HLS

MODIFIED NO. ?

PHARMACOLOGY

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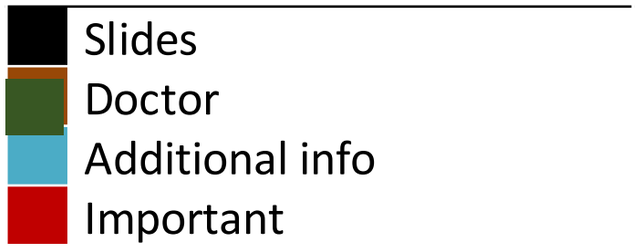
Antivirals

Color code



The head of a pin can hold five hundred million rhinoviruses (cause of the common cold). One sneeze can generate an aerosol of enough cold viruses to infect thousands of people!

Antiviral chemotherapy

- **Virus Structure and Replication**

  Viruses are the smallest infective agent, effectively consisting of nucleic acid (DNA or RNA) enclosed in a protein coat.

  Viruses are intracellular parasites with no, or little, metabolic machinery of their own.

  They have to borrow the biochemistry of the host cell to succeed and grow (this is what makes selective antiviral therapy so difficult).

Antiviral chemotherapy

·The virus attaches to specific receptors on the host cell surface which are normal membrane components.Usually ion channels, neurotransmitter receptors.

• The receptor/virus complex enters the cell by receptor-mediated endocytosis during which the virus coat maybe removed.

- **The nucleic acid of the virus then hijacks the cellular machinery for replicating viral nucleic acids and proteins for the manufacture of new virus particles,and that's the major problem because the body doesn't have control on the virus itself even with the drugs that taken .**

- Remember this: treatment must occur before or during the virus flare. Either we treat early, or we do not treat at all, except for HIV, which integrates into the human genome. Worldwide, 70% of HIV cases are attributed to homosexual transmission.
- **All the antiviral drugs work on the replication not symptoms . Unlike cancer cells, the immune system fights against the viruses.**

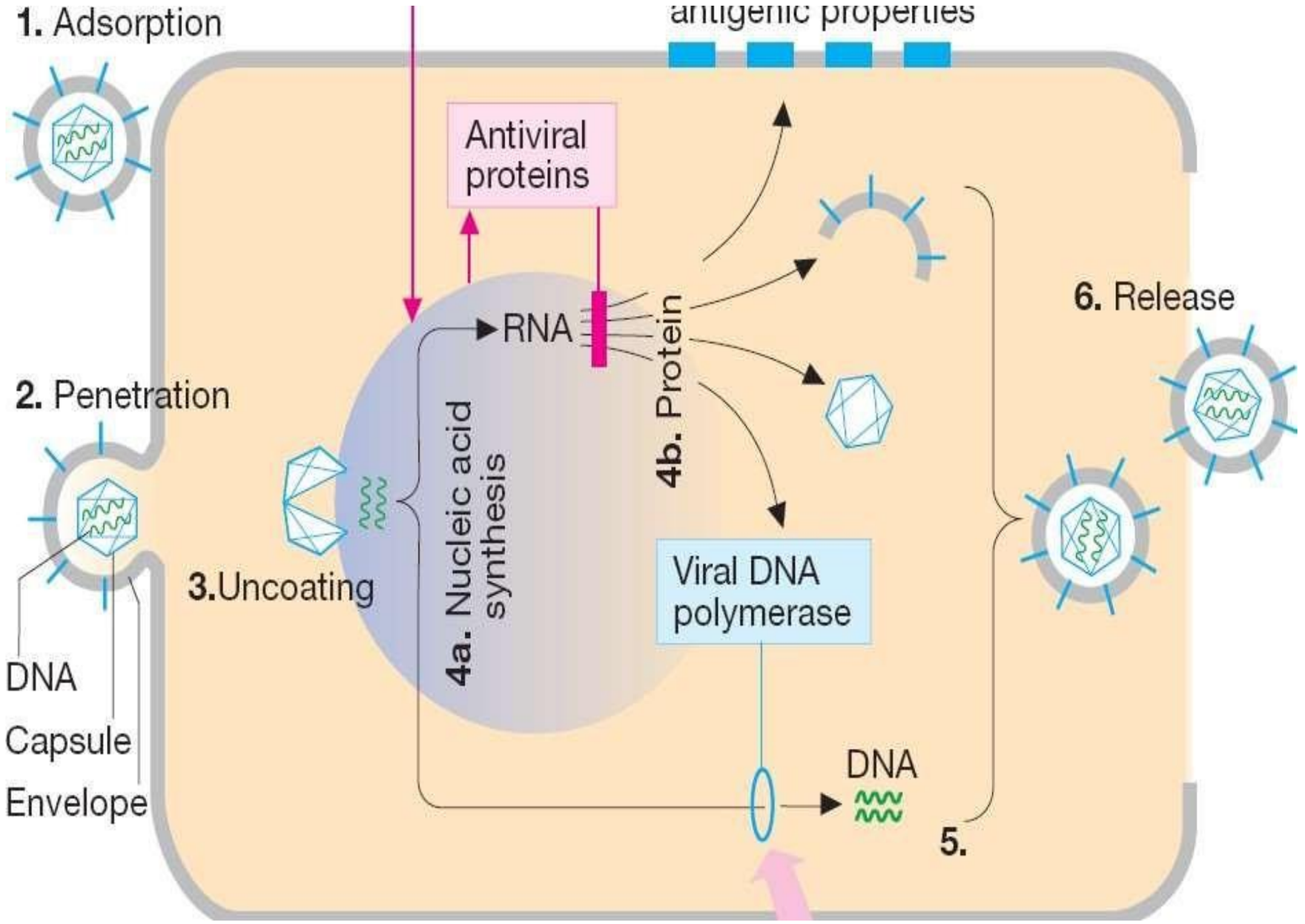
- **Flare : is a tremendous replication that happens within 24 hours of symptoms,** "flare" is a worsening of the disease process and ends at 48 hours.

Antiviral chemotherapy

- **The genome of DNA viruses enters the cell nucleus and uses host RNA polymerase to produce virus-specific proteins.**

- **After assembly of coat proteins around the viral DNA, complete virions are released by budding or after cell lyses.**

- **Generally, RNA virus replication occurs solely in the cytoplasm and doesn't involve the cellular nucleus. (influenza are an exception since they have a requirement for active cellular transcription).**


1. Adsorption
antigenic properties
Antiviral proteins
RNA
4b. Protein
6. Release
2. Penetration
3.Uncoating
4a. Nucleic acid synthesis
Viral DNA polymerase
DNA
Capsule
Envelope
DNA
5.

Treatment of Herpesviruses (DNA viruses)
Varicella-zoster,
Cytomegalavirus,
Herpes simplex

Varicella-zoster causes shingles

Cytomegalovirus causes respiratory problems in children(pneumonia) , also can cause retinitis in retina

Herpes simplex (the most common virus) causes labialis (oral herpes) and can also cause ulcers in the vagina.

We will begin with a time series of treatment

Anti-metabolites

- "False" DNA building blocks **or nucleosides.** A nucleoside consists of a nucleobase and the sugar deoxyribose.

