1- Fusion inhibitors: Enfuvirtide AND Maraviroc

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

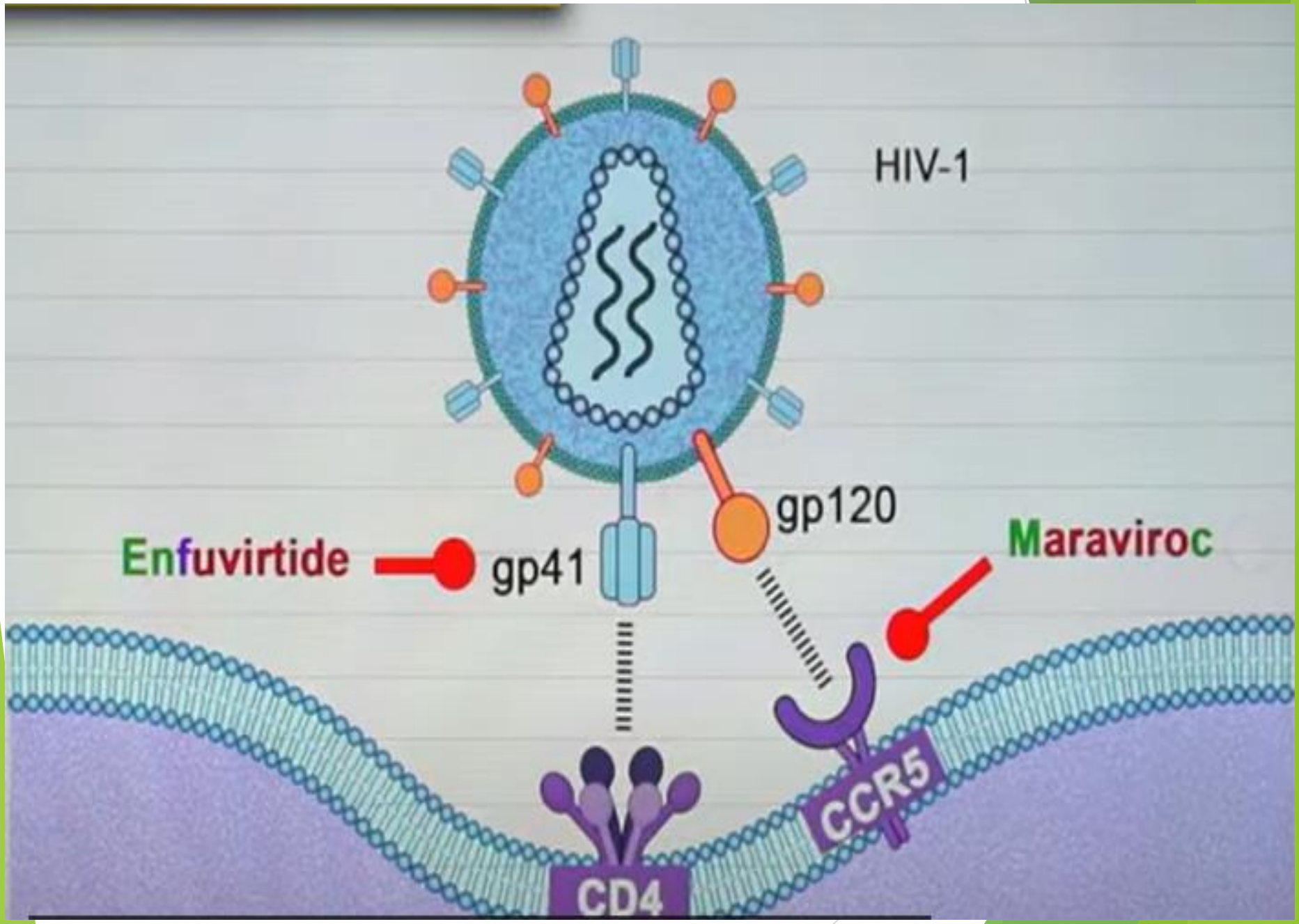
- **Mechanism of action:**

- 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

Mechanism of Action	Major Drugs
1-Block viral penetration/uncoating	**Amantadine**, enfuvirtide, maraviroc
2-Inhibit viral DNA polymerases	**Acyclovir, foscarnet, ganciclovir**
3-Inhibit viral RNA polymerases	**Foscarnet**
4-Inhibit viral reverse transcriptase	Zidovudine, didanosine, zalcitabine, lamivudine, stavudine, nevirapine, efavirenz
5-Inhibit viral aspartate protease	lndinavir, ritonavir, saquinavir, nelfinavir
6-Inhibit viral neuraminidase	**Zanamivir, oseltamivir**

Thank You!!!