

***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.**

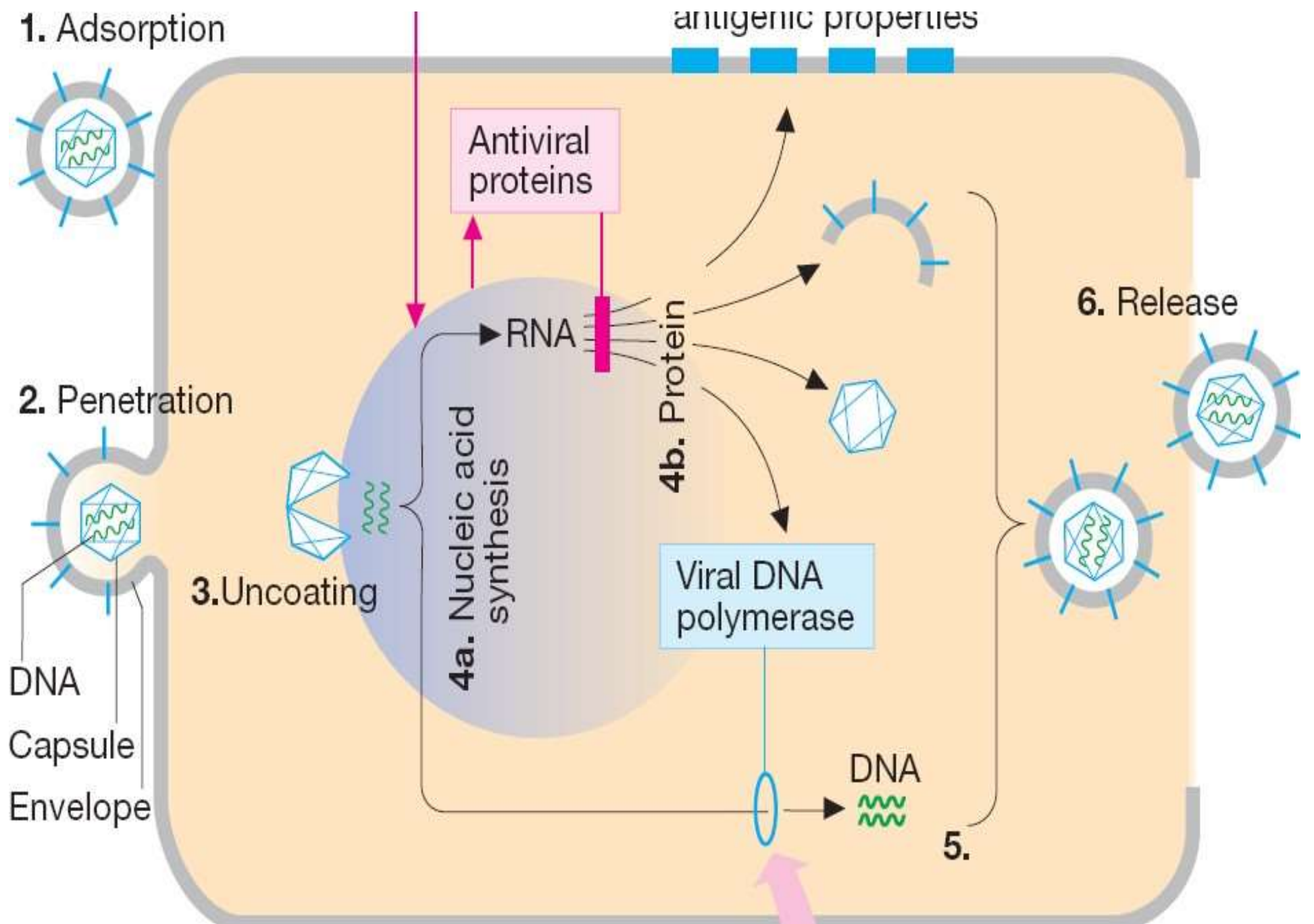
**They have to borrow the biochemistry of the host cell to succeed and grow (this is what makes selective antiviral therapy so difficult).**

# 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 may be 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.**

# 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).**



**Treatment of Herpesviruses**  
**Varicella-zoster,**  
**Cytomegalavirus,**  
**Herpes simplex**

# 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.

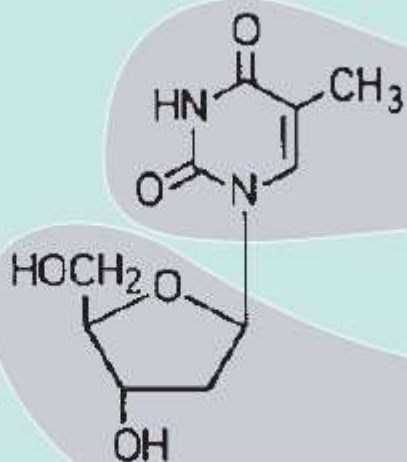
Antimetabolites = incorrect DNA building blocks

Correct:

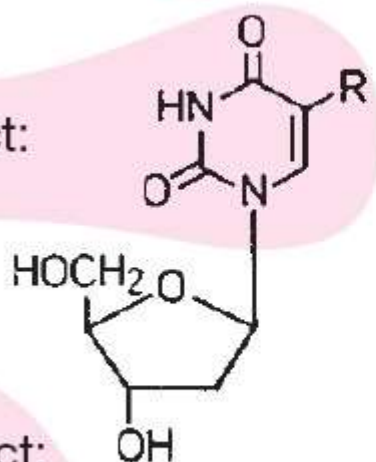
Thymidine

Thymine

Desoxyribose



Incorrect:



- R: - I Idoxuridine  
- CF<sub>3</sub> Trifluridine  
- C<sub>2</sub>H<sub>2</sub> Edoxudine

Insertion into DNA instead of thymidine

Vidarabine

Acyclovir

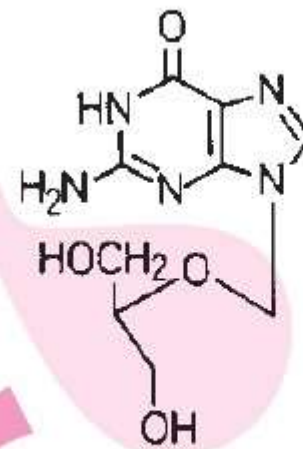
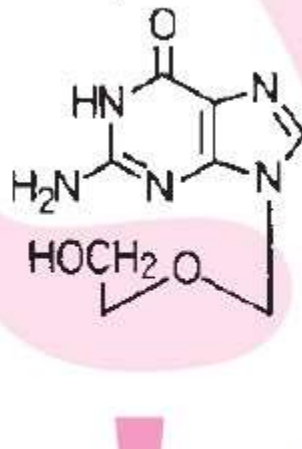
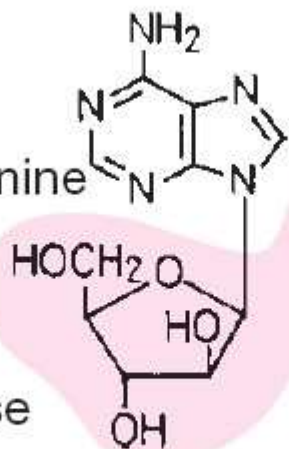
Ganciclovir

