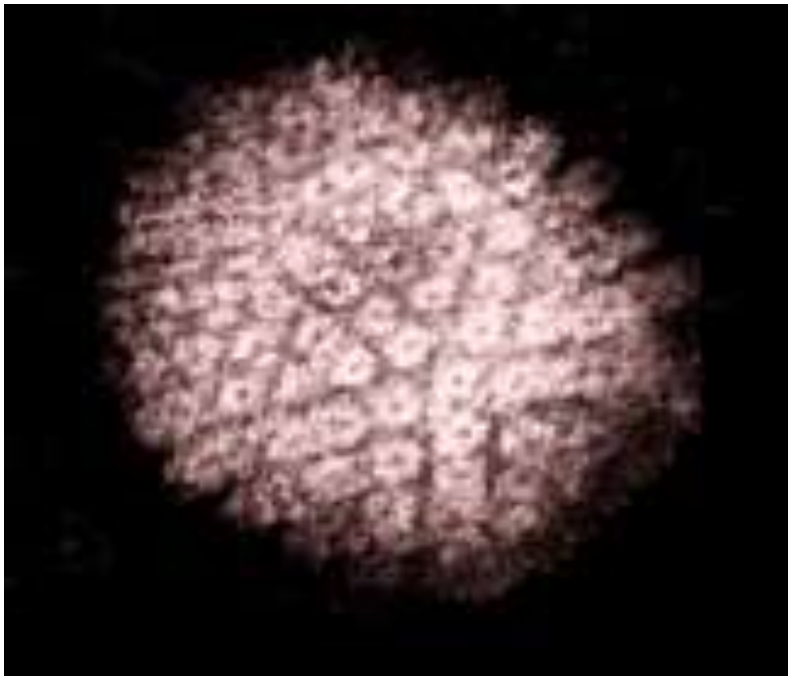
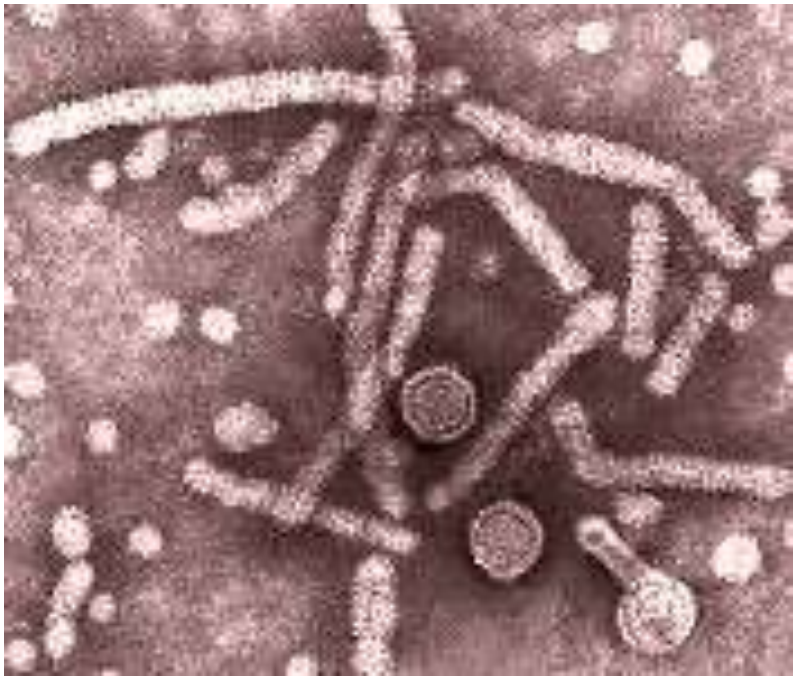
The head of a pin can hold five hundred million rhinoviruses (cause of the common cold). One sneeze can generate an aerosol of enough cold viruses to infect thousands of people!

DNA-containing Viruses:



Herpes Virus

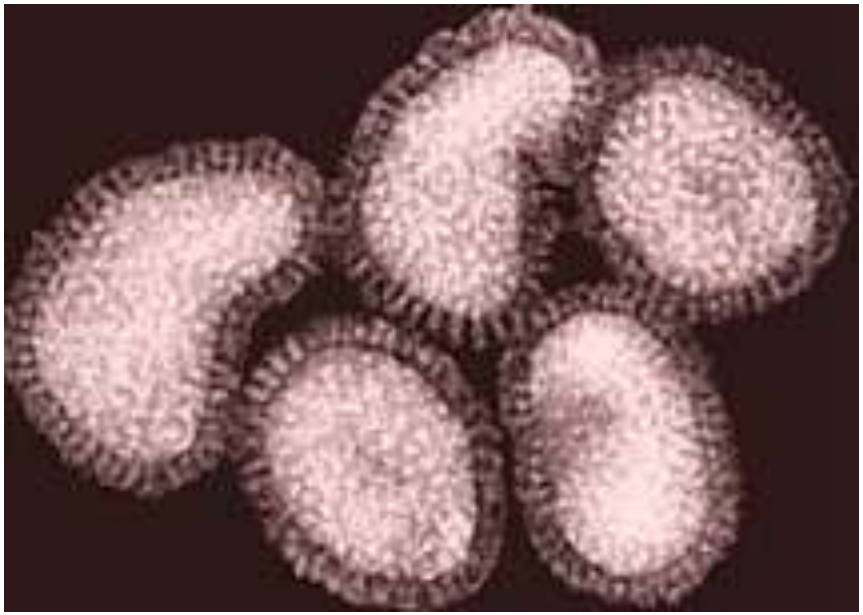
Herpes viruses are found in a wide range of hosts; at least seven different species are known to infect humans, including herpes simplex.



