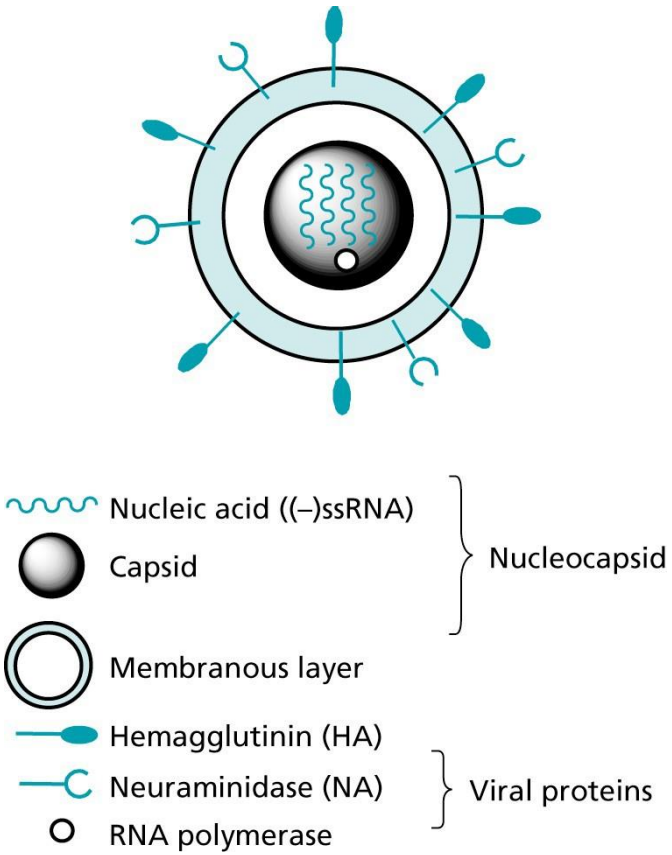
Antiviral Drugs

Structure of viruses

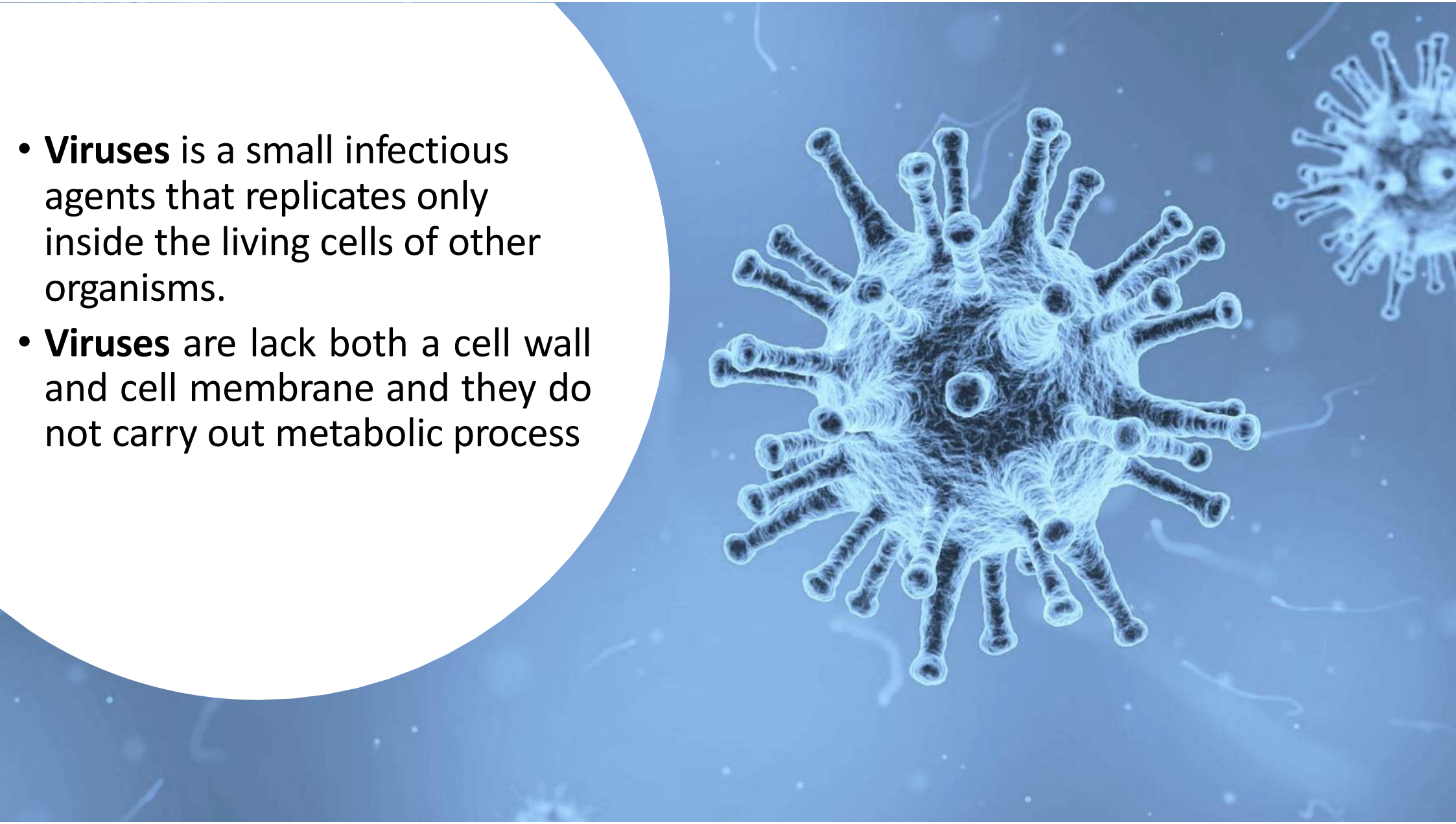
structure of the influenza virus

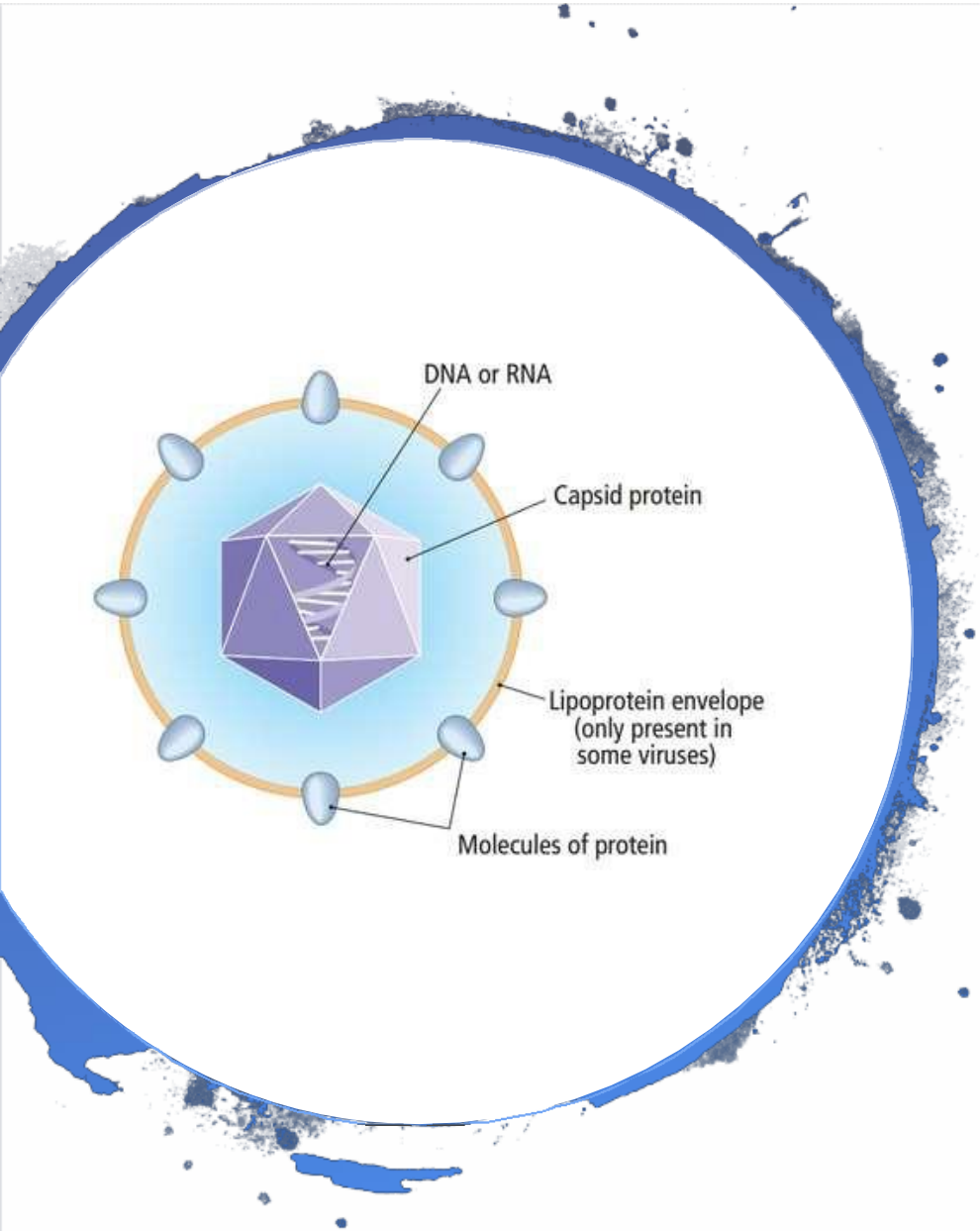


- **DNA-viruses**: poxviruses, herpes, adenoviruses, papillomaviruses.
Contain mostly double-stranded DNA, a small number single-stranded DNA.
DNA viruses enter the cell nucleus and direct the generation of new viruses.

- **RNA-viruses**: influenza, measles, mumps, cold, meningitis, poliomyelitis, retroviruses (AIDS, T-cell leukemia), arenaviruses.
Contain largely single-stranded RNA (ssRNA).
RNA viruses do not enter the cell nucleus (except the influenza virus).
RNA retroviruses uses the viral reverse transcriptase to make a DNA copy of the viral RNA, which is then integrated into the host genome.

- **Viruses** is a small infectious agents that replicates only inside the living cells of other organisms.
- **Viruses** are lack both a cell wall and cell membrane and they do not carry out metabolic process





Viral particles consist of two to three parts :

1. Genetic material , either DNA or RNA
2. Protein coat (Capsid), which surrounds and protects the genetic material
3. Envelope of lipid , lipid layer that surround the protein coat when they are outside cell

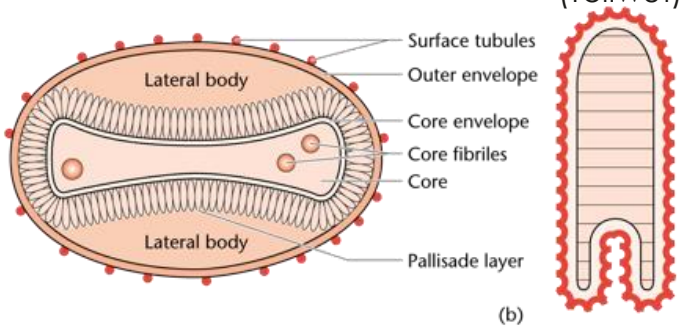
- Viruses cannot reproduce on their

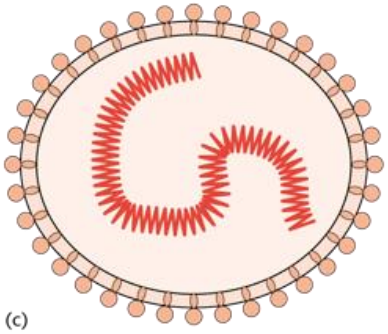
Own , they use host's metabolic processes and so few drugs are selective enough to prevent viral replication

Virus Structure

Rabiesvirus
(Tollwut)

