Antiviral drugs

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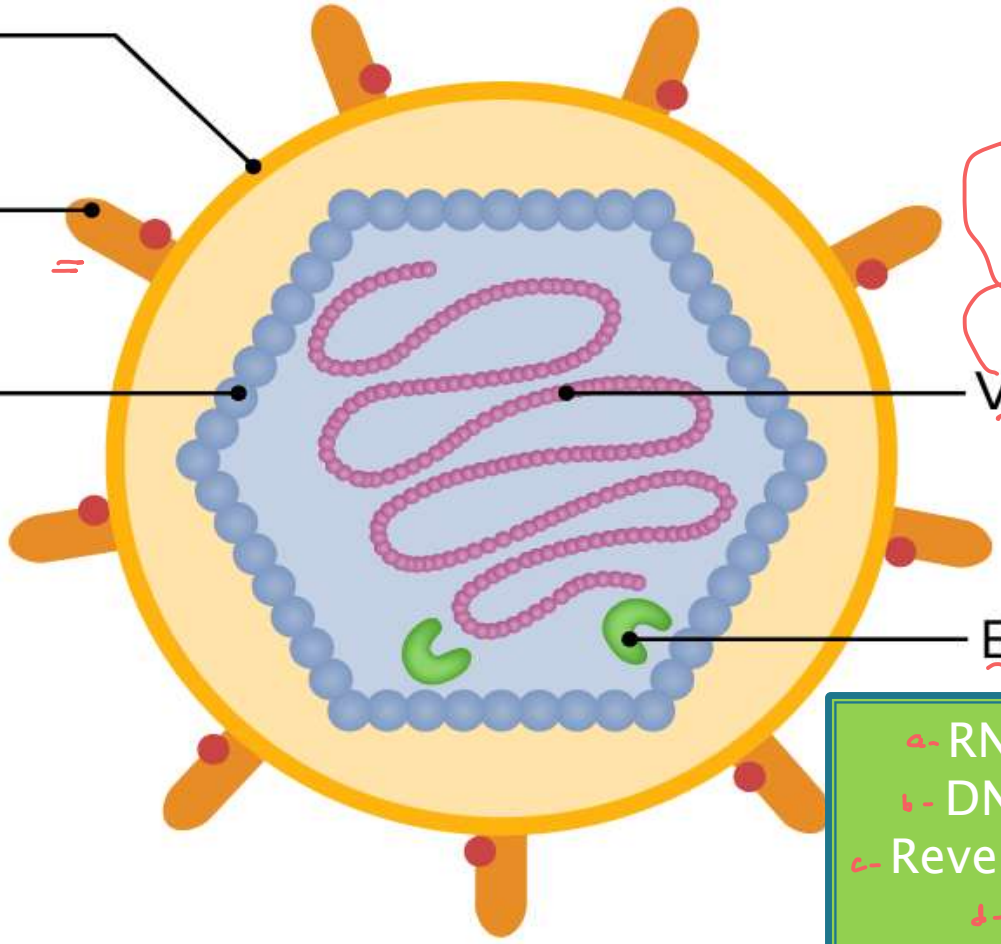
1- what does Virus structure composed of? 2- what're the enzymes? 3- what're the steps of Viral replication?