Adenine

Guanine

Guanine

Arabinose



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.**
- **Acyclovir triphosphate inhibits viral DNA polymerase resulting in chain termination.**

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

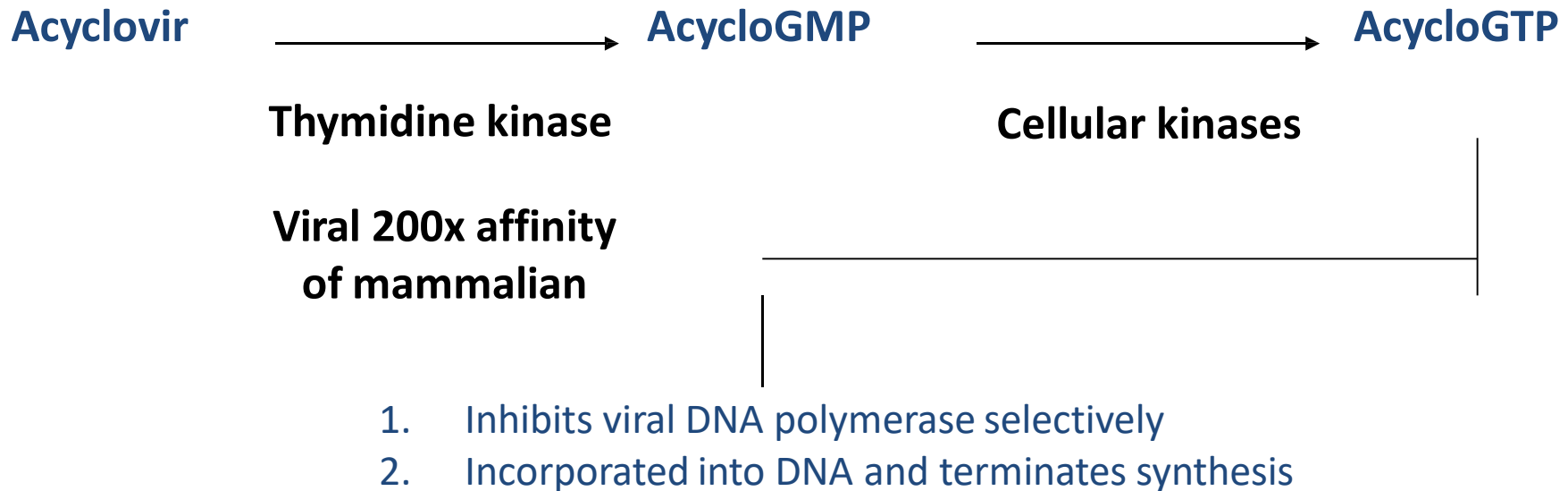
**Acyclovir is active against herpes simplex and varicellar-zoster virus.**

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

# Acyclovir

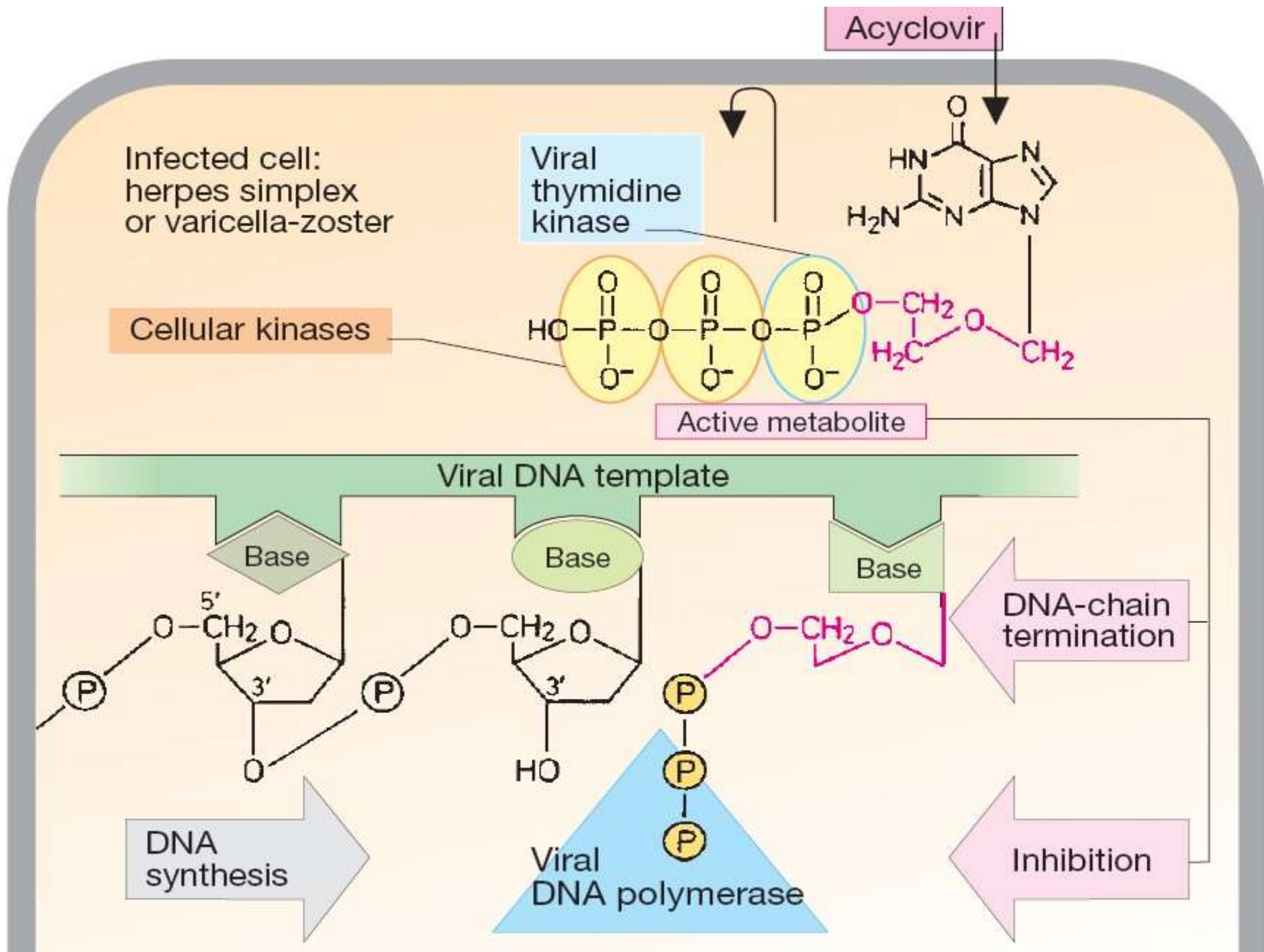
and Valacyclovir (pro-drug, better availability)

A Guanine analogue with antiviral for Herpes group only



**Resistance:**

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



# Acyclovir

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 recurrences of genital herpes.