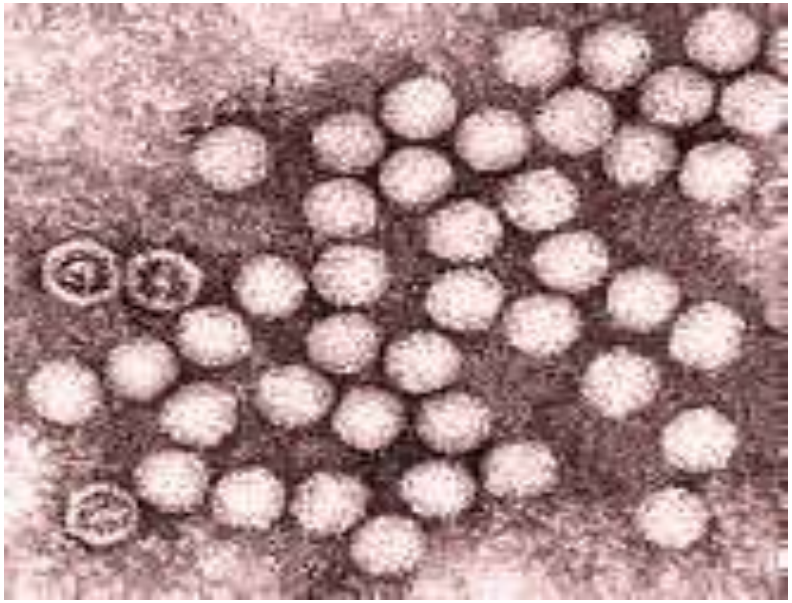
Hepatitis B

Hepatitis B virus causes both acute and chronic liver infections in humans. An unusual feature of these infections are the length of time they last; up to several months in acute infections, and many years (or for life) in chronic infections.

RNA-containing Viruses



Influenza
causes acute upper respiratory disease in humans, usually accompanied by a fever.



Enterovirus
belong to one of the largest families of viruses; others in this family include rhinoviruses (which cause the common cold), cardioviruses, apthoviruses and hepatoviruses (which cause hepatitis A). Enteroviruses usually reproduce in the intestine..

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.**

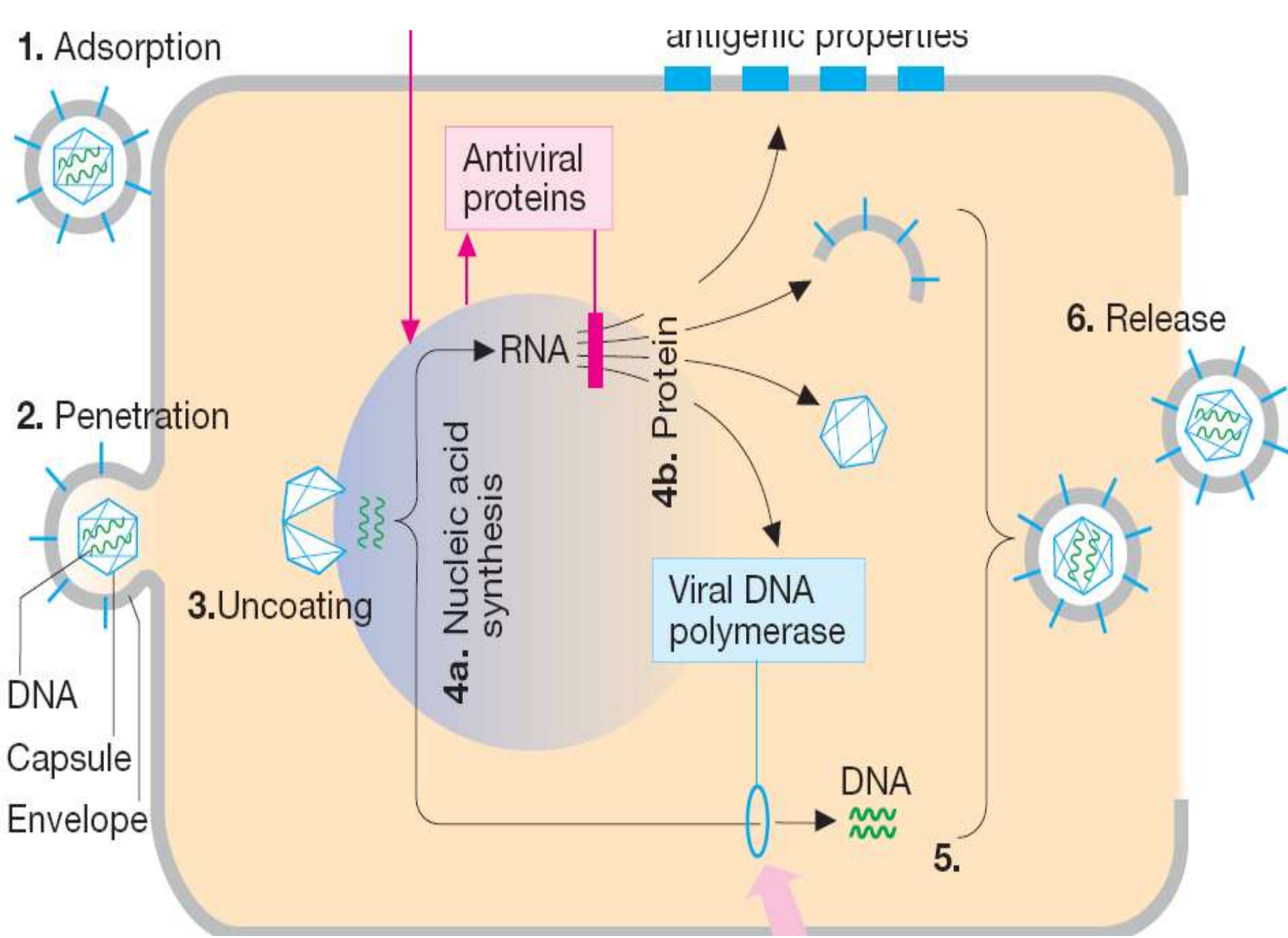
- **The nucleic acid of the virus then hijacks the cellular machinery for replicating viral nucleic acids and proteins for the manufacture of new virus particles.**

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).**


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

General principles: Viral diseases

DNA-based viruses	Resultant disease
Herpes simplex types 1, 2	herpes (skin); encephalitis (brain)
Varicella zoster	chickenpox (children)
Herpes zoster	shingles (adult)
Human papillomavirus	warts (plantar, genital), cancer
Epstein-Barr virus	Mononucleosis ("mono"); Burkitt's lymphoma; nasopharyngeal carcinoma
Poxvirus	smallpox; chickenpox

RNA-based viruses	Resultant disease
HIV-1, HIV-2	HIV; AIDS
Rhinovirus	respiratory/GI infections ("common cold")
Hepatitis A	Hepatitis
Influenza A, B, C viruses	Influenza A, B, C

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.