Virus structures



① Envelope

② Envelope protein

③ Capsid → spike protein for attachment

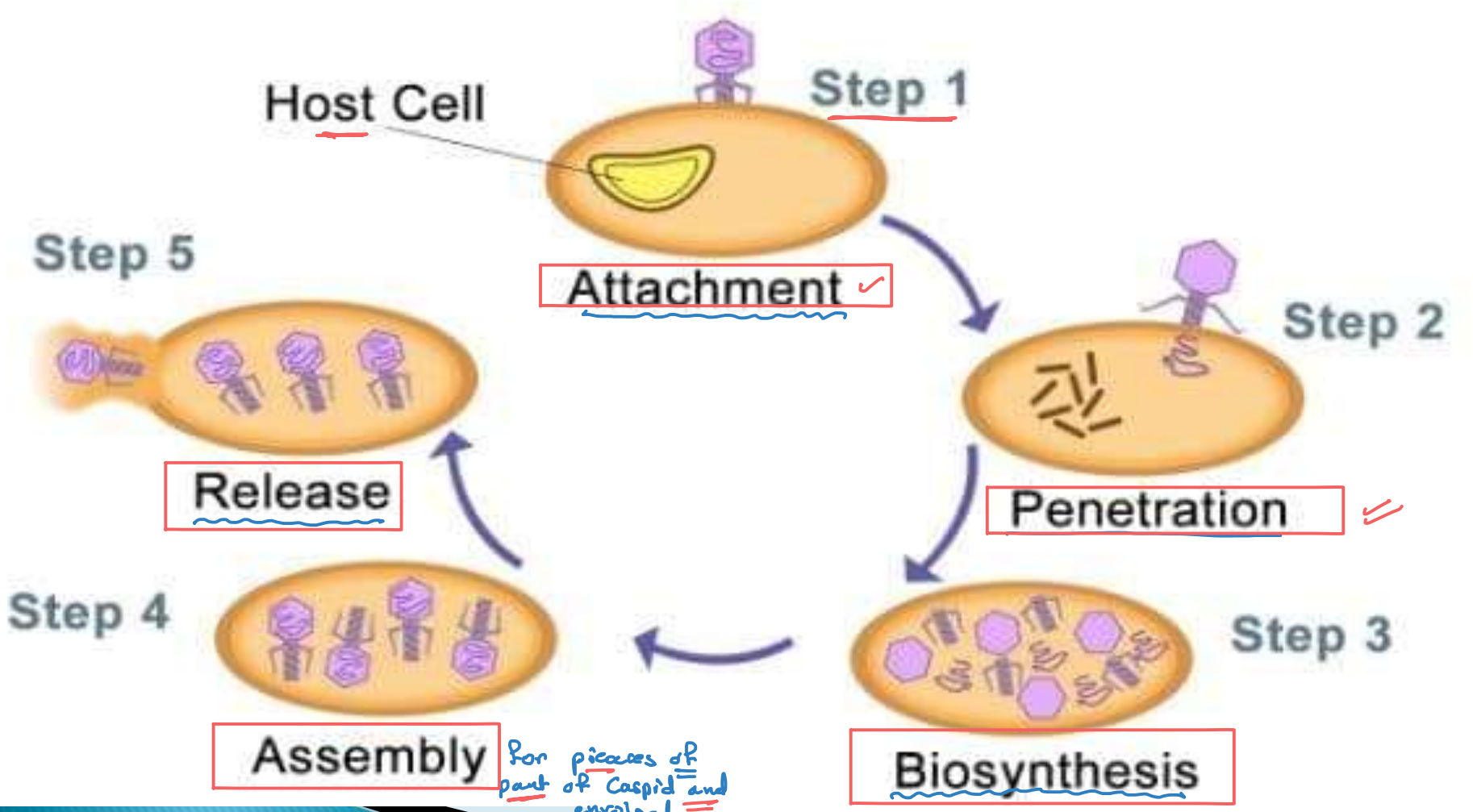
① RNA OR ② DNA GENOME

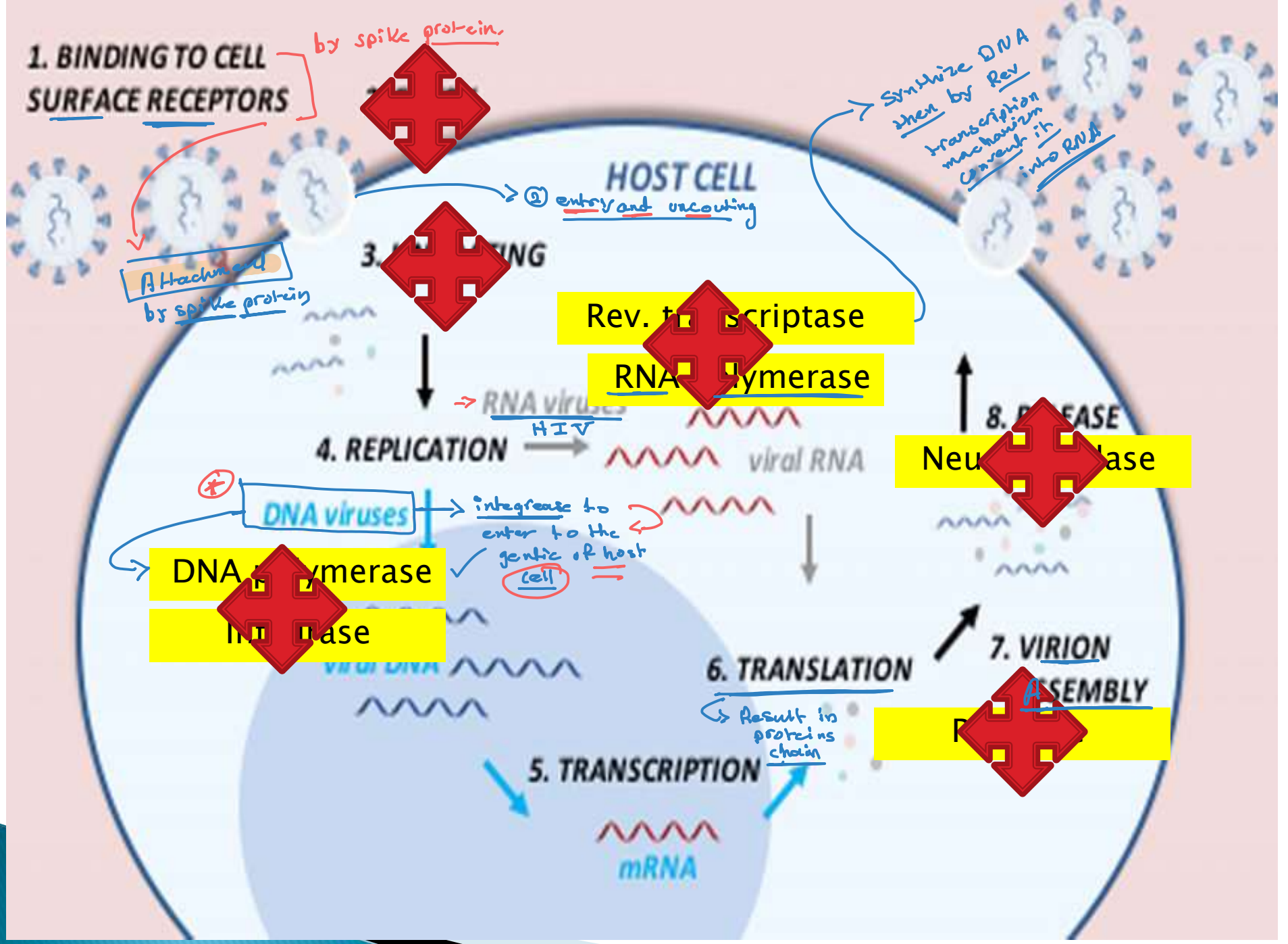
④ Viral genome

⑤ Enzyme

a- RNA polymerase
b- DNA polymerase
c- Reverse transcriptase
d- Integrase
e- Protease
f- Neuraminidase

Steps of virus replication




1. BINDING TO CELL SURFACE RECEPTORS
by spike protein
Attachment by spike protein
HOST CELL
② entry and uncoating
3. [illegible]ING
RNA viruses
HIV
4. REPLICATION
viral RNA
DNA viruses
integrase to enter to the genetic of host cell
DNA [illegible]ymerase
[illegible]ase
6. TRANSLATION
Result in proteins chain
5. TRANSCRIPTION
mRNA
Rev. t[illegible]scriptase
RNA [illegible]ymerase
Synthize DNA then by Rev transcription machanizm convert it into RNA
8. [illegible]EASE
Neu[illegible]ase
7. VIRION
[illegible]SEMBLY

→ what are the steps that we can target to stop the replication of Virus?