Poxvirus

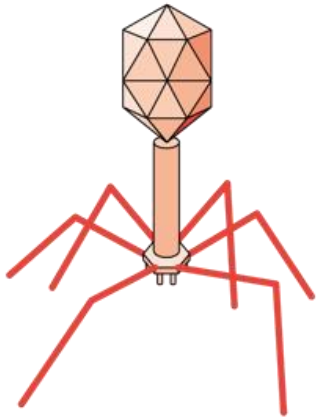




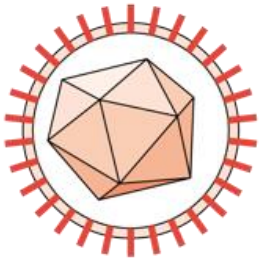
Poxvirus

Mumpsvirus

T-virus

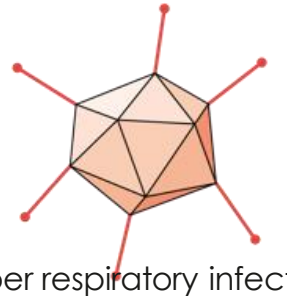


Coliphage Lambda



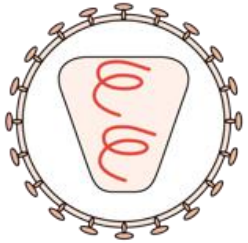
Herpes Simplex

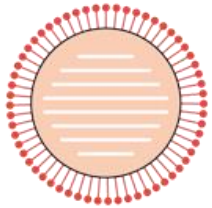
Adenovirus



upper respiratory infections

HIV



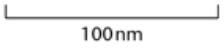


Influenzavirus

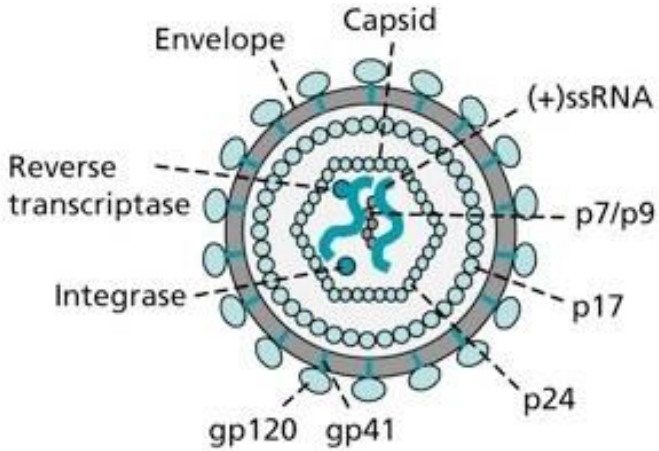
Tobacco Mosaic

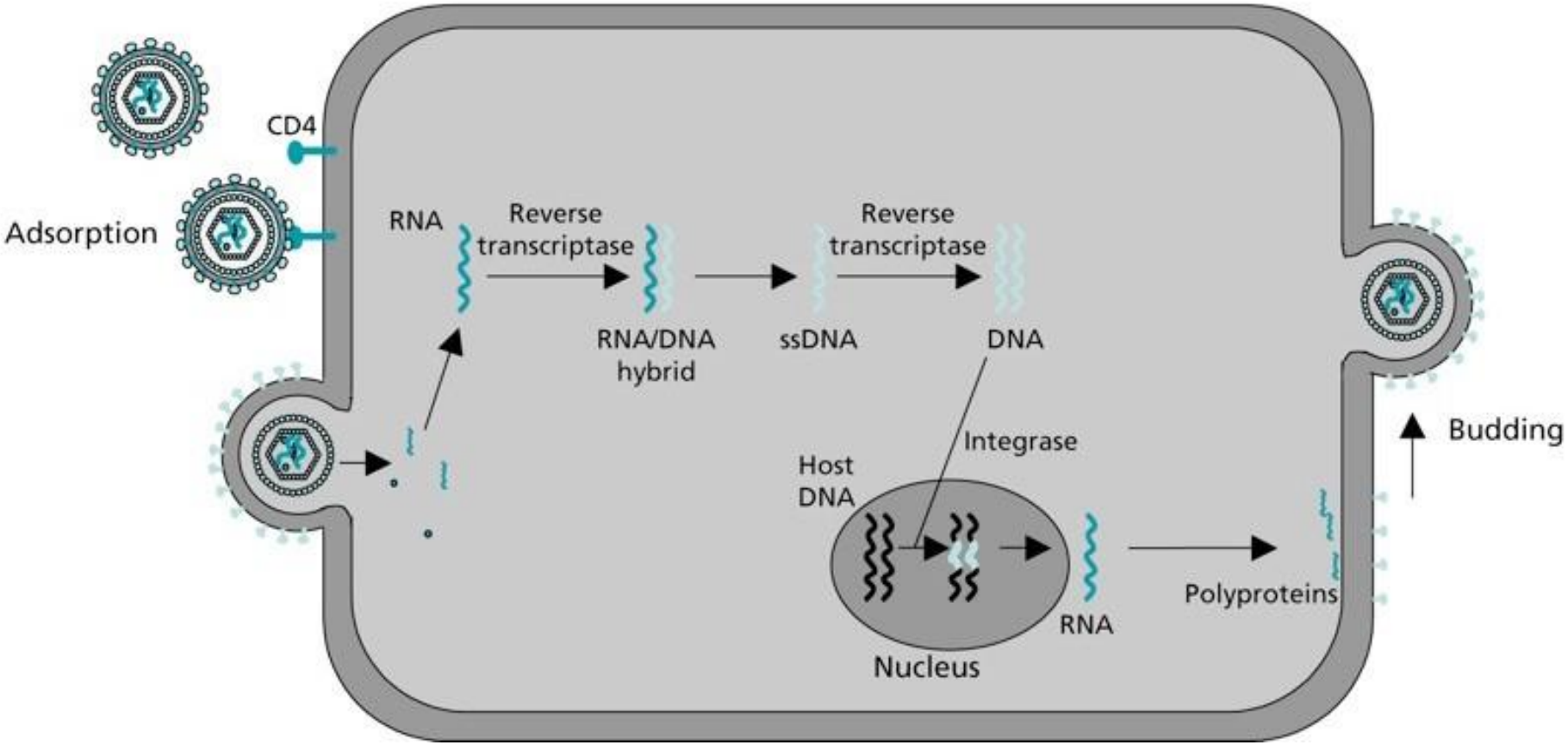
Simian

Rhino

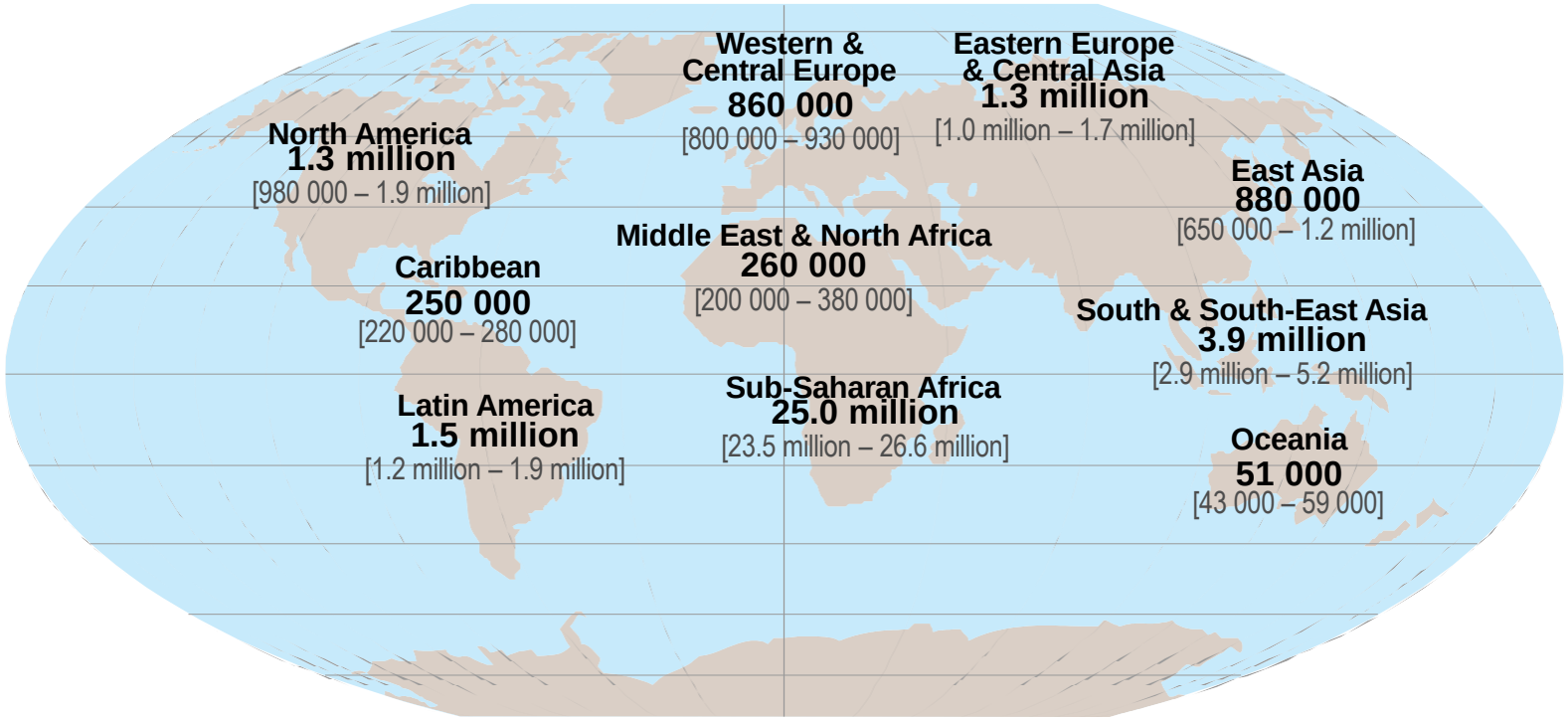


The HIV virus structure and the HIV life cycle





Adults and children estimated to be living with HIV

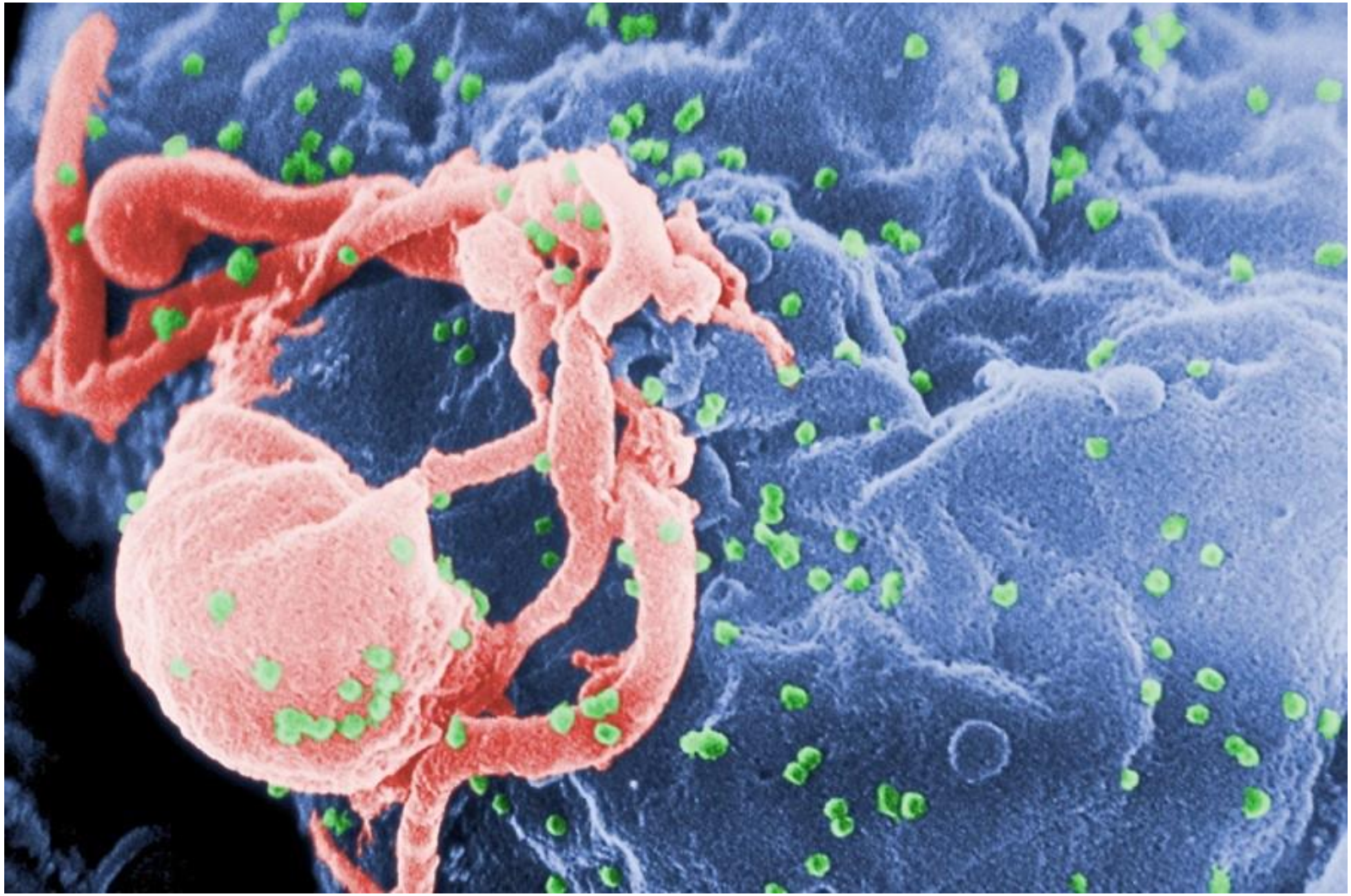


Total: 35.3 million [32.2 million – 38.8 million]