- 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.
- 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, uncommon with adequate hydration and avoidance of rapid infusion rate.**

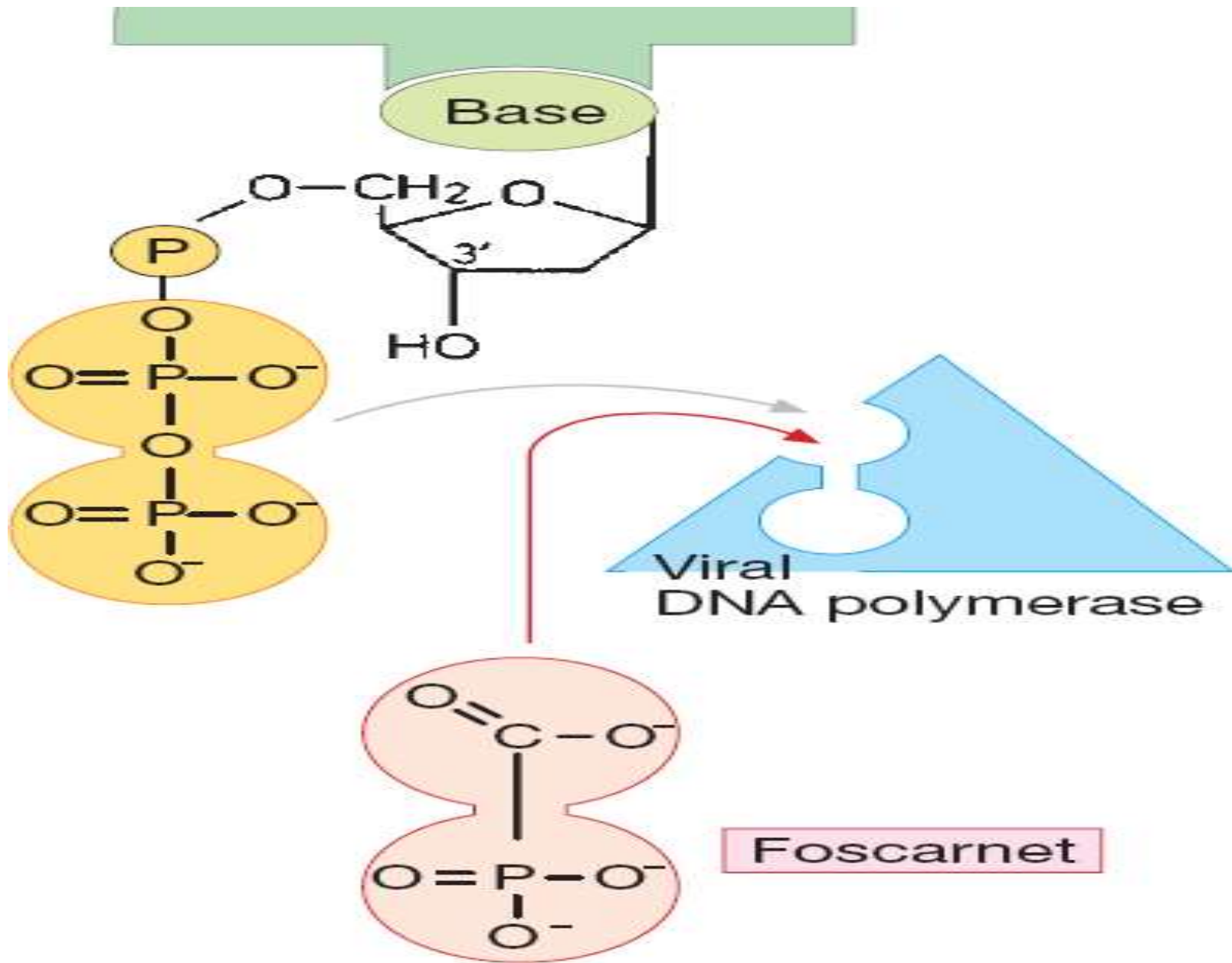
# Ganciclovir

- Mechanism like Acyclovir **however**
- Active against all Herpes viruses including CMV (100 time than acyclovir)
- 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.

# Foscarnet

- **An inorganic pyrophosphate analog**
- **Active against Herpes (I, II, Varicella , CMV), including those resistant to Acyclovir and Ganciclovir.**
- **Direct inhibition of DNA polymerase and Reverse Transcriptase**
- **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.**





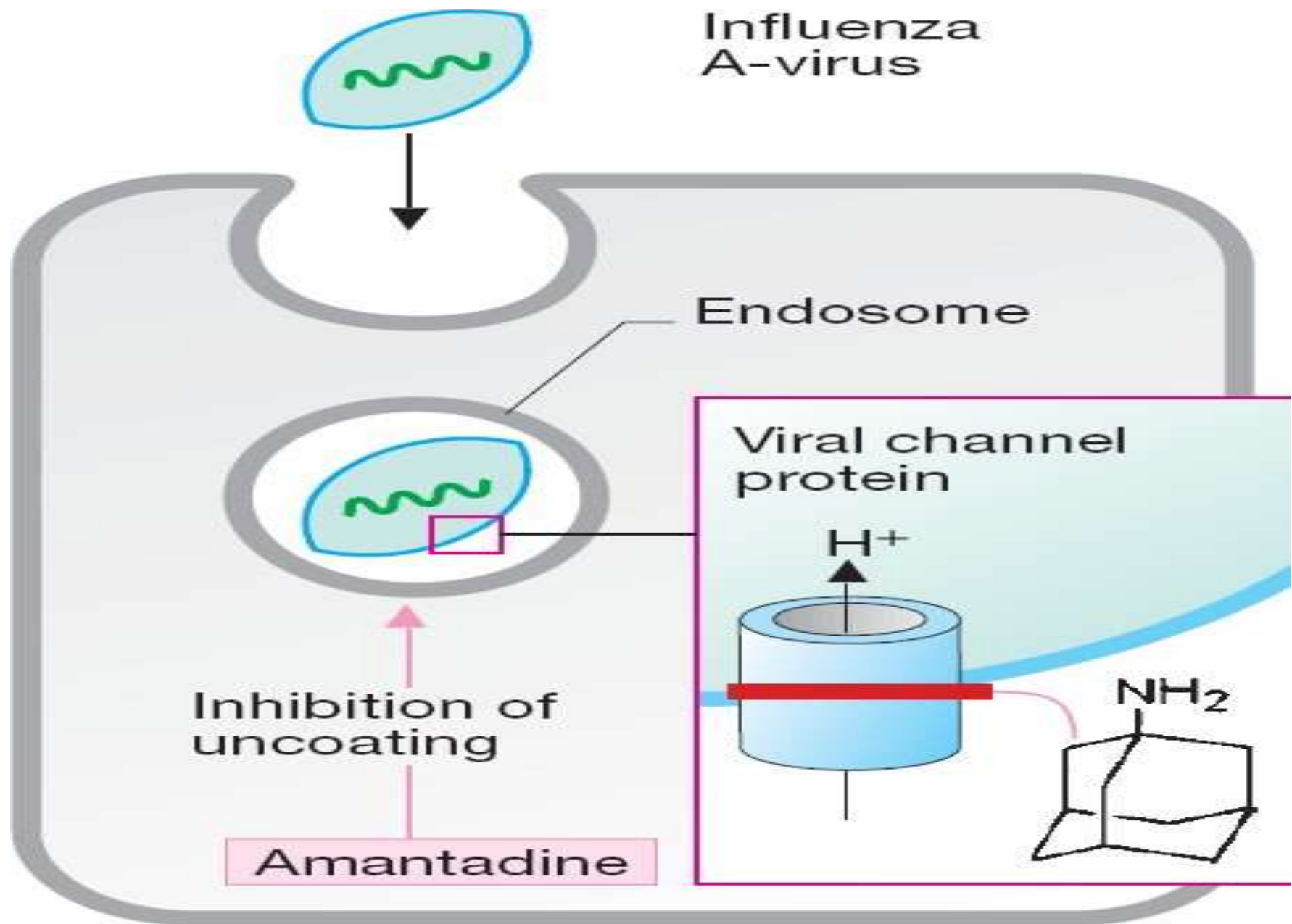
**Treatment of respiratory virus infection**

