بسم الله الرحمن الرحيم

Pharmacology

﴿ وَقُل رَّبِّ أَدْخِلْنِي مُدْخَلَ صِدْقٍ وَأَخْرِجْنِي مُخْرَجَ صِدْقٍ وَاجْعَل لِّي مِن لَّدُنكَ سُلْطَانًا نَّصِيرًا ﴾

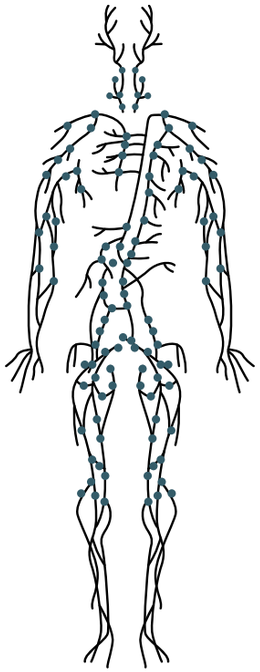
ربنا آتنا من لدنك رحمة وهيئ لنا من أمرنا رشدًا

Final | Lecture 8

Anti-viral

Written by: Raghad Altiti

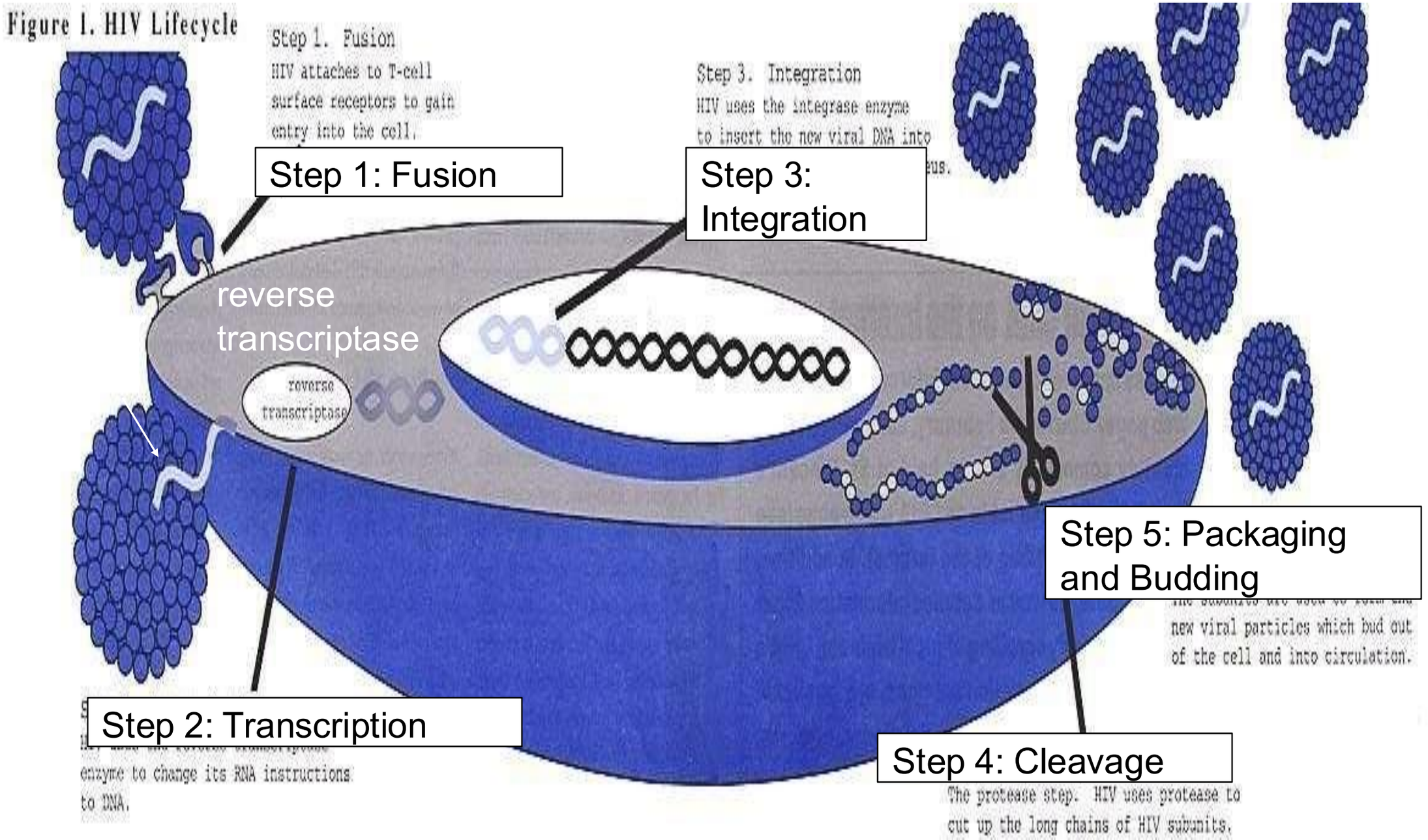
Reviewed by: Layan Fawarseh



Un-explained slides have been removed from this file, with the exception of two figures that have been retained.

Antiretroviral agents

HIV Life Cycle



Regarding the previous slide

- HIV is a major chronic disease that patients must manage throughout their lives. Currently, there are around 40 million people living with HIV worldwide, with an estimated 1.2 million new infections each year (incidence). Fortunately, there are many effective medications available that can control the virus and prevent death, though they require continuous management.

- Understanding the HIV life cycle is extremely important, as drug development focuses on targeting different stages of this cycle.

Check slide 17 for notes regard this slide

(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)

- **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.**

Regarding the previous slide

- To reduce the number of mutations, since we are dealing with an RNA virus, we use a regimen of multiple drugs (a cocktail) to maintain constant pressure on the virus. However, resistance can develop very quickly, which is why we use what's called **HAART (Highly Active Antiretroviral Therapy)**. In this approach, the patient receives three drugs that have **different mechanisms of action** and **distinct side effects**.
- In the treatment of **HIV** and **hepatitis**, however, we sometimes use drugs with the **same mechanism of action** (such as Protease Inhibitors – slide 13). This is done to **inhibit liver metabolism** of the drug and **increase its concentration** in the blood. For example, the antiretroviral drug **ritonavir** is used in HIV treatment in combination with **saquinavir** to raise the blood level of saquinavir, ritonavir also is used in hepatitis treatment.

Azidothymidine (Zidovudin(AZT)) (The prototype)

- **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**