World Health Organization

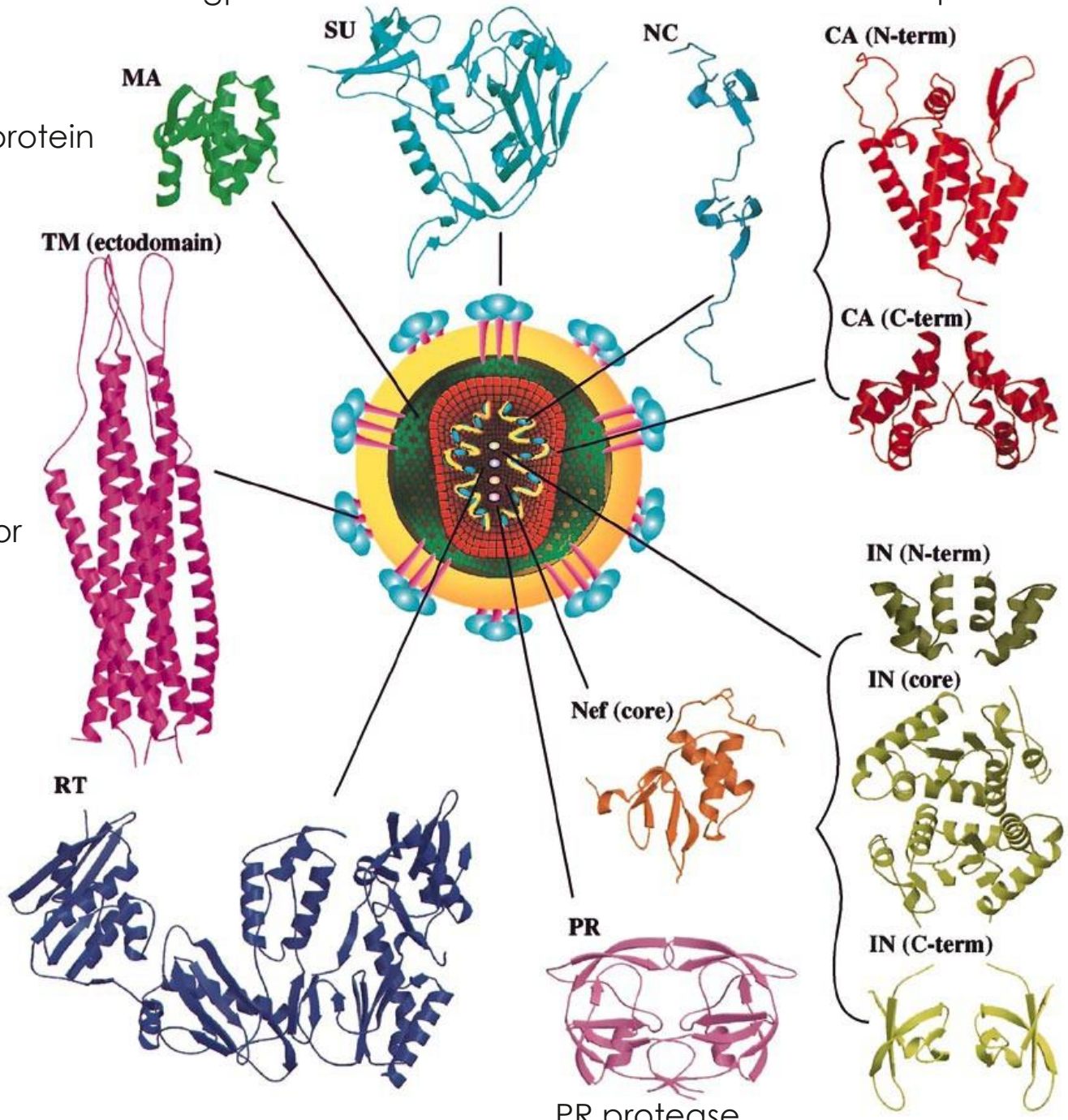
UNAIDS

Scanning electron micrograph of HIV-1 budding from a cultured lymphocyte

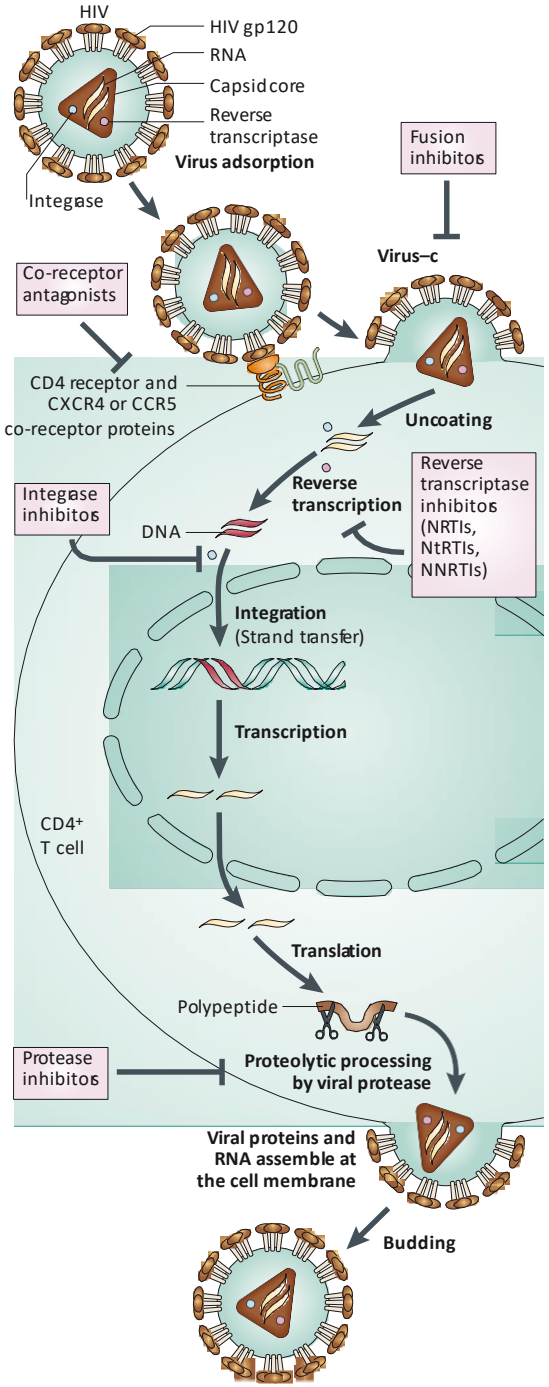


Structural Biology of HIV-1

Summers, J. Mol. Biol. 285 (1999),1-32



The various stages during viral infection



- **Attachment** of the virus to the host cell membrane via binding of molecules of the outer surface of the virion to a receptor molecule on the host cell (protein or carbohydrate)

- **Penetration and uncoating** of the virus and subsequent release of the virions into the host cell. Some viruses inject their material, others enter the cells intact (via endosomal entry) and are uncoated inside.

- Retroviruses (e.g. HIV):**reverse transcription** of viral RNA into DNA

- **Integration of the viral DNA into the host cell genome**

- Some viruses (e.g. HIV) use the cellular system for gene **duplication and translation**, while others (herpes) uses their own system to produce mRNA coding for viral proteins (early genes)

- **Synthesis and assembly of nucleocapsids** (late genes): Synthesis of capsid proteins that self-assemble to form the capsid.

- **Virion release**: Release of the naked virions by cell lysis, where the cell is destroyed. Alternatively, the viruses with envelopes can be released by a process known as budding, in which the nucleocapsid is wrapped by the membrane and pinched off.

Strategies for Antiviral Drug Development

- inhibition of virus adsorption
- inhibition of virus-cell fusion
- inhibition of the HIV integrase (HIV)
- inhibition of viral DNA or RNA synthesis
  - inhibitors of viral DNA polymerase
  - inhibitors of the reverse transcriptase
  - acyclic nucleoside phosphonates
- viral protease inhibition
- viral neuraminidase inhibition (influenza)
- inhibition of IMP dehydrogenase
- inhibition of S-adenosylhomocysteine hydrolase

Viral attachment and entry are blocked by:

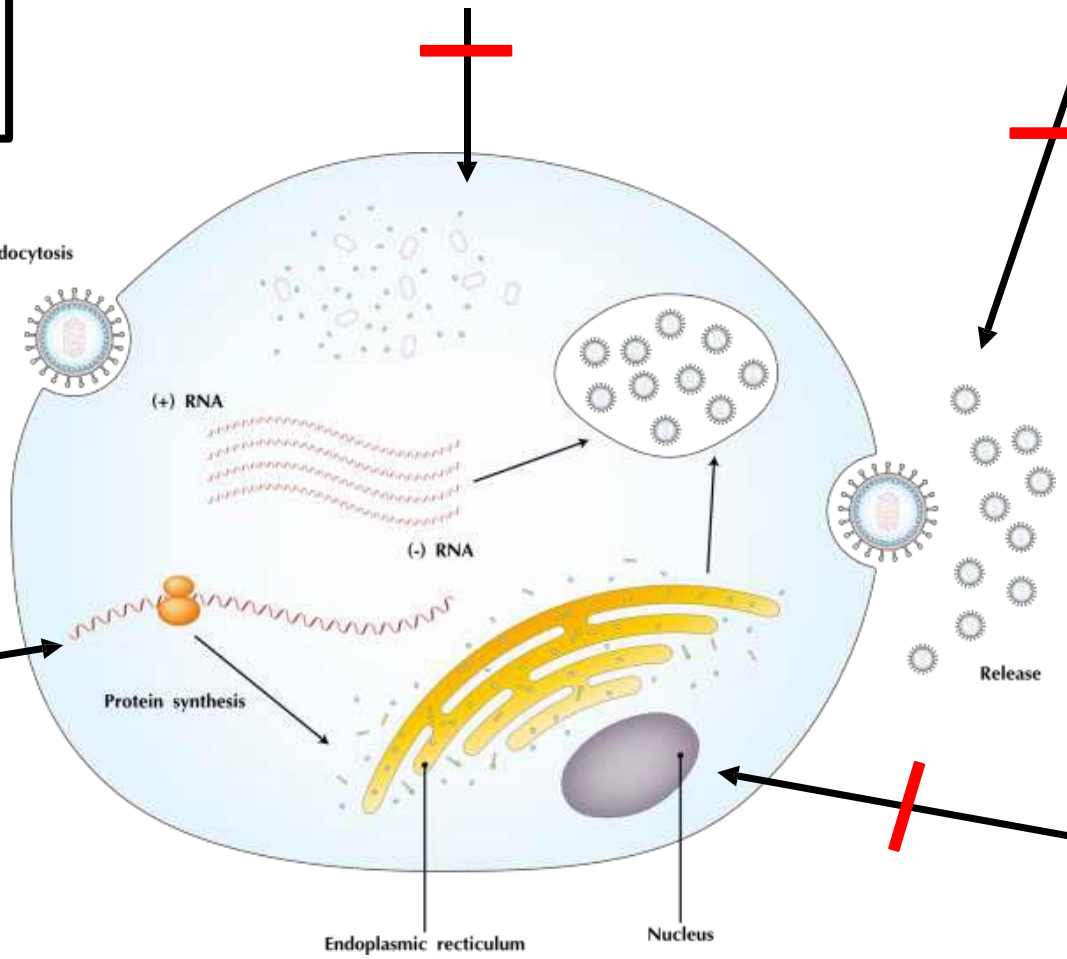
- Enfuvirtide(HIV)
- Maraviroc(HIV)
- Docosanol(HSV)
- Palivizumab (RSV)

Uncoating are blocked by:

- Amantadine (influenza)
- Rimantadine(influenza)

Viral release are blocked by:

- Neuraminidase inhibitors(Influenzas)



Protein processing are blocked by:

- Protease inhibitors (HIV)

Nucleic acid synthesis are blocked by:

- Nucleoside reverse transcriptase Inhibitors NRTI (HIV,HBV)
- Non-Nucleoside reverse transcriptase Inhibitors NNRTI (HIV)
- Acyclovir (HSV)
- Foscarnet(CMV)

Targets for Antiviral Drugs

Approach	Target virus(es)	Compounds approved	Selected compounds in development for the indicated target virus
Virus adsorption inhibitors	HIV, HSV, CMV, RSV and other enveloped viruses		Polysulphates, polysulphonates, polycarboxylates, polyoxometalates, chicoric acid, zintevir, cosalane derivatives, negatively charged albumins
Virus–cell fusion inhibitors	HIV, RSV and other paramyxoviruses		HIV: AMD3100, TAK779 and T20 derivatives
Viral DNA polymerase inhibitors	Herpesviruses (HSV-1, -2, VZV, CMV, EBV, HHV-6, -7, -8)	Acyclovir, valaciclovir, ganciclovir, valganciclovir, penciclovir famciclovir, brivudin*, foscarnet	Bicyclic furopyrimidine nucleoside analogues, A5021, cyclohexenylguanine
Reverse transcriptase inhibitors	HIV	NRTIs: zidovudine, didanosine, zalcitabine, stavudine, lamivudine‡, abacavir NNRTIs: nevirapine, delavirdine, efavirenz	Emtricitabine, amdoxovir Emivirine, UC781, DPC083, TMC125 (R165335)
Acyclic nucleoside phosphonates	DNA viruses (polyoma-, papilloma-, herpes-, adeno- and poxviruses), HIV, HBV	CMV: cidofovir HIV: tenofovir	HBV: adefovir
Inhibitors of processes associated with viral RNA synthesis	HIV, HCV		
Viral protease inhibitors	HIV, herpesviruses, rhinoviruses, HCV	HIV: saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, lopinavir	HIV: atazanavir, mozenavir, tipranavir Human rhinovirus: AG7088
Viral neuraminidase inhibitors	Influenza A and B virus	Zanamivir, oseltamivir§	RWJ270201
IMP dehydrogenase inhibitors	HCV, RSV	Ribavirin‖	Mycophenolic acid, EICAR, VX497
S-adenosylhomocysteine hydrolase inhibitors	(–)RNA haemorrhagic fever viruses (for example, Ebola)		

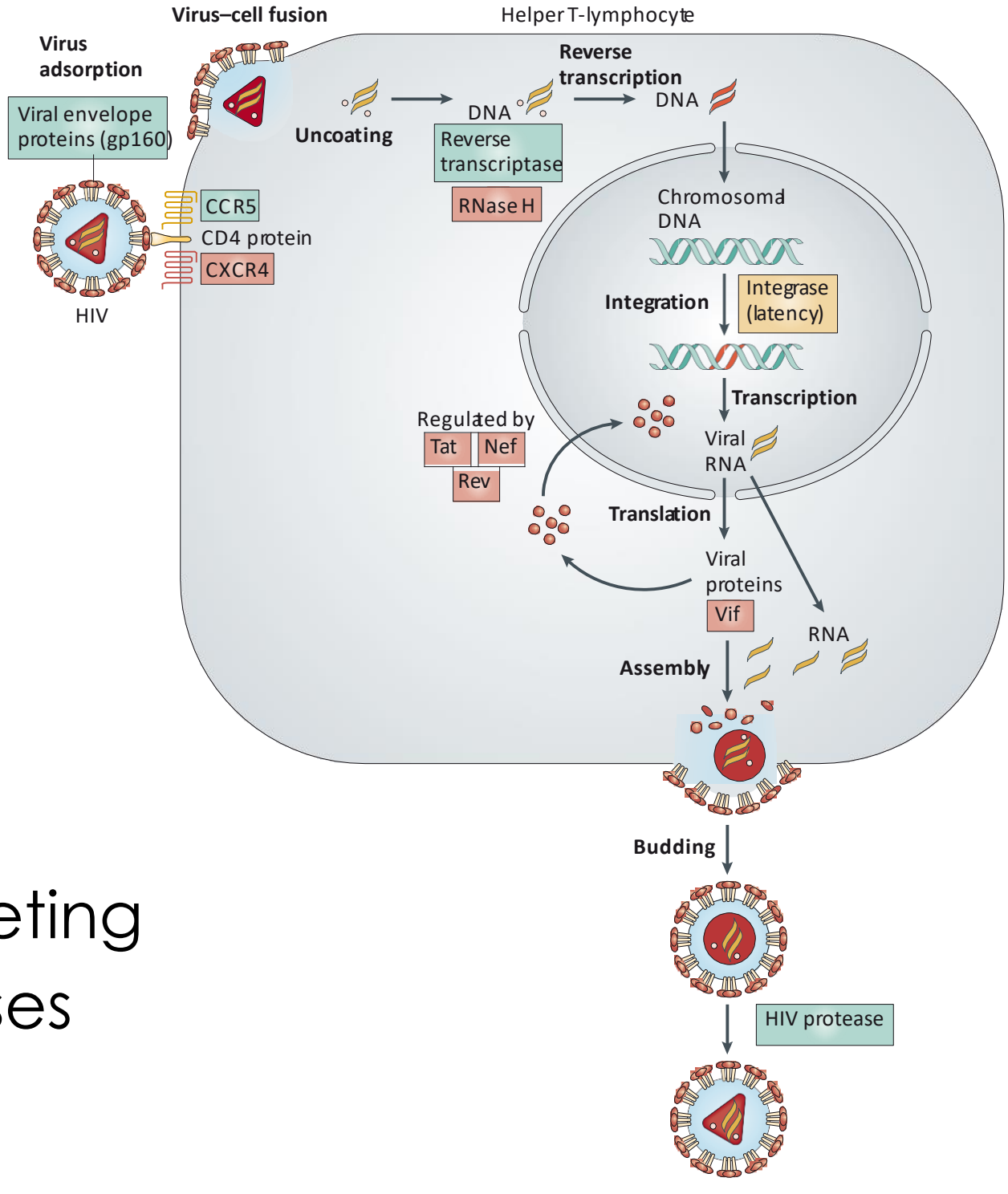
‡ Lamivudine is also approved for the treatment of HBV.