**Influenza A & B**

**Respiratory syncytial virus (RSV)**

# 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.**



# 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 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

# 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

# oseltamivir

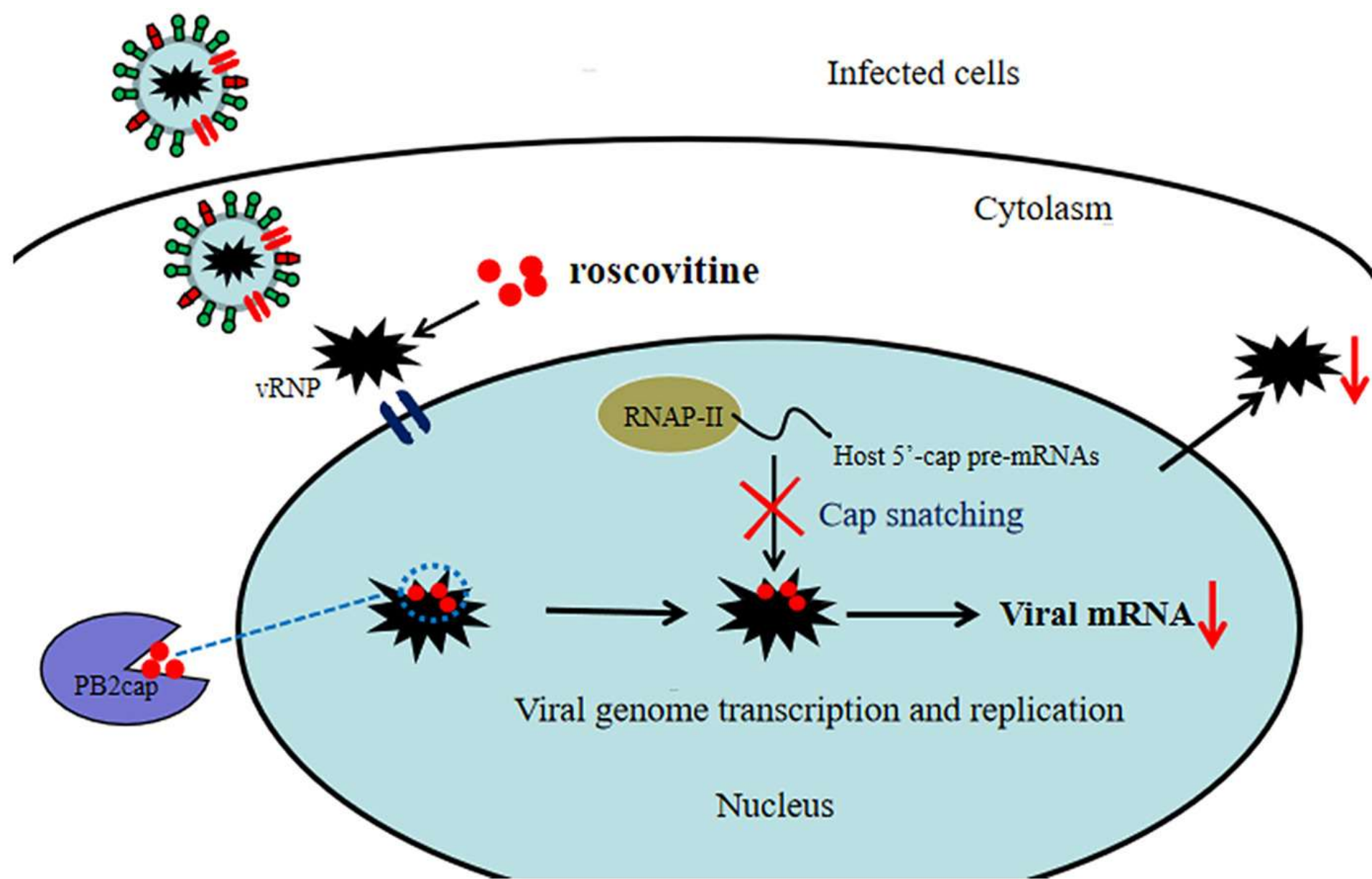
- Early administration is crucial because replication of influenza virus peaks at 24–72 hours after the onset of illness.
- When a 5-day course of therapy is initiated within 36–48 hours after the onset of symptoms, the duration of illness is decreased by 1–2 days compared with those on placebo,
- severity 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.