- **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,** In addition to fatigue, lipodystrophy and fat distribution disorders, however, we don't see them usually.
- There is another drug "Didanosine (Dideoxyinosine)" but its slide was skipped in the lecture.

Regarding the previous slide

سبحان الله العظيم

- These drugs act as **antimetabolites**, meaning they provide **faulty metabolites** (they are 5 drugs but you only need to memorize the prototype drug) that mimic natural nucleotides. When the virus incorporates these faulty molecules during replication—or during **reverse transcription** in the case of HIV—it causes **premature chain termination** and **stops viral replication**.
- Unlike drugs such as acyclovir, which are selectively activated by viral enzymes, these antimetabolites are **activated by human enzymes** through the addition of phosphate groups. Because of this, they **lack selectivity** for infected cells and can affect normal cells as well, particularly those in the **bone marrow**. However, **this toxicity is not always significant**. For example, AZT (zidovudine), a **nucleoside reverse transcriptase inhibitor (NRTI)**, is usually given in **low doses**, which minimizes the risk of bone marrow suppression. Additionally, because the **HIV virus replicates so quickly**, it tends to use the drug before it can reach and harm the bone marrow.
- In the past, high doses were used because therapy involved a single drug (monotherapy) rather than the combination regimens used today. This increased the risk of bone marrow toxicity, especially if patients accidentally overdosed, this may still be a complication these days so it should be taken into consideration.
- Moreover, these drugs can **enter the mitochondria** and incorporate in mito-DNA which may cause “DNA toxicity”, where they may **inhibit mitochondrial function**. This can lead **to lactic acidosis, liver failure, and lipodystrophy** as potential side effects.

Non-nucleoside Non-competitive RT inhibitors

- These drugs are used only in specific cases, as they target viral proteins that are highly mutable in RNA viruses, leading to rapid development of resistance. Therefore, they must be administered as part of a combination regimen.