- In antimetabolites, one of the components is defective. In the body, the abnormal nucleosides undergo bioactivation by attachment of three phosphate residues

- **Acyclovir** has both specificity of the highest degree and optimal tolerability, because it undergoes bioactivation only in infected cells, where it preferentially inhibits viral DNA synthesis.

- An anti-metabolite is used to stop uncontrolled replication, whether in transcription or translation. It targets infected cells as well as bone marrow, causing pancytopenia(bone marrow suppression), as seen with false metabolite vidarabine and Ganciclovir (old drugs).

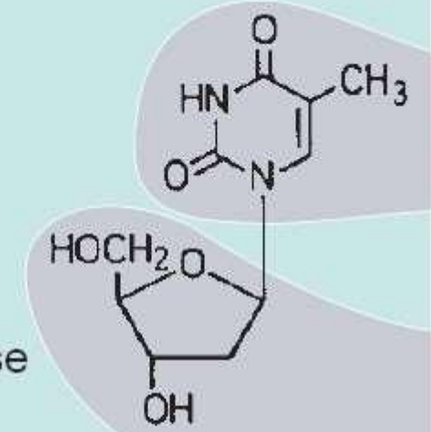
Antimetabolites = incorrect DNA building blocks

Correct:

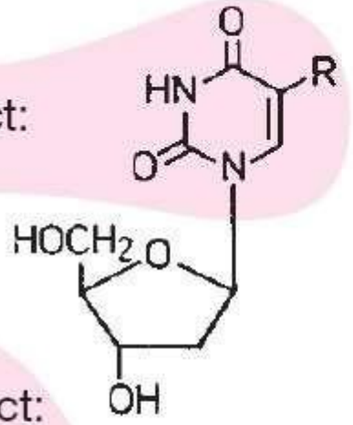
Thymidine

Thymine

Desoxyribose



Incorrect:

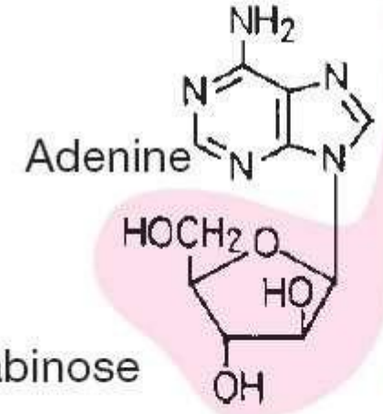


R: - I Idoxuridine
- CF_3 Trifluridine
- C_2H_2 Edoxudine

Insertion into DNA instead of thymidine

Incorrect:

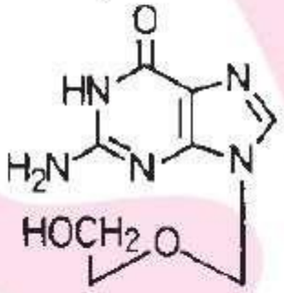
Vidarabine



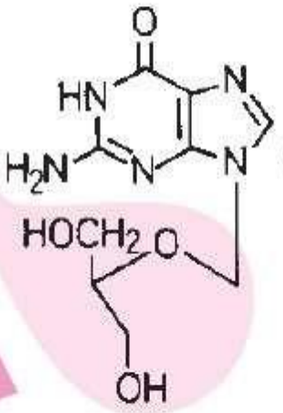
Adenine

Arabinose

Acyclovir



Ganciclovir



Guanine

Inhibition of viral DNA polymerase

Acyclovir

- **A virally coded thymidine kinase (specific to H.simplex and varicella-zoster virus) performs the initial phosphorylation step; the remaining two phosphate residues are attached by cellular kinases.** In the past, all three phosphate groups were attached by cellular kinases, which is why bone marrow suppression occurred.

- The main breakthrough is that the HSV selectively activates the Acyclovir like Zovirax drug which are used in children for treating ulcers.
- Genetic ulceration is more common in the western countries because of the sexual practices.

- **Acyclovir triphosphate inhibits viral DNA polymerase resulting in chain termination** by two mechanisms: either by incorporating into the DNA and blocking it, or by binding directly to the polymerase, which is sufficient to inhibit polymerization.

- **It is 30-fold more potent against the virus enzyme than the host enzyme.**

- **Acyclovir is active against herpes simplex and varicellar- zoster virus.**

- **It is rapidly broken down in cells, is orally active and is relatively non-toxic systemically.**

Acyclovir

and Valacyclovir (pro-drug, better availability)