# 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.



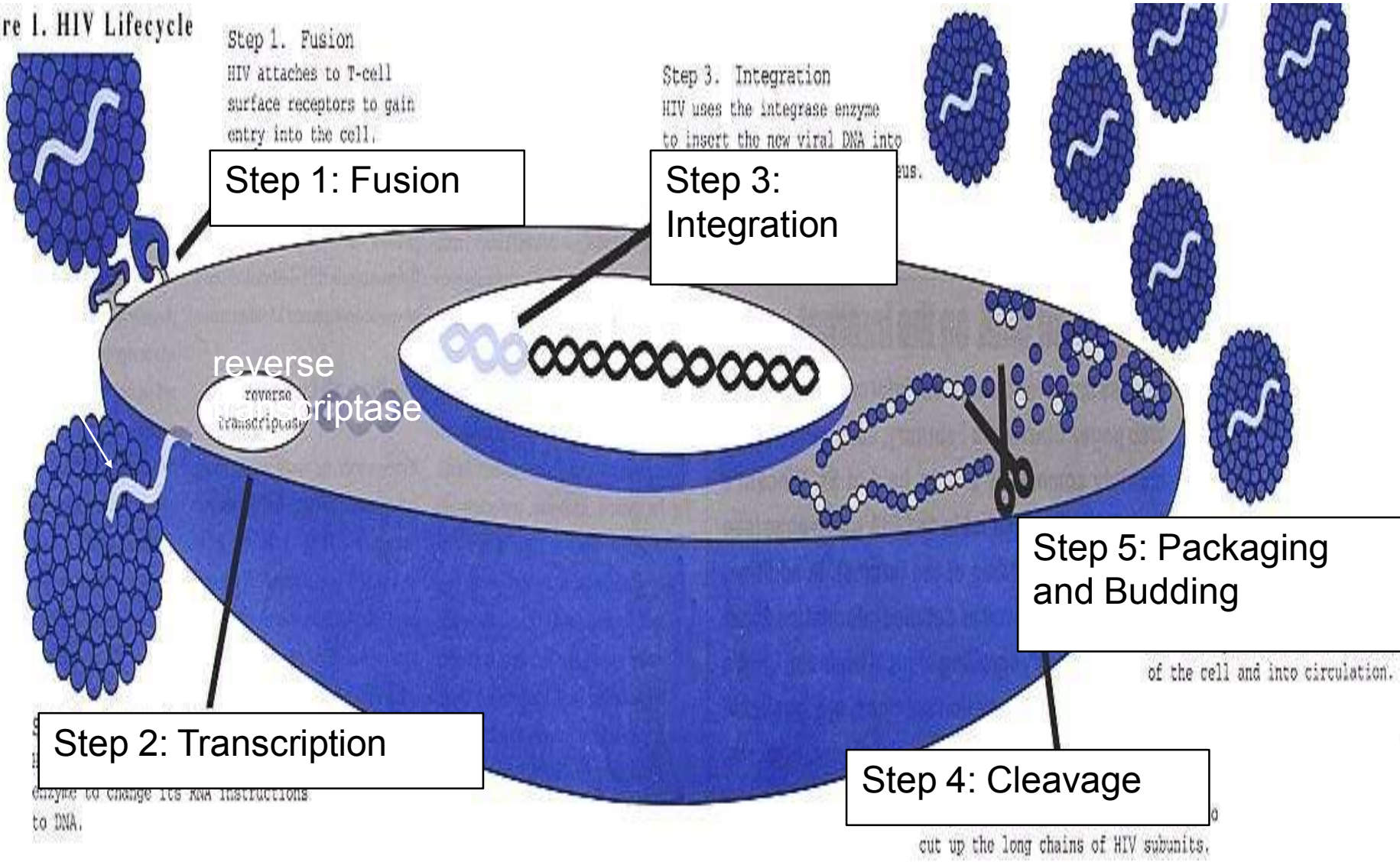
# Ribavirin

- 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

Figure 1. HIV Lifecycle



# 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
- 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
- (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**

**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**

**NNRTI's: Adverse Effects**

**RASH!!**

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

# 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.
- They are orally active, side effects include GI disturbances and hyperglycemia, interact with cytochrome P450. **buffalo hump**

