Charting New Horizons in Education

Antiviral drugs

20

pharmacology

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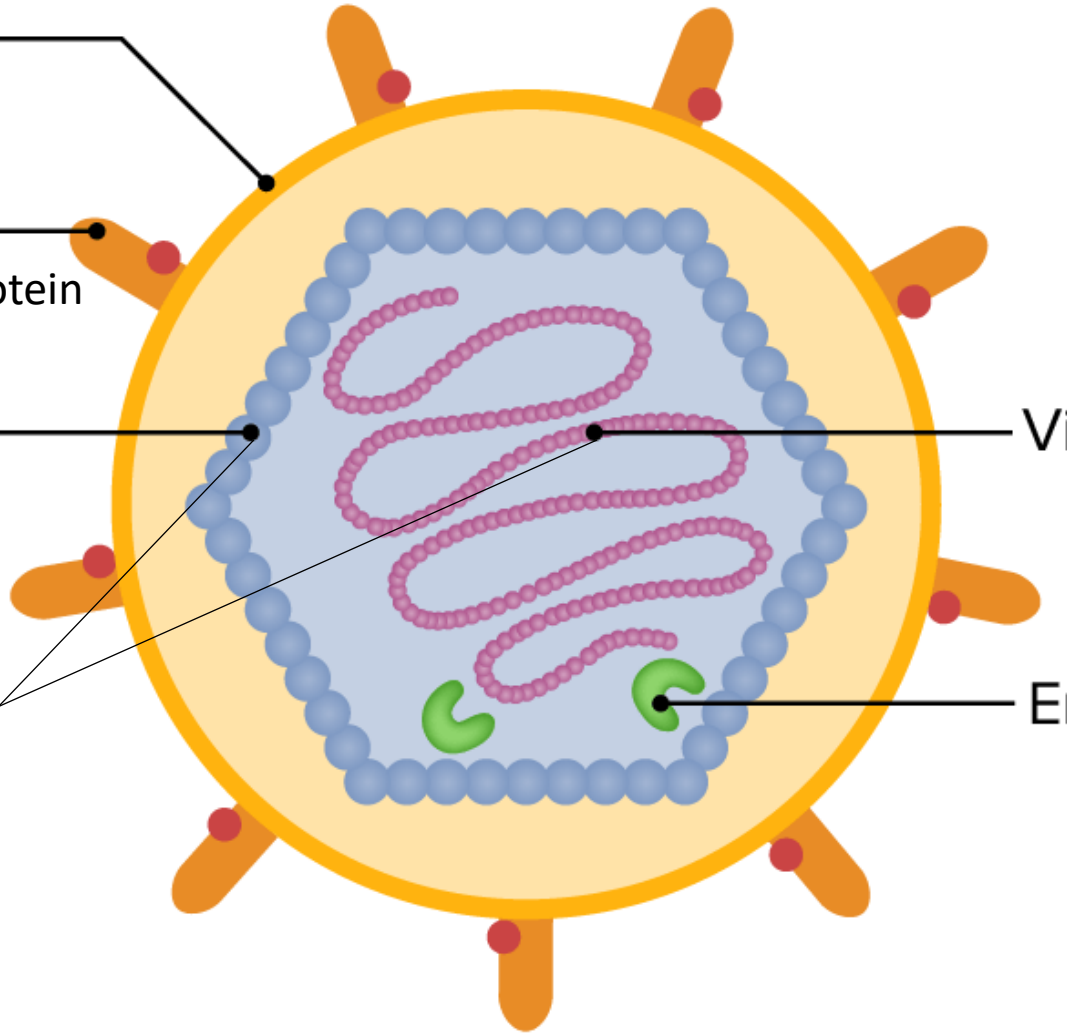
Overview

Viruses are obligate intracellular parasites. They lack both a cell wall and a cell membrane, and they do not carry out metabolic processes.

Virus replication:

- It has no metabolic machinery. Viruses use much of the host's 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)