1- prevent the entry, attachment
↳ effusion inhabitors.

2- prevent the uncoating

3- inhabit the RNA polymaes or DNA

4- inhabit the integrase

5- inhabit the protease.

1- what're the classification of antiviral drug?

Antiviral drugs:

- a- **Anti-herpetic drugs** ↳ DNA Viruses
- b- **Anti-influenzal drugs** RNA Viruses.
- c- **Anti-HIV drugs**

Anti-hepatitis drugs

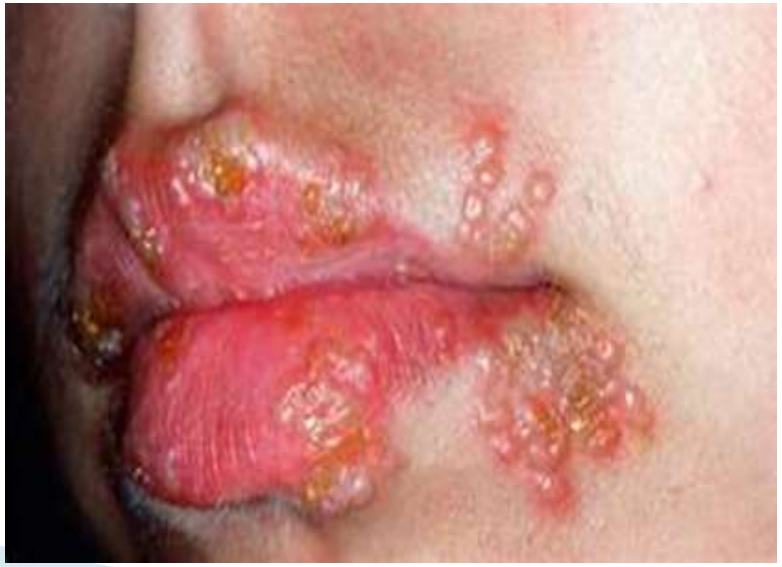
1- what're the feature of analoge drug?
2- what're the type of anti-herplic drug?

-Anti-herpetic drugs (DNA VIRUS)