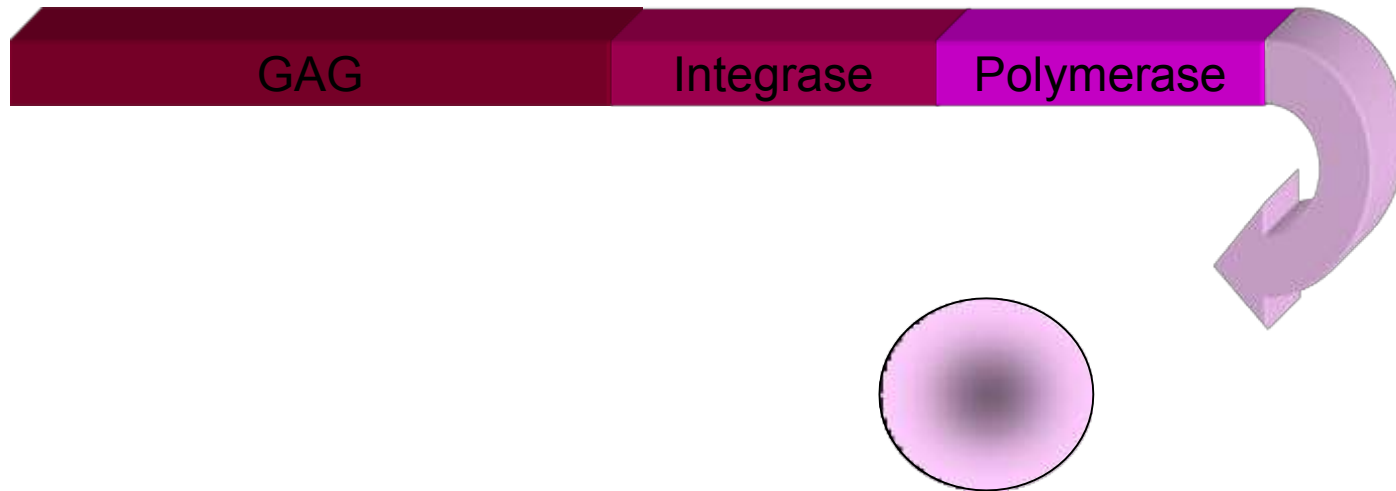
# Anti-Viral Chemotherapy

GAG/POL polyprotein



**Retrovirus --- HIV**

# Anti-Viral Chemotherapy



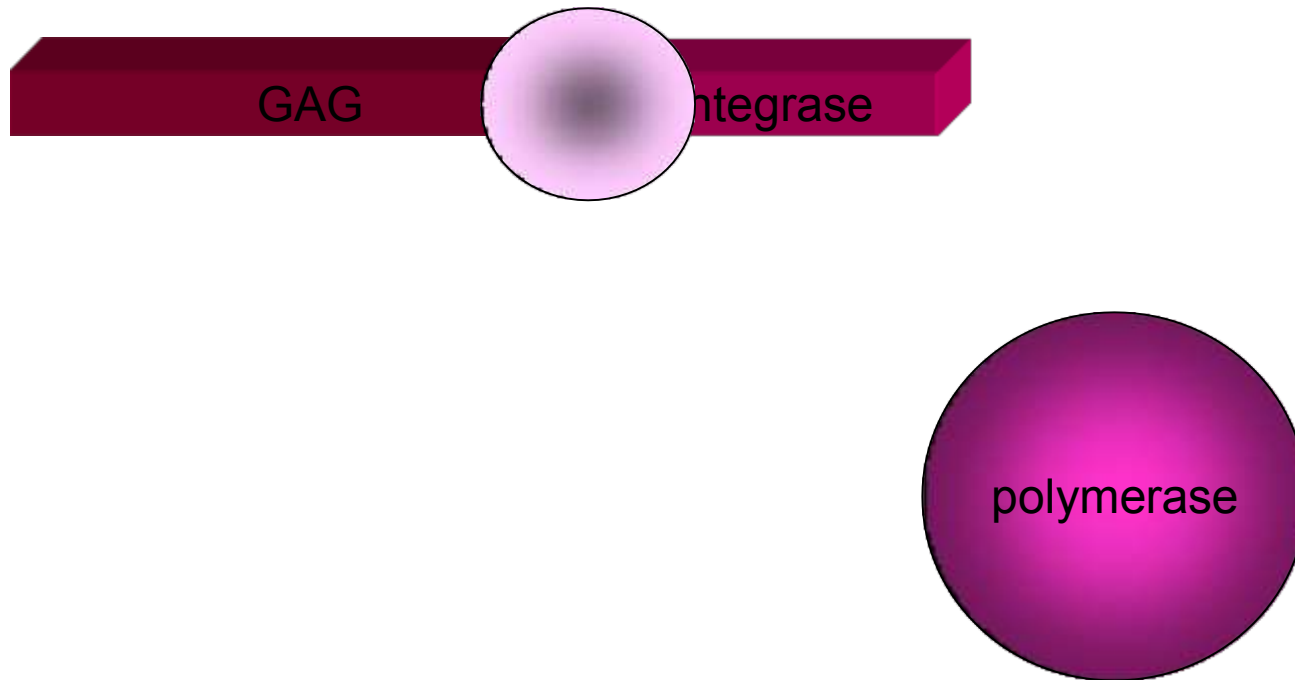
Protease folds and cuts itself free

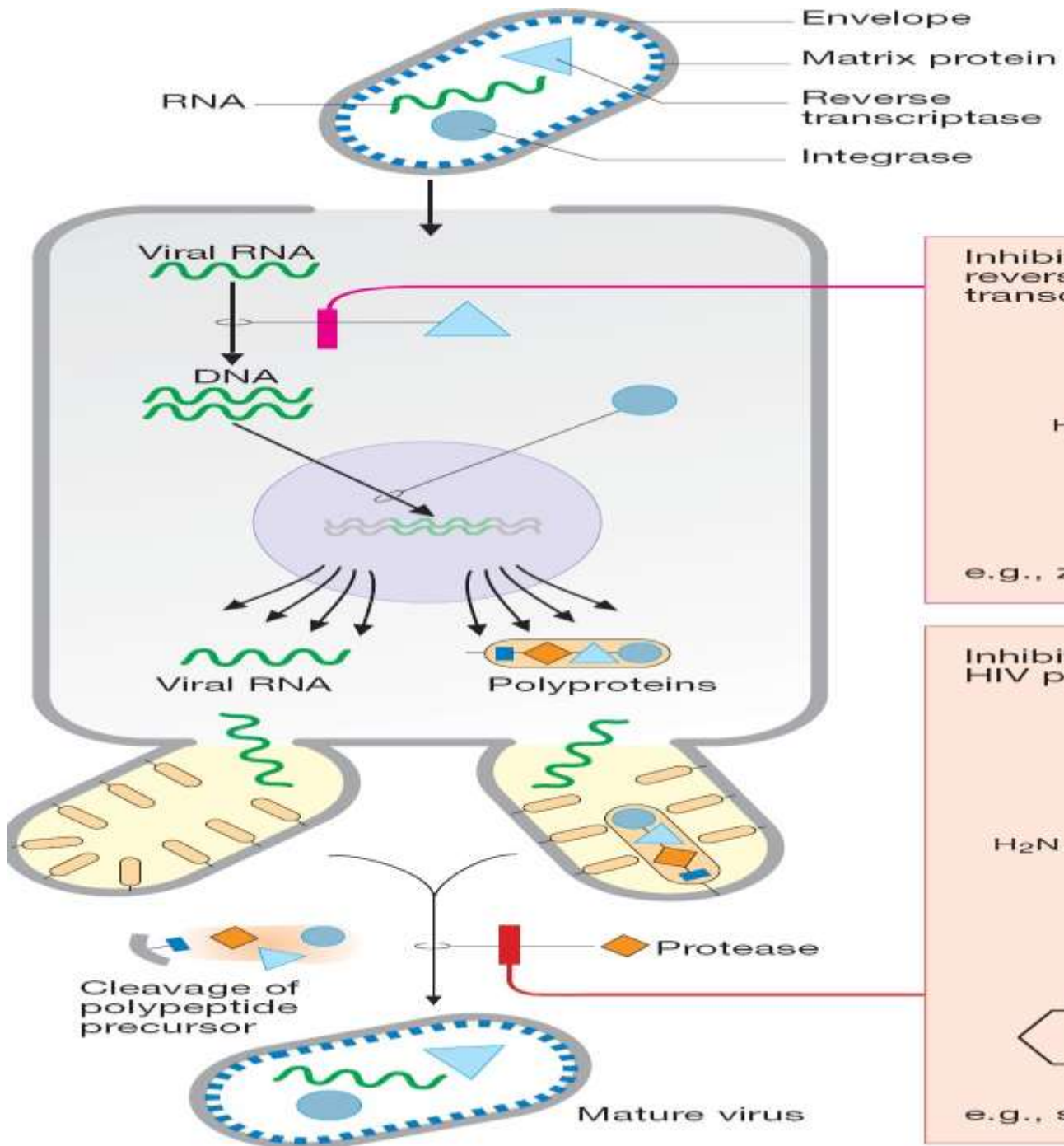
# Anti-Viral Chemotherapy



Protease cuts at a site between the integrase and polymerase

# Anti-Viral Chemotherapy





**Inhibitors of reverse transcriptase**

Cc1nc(=O)n(c1=O)CN2C=CN=C2CO

e.g., zidovudine

**Inhibitors of HIV protease**

CN1C(=O)N(C(=O)N1Cc2ccc3ccccc32)C(O)CC4CC5CC6CC7C(=O)N(C)C(C)C7CC6CC5CC4