Acyclovir +ester group= Valacyclovir

A Guanine analogue with antiviral for Herpes group only

Acyclovir → **AcycloGMP** → **AcycloGTP**

Thymidine kinase

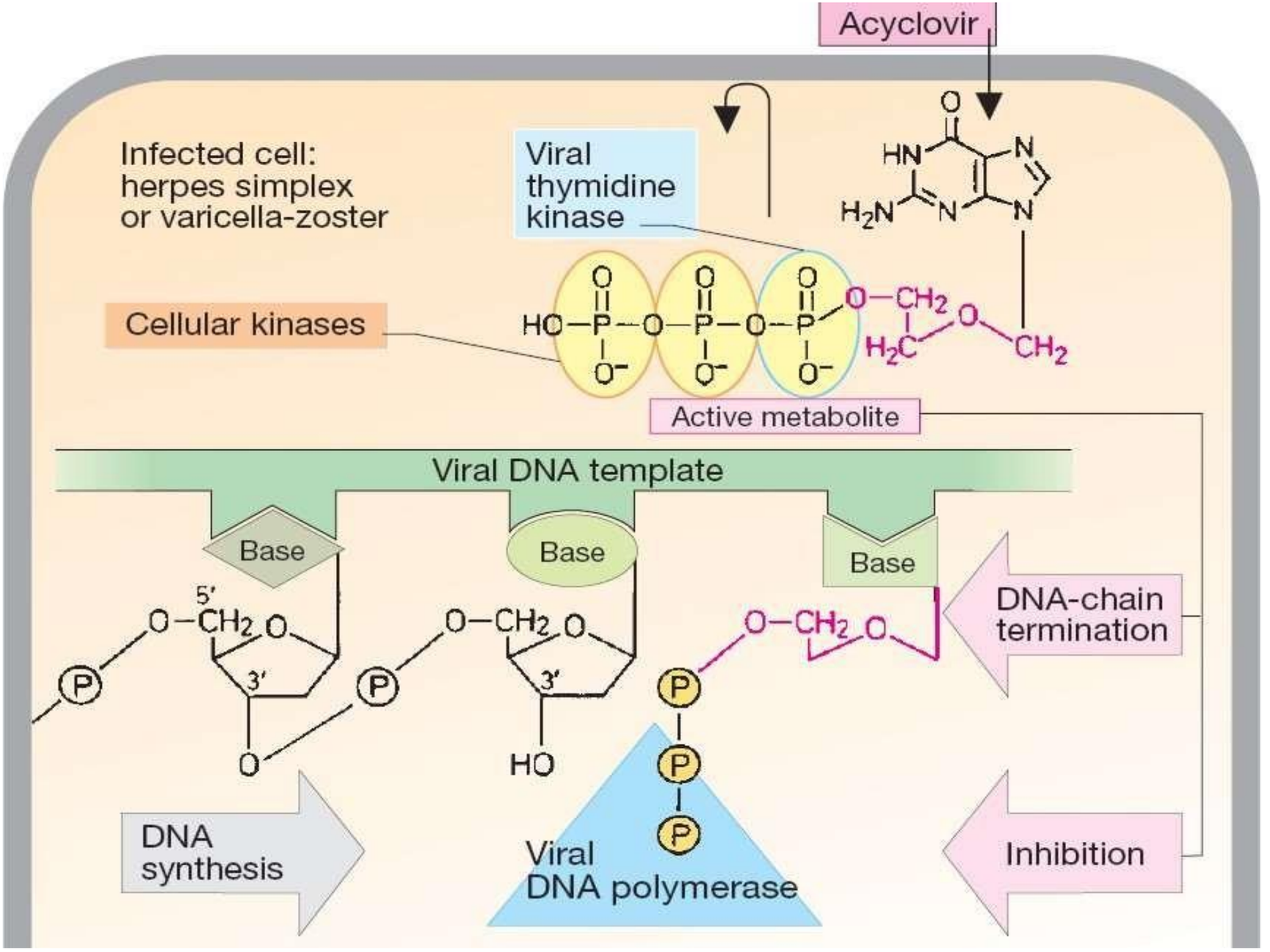
Viral 200x affinity of mammalian

Cellular kinases

1. Inhibits viral DNA polymerase selectively
2. Incorporated into DNA and terminates synthesis

Valacyclovir is a pro-drug with better availability due to a transporter that facilitates its entry into the body. It consists of acyclovir with an added ester group, forming valacyclovir. It is typically given twice daily, and once daily as a prophylactic. Once inside the cell, the ester group is removed, converting it back to Acyclovir and get phosphorylated by thymidine kinase

Resistance:
1. ↓ activity of thymidine kinase
2. altered DNA polymerase


Acyclovir
Infected cell:
herpes simplex
or varicella-zoster
Viral
thymidine
kinase
Cellular kinases
Active metabolite
Viral DNA template
Base
Base
Base
DNA-chain
termination
DNA
synthesis
Viral
DNA polymerase
Inhibition

Acyclovir

It's teratogenic

Acyclovir is used to treat:

- **Herpes simplex infections (genital herpes, and herpes encephalitis).**
- **Chickenpox in immuno-compromised patients.**
- **Prophylactically in patients treated with immunosuppressant drugs or radiotherapy who are in danger of infection by reactivation of latent virus.**
- **Prophylactically in patients with frequent recurrence of genital herpes** or recurrences following ulcers. For example, having four ulcer recurrences in one year indicates a high viral load.

Prophylaxis is the primary use for Acyclovir, as treatment only shortens the duration of symptoms but does not prevent the viral flare .

In prophylaxis, a half-dose of acyclovir is used. Acyclovir has poor bioavailability, so it is administered four times a day at a dose of 500 mg.

- Oral acyclovir has multiple uses. In first episodes of genital herpes, oral acyclovir shortens the duration of symptoms by approximately 2 days, the time to lesion healing by 4 days, and the duration of viral shedding by 7 days. In recurrent genital herpes, the time course is shortened by 1–2 days.
- Without treatment, genital herpes typically lasts 7 days, but with treatment, it can be reduced to 5 days.

- Oral acyclovir is only modestly beneficial in recurrent herpes labialis.
- Topical acyclovir cream is substantially less effective than oral therapy for primary HSV infection. It is of no benefit in treating recurrent genital herpes.

Acyclovir

- **Common adverse drug reactions are nausea, vomiting, diarrhea and headache.**

- **Additional common adverse effects, when acyclovir is administered IV, include :**
  Renal insufficiency and neurologic toxicity

However, incommon with adequate hydration and avoidance of rapid infusion rate.

So if the drug has kidney toxicity the patient should be hydrated

Also, Patients with varicella zoster are treated with acyclovir four times a day or valacyclovir twice a day.

Ganciclovir

It's teratogenic

- **Mechanism like Acyclovir however it doesn't have A virally coded thymidine kinase**
- **Active against all Herpes viruses including CMV (100 time than acyclovir). (but we use it only with CMV)**

- **Low oral bioavailability given I.V.**

- **Most common adverse effect: bone marrow suppression (leukopenia 40%, thrombocytopenia 20%) and CNS effects (headache, behavioral, psychosis, coma, convulsions).**

- **1/3 of patients have to stop because of adverse effects**

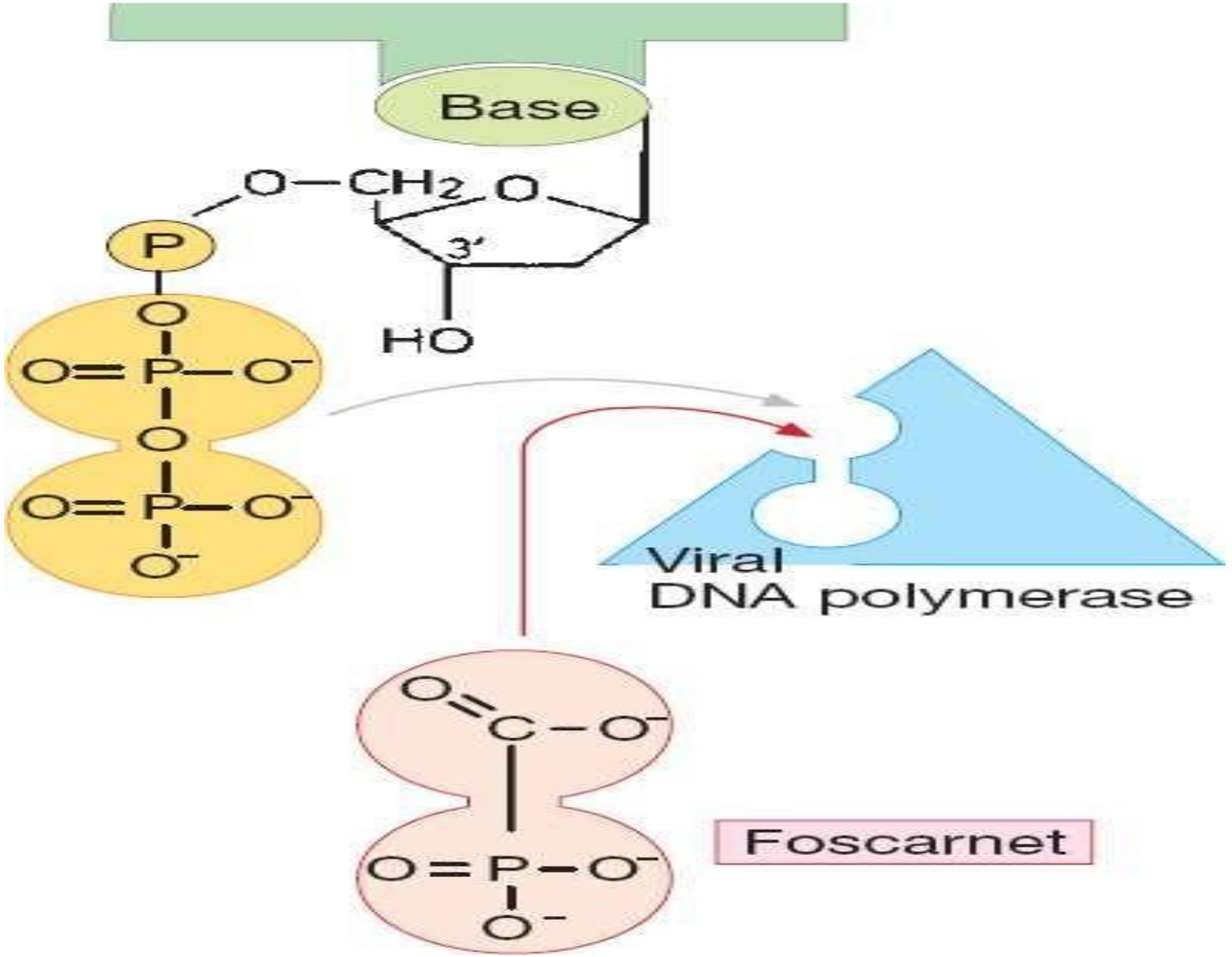
- **Drug of choice for CMV infections: retinitis, pneumonia, colitis.**
- After COVID-19, there has been a flare-up of cytomegalovirus, and the lung microbiome and immunocompetence have changed because we were not exposed to viruses or able to build resistance for two years.
- The doctor advised to conduct research on how CMV has changed and is now causing pneumonia, especially in children.