1. **bind to viral RT, inducing conformational changes that result in enzyme inhibition**
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 Memorize this (the oldest and the prototype)	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

- **Nevirapine Approved for AIDS patients, Good blocker of mother to child transmission (perinatal - breast feeding)**
- **Single dose at delivery reduced HIV transmission by 50%**
- **Single dose to baby by 72 hours**

➢ The transmission rate of AIDS has markedly declined, primarily because the majority of cases—approximately 70%, particularly among mothers—are now effectively controlled. Nevirapine, once a highly effective antiretroviral, is considered teratogenic during the early stages of pregnancy but not in the third trimester, as fetal organ development is complete by that time. Consequently, it may be safely administered during delivery to reduce the risk of vertical transmission. Nevertheless, the widespread emergence of resistance has diminished its overall efficacy (it declines from 50% to ~20%), although it remains in limited clinical use.

- **NNRTI's: Adverse Effects RASH!!**

CNS effects (e.g. sedation, insomnia, vivid dreams (Very important side effect -especially in Nevirapine-) **, dizziness, confusion, feeling of "disengagement")**

- In pregnancy , a regimen of oral zidovudine beginning between 14 and 34 weeks of gestation, intravenous zidovudine during labor, and zidovudine syrup to the neonate from birth through 6 weeks of age has been shown to reduce the rate of vertical (mother-to-newborn) transmission of HIV by up to 23%.

Rash

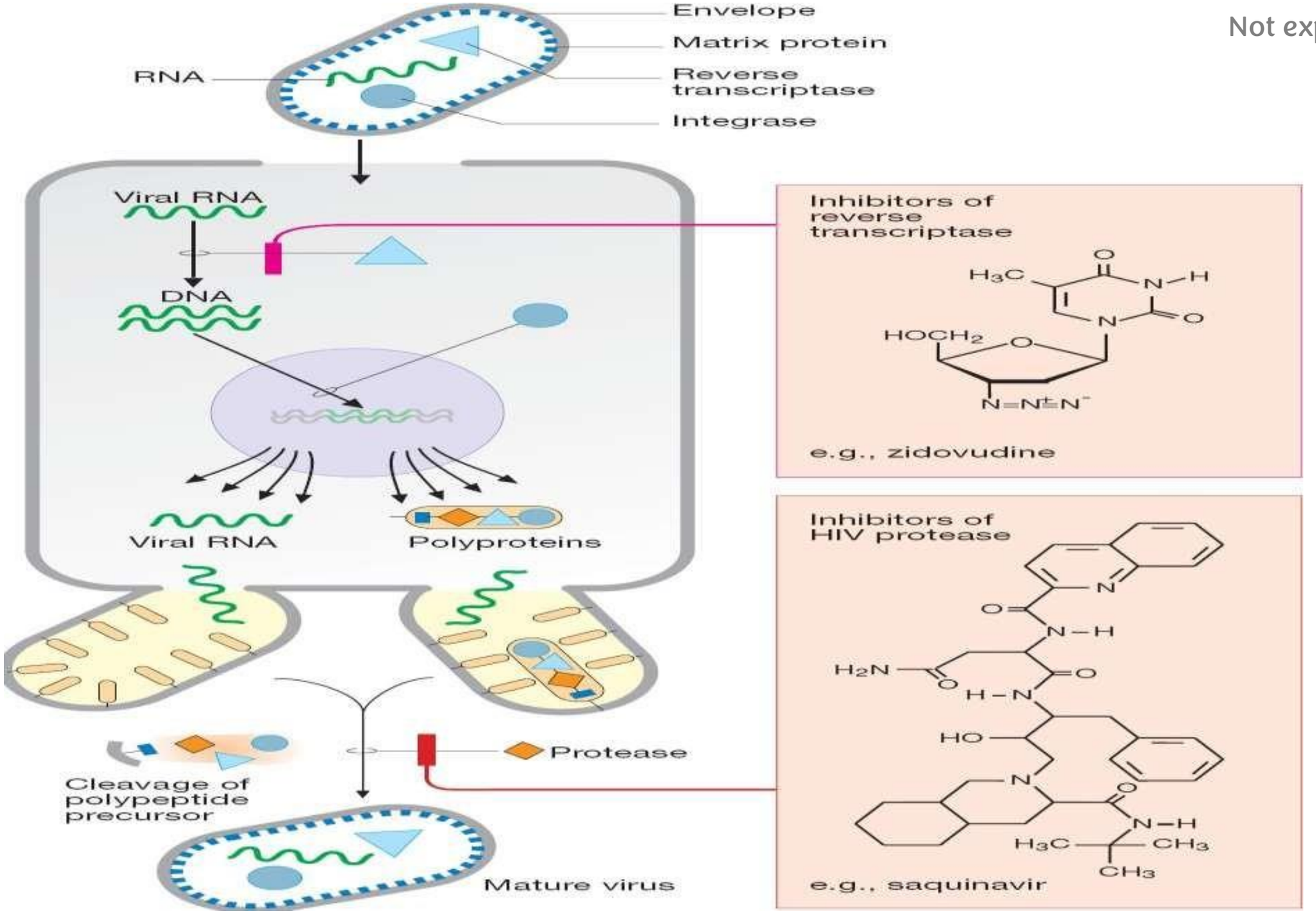
- Rash, occurs in up to 20% of patients, usually in the first 4–6 weeks of therapy.
- Although typically mild and self-limited, rash is dose- limiting in about 7% of patients. Women appear to have an increased incidence of rash.
- When initiating therapy, **gradual dose escalation** over 14 days is recommended to decrease the incidence of rash.