§ In addition to zanamivir and oseltamivir, amantadine and rimantadine have been approved as anti-influenza drugs, but these compounds are targeted at the viral uncoating process, not the viral neuraminidase.

‖ Ribavirin is used in combination with interferon-α for HCV.

CMV, cytomegalovirus; EBV, Epstein–Barr virus; EICAR, 5-ethynyl-1-β-D-ribofuranosylimidazole-4-carboxamide; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IMP, inosine 5≠-monophosphate; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; RSV, respiratory syncytial virus; VZV, varicella-zoster virus.

Drugs targeting HIV viruses



ANTIVIRAL AGENTS

1. **Entry and Fusion Inhibitors**
2. **Uncoating Inhibitors**
3. **Nucleic acid inhibitors**
   - **a) Viral DNA protease inhibitors**
   - **b) Reverse transcriptase inhibitors**
4. **Integrase inhibitors**
5. **Protease inhibitors**
6. **Release inhibitors (Neurominidase inhibitors)**
7. **Others**

Antiviral Drugs on the Market in the US (2007)

Name	Trade name	Company	Launched
Nucleoside or nucleotide reverse-transcriptase inhibitors			
Zidovudine	Retrovir	GlaxoSmithKline	1987
Didanosine	Videx	Bristol–Myers Squibb	1991
Zalcitabine	HIVID	Roche	1992
Stavudine	Zerit	Bristol–Myers Squibb	1995
Lamivudine	Epivir	GlaxoSmithKline, Shire Pharmaceuticals	1998
Abacavir	Ziagen	GlaxoSmithKline	1999
Tenofovir disoproxil fumarate	Viread	Gilead	2001
Emtricitabine	Emtriva	Gilead	2003
Non-nucleoside reverse-transcriptase inhibitors			
Nevirapine	Viramune	Boehringer Ingelheim	1996
Efavirenz	Sustiva, Stocrin	Bristol–Myers Squibb, Merck	1998
Delavirdine	Rescriptor	Pharmacia & Upjohn, Agouron, Pfizer	1999
Protease inhibitors			
Saquinavir	Invirase	Hoffmann-La Roche	1995
Indinavir	Crixivan	Merck	1996
Ritonavir	Norvir	Abbott, GlaxoSmithKline	1996
Nelfinavir	Viracept	Agouron, Pfizer	1997
Amprenavir	Agenerase, Prozei	Vertex	1999
Lopinavir + ritonavir	Kaletra, Aluvia	Abbott	2000
Atazanavir	Reyataz, Zrivada	Bristol–Myers Squibb, Novartis	2003
Fosamprenavir	Lexiva, Telzir	Vertex, GlaxoSmithKline	2003
Tipranavir	Aptivus	Boehringer Ingelheim	2005
Darunavir	Prezista	Tibotec	2006
Entry inhibitors			
Enfuvirtide	Fuzeon	Trimeris, Roche	2003
Maraviroc	Celsentri, Selzentry	Pfizer	2007

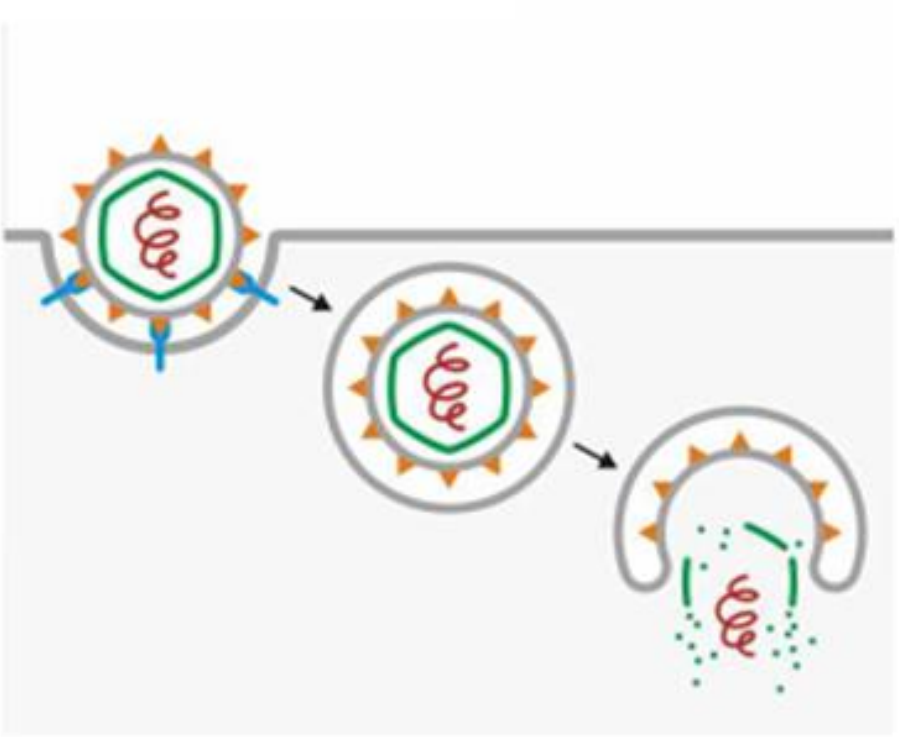
1. Entry Inhibitors

The most common drugs that prevent the virus from entering CD4 cells are:

-Maraviroc

-Enfuvirtide

-Docosanol



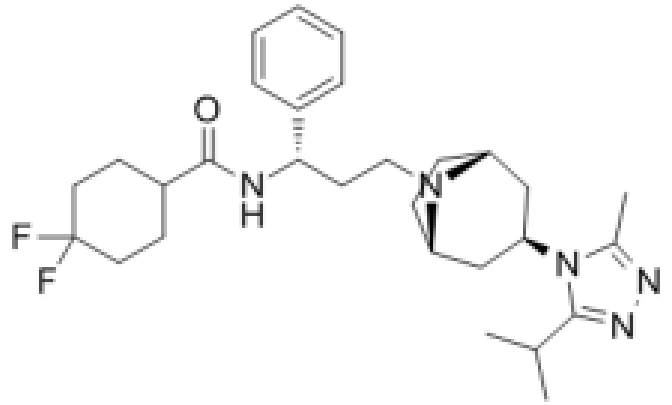
Maraviroc:

-It is new class of antiretroviral agents that targets a host protein, the chemokine receptor CCR5, rather than a viral target.

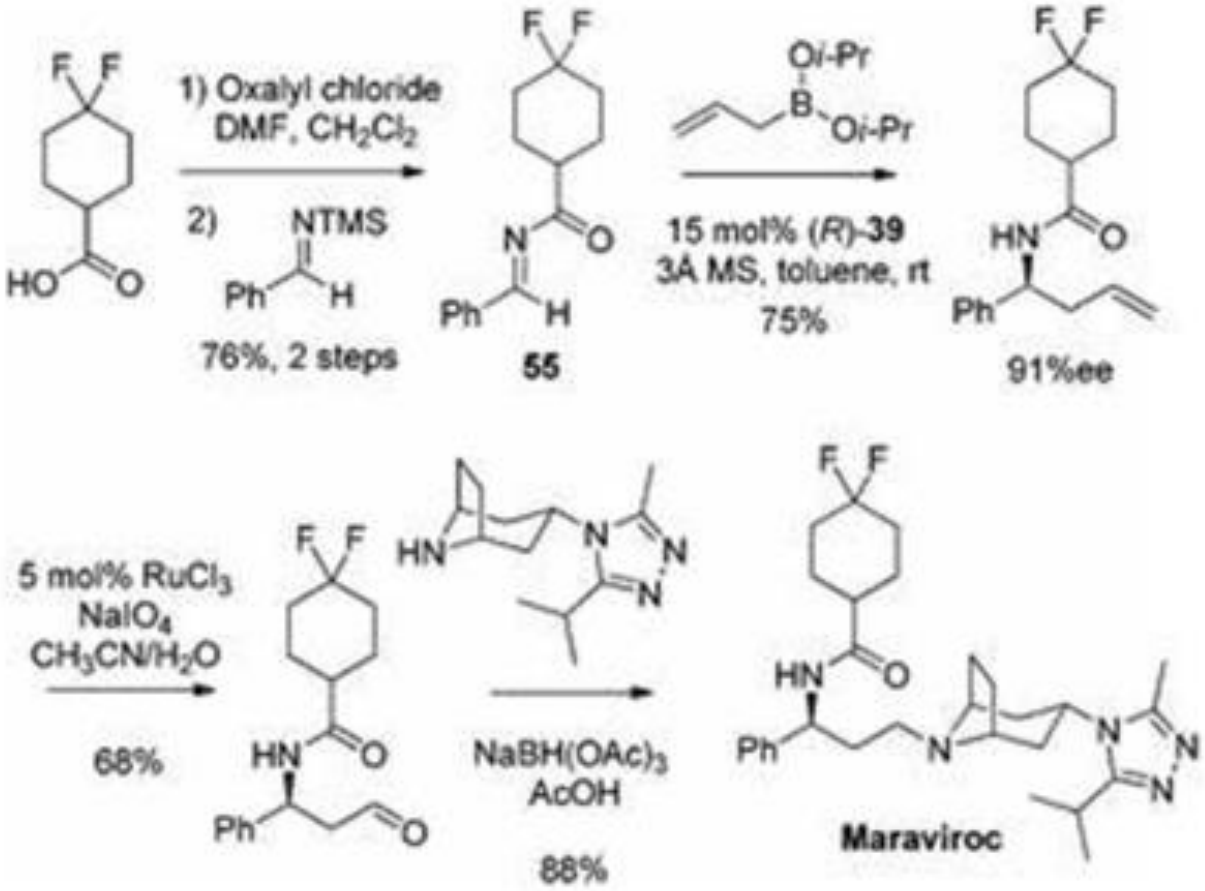
-Binding to this cell-surface protein.

-block human immunodeficiency virus type 1 (HIV-1) attachment to the coreceptor and prevents the virus from entering $CD4^+$ cells.

-Maraviroc is a substrate of cytochrome P450 (CYP3A) and *p*-glycoprotein, and has clinically significant interactions with other drugs including efavirenz and rifampin.



Synthesis of Maraviroc:

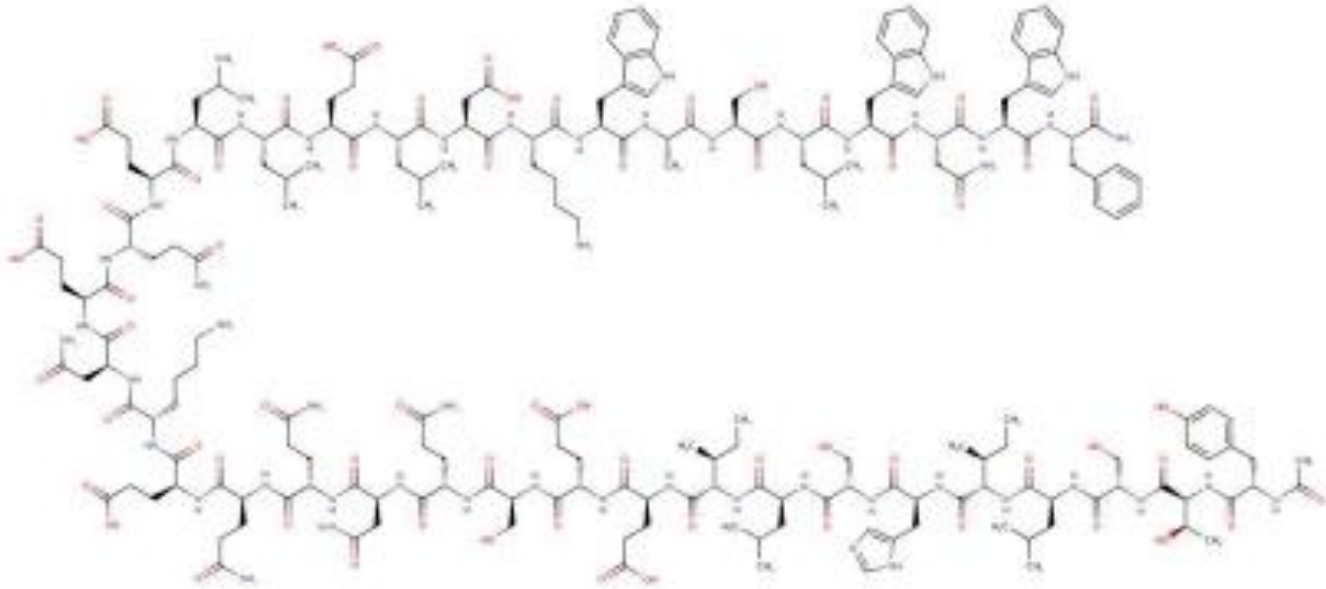


Enfuvirtide

•New class of antiviral drug, fusion inhibitors, which interferate with penetration of HIV-1 in the cells.

•Exhibits potent and selective inhibition of membrane of viral and cells.