Foscarnet

- **An inorganic pyrophosphate analog**
- **Active against Herpes (I, II, Varicella , CMV), including those resistant to Acyclovir and Ganciclovir.(we usually use it for certain conditions ,mentioned below)**
- **Direct inhibition of viral DNA polymerase (very selective to it) and Reverse Transcriptase**

so, keep the drug away as this could lead to mutations in the viral DNA polymerase and a loss of its activity.

- **Nephrotoxicity (25%) most common side effect**
- **Use: (1) CMV retinitis and other CMV infections instead of ganciclovir**
  (2) H. simplex resistant to Acyclovir.
  (3) HIV.


Base
O—CH2 O
3′
P
HO
Viral
DNA polymerase
Foscarnet

Treatment of respiratory virus infection

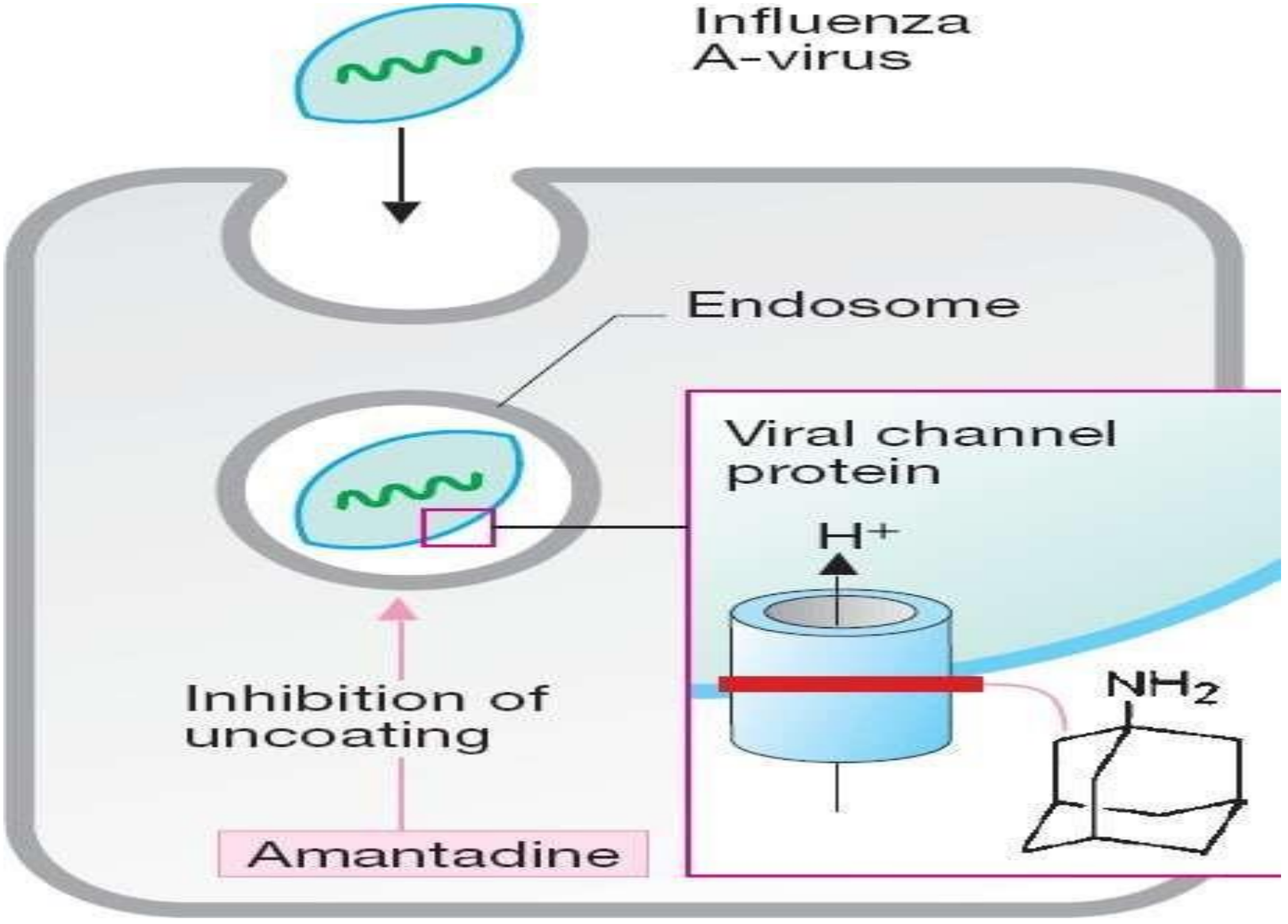
Influenza A & B

Respiratory suncytial virus (RSV)

This slide is not required because they are old drugs

Attachment Inhibitors

- The primary antiviral mechanism of Amantadine and Rimantadine is to block the viral membrane matrix protein, which function as an ion channel that is required for the fusion of the viral membrane with the cell membrane.
- Their clinical use is limited to Influenza A infection.
- They are very effective in preventing infection if the treatment is begun at the time of-or prior to- exposure to the virus.