Protease Inhibitors

Remember we never use them alone as they target the proteins!

- **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.**
- **They are orally active, side effects include GI disturbances and hyperglycemia, interact with cytochrome P450.** **buffalo hump**
- Most HIV patients use them and they have high drug-drug interactions and low lipid metabolism causing fat redistribution

Not explained



New targets

- **Enfuvirtide is Peptides derived from gp41 can inhibit infection, probably by blocking the interaction of gp41 with cell membrane proteins during fusion.** Active against only HIV 1 fusion.

Prototype

- **Raltegravir (Integrase Inhibitor) targets integrase** -with rare side effects-, integrase is **an HIV enzyme that integrates the viral genetic material into human chromosomes, a critical step in the pathogenesis of HIV**, this drug can serve both as a prophylactic agent to prevent HIV infection and as part of therapeutic regimens (HAART) for patients who are already infected.

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

Active against both HIV 1&2 fusion.

Regarding the previous slide

- In cases of sexual exposure to HIV, **post-exposure prophylaxis (PEP) with raltegravir -mainly-** should ideally be initiated within 8 hours, and no later than one week after exposure.
- To prevent occupational transmission—for example, through needlestick injuries—raltegravir is administered in combination with zidovudine (NRTI) for one month. An NNRTI may also be added. The rationale for combining raltegravir with NRTIs or NNRTIs is to minimize the risk of resistance development, which may arise due to mutations in the viral integrase protein. Importantly, resistance to raltegravir implies cross-resistance to other integrase inhibitors as well.
- Enfuvirtide and maraviroc are typically reserved for cases where there is resistance to standard regimen.

(HAART)

PI: Protease inhibitors

- **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)

NRTIs are essential components of all antiretroviral regimens, functioning as the main inhibitors that suppress viral load and inhibit ongoing replication by targeting the reverse transcriptase enzyme.

- **The trouble with all of these complicated drug regimens is compliance. The components of HAART must be taken different times.** As patient find it hard to administer the drug along the day.
- **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.**

لا حول ولا قوة إلّا بالله
العلي العظيم

Treatment of respiratory virus infection Influenza A & B

Respiratory suncytial virus (RSV)

Usually self-limited

Regarding the previous slide

- Viral flare: infection within 24-48 hours causes high jacking or high replication increasing the virus load and expressing serious symptoms.
- So, if we started treating the patient after 3 days ,for example, we are basically trying to decrease the infection duration.
- As the drugs that we give for the influenza try to treat the flare itself **(should be given within 24-48 hours)** so giving the drug only decrease the duration of infection by 1-2 days.