1-Acyclovir, famciclovir, valacyclovir

2-Ganciclovir, Valganciclovir

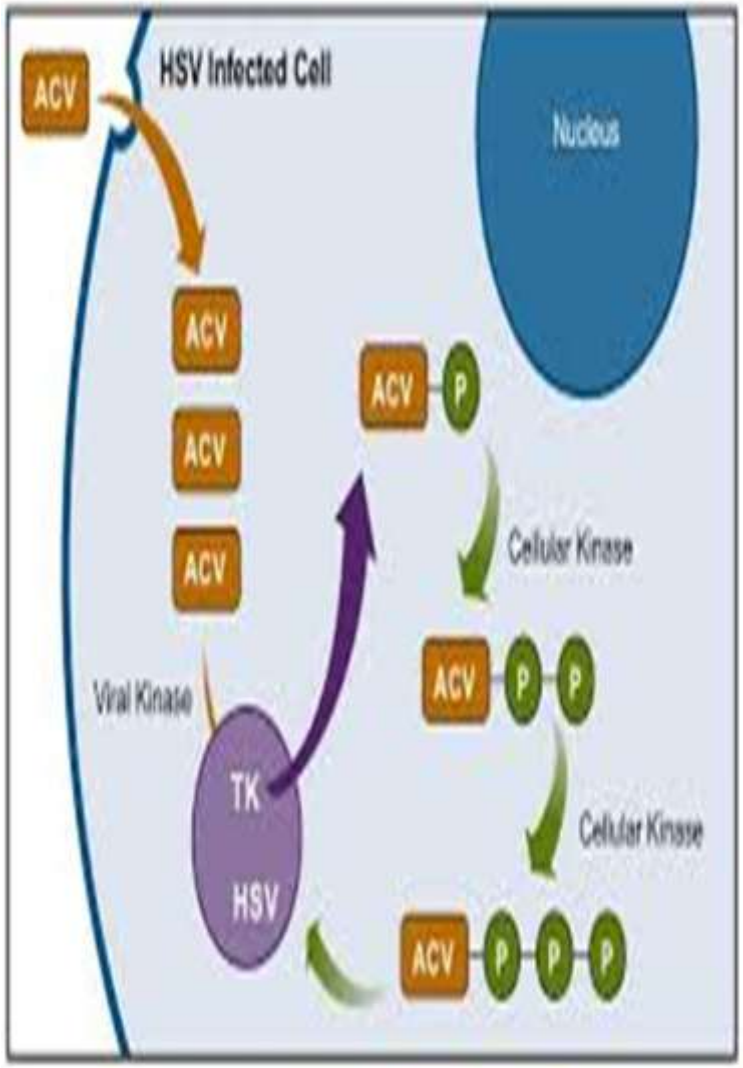
3-Foscarnet



1-Acyclovir- famciclovir- valacyclovir

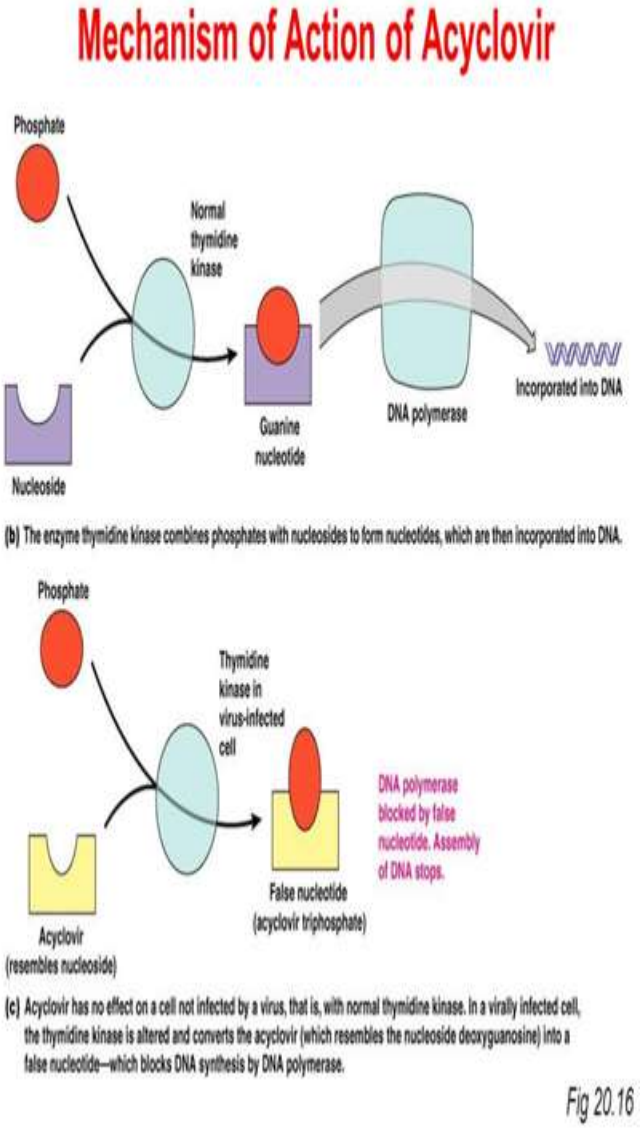
Activation Guanosine analogs

- 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