e.g., saquinavir



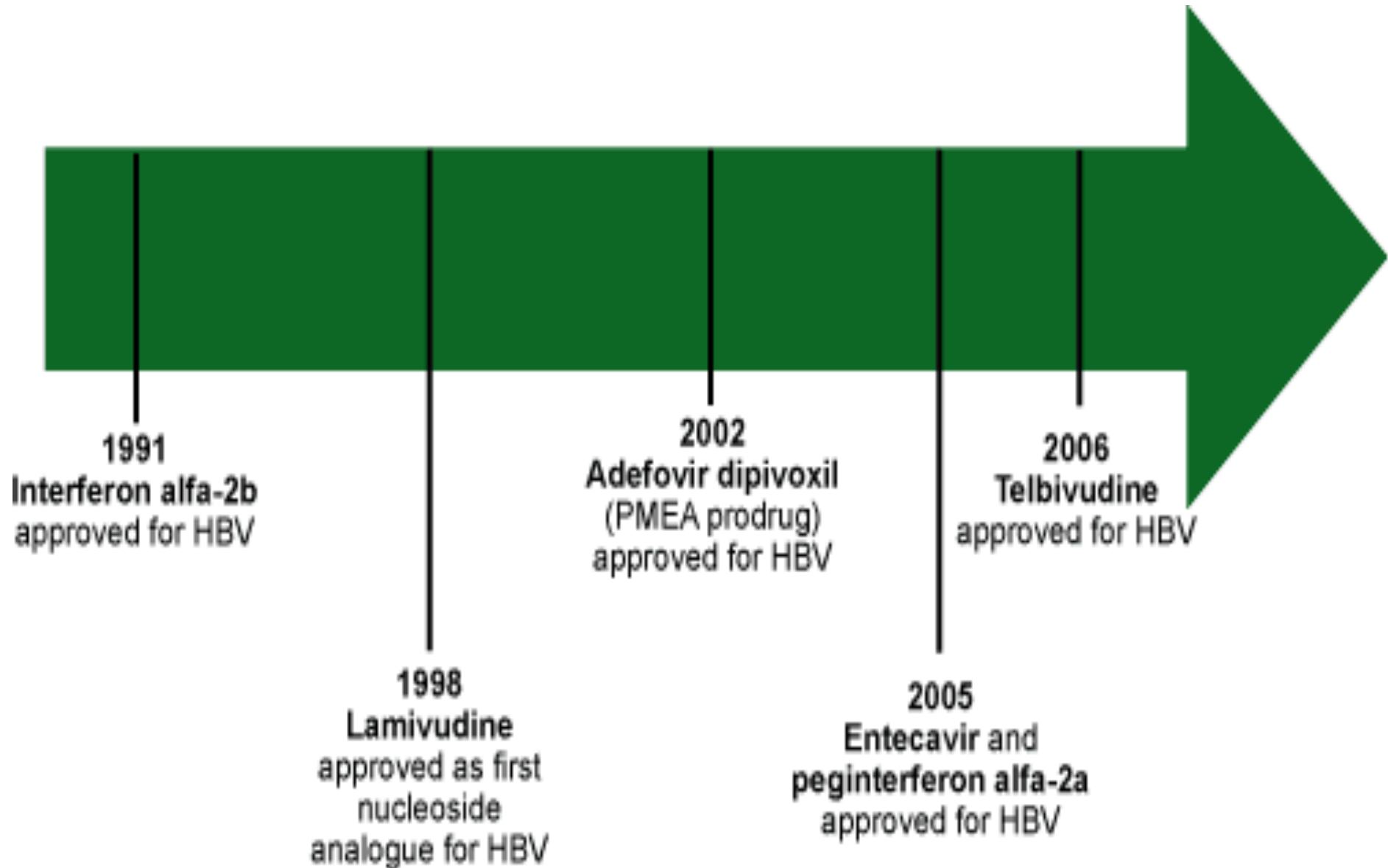
# New targets

- **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)

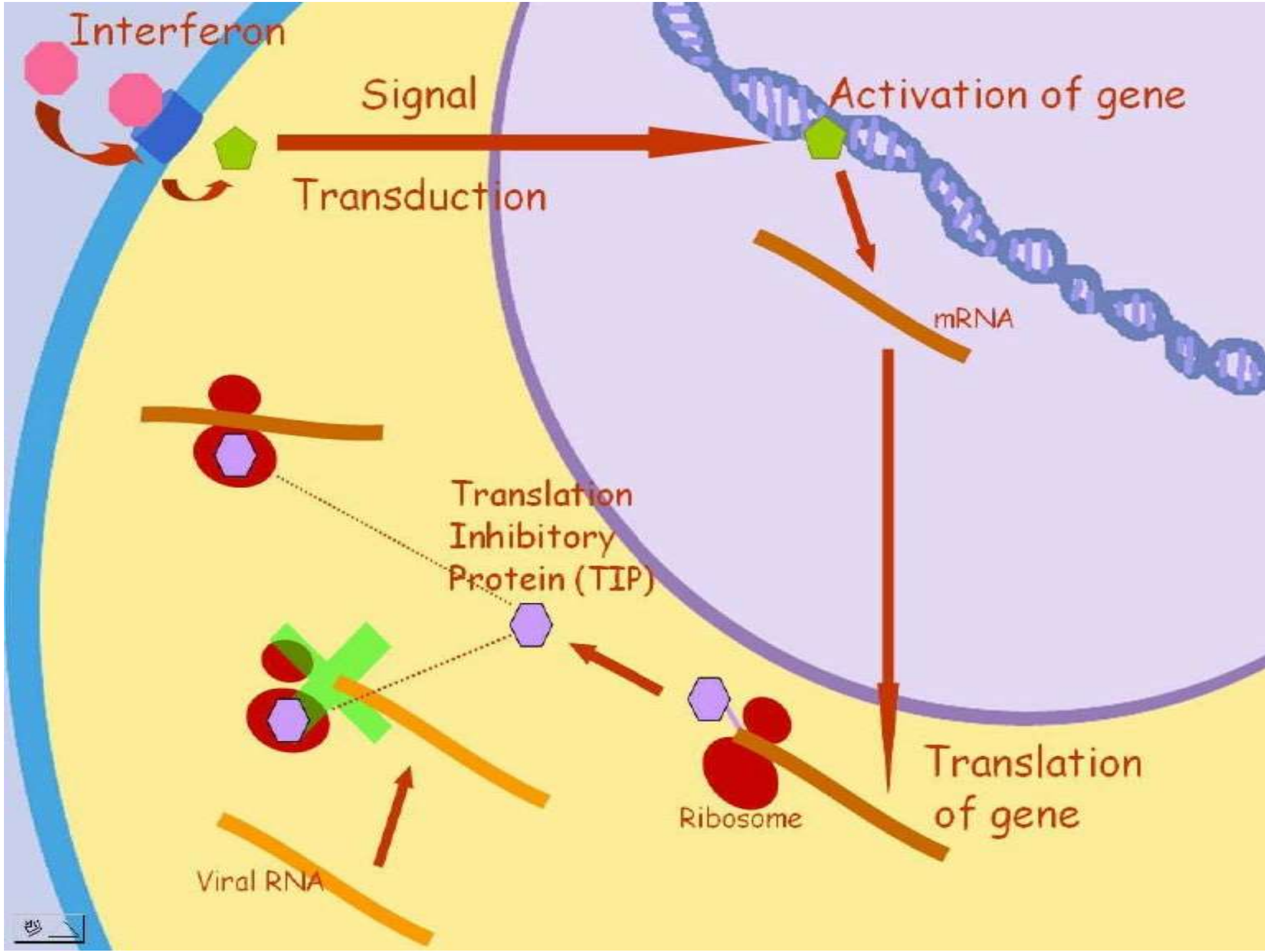
- **Highly active anti-retroviral therapies**
- **Combination therapies (triple drug cocktail, HAART) are very effective and can reduce viral load in the patient below detectable levels implying that HIV replication has ceased.**  
examples (1) **NNRTI–Based Regimens (1-NNRTI + 2NRTIs)**  
(2) **PI-Based Regimens (1 or 2 PIs + 2 NRTIs)**
- **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.**