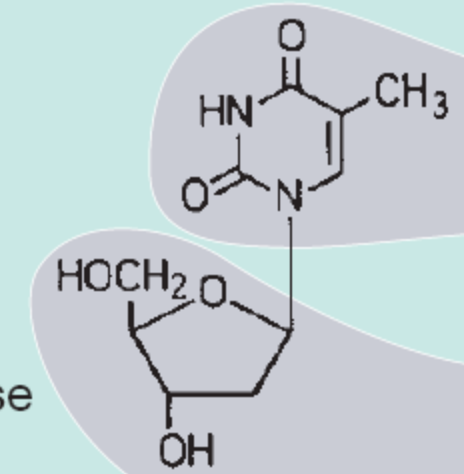
Antimetabolites = incorrect DNA building blocks

Correct:

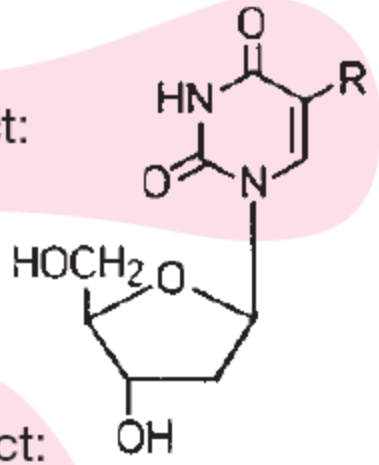
Thymidine

Thymine

Desoxyribose



Incorrect:

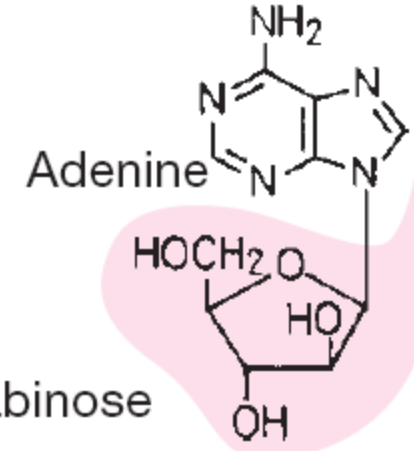


R: - I Idoxuridine
- CF_3 Trifluridine
- C_2H_2 Edoxudine

Insertion into DNA instead of thymidine

Incorrect:

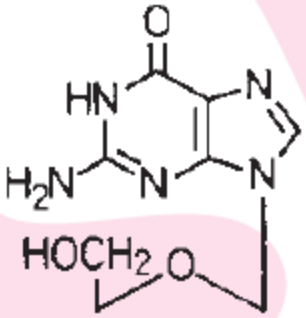
Vidarabine



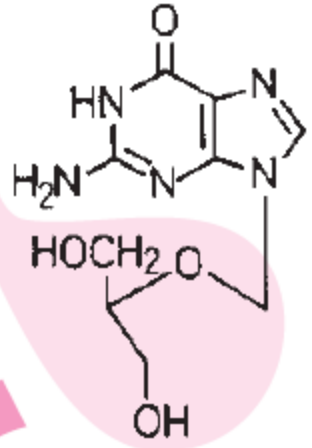
Adenine

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.**

- **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

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

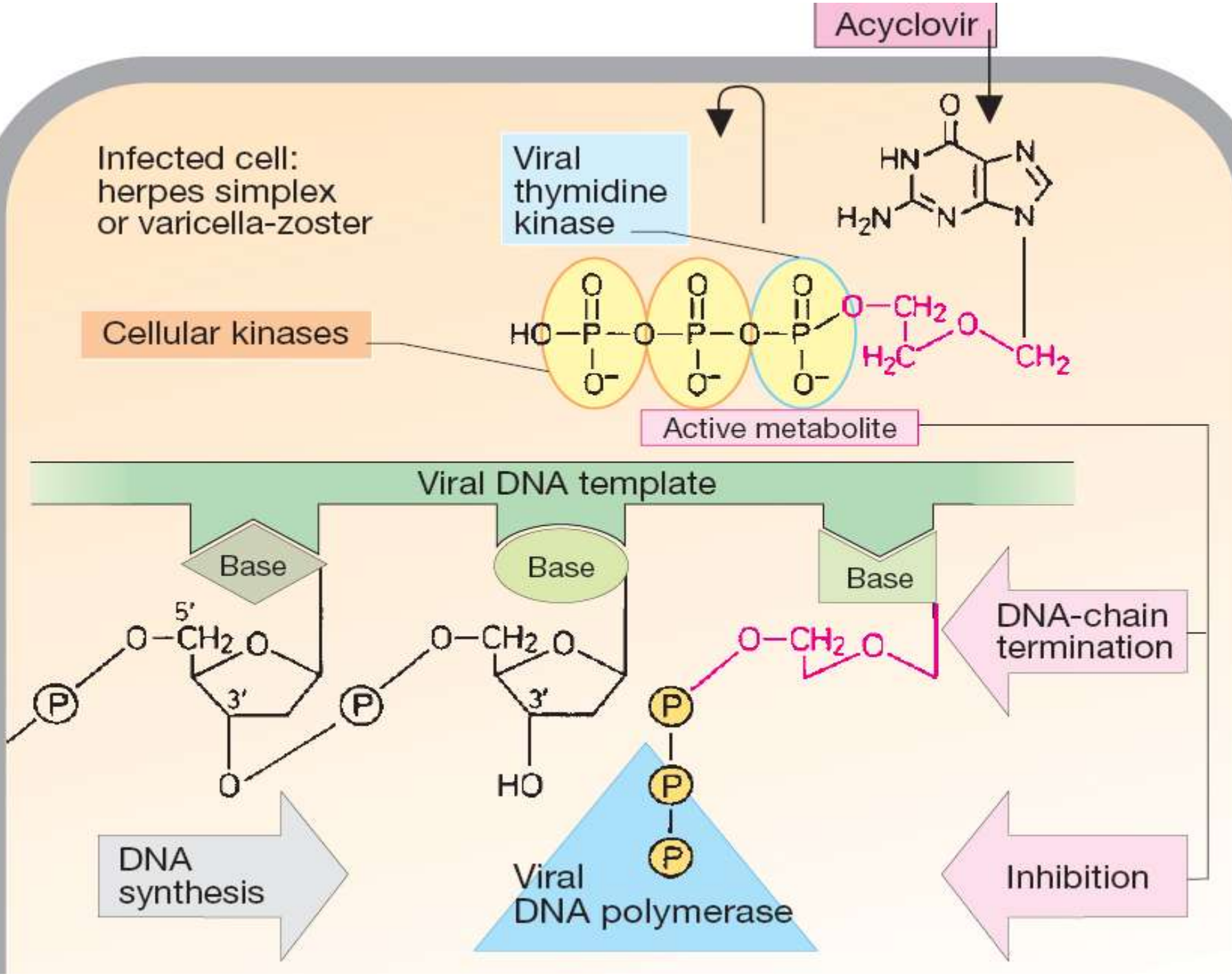
Thymidine kinase

Viral 200x affinity of mammalian

Cellular kinases

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

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

Acyclovir is used to treat:

- **Herpes simplex infections (oral labialis, 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.