Influenza
A-virus
Endosome
Viral channel
protein
H+
NH2
Inhibition of
uncoating
Amantadine

This slide is not required because they are old drugs

Attachment Inhibitors

- **Side effects of Amantadine are mainly associated with the CNS, such as ataxia and dizziness.**
- **While Rimantadine produce little CNS effect because it does not penetrate the blood brain barrier.**
- **Both should be used with caution in pregnant and nursing women.**

Neuroaminidase inhibitors

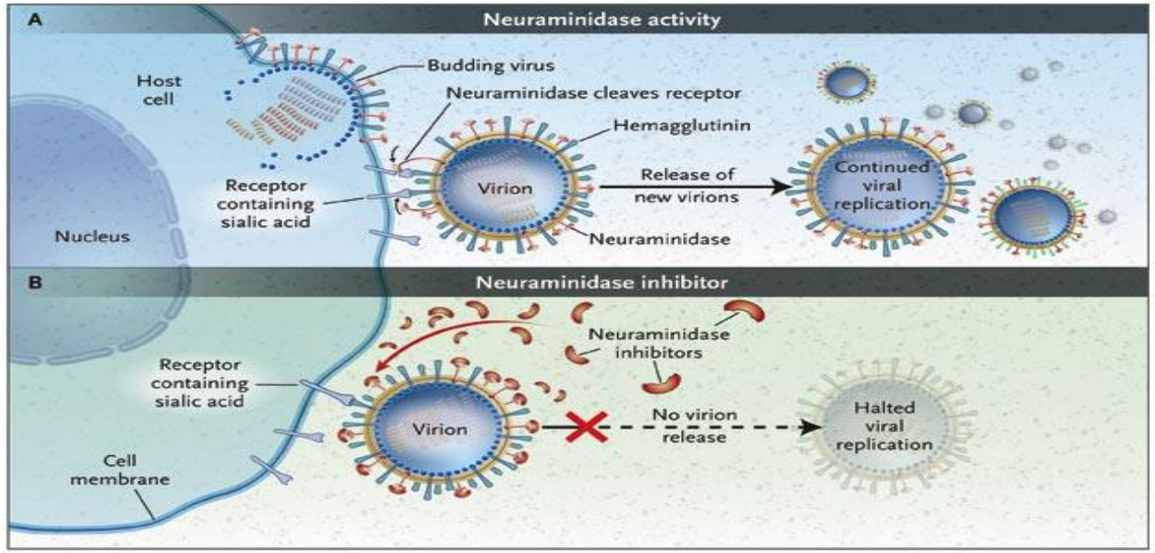
Oseltamivir (tamiflu) and Zanamavir (inhalation)

Viral neuraminidase catalyzes cleavage of terminal sialic acid residues attached to glycoproteins and glycolipids, a process necessary for release of virus from host cell surfaces.

- **Neuraminidase inhibitors thus prevent release of virions from infected cell** so, Don't use this drug

- Neuraminidase is an enzyme produced by certain pathogens that modifies the host's response to infection. It cleaves N-acetylneuraminic acid (NAN) from cell surfaces, leading to the production of pyruvate.

- Extra picture



Neuroaminidase inhibitors

- **Administration of neuraminidase inhibitors is a treatment that limits the severity and spread of viral infections.**

- **Neuraminidase inhibitors are useful for combating influenza infection:**

  zanamivir, administered by inhalation;

  oseltamivir, administered orally.

- **Toxicities**

– **Exacerbation of reactive airway disease by zanamavir**

– **Nausea and vomiting for oseltamivir**

- This drug is associated with flare issues , so it must be started within 48 hours of the onset of symptoms such as sore throat, runny nose, or fever.
- It is effective against the H5N1 (The bird flu virus).

oseltamivir

- Early administration is crucial because replication of influenza virus peaks at 24–72 hours after the onset of illness.
- When a 5-day course of therapy is initiated within 36–48 hours after the onset of symptoms, the duration of illness is decreased by 1–2 days compared with those on placebo, However, do not prescribe this drug, as 1–2 days of symptom relief does not justify losing one of the last effective treatment options.
- severity is diminished, and the incidence of secondary complications in children and adults decreases.
- Once-daily prophylaxis is 70–90% effective in preventing disease after exposure (in immunocompromised patients).

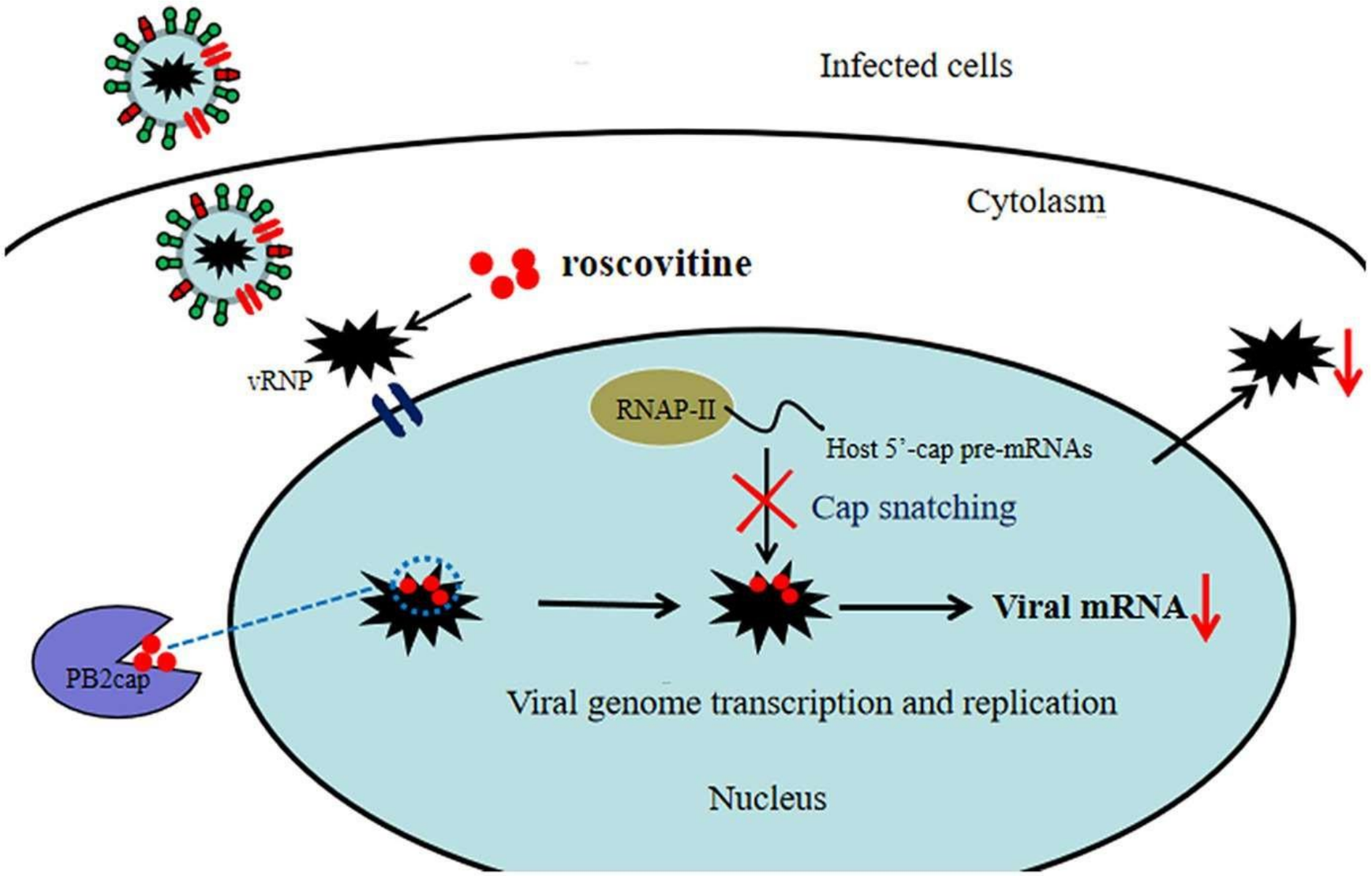
Cap-dependent endonuclease inhibitor

Baloxavir marboxil

inhibit influenza virus' cap dependent endonuclease activity (**cap snatching)**.

cap snatching: the first 10 to 20 residues of a host cell RNA are removed (snatched) and used as the 5’ cap and primer to initiate the synthesis of the nascent viral mRNA.