Neuroaminidase inhibitors

Oseltamivir (Tamiflu) and Zanamavir

- Mechanism of action:

- **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.**

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,

- 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,** may be given to immunocompromised in some cases.

Cap-dependent endonuclease inhibito

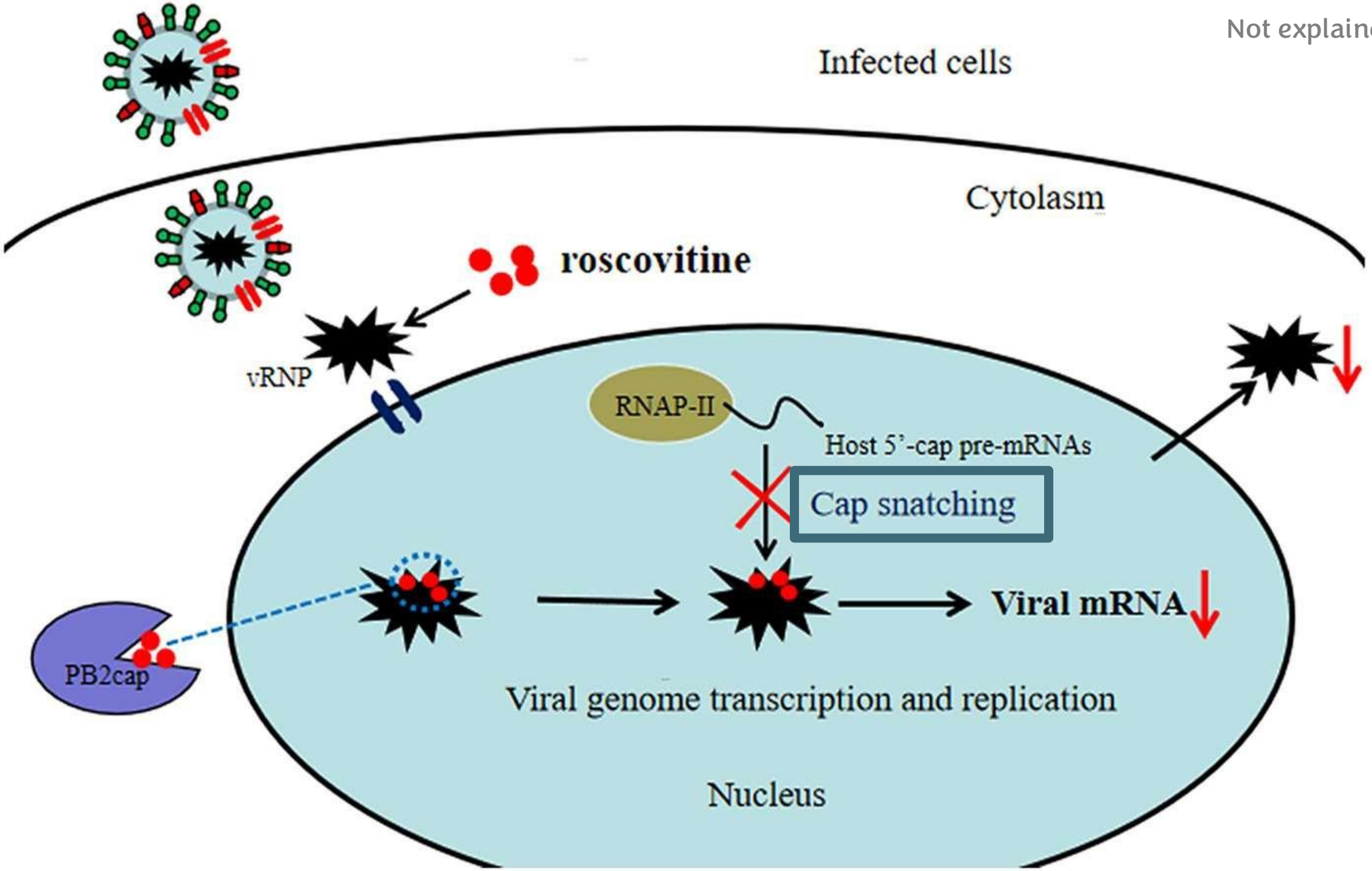
Baloxavir marboxil Taken once daily

- How can the viral RNA fit the human ribosome? Well, it have an endonuclease that use **"cap snatching"** mechanism

- 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.