Drink water ... 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

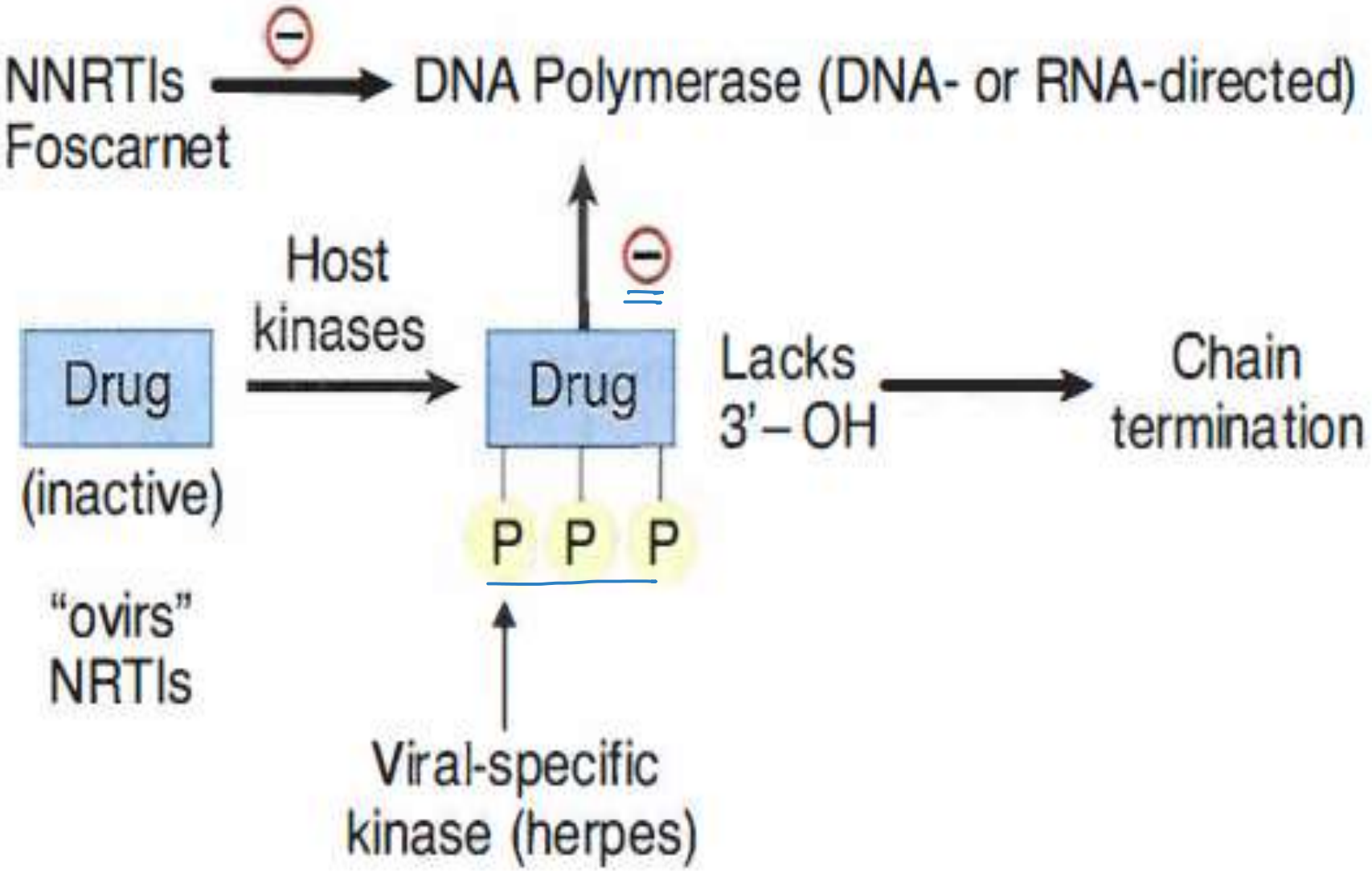
Notes:

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

3-Foscarnet

Not need for activation

- ✓ 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)