Structure of the virus



Envelope

Envelope protein
Glycoprotein Spikes

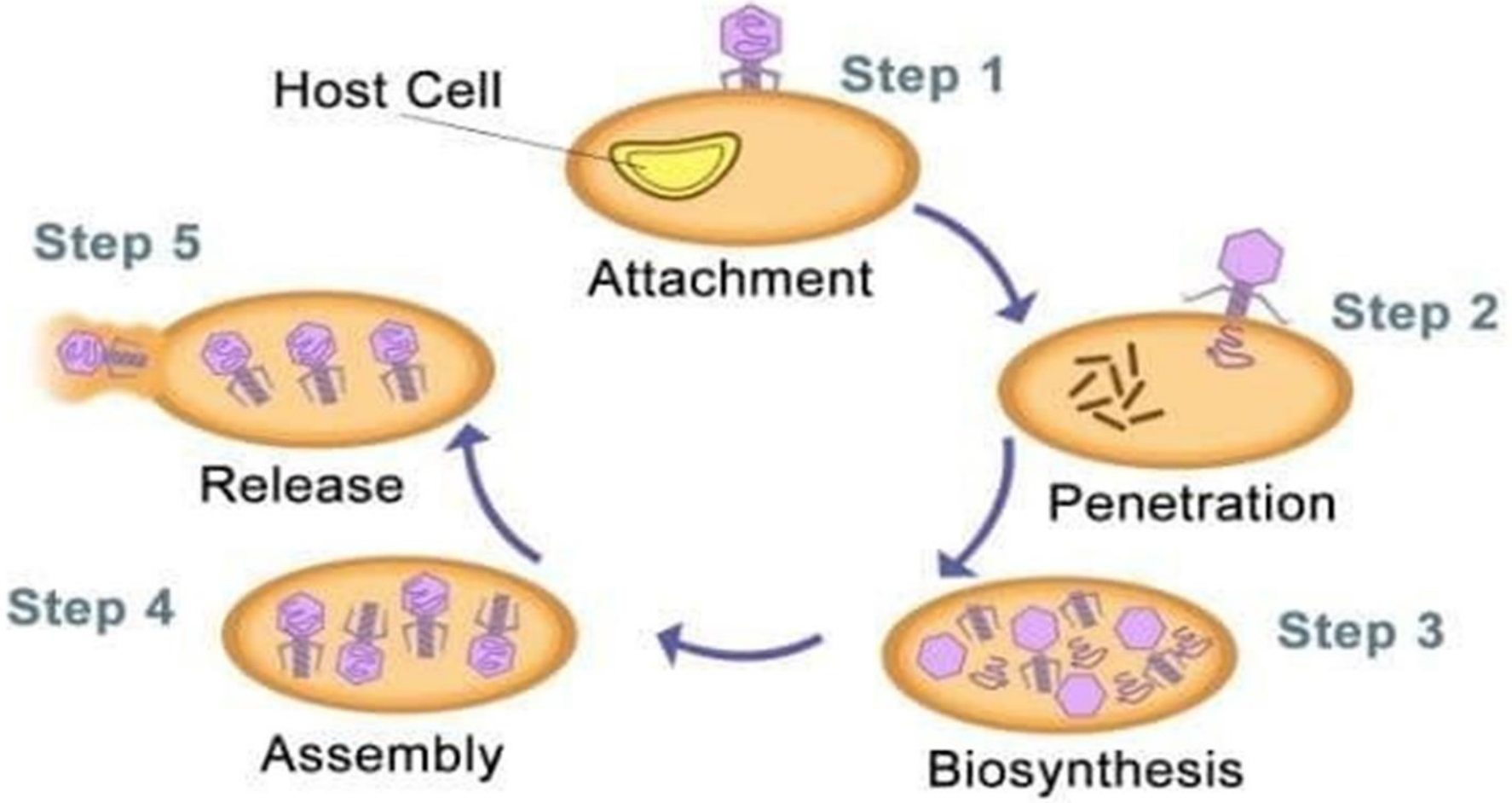
Capsid

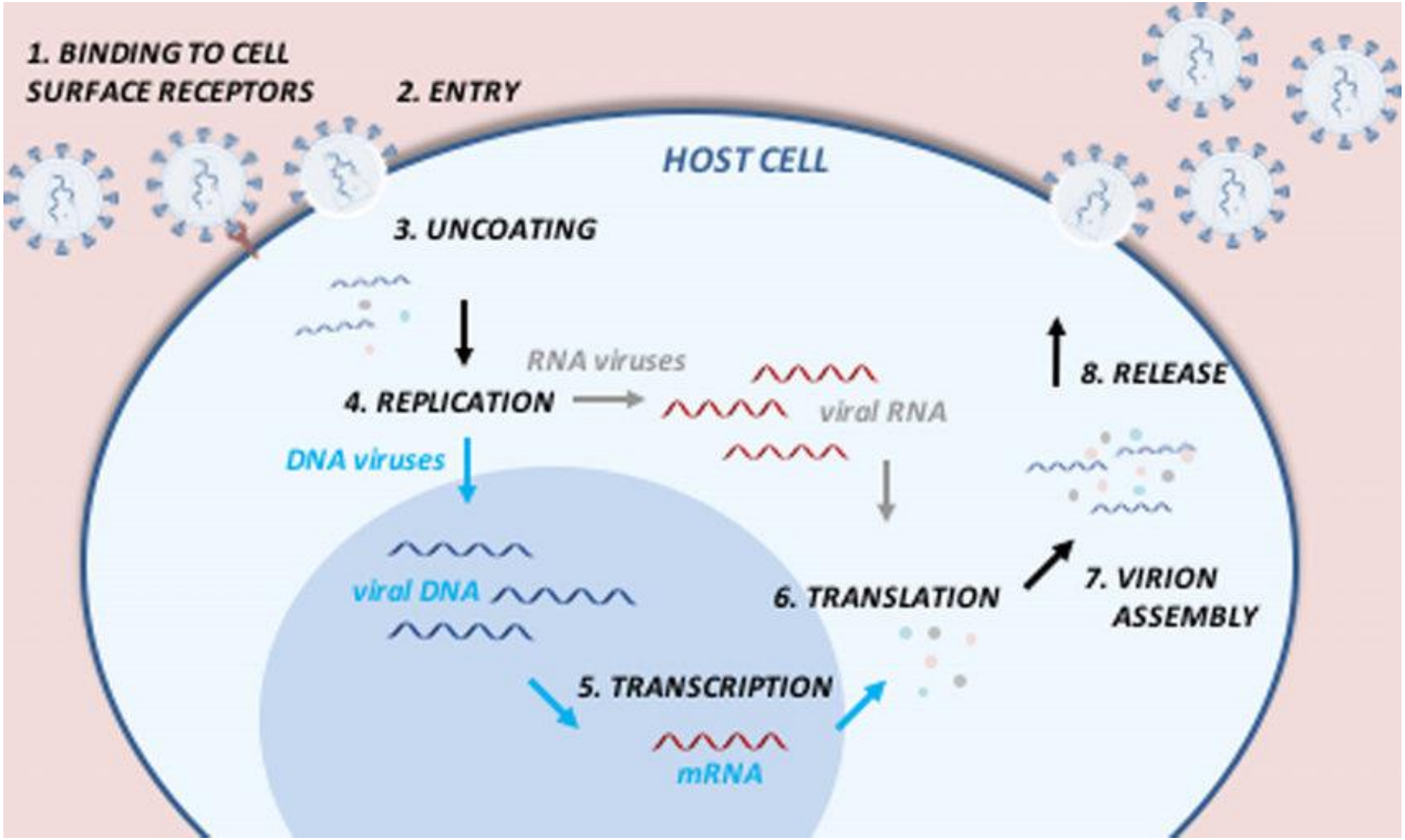
Capsid+genome=nucleocapsid

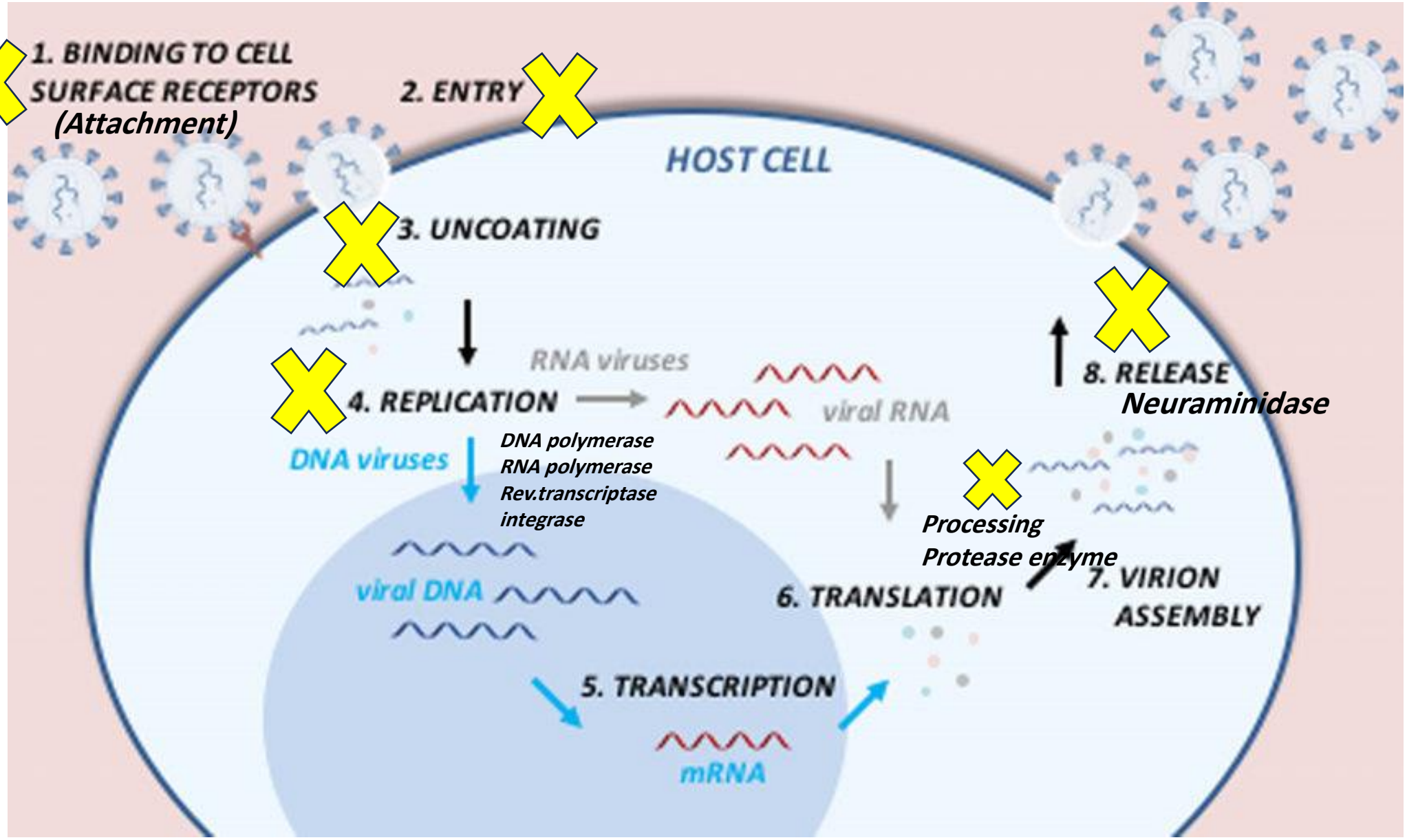
Viral genome
DNA/RNA

Enzyme
Protease
Integrase
Polymerase