•Showed significantly efficacy in the combination with other antiviral drugs in early stadium of HIV infection and in patients with antiretroviral resistention

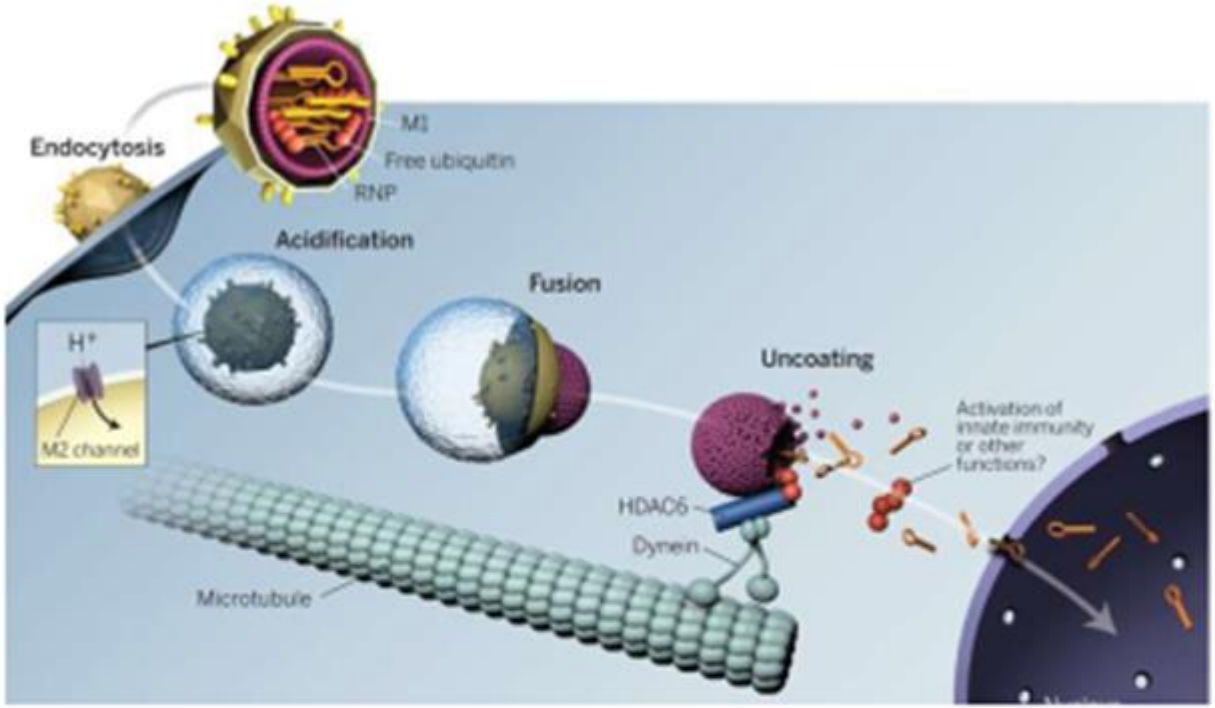


• Dose of Fuzeon for treating adults with HIV or AIDS is Fuzeon 90 mg (1 mL) injected twice daily just under the skin

• Enfuvirtide therapy costs an estimated US$25,000 per year in the United States

DOCOSANOL

- Saturated 22-carbon aliphatic alcohol.
- Inhibits FUSION between plasma membrane and HSV envelope resulting in prevention of viral entry into cells and subsequent viral replication.
- Only for orolabial HERPES

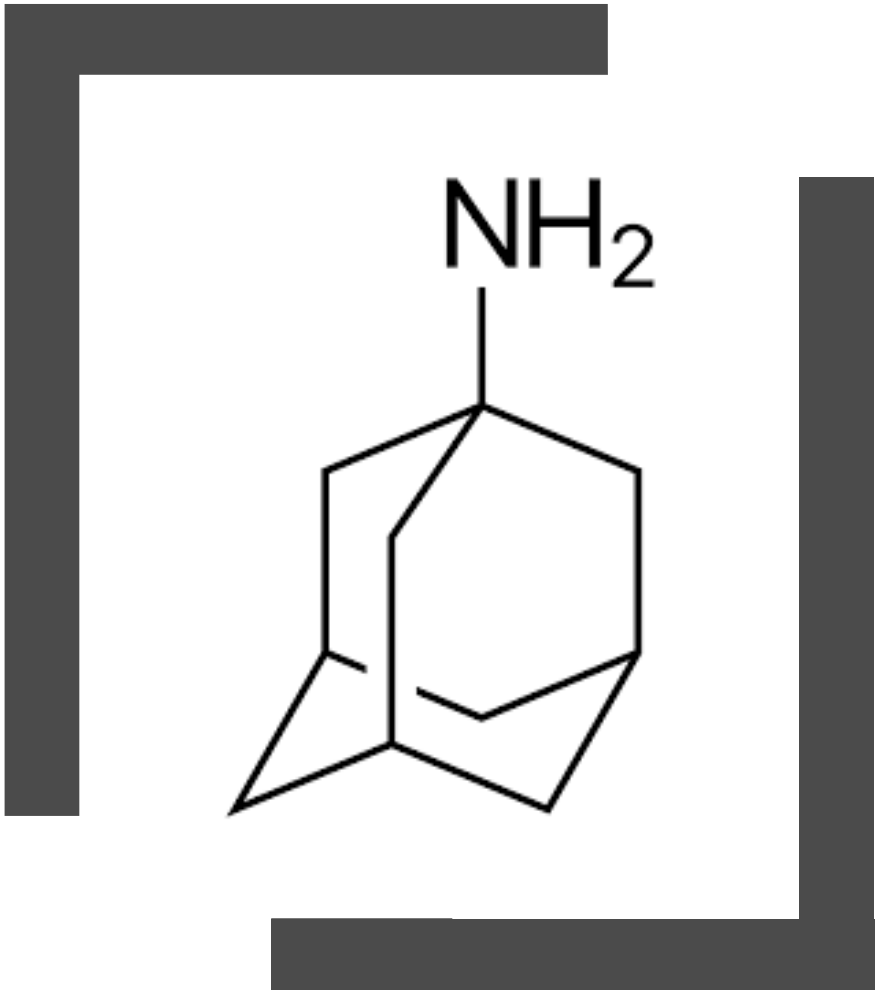


2. Uncoating Inhibitors

Amantadine and Rimantadine :

They are hydrophobic amines (weak organic bases) with clinical against influenza **A** only.

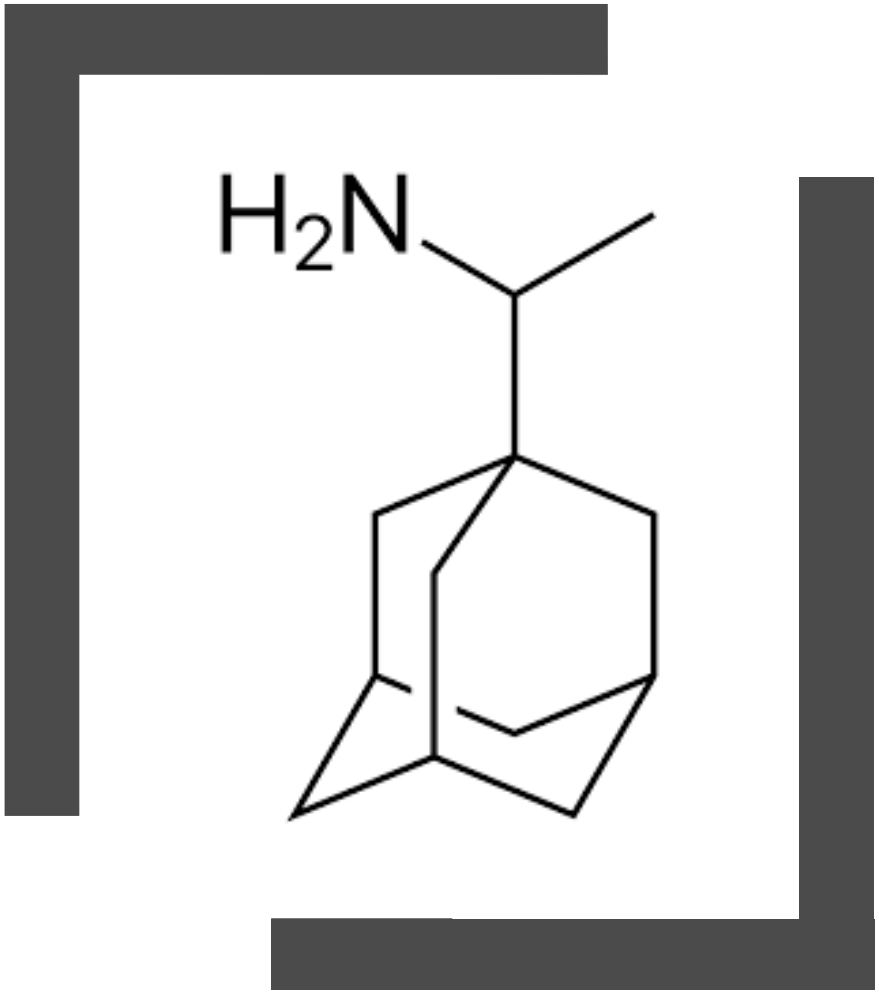
Can reduce severity of illness if started within 48 hrs of onset of symptoms .



2. Uncoating inhibitors

Amantadine :

Amantadine (1-aminoadamantane) and its methyl derivative inhibit the uncoating of the viral RNA within the infected host cells thus preventing its replication

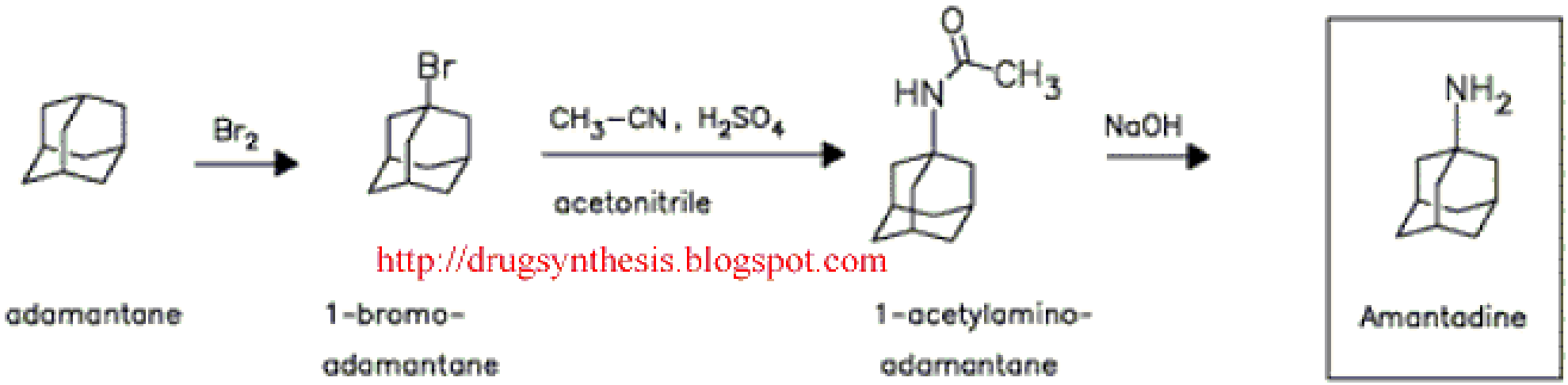


Uncoating inhibitors

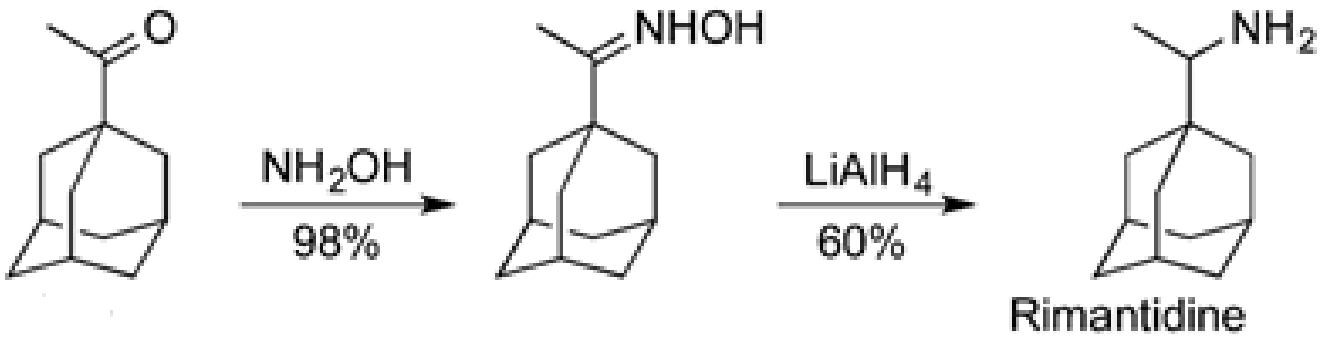
Rimantadine:

Interfere with virus uncoating by inhibiting release of specific protein also its more effective than amantadine .