→ prevent a- attachment, b- penetration and c- uncoating

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

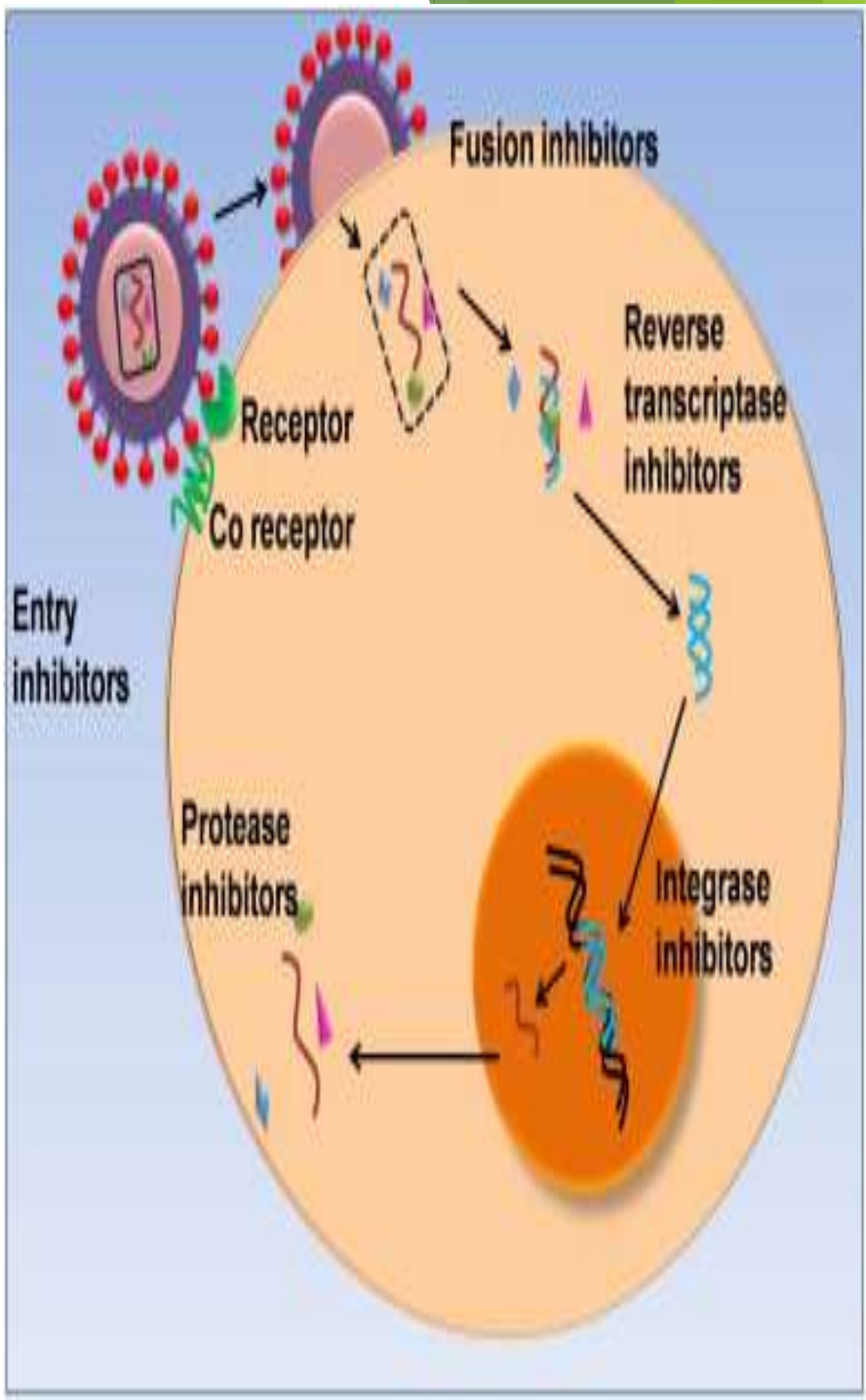
- **Mechanism of action:**

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

Anti-HIV drugs

- Fusion inhibitors
- Reverse transcriptase inhibitors (NRTIs).
  - They classify this type of drug according to nucleotide analogs.
- *Protease inhibitors (PIs).* prevent the assembly.
- *Integrase inhibitors*



- Highly active antiretroviral therapy **(HAART)** is often initiated on the time of diagnosis.

if the patient diagonsed with HIV, He/she has to start treatment with HAART, because HIV is high resistance.

- 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).
- 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. [protect fetus from HIV]

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, which then allow the assembly and maturation of new viruses.
  - PIs act by ***inhibiting*** this enzyme.
- ***Ritonavir*** 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 integration of viral genome in host cell DNA.