Docosanol

- Docosanol is a saturated 22-carbon aliphatic alcohol that inhibits fusion between the plasma membrane and the HSV envelope, thereby preventing viral entry into cells and subsequent viral replication.

- Topical docosanol 10% cream is available without a prescription; application site reactions occur in approximately 2% of patients.

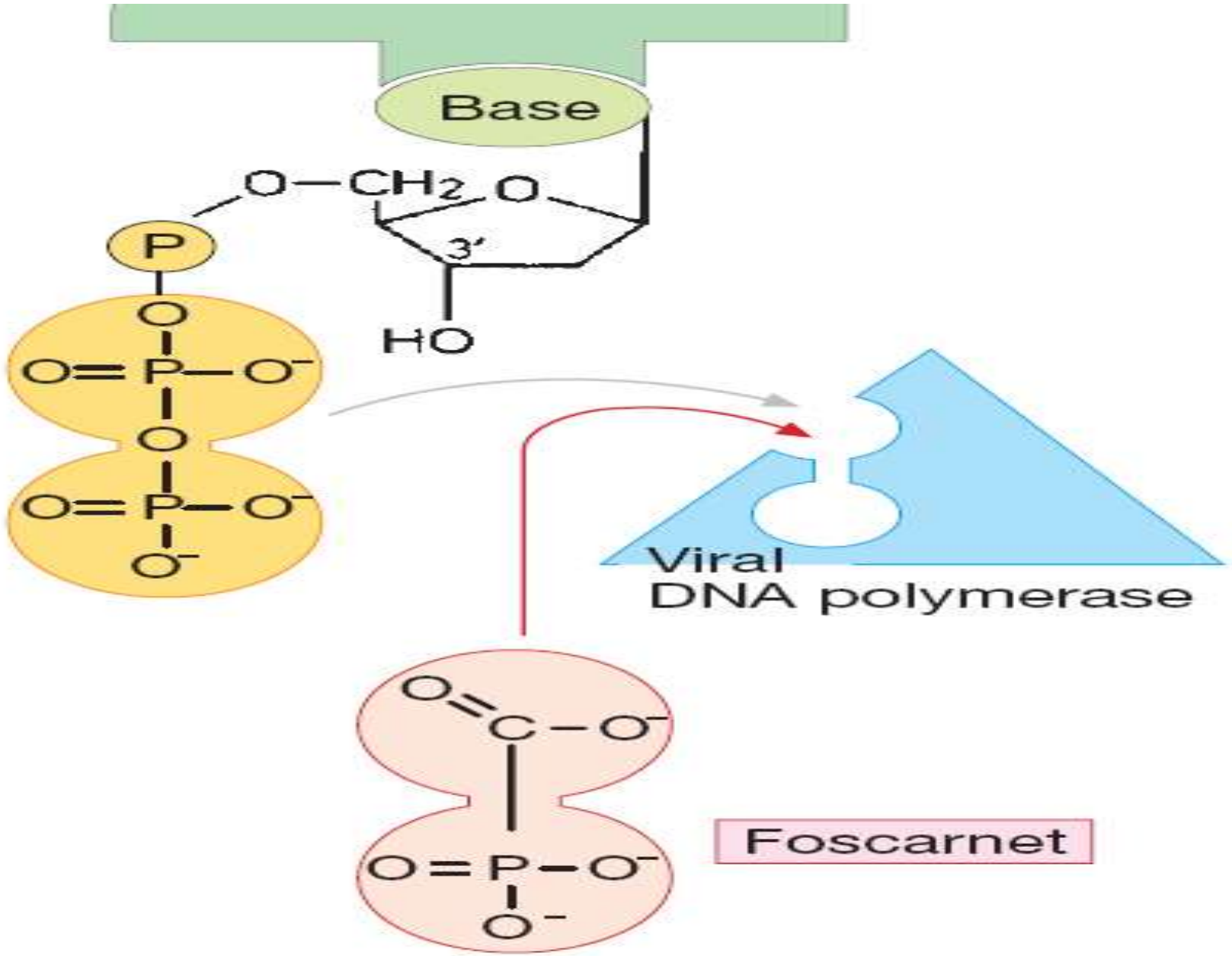
- When applied within 12 hours of the onset of prodromal symptoms, five times daily, median healing time was shortened by 18 hours compared with placebo in recurrent orolabial herpes.

Ganciclovir

- **Mechanism like Acyclovir**
- **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, cnvulsions).**
- **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 or ……..**
  (2) H. simplex resistant to Acyclovir.
  (3) HIV.


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

Vidarabine

- **Inhibits virally induced DNA polymerase more strongly than it does the endogenous enzyme.**

- **Vidarabine is a chain terminator and is active against herpes simplex, varicella zoster, and vaccinia are especially sensitive.**

- **Its use is now limited to topical treatment of severe herpes simplex infection. Before the introduction of the better tolerated acyclovir, vidarabine played a major part in the treatment of herpes simplex encephalitis.**

- **Its clinically used in treatment of immunocompromised patients with herpetic and vaccinia keratitis and in keratoconjunctivitis.**