Reverse transcriptase

Steps of viral replication



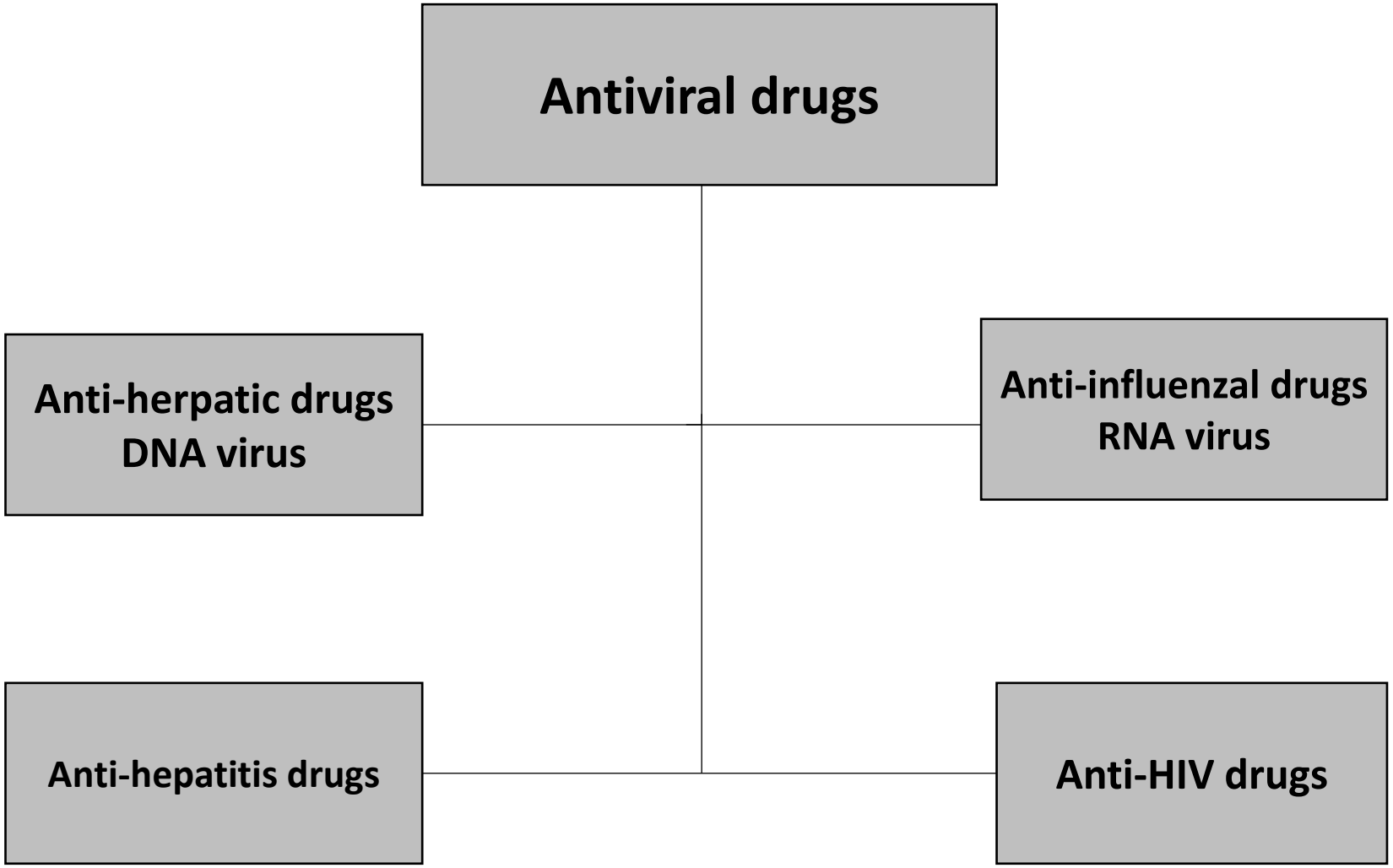

1. BINDING TO CELL SURFACE RECEPTORS
2. ENTRY
HOST CELL
3. UNCOATING
RNA viruses
4. REPLICATION
viral RNA
8. RELEASE
DNA viruses
viral DNA
6. TRANSLATION
7. VIRION ASSEMBLY
5. TRANSCRIPTION
mRNA