Synthesis of Amantadine



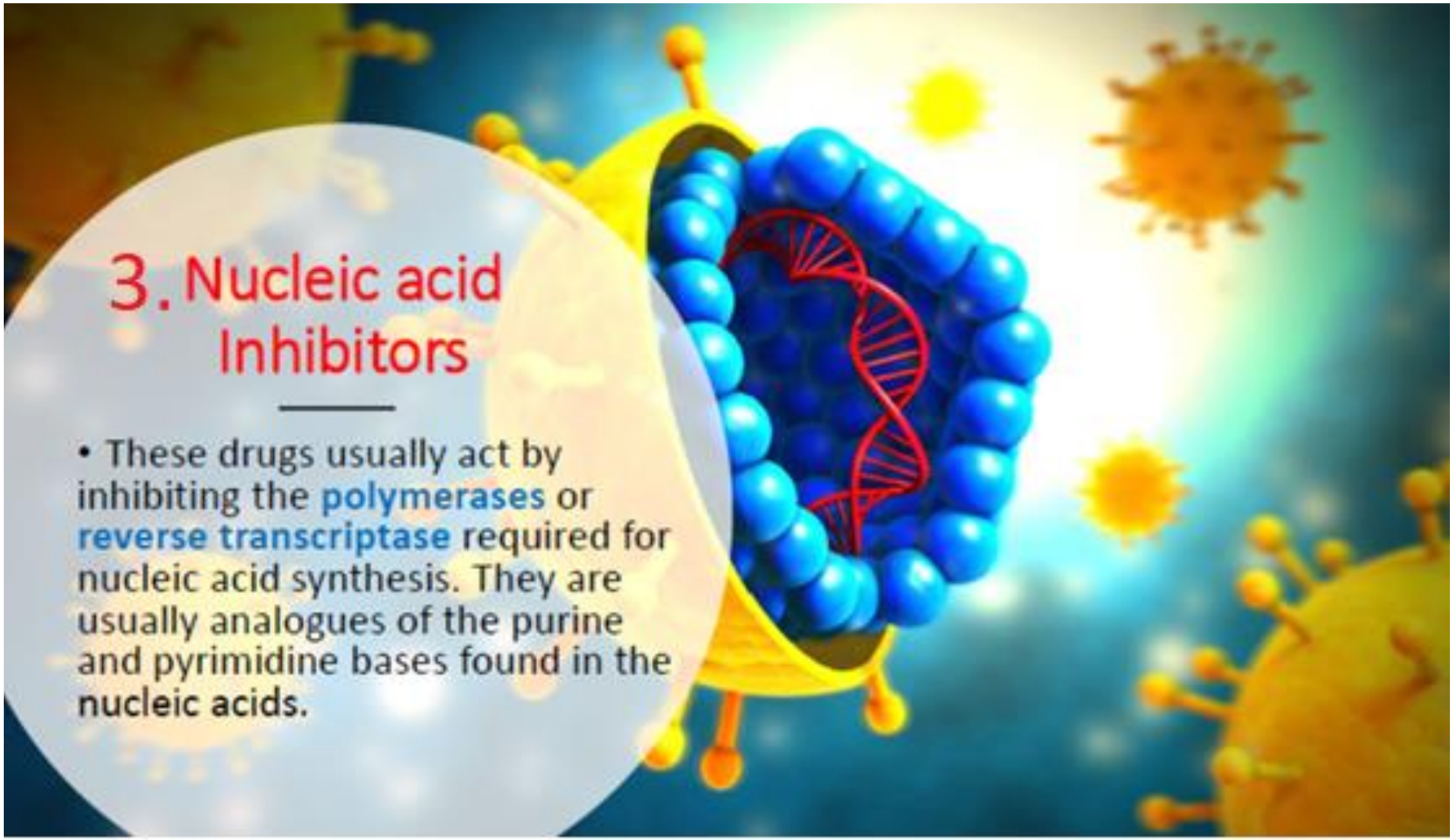
Synthesis of Rimantadine



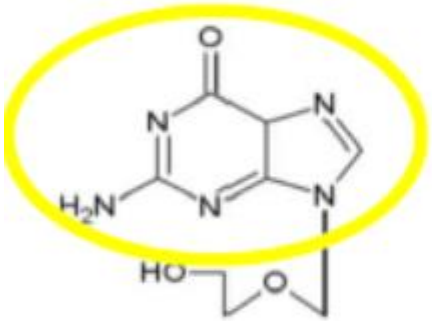
Rimantidine

EC_{50} (Influenza AH2N2)[261] = 14 µM

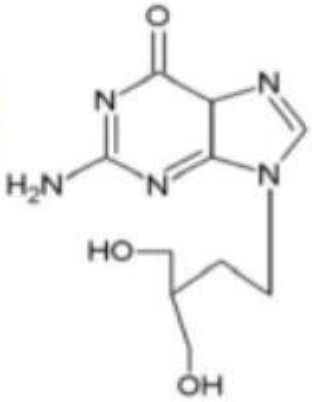
EC_{50} (Influenza AH3N2)[261] = 0.4 µM


3. Nucleic acid Inhibitors
• These drugs usually act by inhibiting the polymerases or reverse transcriptase required for nucleic acid synthesis. They are usually analogues of the purine and pyrimidine bases found in the nucleic acids.

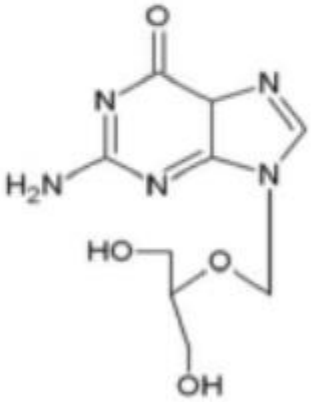
3a. Inhibitors of viral DNA polymerase



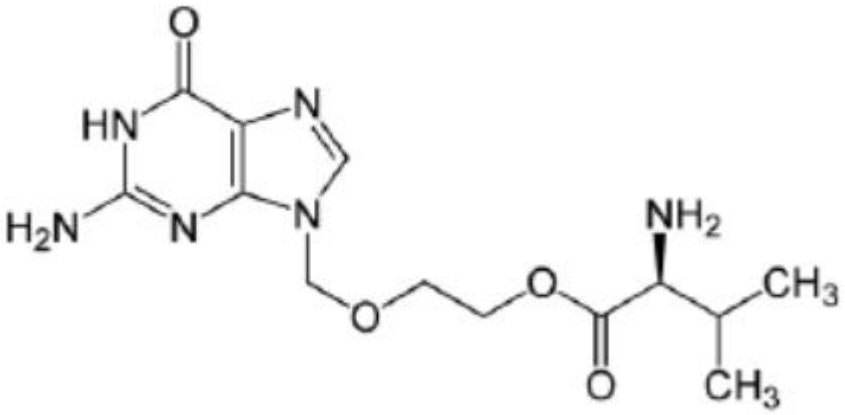
Acyclovir (ACV)



Penciclovir (PCV)



Ganciclovir (GCV)



Valaciclovir (prodrug of ACV)

Acyclovir

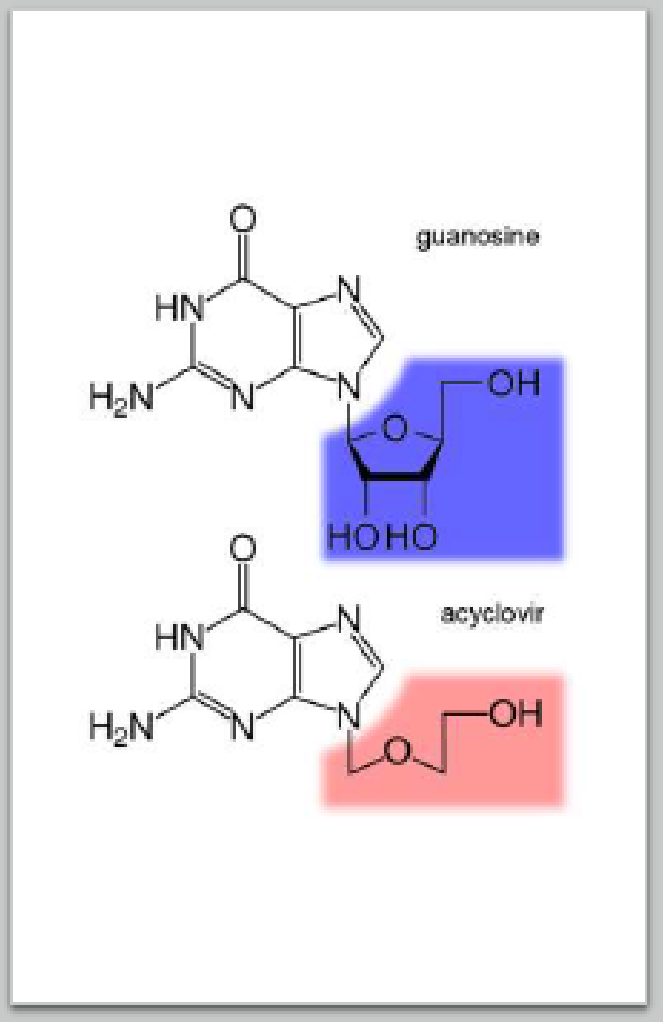
- is the prototypic antiherpetic therapeutic agent. Herpes simplex virus (HSV) types 1 and 2,varicella-zoster virus (VZV) (i.e. chickenpox and shingles).

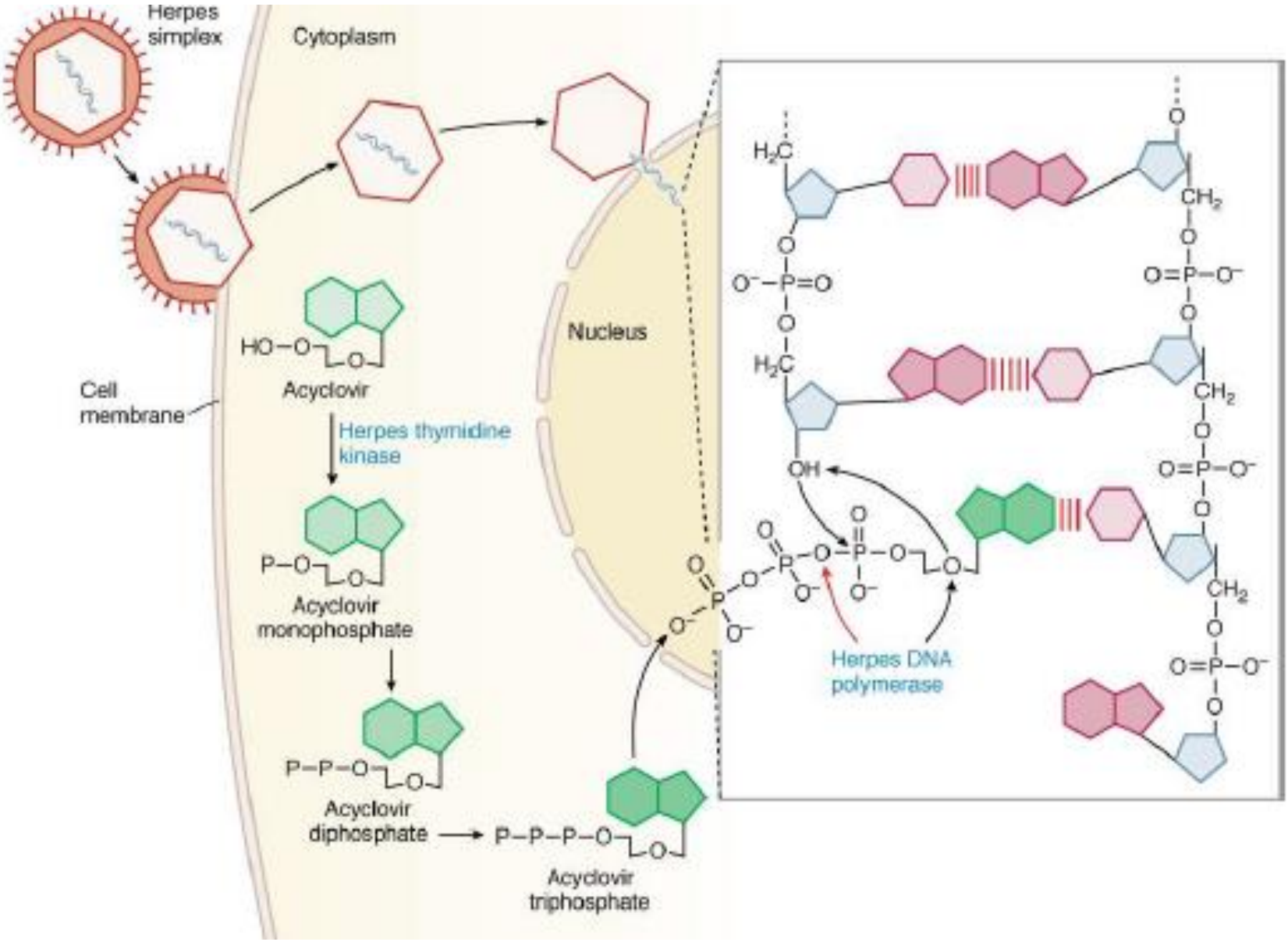
- Acyclovir has a nucleoside-like structure
- it lacks the complete sugar ring.
- In virally infected cells, it is phosphorylated to form a triphosphate which is the active agent, and so acyclovir is a prodrug

- Acyclovir triphosphate prevents DNA replication in two ways.

Firstly, it can bind to DNA polymerase and inhibit it.

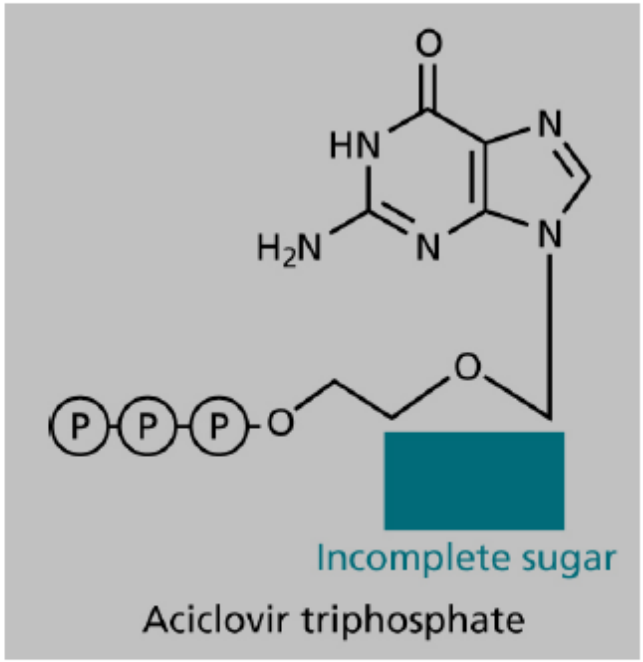
Secondly, the drug acts as a chain terminator



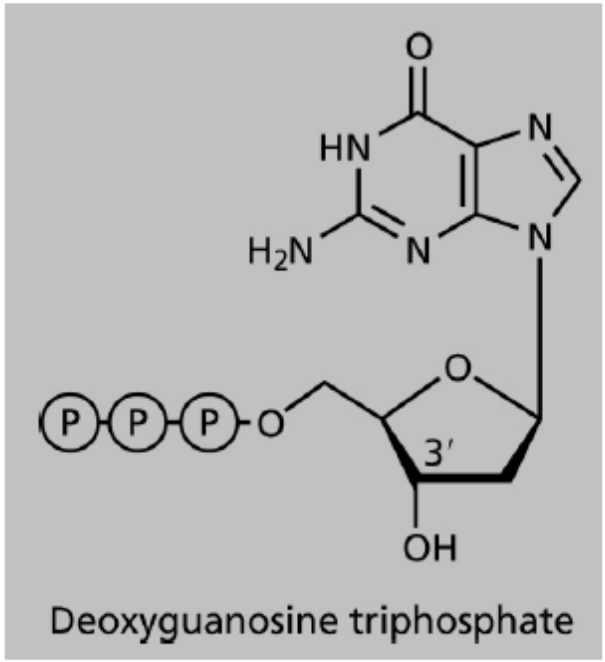

Herpes simplex
Cytoplasm
Nucleus
Cell membrane
Acyclovir
Herpes thymidine kinase
Acyclovir monophosphate
Acyclovir diphosphate
Acyclovir triphosphate
Herpes DNA polymerase