-After the virus is endocytosed and the RNA is released, it hijacks the cellular machinery. Part of the viral RNA is transcribed using cellular ribosomes. Before the premature RNA becomes mature, it undergoes splicing. A methyl guanine cap is added to the 5’ end, and a poly-A tail is added to the 3’ end. This cap is important for the ribosome to recognize the RNA and translate it. However, the viral RNA lacks this cap, so it uses endonuclease to steal the 5`cap (cap snatching).
-It is a Japanese drug.
-The resistance begins(10%), despite it is a new drug.


Infected cells
Cytolasm
roscovitine
vRNP
RNAP-II
Host 5'-cap pre-mRNAs
Cap snatching
Viral mRNA
PB2cap
Viral genome transcription and replication
Nucleus

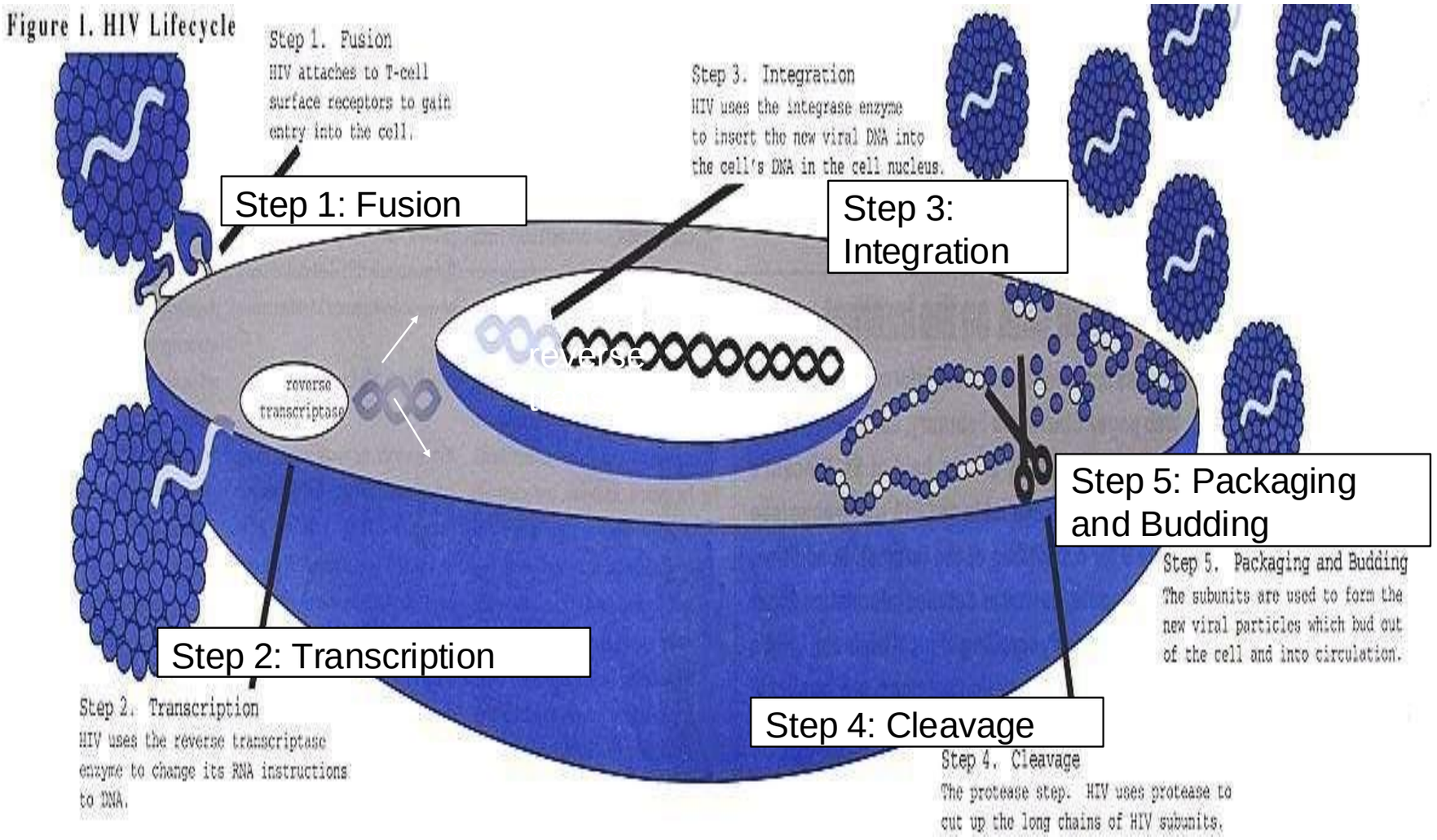
This slide is not required

Ribavirin

- **It is an antimetabolite that inhibits influenza RNA polymerase non-competitively *in vitro* but poorly in vivo.**
- **An aerosol form is used against RSV (respiratory syncytial virus) and the drug is used intravenously against Lassa fever.**
- **Adverse reactions includes: Anemia due to hemolysis and bone marrow suppression**

Antiretroviral agents

HIV Life Cycle



HIV, an RNA virus, has two important enzymes:

1. **Reverse transcriptase** – Converts viral RNA to DNA.
2. **Integrase** – Inserts the new viral DNA into the host cell's DNA within the cell nucleus.

Once integrated, the viral DNA is transcribed, translated, and replicated within helper T cells. Treatment is difficult because the virus hijacks these T cells, making it difficult to eliminate.