1. BINDING TO CELL SURFACE RECEPTORS (Attachment)
2. ENTRY
HOST CELL
3. UNCOATING
RNA viruses
4. REPLICATION
viral RNA
8. RELEASE
Neuraminidase
DNA viruses
DNA polymerase
RNA polymerase
Rev.transcriptase
integrase
Processing
Protease enzyme
viral DNA
6. TRANSLATION
7. VIRION ASSEMBLY
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


Antiviral drugs
Anti-herpatic drugs
DNA virus
Anti-influenzal drugs
RNA virus
Anti-hepatitis drugs
Anti-HIV drugs

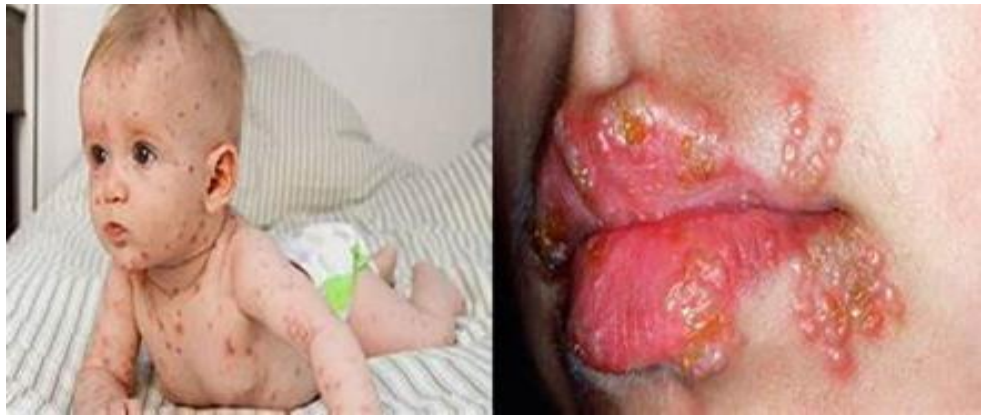
Anti-herpatic drugs (DNA virus)
((nucleotide analogues))

Acyclovir, famciclovir, valacyclovir

Ganciclovir, Valganciclovir

Famciclovir

DRUG	ROUTE
Acyclovir	IV
Valacyclovir	Oral
Ganciclovir	IV
Valganciclovir	oral



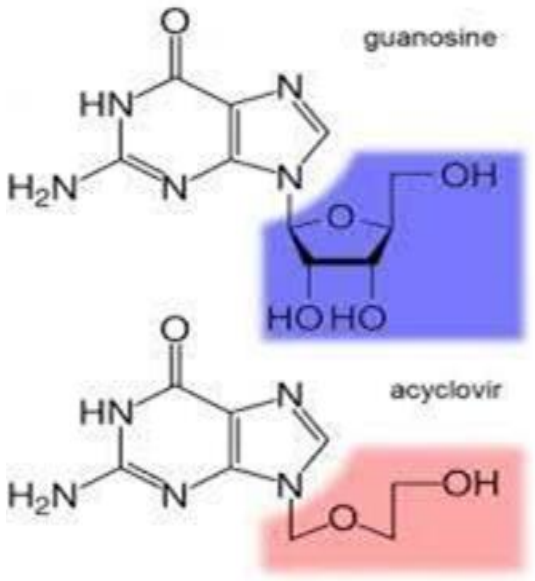
Acyclovir, famciclovir, valacyclovir

A nucleotide analogue drug typically means two things:
1.It is administered as a **prodrug** (an inactive form that requires activation within the body) so it undergoes **phosphorylation** within the body to become active and mimic natural nucleotides.
2. It **competes** with natural nucleotides for incorporation by the viral DNA polymerase during DNA synthesis. Once incorporated, the analogue will dominate the process, leading to **chain termination** and inhibiting viral replication

Acyclovir, famciclovir, valacyclovir

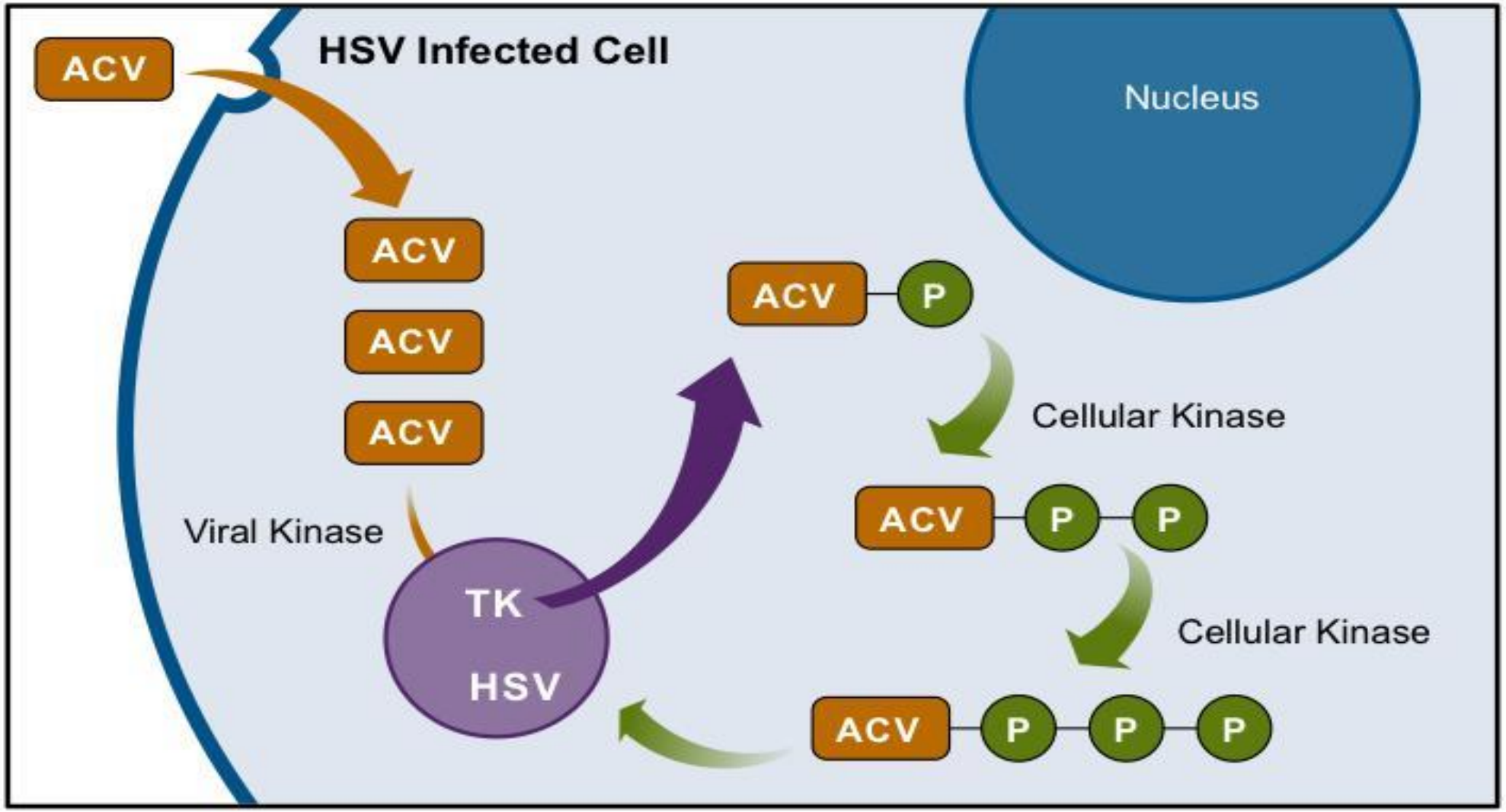
Activation:

- Guanosine analogs.
- Mono-phosphorylated by HSV/VZV thymidine kinase (TK)(not phosphorylated in uninfected cells → few adverse effects).



- Acyclovir and famciclovir are activated only by thymidine kinase in infected cells. This is a significant advantage because it makes them highly **selective** for virus-infected cells, minimizing their effects on uninfected cells and reducing toxicity.

They are further activated by host-cell kinases to the triphosphates



Triphosphates are substrates for viral DNA polymerase →

incorporated into the DNA molecule →

chain terminates

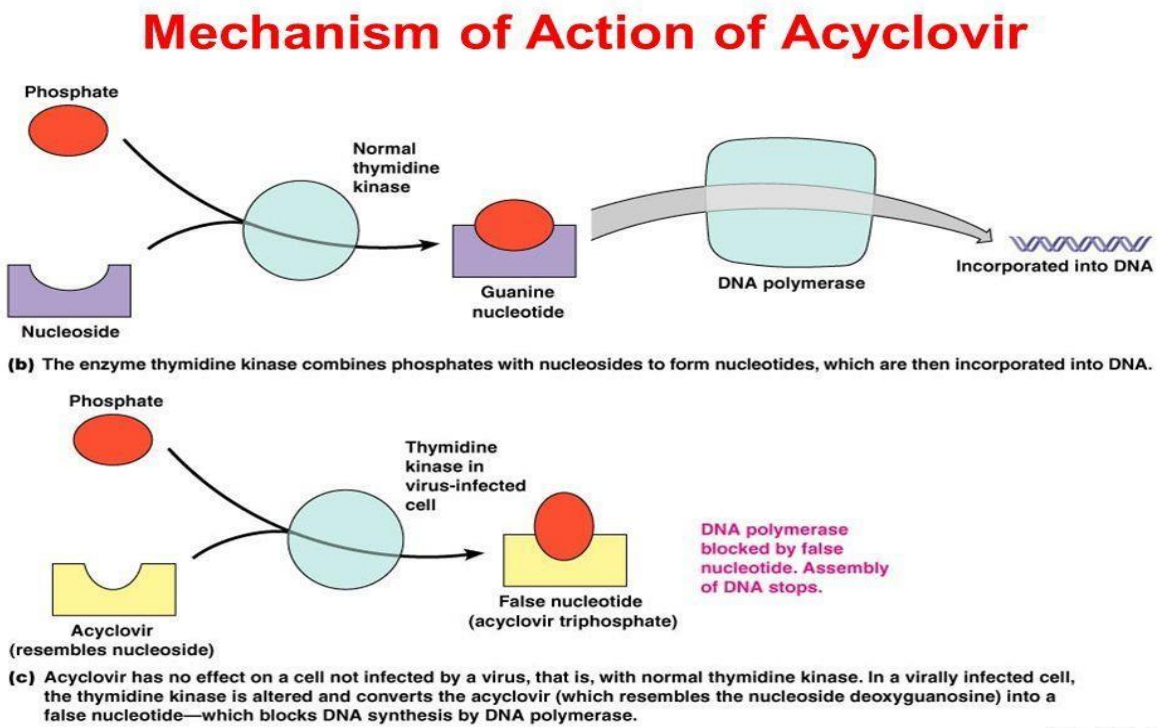


Fig 20.16

After activation by the phosphate group added by viral thymidine kinase, human cellular kinases add two more phosphate groups, converting it into acyclovir triphosphate. In this active form, it competes with natural nucleotides for incorporation by viral DNA polymerase, leading to chain termination (defective DNA synthesis), ultimately stopping viral replication and killing the virus.

Clinical uses:

-Treatment of herpes simplex and varicella zoster virus infections

-Prophylaxis in immuno-compromized patients . (To prevent the dormant virus from becoming active, as it is reactivated when immunity decreases.)

-No role in post-herpetic neuralgia

-famciclovir : For herpes zoster

-Valacyclovir is a prodrug of acyclovir (oral=IV acyclovir)

Toxicity:

-Crystalluria & nephropathy SO Maintain good hydration

Ganciclovir

Activation: Monophosphorylated by CMV kinase → effective against CMV.

Mechanism of action: Like acyclovir.

Clinical uses:

-Treatment & prophylaxis of Cytomegalovirus infection (especially immuno-compromized patients).