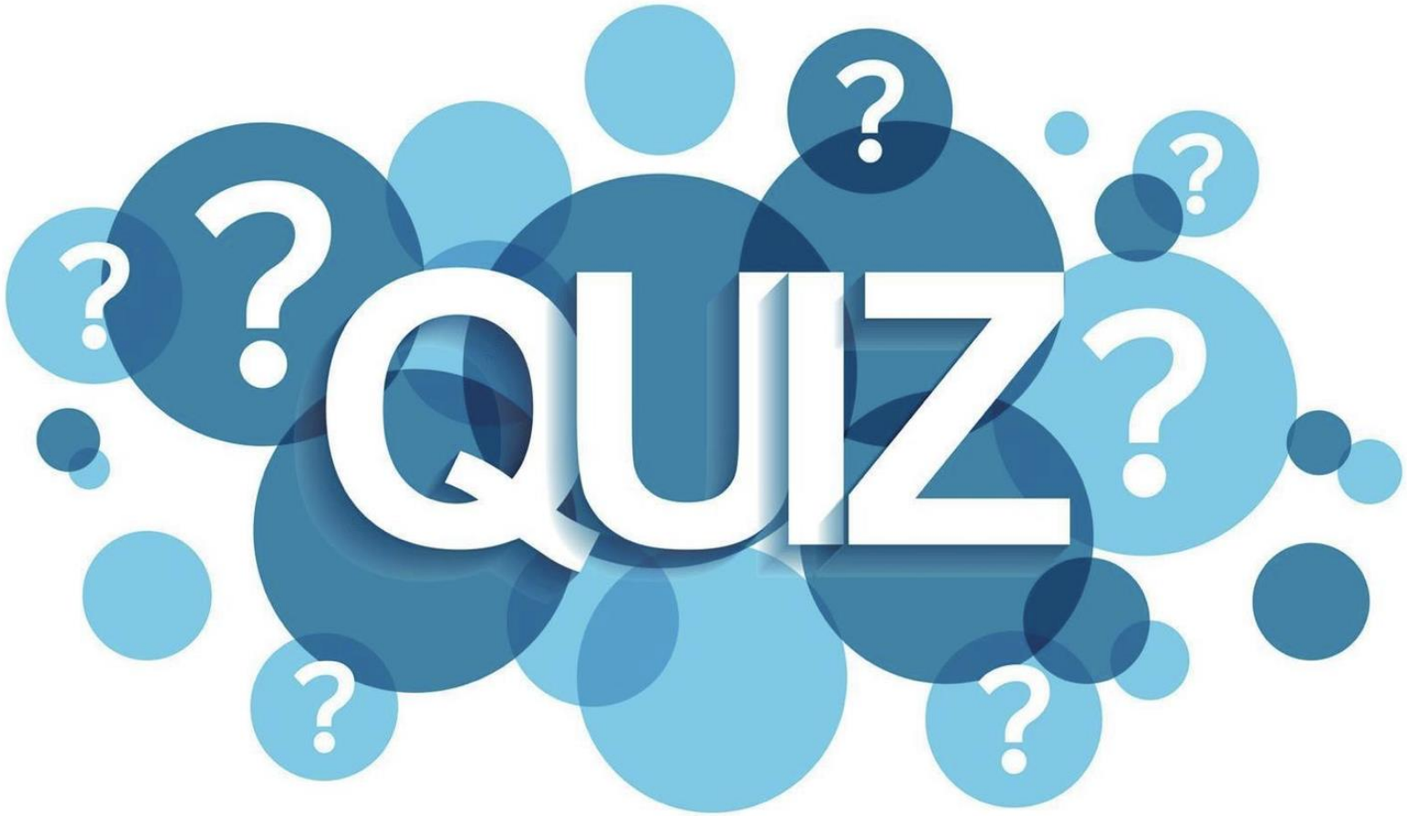
- Baloxavir marboxil inhibit influenza virus' cap dependent endonuclease activity (cap snatching).

Not explained



Pharmacology Quiz 8

الحمد لله رب العالمين



For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			