Inhibitors of viral DNA or RNA synthesis

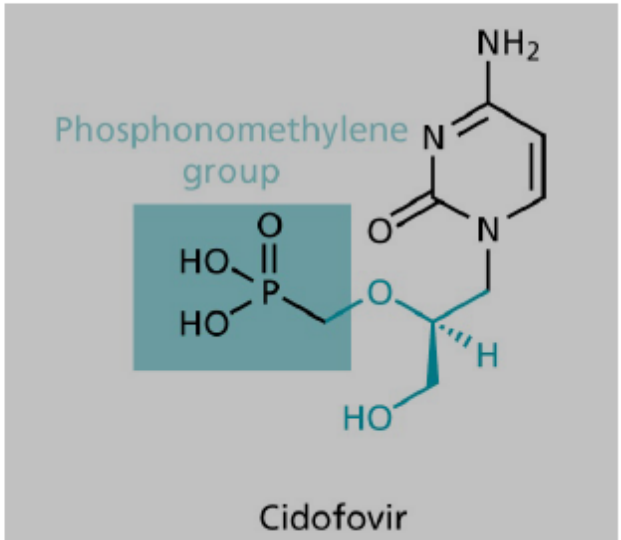
- **DNA viruses**: First step is replication of viral DNA. Inhibitors of the latter are nucleoside analogues. These are sufficiently similar to the "normal" nucleosides, so that they can serve as substrates for the viral DNA polymerases. Since the sugar lacks the 3' hydroxyl group they act as chain terminators:



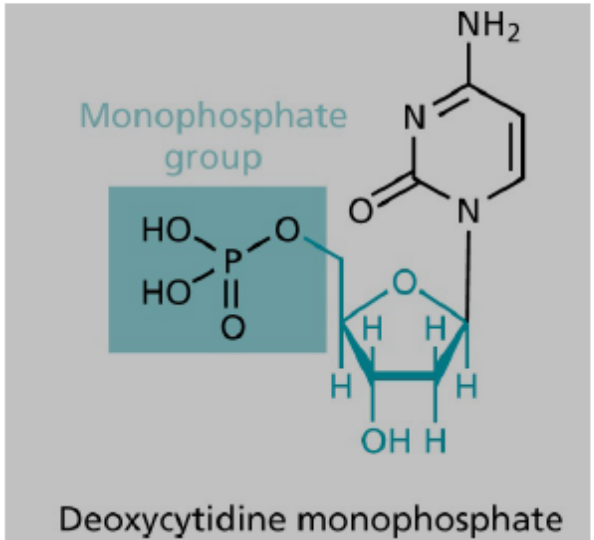
Aciclovir triphosphate



Deoxyguanosine triphosphate

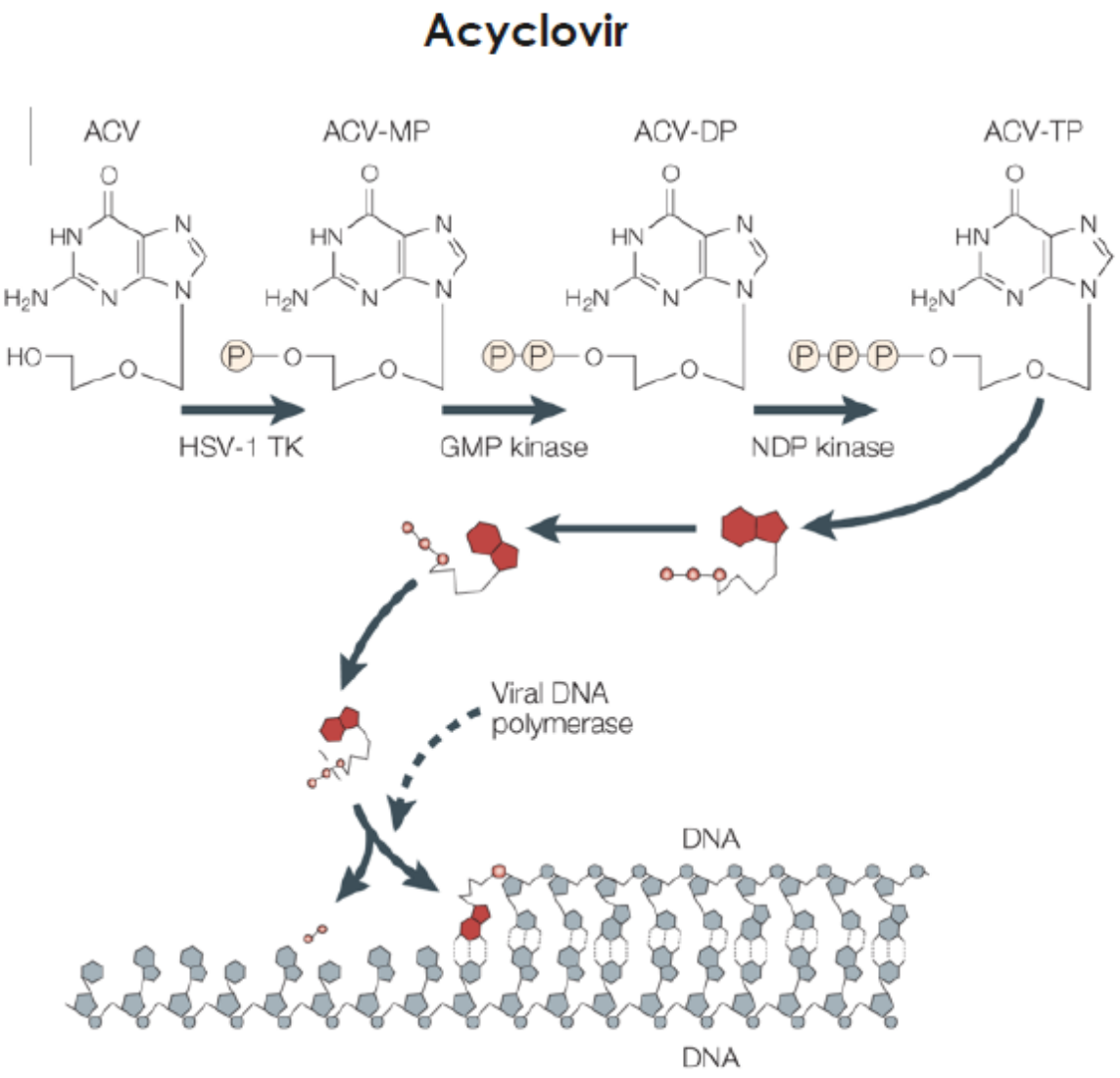


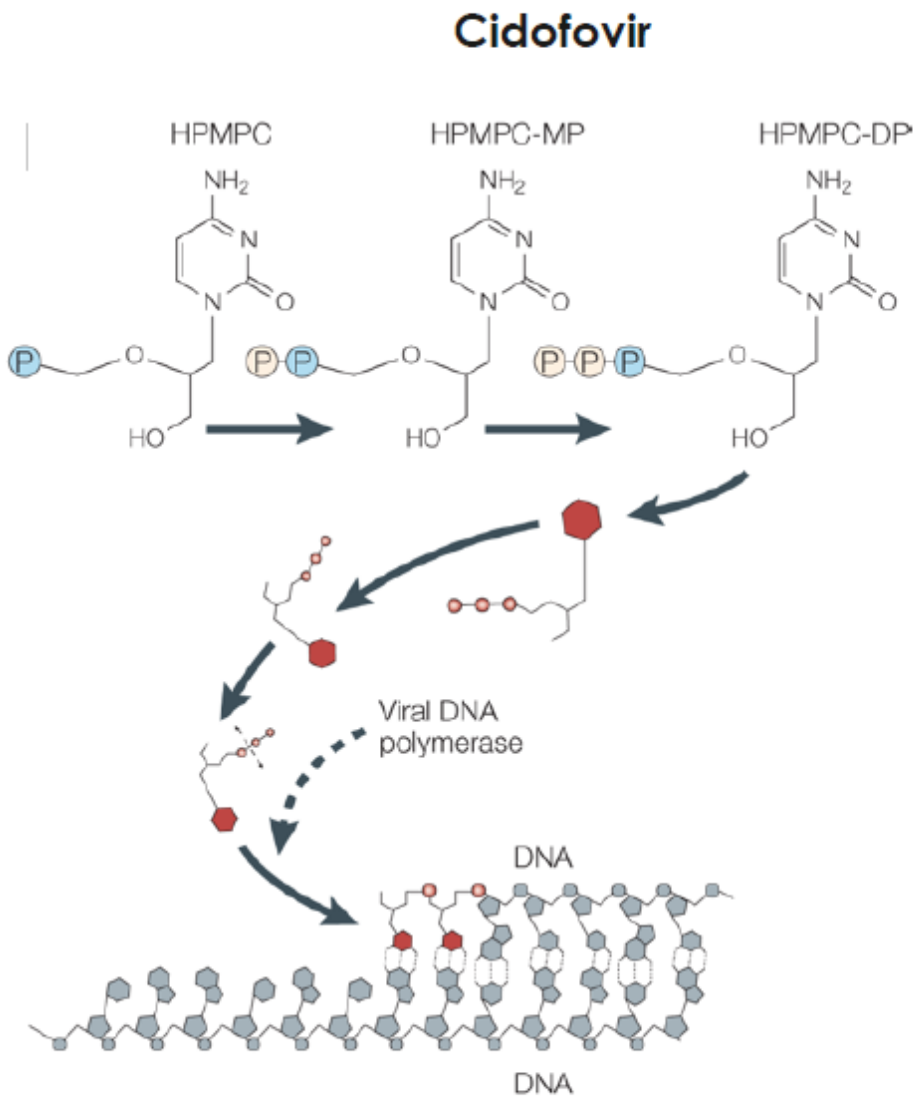
Cidofovir



Deoxycytidine monophosphate

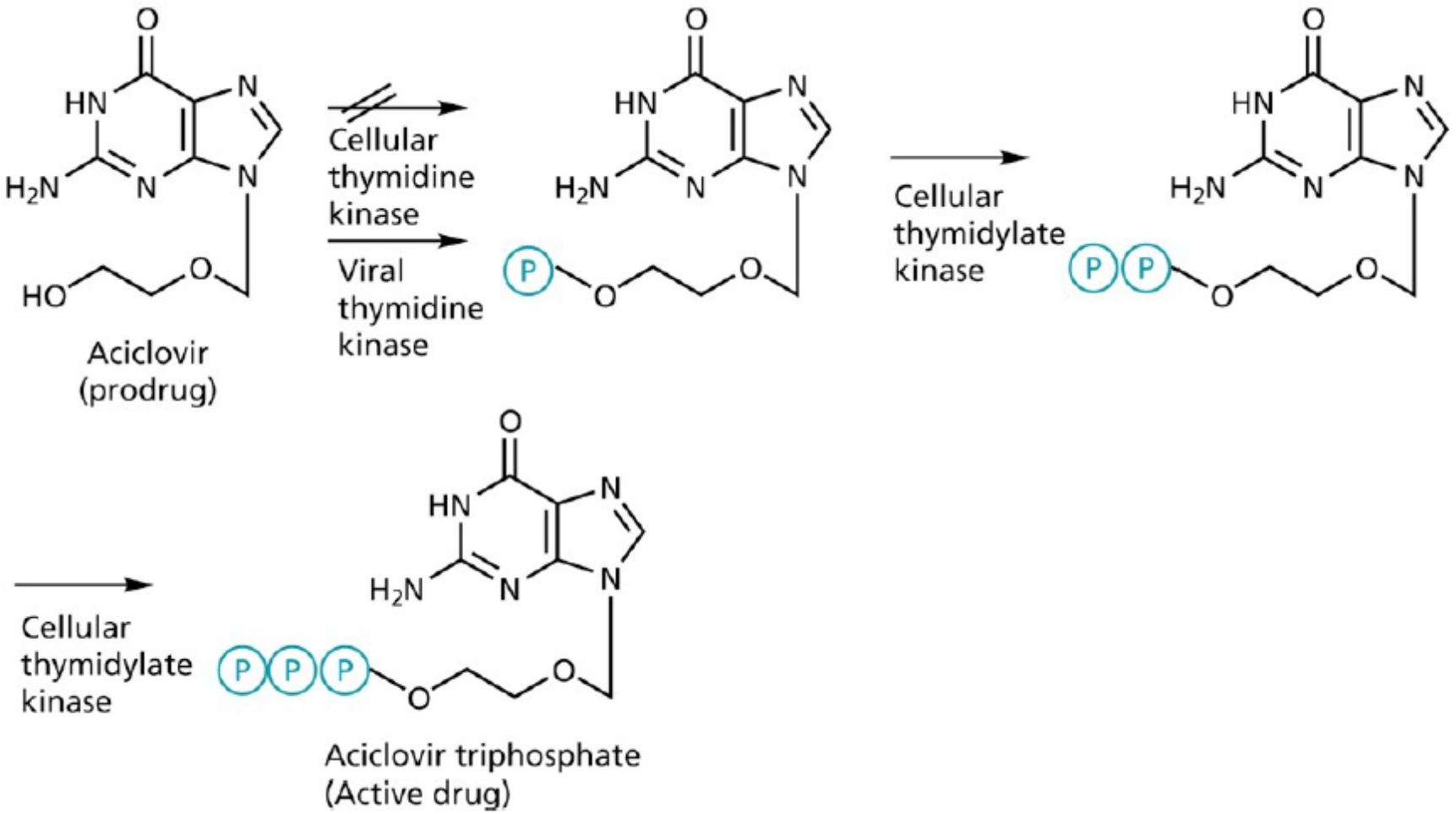
Chain terminators for viral DNA polymerases