Azidothymidine (Zidovudin(AZT))

- **It is a potent antagonist of reverse transcriptase, It is a chain terminator.**

- **Cellular enzyme phosphorylate AZT to the triphosphate form which inhibits RT and causes chain termination (anti-metabolite)**

- **It is widely use in the treatment of AIDS (The only clinical use).**

- **AZT is toxic to bone marrow, for example, it cause severe anaemia and leukopenia In patient receiving high dose.**

Headache is also common

Didanosine (Dideoxyinosine)

- **Didanosine act as chain terminators and inhibitors of reverse transcriptase because they lack a hydroxyl group.**
- **Is phosphorylated to the active metabolite of dideoxyadenosine triphosphate**
- **It is used in the treatment of AIDS (second drug approved to treat HIV-1 infection).**
- **They are given orally,**
- **and their main toxicities are pancreatitis, peripheral neuropathy, GI disturbance, bone marrow depression.**

Non-nucleoside Non-competitive RT inhibitors

(1) bind to viral RT, inducing conformational changes that result in enzyme inhibition (direct inhibitor of reverse transcriptase)

(2) Combination therapy with AZT (resistant mutants rapidly emerge, little use in monotherapy)

(3) Resistance mutations will be at different sites

Generic Name	Trade Name	Usual Dose
Nevirapine	Viramune®	200 mg QD x14 days, then 200 mg BID
Delavirdine	Rescriptor®	400 mg TID
Efavirenz	Sustiva™	600 mg QD

Non-nucleoside Non-competitive RT inhibitors

It isn't teratogenic

Nevirapine **Approved for AIDS patients, Good blocker of mother to child transmission(vertical transmission)(perinatal -breast feeding)**

- **Single dose at delivery reduced HIV transmission by 50%**
- **Single dose to baby by 72 hours**

NNRTI's: Adverse Effects

RASH!!

CNS effects (e.g. sedation, insomnia, vivid dreams, dizziness, confusion, feeling of "disengagement")

We use dose escalation, starting with a low dose and gradually increasing it. For the first 14 days, we administer half the dose, then increase it while monitoring the patient for any signs of rash.

Rash

Rash, occurs in up to 20% of patients, usually in the first 4–6 weeks of therapy.

Although typically mild and self-limited, rash is dose- limiting in about 7% of patients. Women appear to have an increased incidence of rash.

When initiating therapy, gradual dose escalation over 14 days is recommended to decrease the incidence of rash.

Protease Inhibitors

- **HIV Protease Inhibitors; have significantly alter the course of the HIV disease.**

- **All are reversible inhibitors of HIV Protease-the viral enzyme responsible for cleavage of viral polyprotein into number of essential enzymes (reverse transcription, polymerase).**

- **Examples are : Saquinavir, and Ritonavir. (navir)**

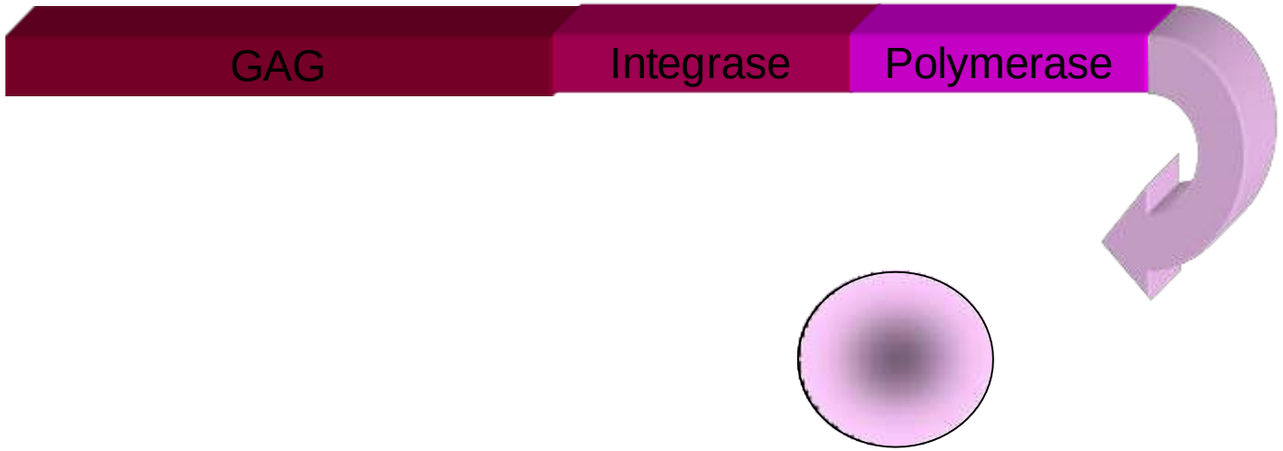
- **They are orally active, side effects include GI disturbances and hyperglycemia, interact with cytochrome P450,** inhibiting it and causing changes in lipid profiles, such as the development of a '**buffalo hump**,' similar to the effects seen with glucocorticosteroids. This causes a change in the treatment regimen to include **both** reverse transcriptase and protease inhibitors, rather than using reverse transcriptase inhibitors alone.