Treatment of respiratory virus infection

Influenza A & B

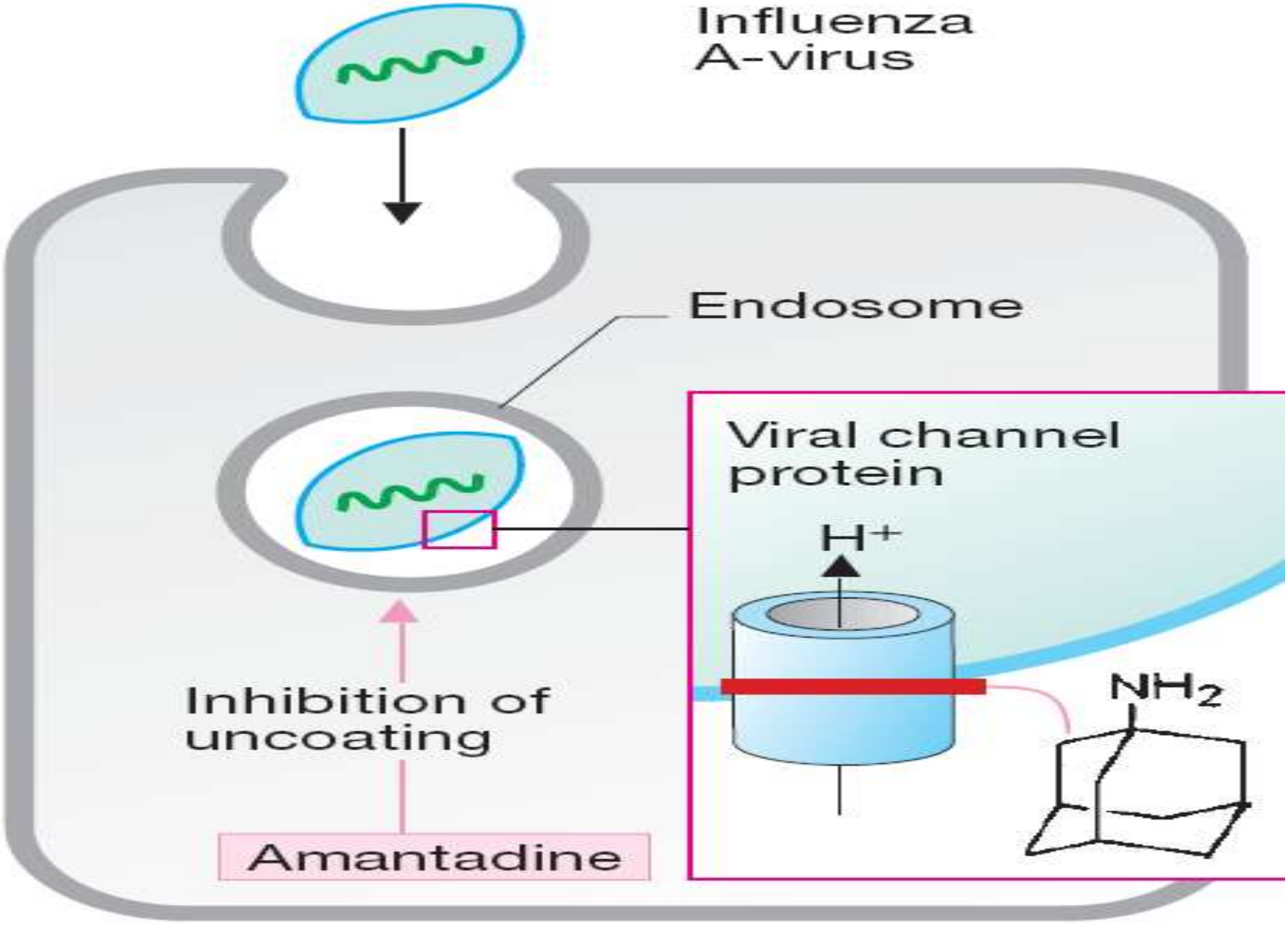
Respiratory suncytial virus (RSV)

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.**


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

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

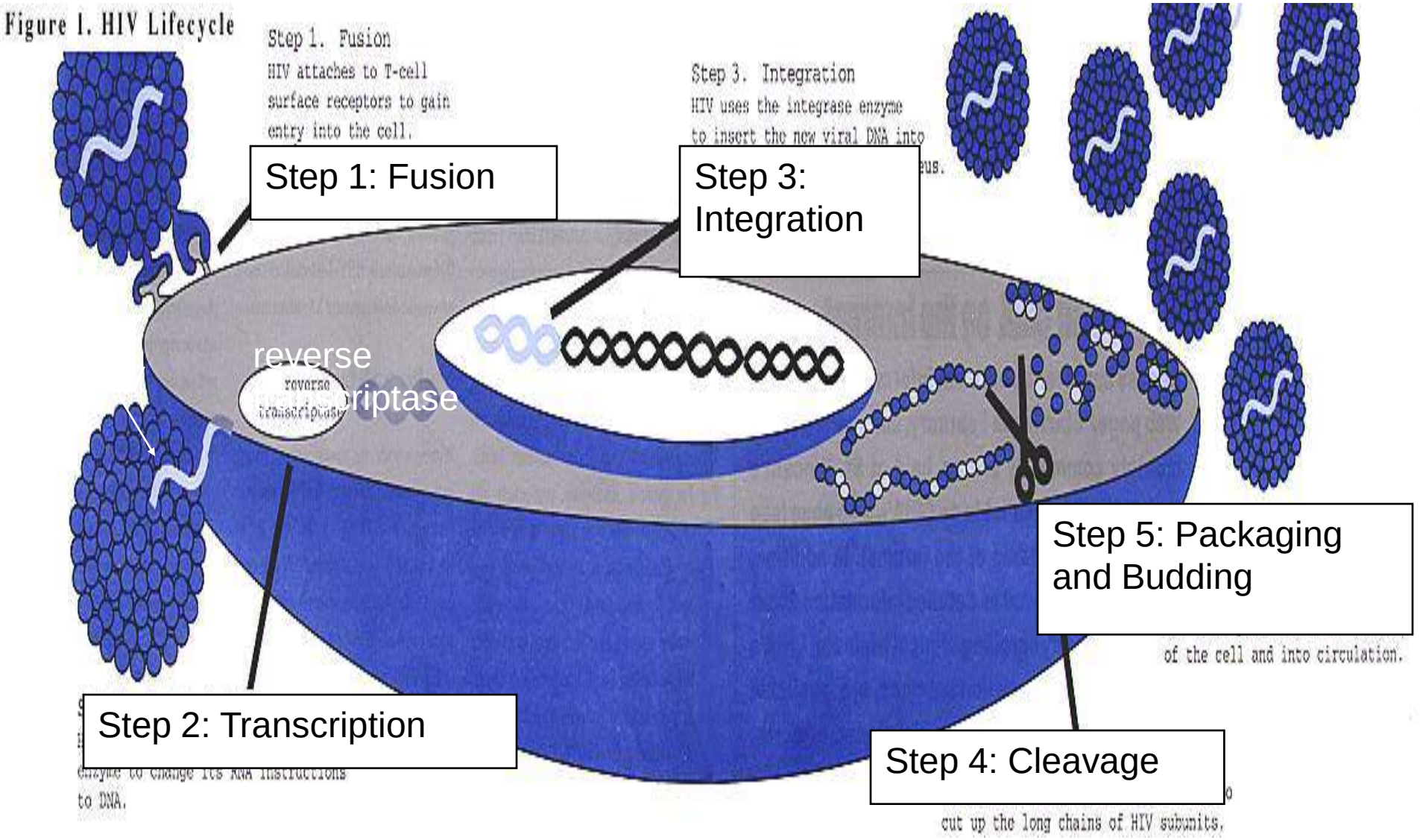
- Early administration is crucial because replication of influenza virus peaks at 24–72 hours after the onset of illness.
- When a 5-day course of therapy is initiated within 36–48 hours after the onset of symptoms, the duration of illness is decreased by 1–2 days compared with those on placebo,
- severity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