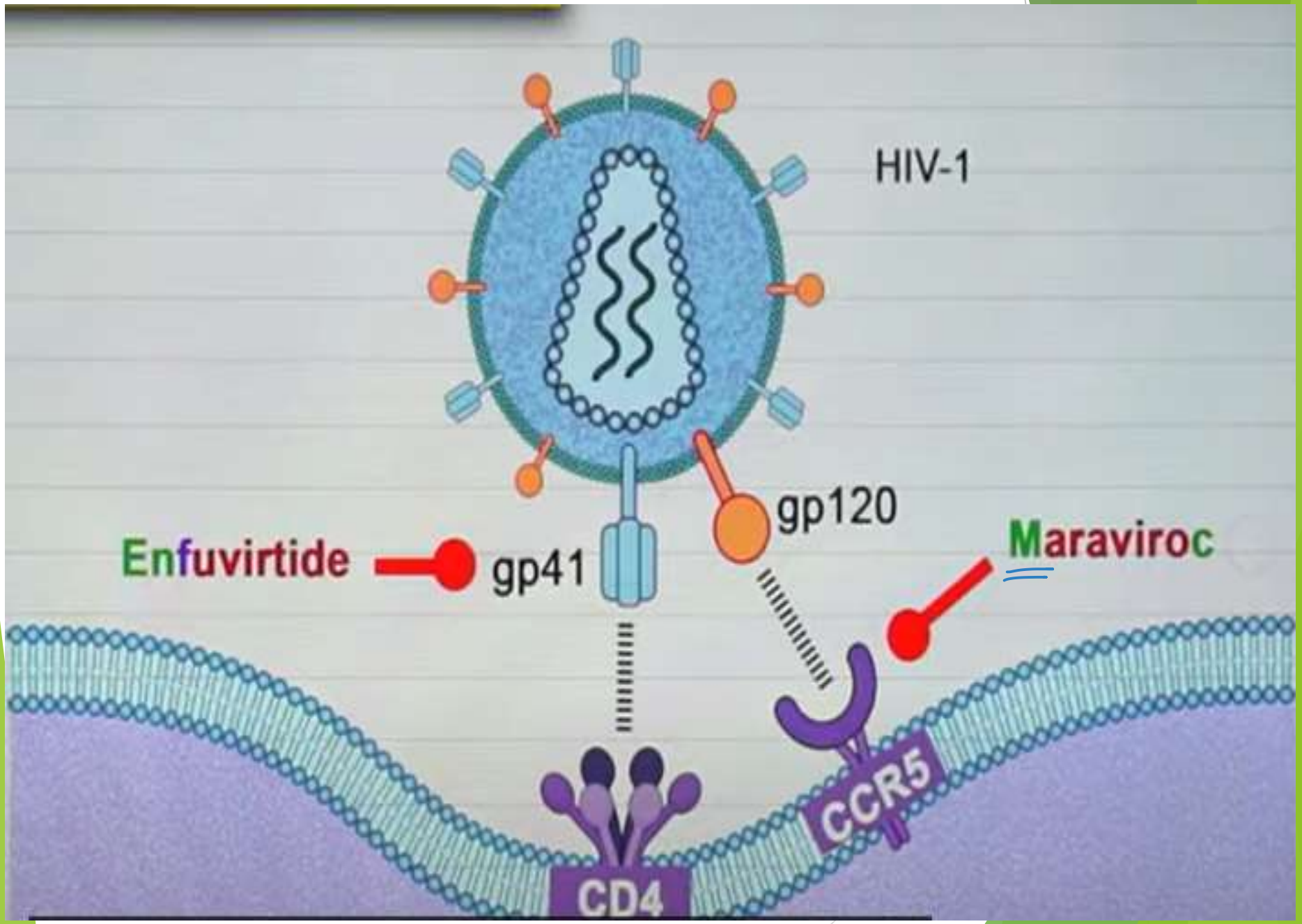
1- Fusion inhibitors: Enfuvirtide AND Maraviroc

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