# Anti-Hepatitis B Virus Agents



# ***Interferons***

- ***Interferon Alfa***
- Endogenous proteins induce host cell enzymes that inhibit viral RNA translation and cause degradation of viral mRNA and tRNA .
- Bind to membrane receptors on cell surface , May also inhibit viral penetration, uncoating, mRNA synthesis, and translation, and virion assembly and release.
- ***Pegylated interferon Alfa***
- A linear or branched polyethylene glycol (PEG) moiety is attached covalently to interferon
- Increased half-life and steady drug concentrations



# ***Interferons***

- **a limited treatment course (ie, only 1 year of therapy),**
- **lack of resistance development.**
- **Disadvantages include a high rate of treatment-related adverse events. flu-like symptoms: increased body temperature, feeling ill, fatigue, headache, muscle pain.**

# Anti-Hepatitis C Virus Agents

- **Approved**
  - **Interferon-alpha (pegylated)**
  - **Ribavirin**
  
- **New drugs**
  - **Protease inhibitors**
  - **Polymerase inhibitors**

# Ombitasvir, paritaprevir, ritonavir (Technivie)



**technivie™**  
ombitasvir, paritaprevir  
and ritonavir tablets



# Ombitasvir, paritaprevir, ritonavir (Technivie)

## Mechanism of Action:

- Combines 2 direct-acting hepatitis C virus antiviral agents with distinct mechanisms of action.
- Ombitasvir inhibits HCV NS5A, and interferes with viral RNA replication and virion assembly.
- Paritaprevir inhibits HCV NS3/4A protease and interferes with HCV coded polyprotein cleavage necessary for viral replication.
- Ritonavir is not active against HCV.
- Ritonavir is a potent CYP3A inhibitor that increases peak and trough plasma drug concentrations of paritaprevir and overall drug exposure (ie, AUC).

# Ombitasvir, paritaprevir, ritonavir (Technivie)

- **Pricing: USTablets** (Technivie Oral)
- 12.5-75-50 mg (2): \$1095.04
- This drug made a once-a-day pill option available to people with HCV type 4 who don't have cirrhosis or who have compensated cirrhosis, meaning their liver has scarring but they do not have any symptoms from it yet.
- It is used with ribavirin, which may boost your chances of a cure.

# Daclatasvir (Daklinza)

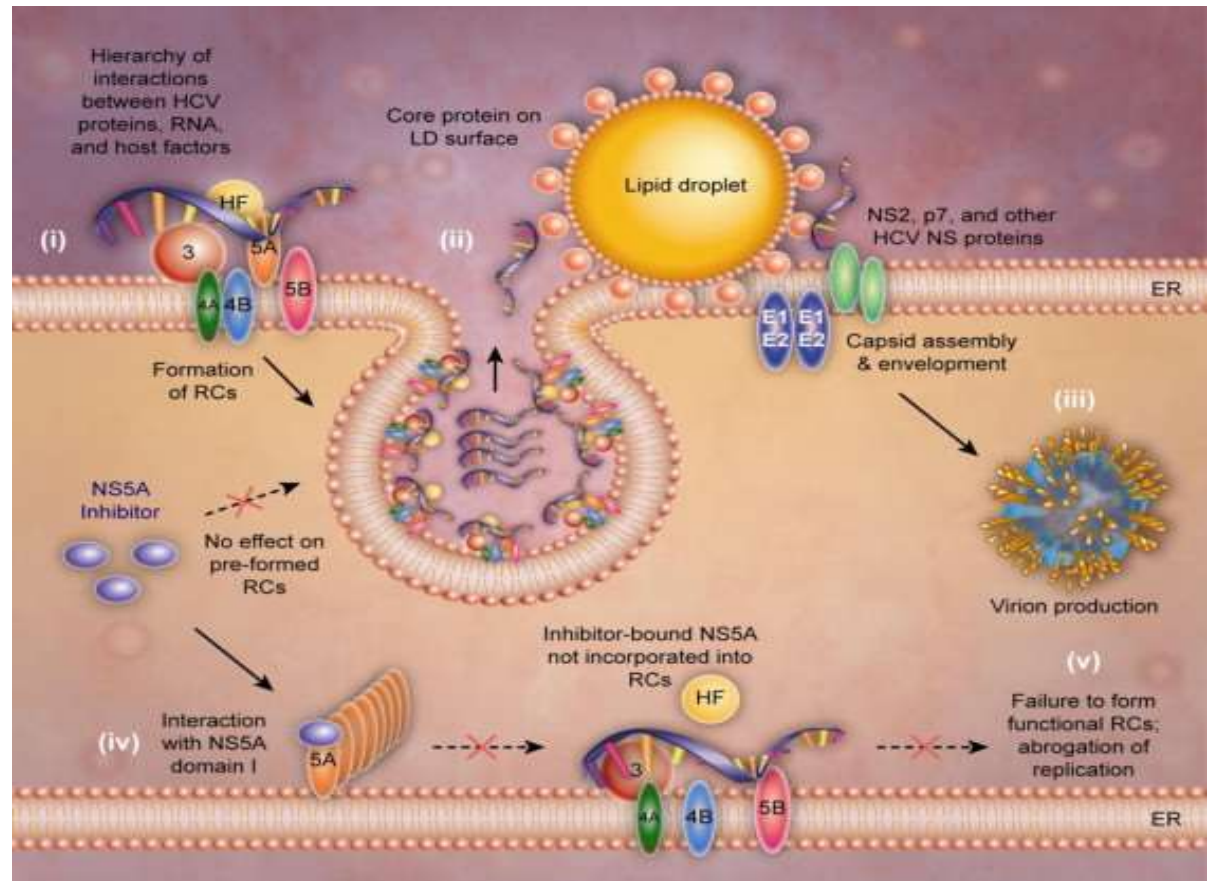
**Pricing: US** Tablets (Daklinza Oral)

30 mg (28): \$25200.00

60 mg (28): \$25200.00

90 mg (28): \$25200.00

- **Pharmacologic Category** Antihepaciviral, NS5A Inhibitor
- This drug is approved to treat people with HCV types 1 or 3. It's a pill you take once a day along with sofosbuvir (Sovaldi) and possibly ribavirin.





- 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%.