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



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.**

Abacavir

- Abacavir is a guanosine analog (Figure 49–2) that is well absorbed following oral administration (83%) and is unaffected by food. The serum half-life is 1.5 hours. The drug undergoes hepatic glucuronidation and carboxylation. Cerebrospinal fluid levels are approximately one third those of plasma.
- Abacavir is often co-administered with lamivudine, and a once-daily, fixed-dose combination formulation is available. Abacavir is also available in a fixed-dose combination with lamivudine and zidovudine.
- High-level resistance to abacavir appears to require at least two or three concomitant mutations and thus tends to develop slowly.
- Hypersensitivity reactions, occasionally fatal, have been reported in up to 8% of patients receiving abacavir and may be more severe in association with once-daily dosing.

- All NRTIs may be associated with mitochondrial toxicity, probably owing to inhibition of mitochondrial DNA polymerase gamma. Less commonly, lactic acidosis with hepatic steatosis may occur, which can be fatal. NRTI treatment should be suspended in the setting of rapidly rising aminotransferase levels, progressive hepatomegaly, or metabolic acidosis of unknown cause. The thymidine analogs zidovudine and stavudine may be particularly associated with dyslipidemia and insulin resistance. Also, some evidence suggests an increased risk of myocardial infarction in patients receiving abacavir or didanosine; this bears further investigation.

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, usually a maculopapular eruption that spares the palms and soles, 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.**

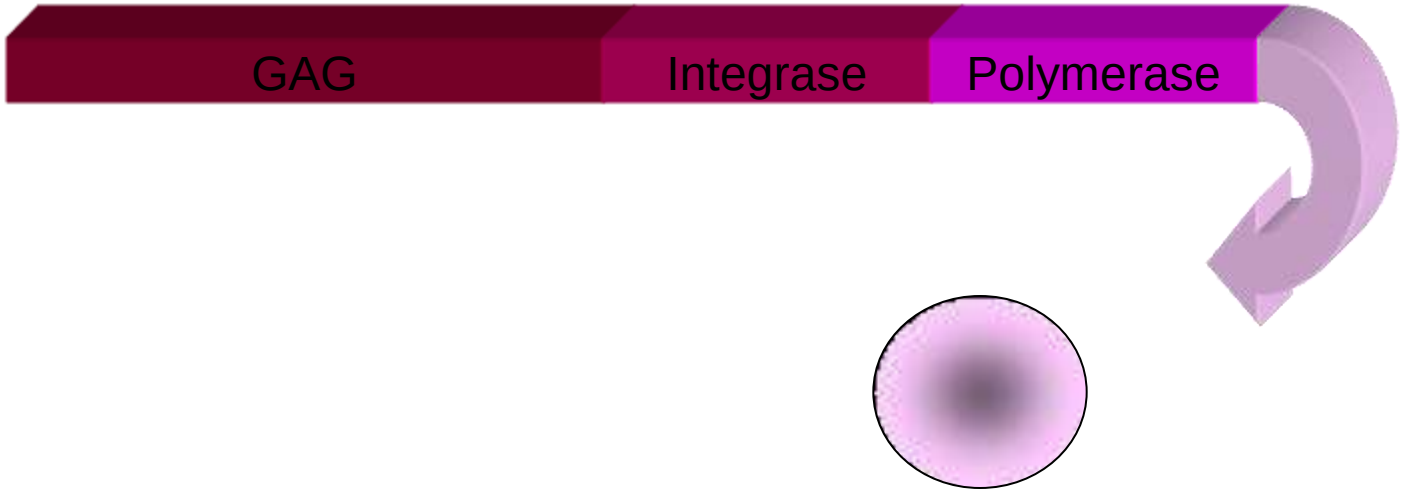
- **They are orally active, side effects include GI disturbances and hyperglycemia, interact with cytochrome P450.** **buffalo hump**