Note: Valganciclovir(ORAL) is a prodrug with better bioavailability (oral replacement for IV ganciclovir)

Toxicity:

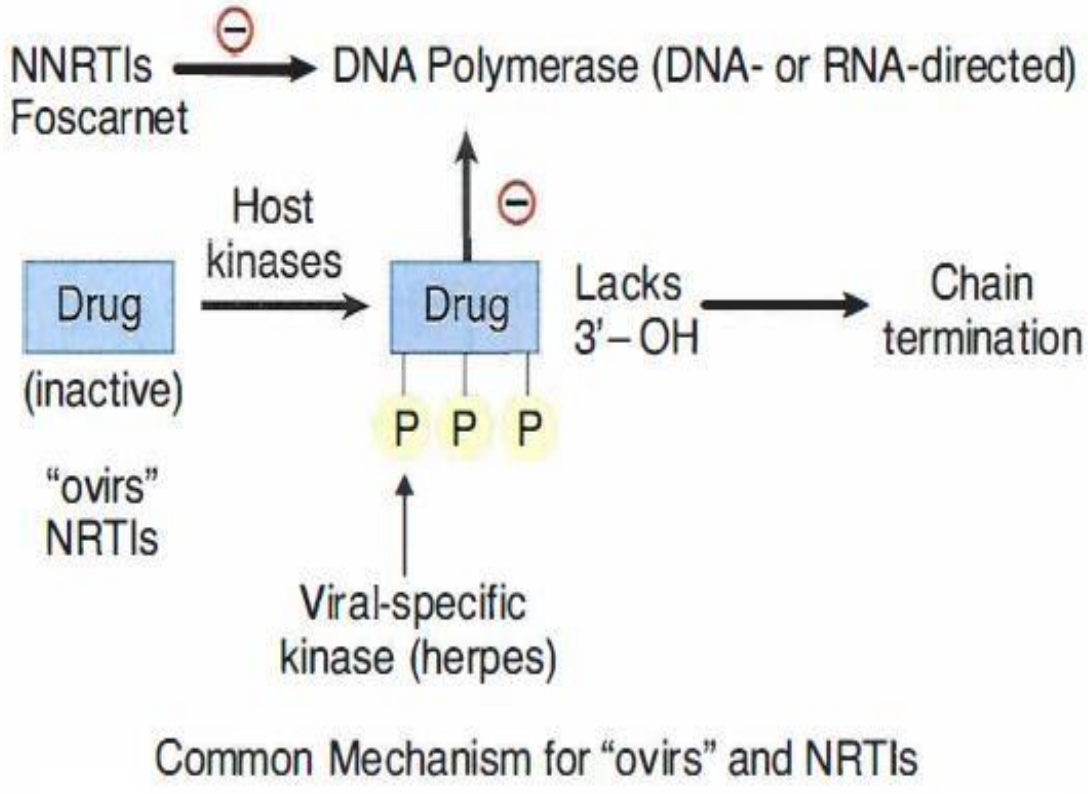
-Myelo-suppression (Leucopenia, thrombocytopenia).

-Nephropathy

Foscarnet

Doesn't require activation by viral or human kinases

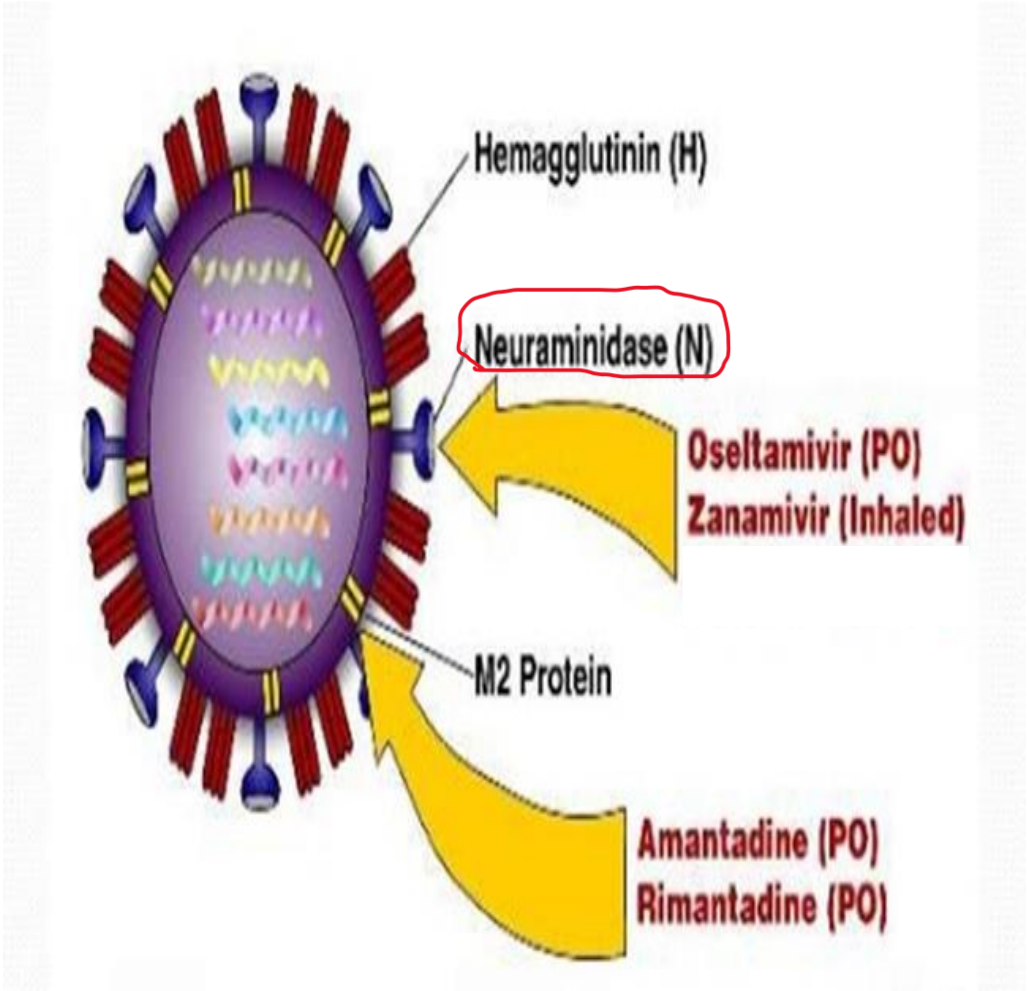
Mechanism of action:
- Inhibition of Viral DNA polymerase
- Inhibition RNA polymerase
- Inhibition HIV reverse transcriptase



Common Mechanism for "ovirs" and NRTIs

Clinical uses:
-Ganciclovir-resistant CMV infection.
-Acyclovir-resistant HSV infection.