Anti-Viral Chemotherapy

GAG/POL polyprotein

Retrovirus --- HIV

Anti-Viral Chemotherapy

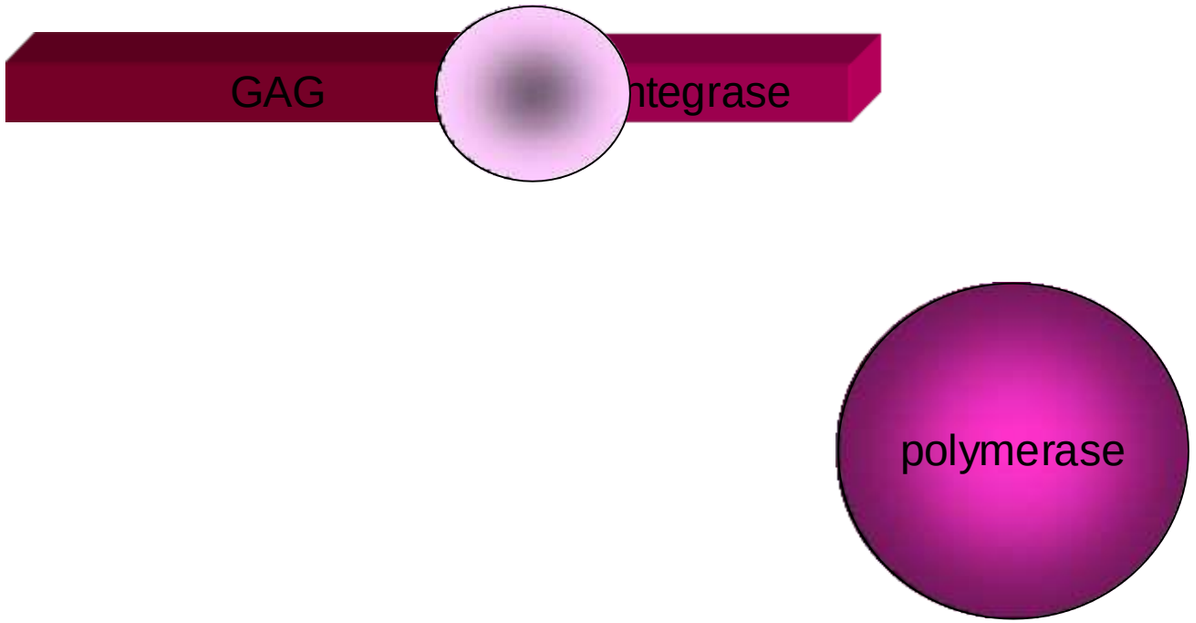


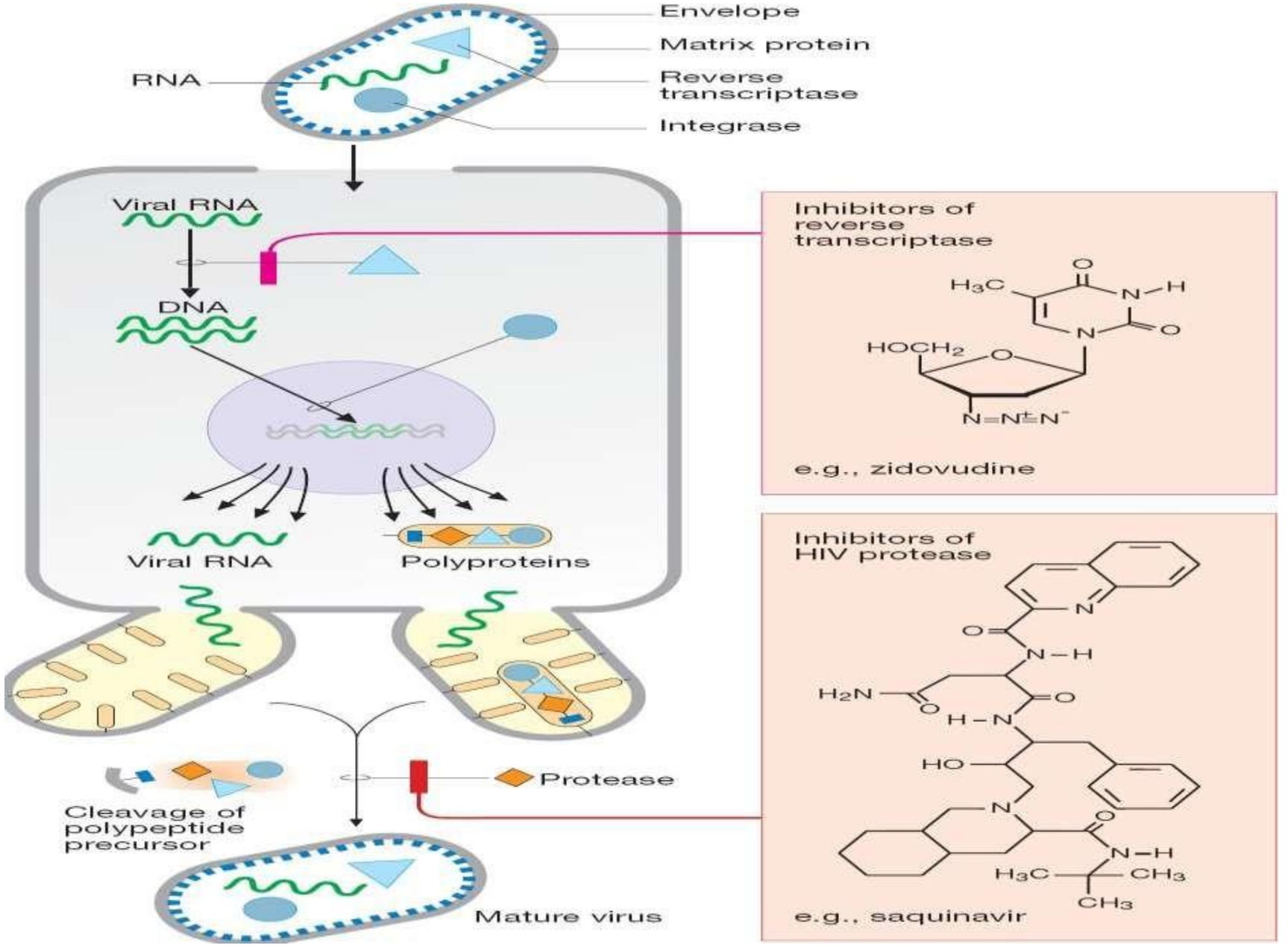
Protease folds and cuts itself free

Anti-Viral Chemotherapy

Protease cuts at a site between the integrase and polymerase

Anti-Viral Chemotherapy




Envelope
Matrix protein
RNA
Reverse transcriptase
Integrase
Viral RNA
DNA
Viral RNA
Polyproteins
Protease
Cleavage of polypeptide precursor
Mature virus
Inhibitors of reverse transcriptase
e.g., zidovudine
Inhibitors of HIV protease
e.g., saquinavir

New targets

- **Enfuvirtide is Peptides derived from gp41 can inhibit infection, probably by blocking the interaction of gp41 with cell membrane proteins during fusion.**

- **Raltegravir (Integrase Inhibitor) targets integrase, an HIV enzyme that integrates the viral genetic material into human chromosomes, a critical step in the pathogenesis of HIV.**

- **Maraviroc It blocks the interaction between chemokine receptor CCR5 and HIV gp120.**

(HAART)

- **Highly active anti-retroviral therapies**

- **Combination therapies (triple drug cocktail, HAART) are very effective and can reduce viral load in the patient below detectable levels implying that HIV replication has ceased.**

  examples (1) NNRTI–Based Regimens (1-NNRTI + 2NRTIs)

  (2) PI-Based Regimens (1 or 2 PIs + 2 NRTIs)

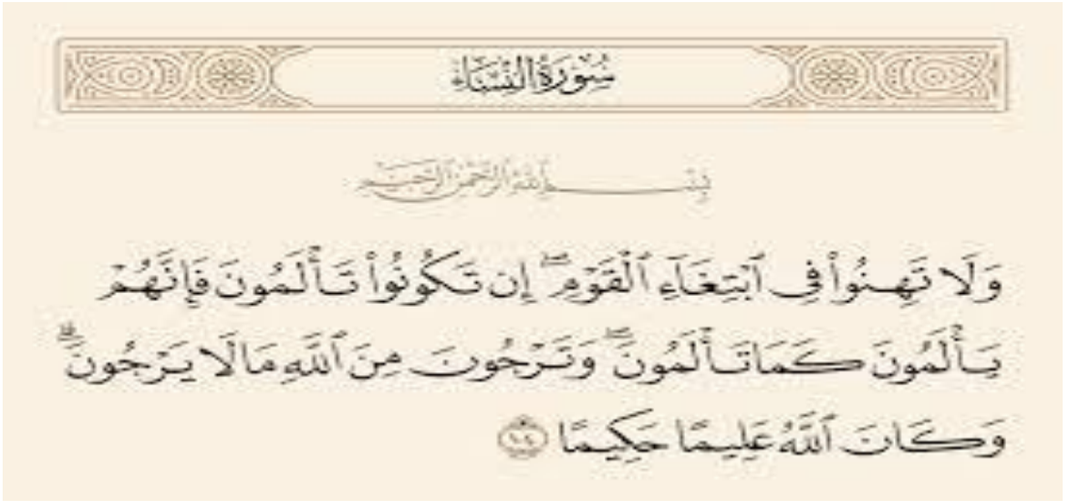
  2NRTIs doesn't change, Because RNA viruses mutate easily, treatment can be challenging and may require combination therapy to prevent resistance.

- **The trouble with all of these complicated drug regimens is compliance. The components of HAART must be taken at different times.**

- **Non-compliance with protease inhibitor therapy is of serious concern as the new virus that emerges is resistant to the inhibitor being taken and also resistant to other protease inhibitors.**

Additional sources

1. Book pages
2. Youtube videos
3. Webpages…etc



VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!