Anti-Viral Chemotherapy

GAG/POL polyprotein

Retrovirus --- HIV

Anti-Viral Chemotherapy

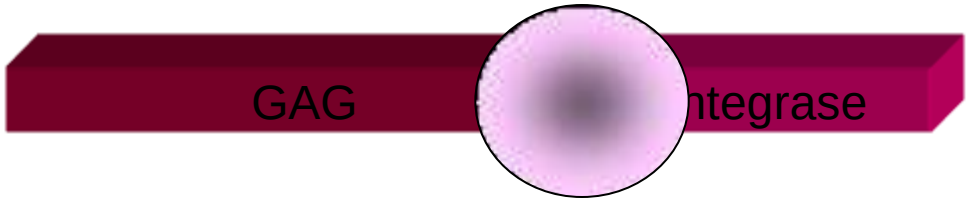


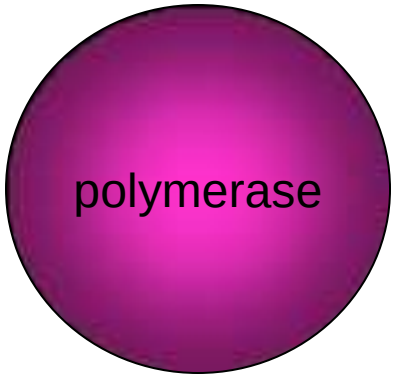
Protease folds and cuts itself free

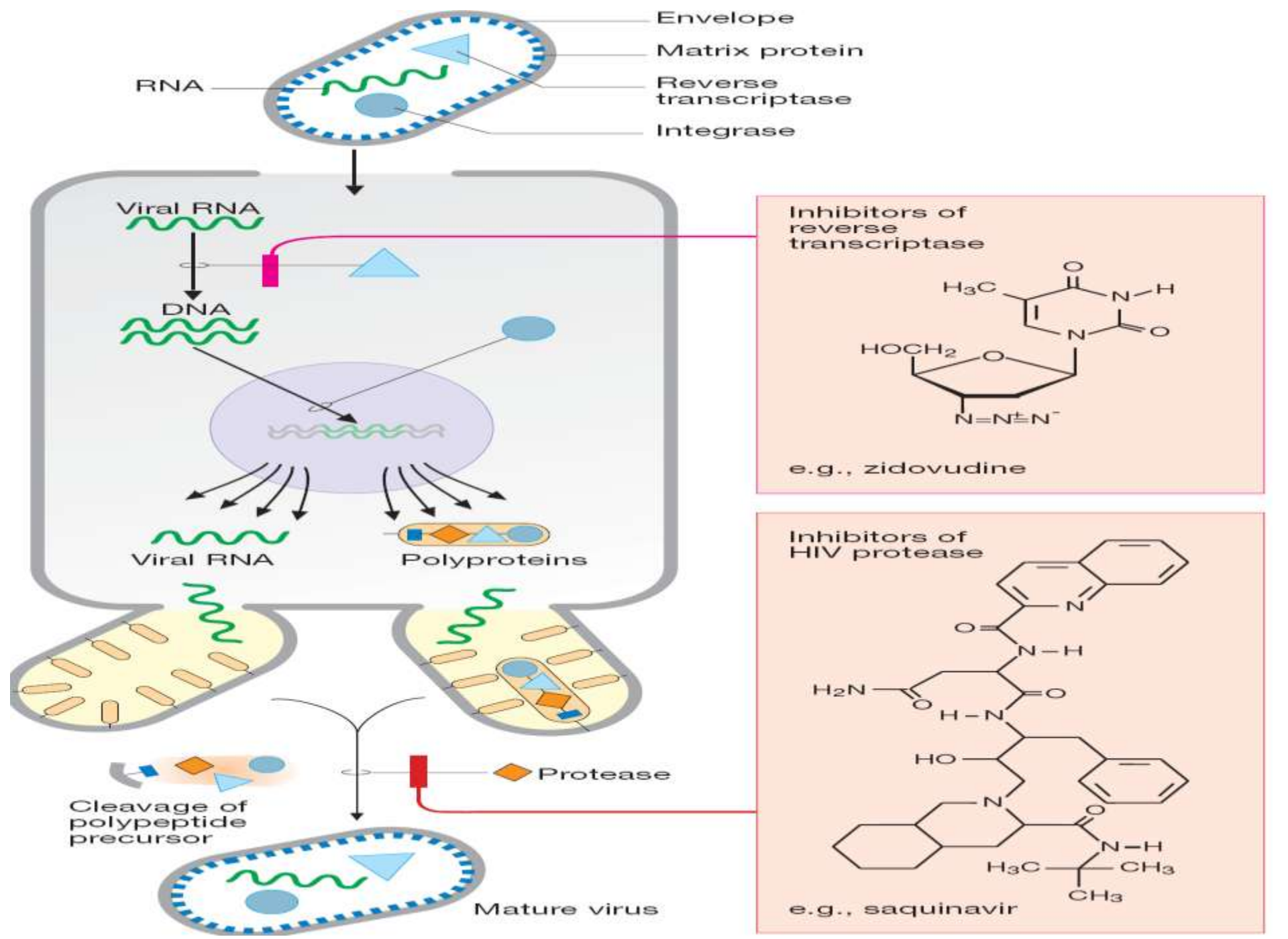
Anti-Viral Chemotherapy

Protease cuts at a site between the integrase and polymerase

Anti-Viral Chemotherapy






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

- **Agents that block fusion of HIV with the host cell by interacting with gp41**

- **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.**

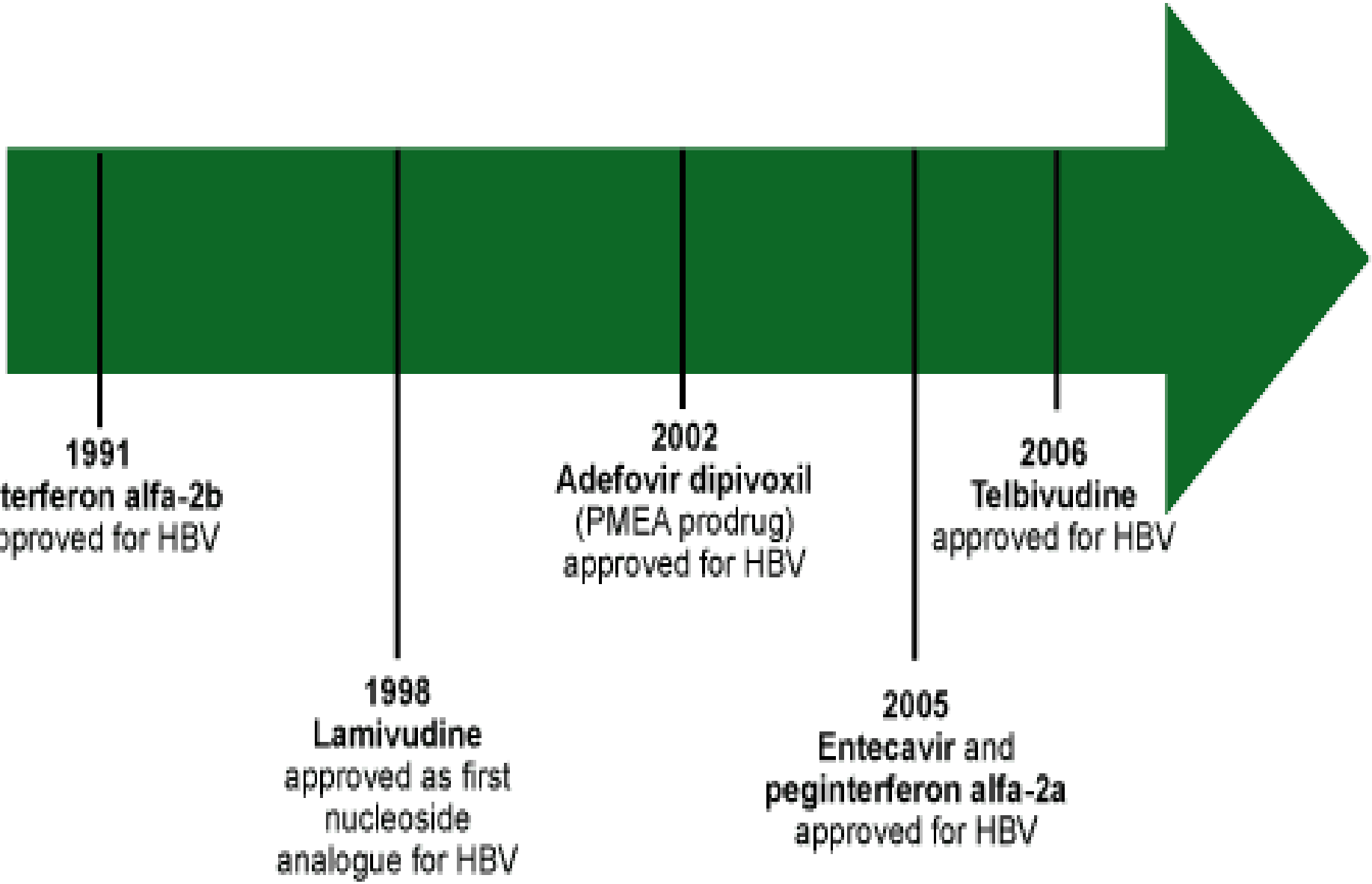
  examples (1) NNRTI–Based Regimens (1-NNRTI + 2NRTIs)