Toxicity:
-Nephrotoxicity
-Electrolyte disturbances that may cause seizures (hypocalcemia & hypomagnesemia)



Anti-influenzal drugs
RNA virals

- Amantadine & Rimantadine
- Oseltamivir & Zanamivir

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

Oseltamivir & Zanamivir

Mechanism of action:

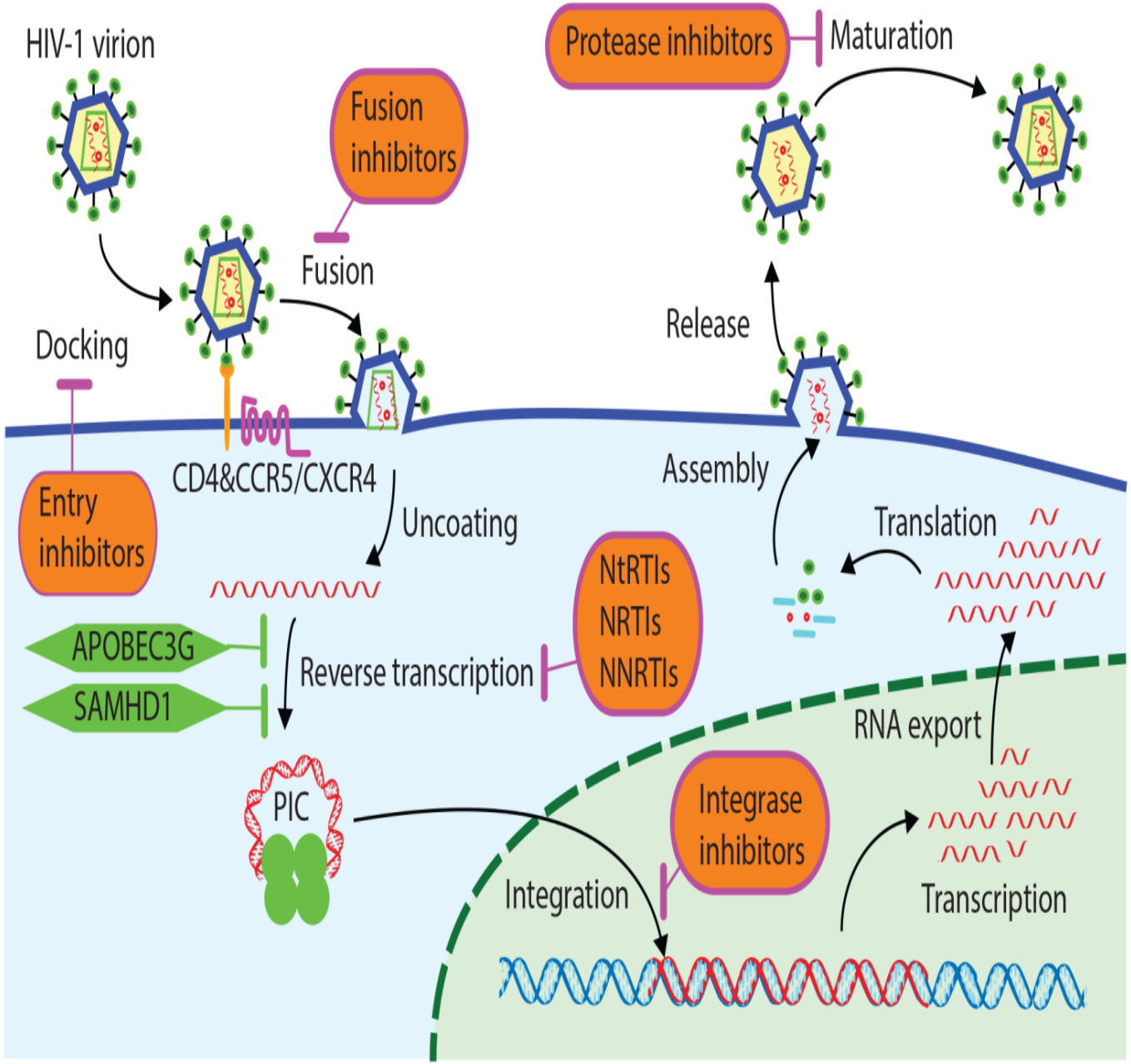
- inhibit neuraminidases of influenza A & B → viral clumping → prevents new viral particles from being released in the body.

Clinical uses:

Prevention & treatment of influenza A & B

Anti-HIV drugs

- Fusion inhibitors
- Reverse transcriptase inhibitors (nucleoside and non-nucleoside) (Main component)
- Protease inhibitors (PIs).
- Integrase inhibitors



- HIV virus is highlyyyyyyyy resistant to drugs ☹
- 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):

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

Nucleoside Reverse transcriptase inhibitors (NRTIs).

- **Zidovudine**
- **Lamivudine**
- **Didanosine**
- **Tenofovire**

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.

NOTE :

- **Zidovudine** : Is used for general prophylaxis and for prevention of vertical transmission in pregnancy.

- Toxicity:

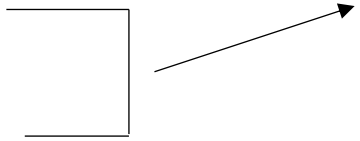
-Bone marrow depression (can be reversed(treated) by granulocyte colony stimulating factor [G-CSF] and erythropoietin).

-Peripheral neuropathy and myopathy.

-Lactic acidosis.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs).

- **Efavirenz**
- **Etravirine**



Mechanism of action:

-Bind to inhibition of reverse transcriptase and chain termination of DNA.
-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 pregnancy.

Protease inhibitors (PIs).