  (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

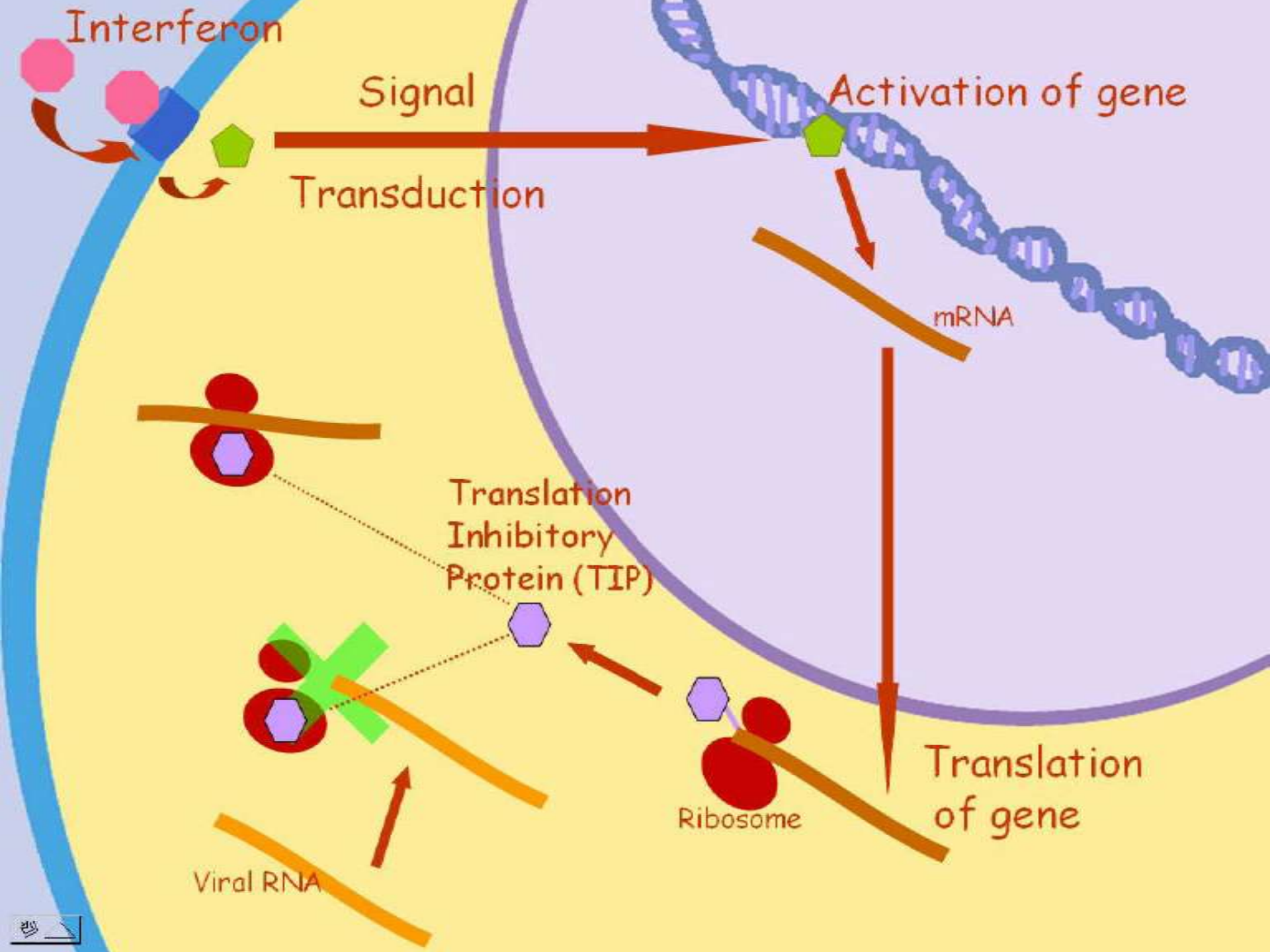


Interferons

- ***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 branced polyethylene gylcol (PEG) moiety is attached covalently to interferon**
- **Increased half-life and steady drug concentrations**

Interferon, mechanism of action:

- 1) binds to cell surface receptors
- 2) induces expression of translation inhibitory protein (TIP)
- 3) TIP binds to ribosome, inhibits host expression of viral proteins


Interferon
Signal
Transduction
Activation of gene
mRNA
Translation
Inhibitory
Protein (TIP)
Ribosome
Translation
of gene
Viral RNA

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 B Virus Agents

- **…….**

- **Entecavir and tenofovir have very strong resistance profiles in treatment-naive patients.**

- **Disadvantages include the need to continue therapy indefinitely and the potential for resistance development.**

Anti-Hepatitis C Virus Agents

- **Approved**
  - **Interferon-alpha (pegylated)**
  - **Ribavirin**

- **In development**
  - **Protease inhibitors**
  - **Polymerase inhibitors**

- 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%.