- **Atazanavir**
- **Lopinavir**
- **Ritonavir**

Mechanism of action:

-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:

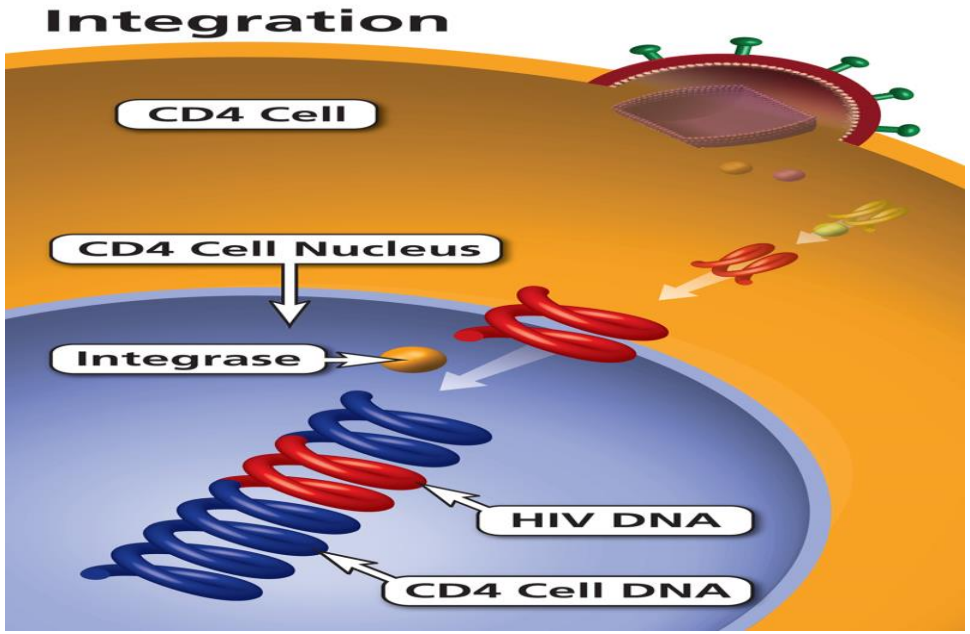
- Hyperglycemia (insulin resistence) &lipodystrophy.
- Nausea & diarrhea.
- Drug-drug interactions.
- N.B. No bone marrow depression.

Integrase inhibitors

- **Raltegravir**
- **Elivtegravir**

Mechanism of action:

Inhibit integration of viral genome in host cell DNA.



Fusion inhibitors

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:

-Injection site reaction and hypersensitivity.

-Increased incidence of bacterial pneumonia

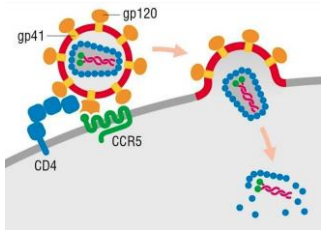
Maraviroc

Mechanism of action:

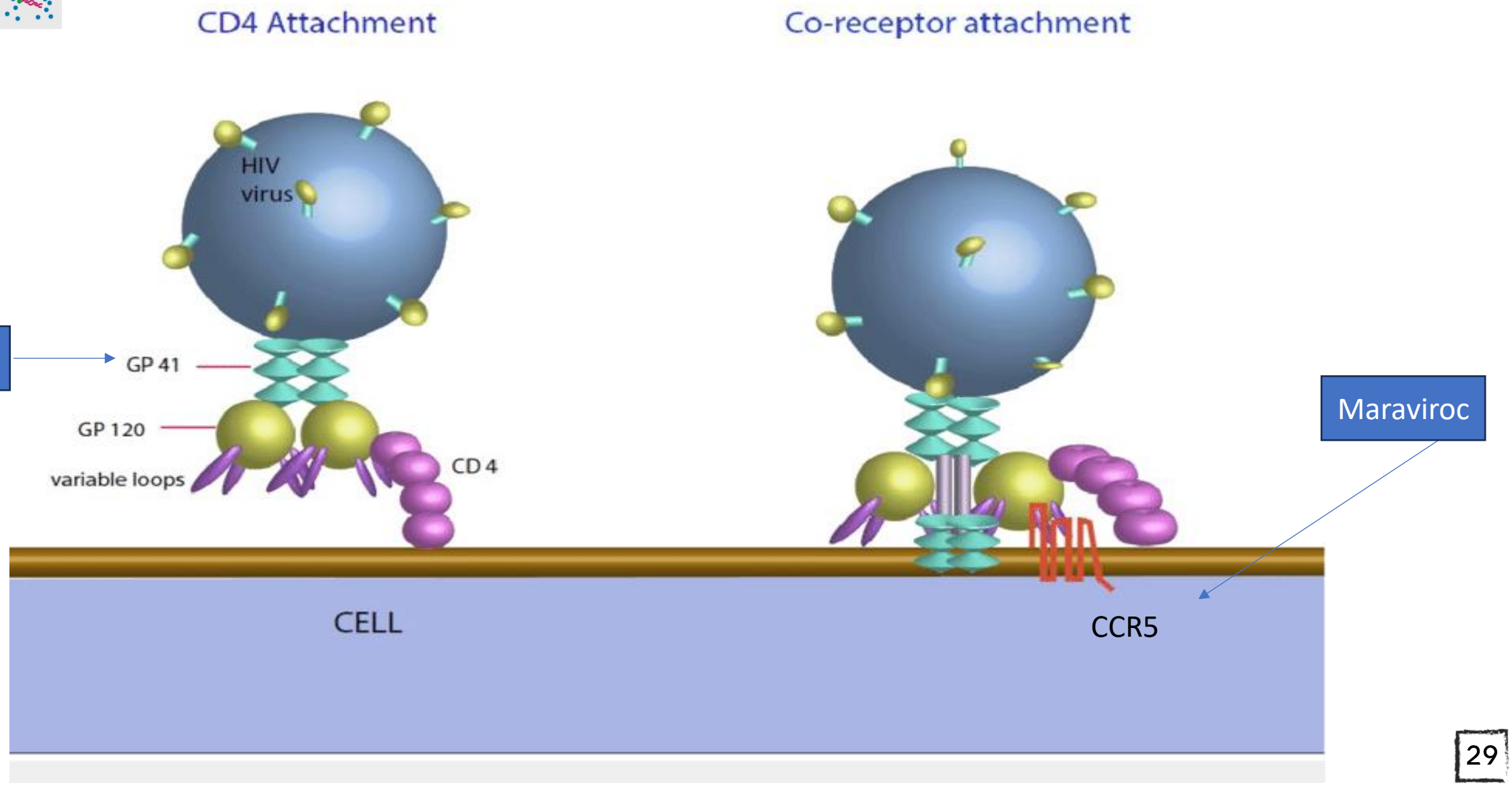
binds specifically and selectively to the membrane host protein CCR5, one of two chemokine receptors necessary for entry of HIV into CD4+ cells
So, it inhibits binding and entry of the virus into immune cells

Adverse effects:

-Cough
-Diarrhea
-Muscle and joint pain



Fusion inhibitors



Enfuvirtide

Maraviroc

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	Indinavir, ritonavir, saquinavir, nelfinavir
6-Inhibit viral neuraminidase	**Zanamivir, oseltamivir**

«Wherever the art of medicine is loved,

there is also a love of humanity.»

- Hippocrates-

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