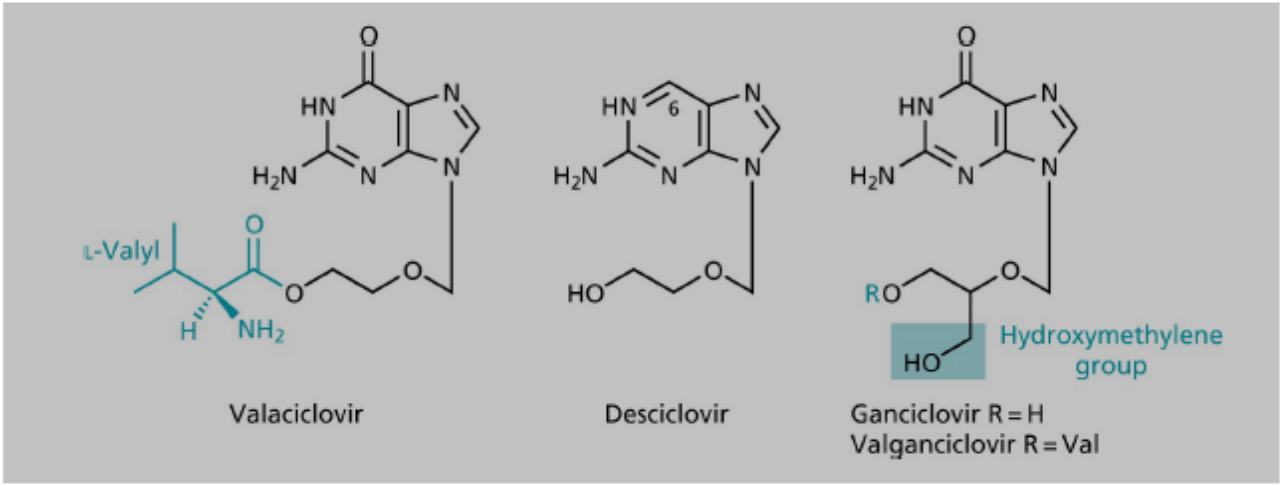


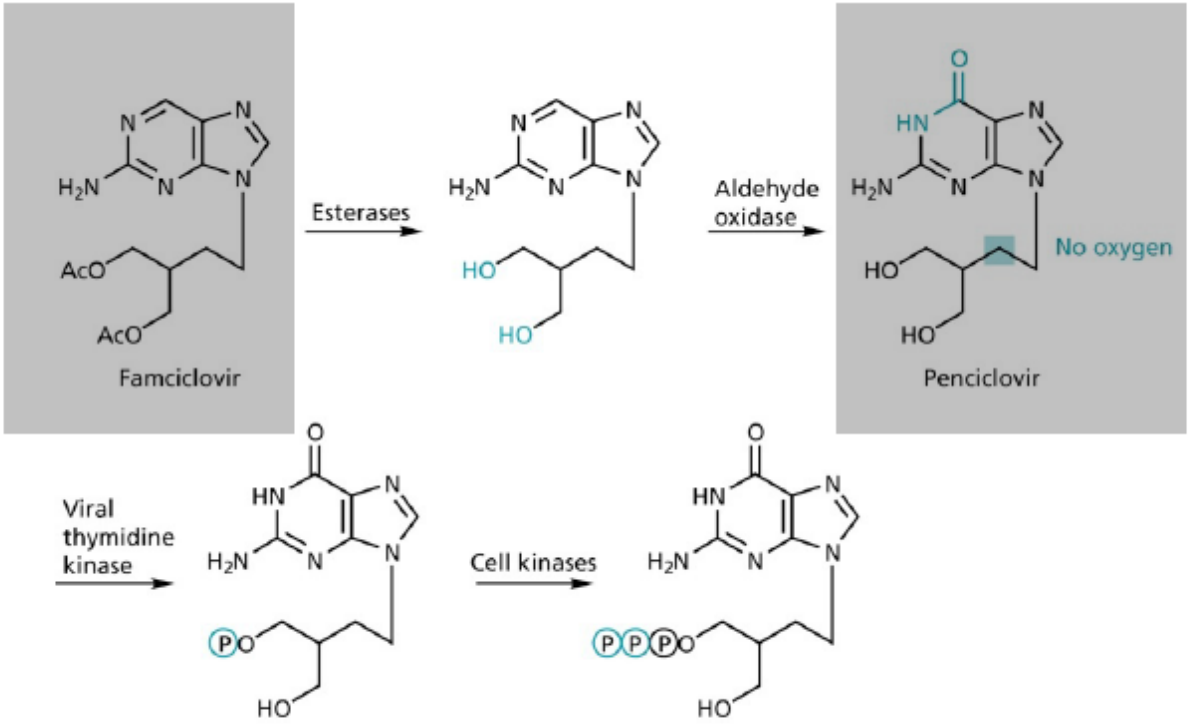
(does not require the presence of a viral thymidine kinase)

- The drugs are prodrugs, that can only be converted into the phosphorylated forms by the viral thymidine kinase and hence do not interfere with DNA synthesis in non-infected cells:



Prodrugs with improved bioavailability





Valacyclovir

- The oral bioavailability of acyclovir is quite low (15– 30%).
- To overcome this, various prodrugs were developed to increase water solubility. Valacyclovir is an **l-valyl ester prodrug** absorbed from the gut far more effectively than acyclovir.

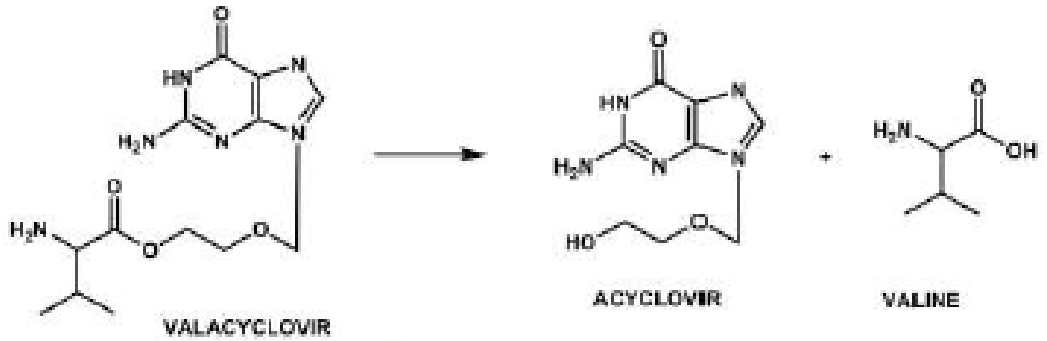
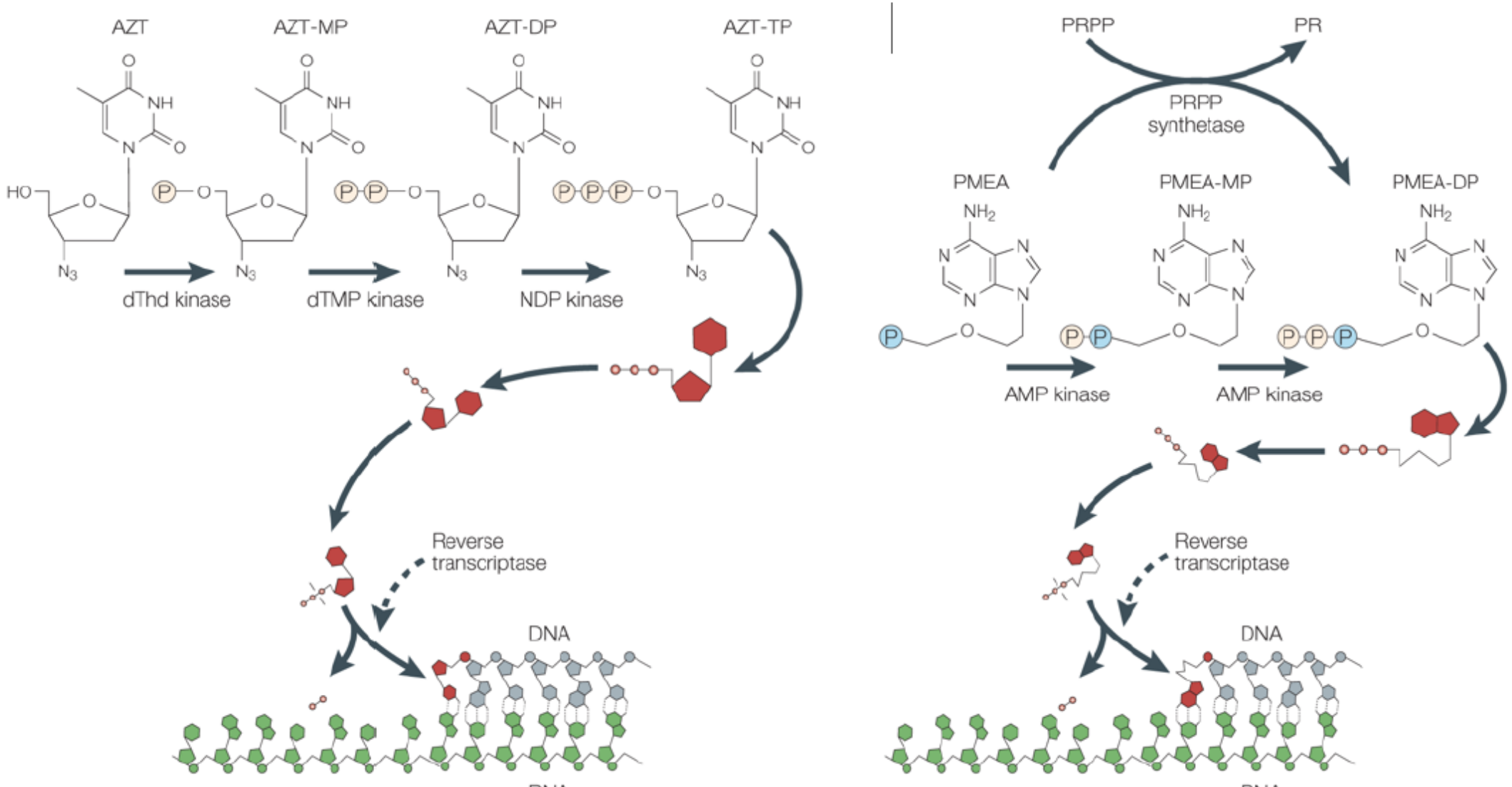


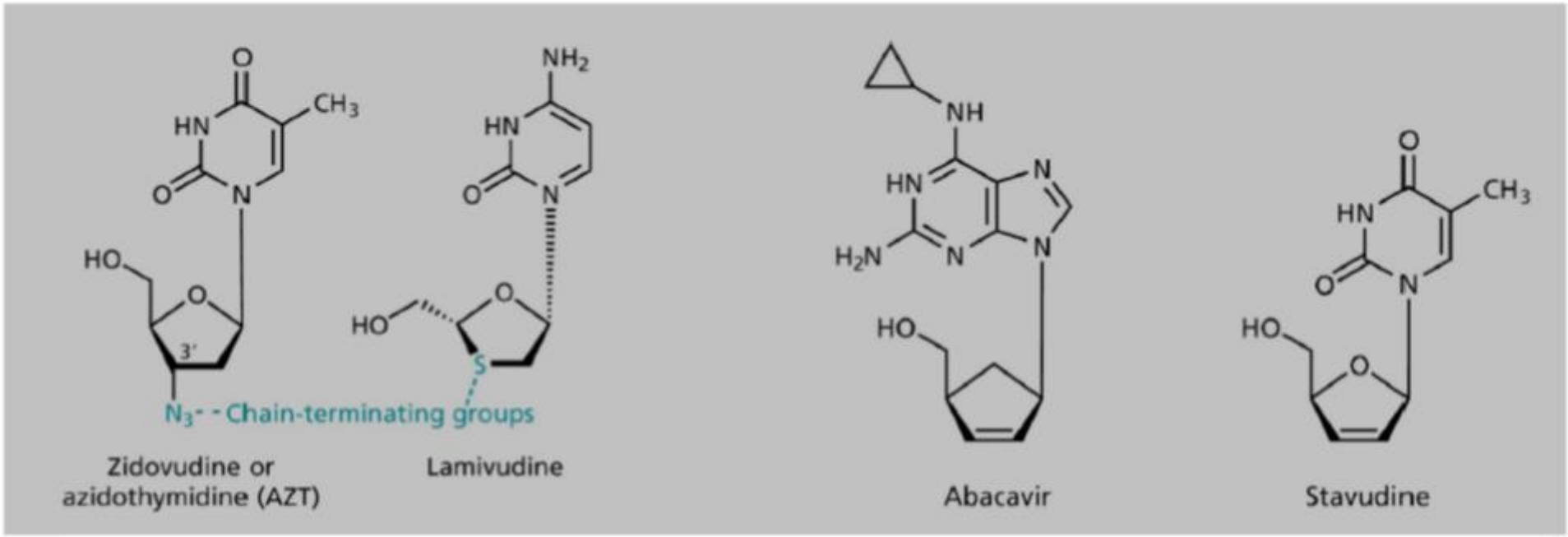
FIGURE 14 - Reaction illustrating the release of acyclovir from its prodrug.

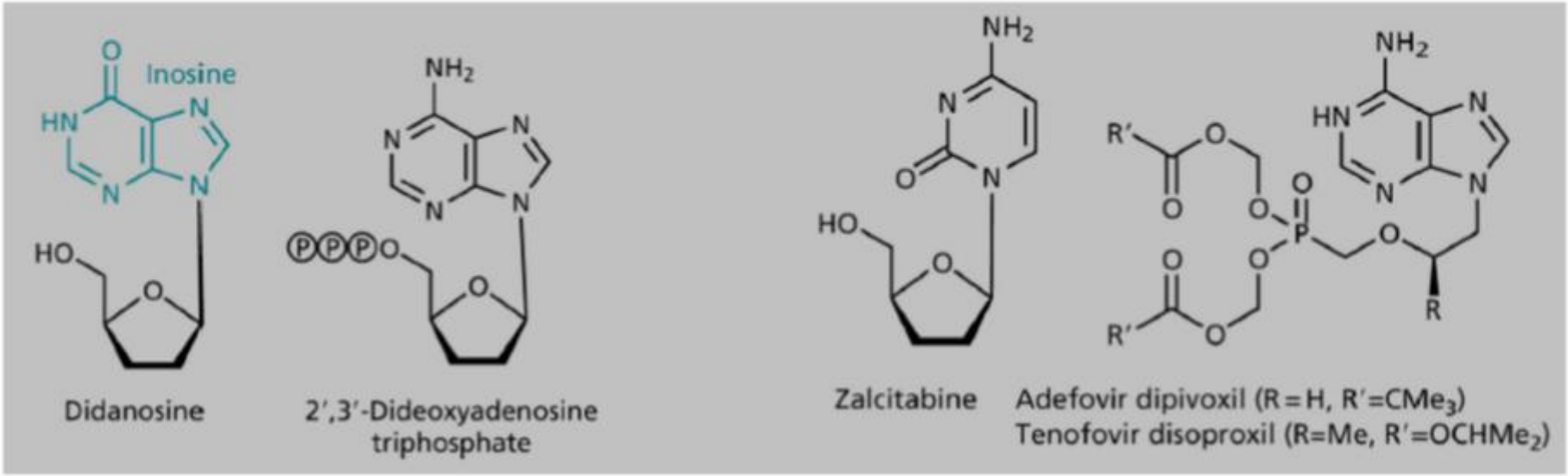
Inhibitors of viral DNA or RNA synthesis

- **RNA viruses**: First step is transcription of viral RNA into DNA by the viral reverse transcriptase. All three phosphorylation steps must be carried out by cellular kinases.



3b. Drugs as inhibitors of the reverse transcriptase

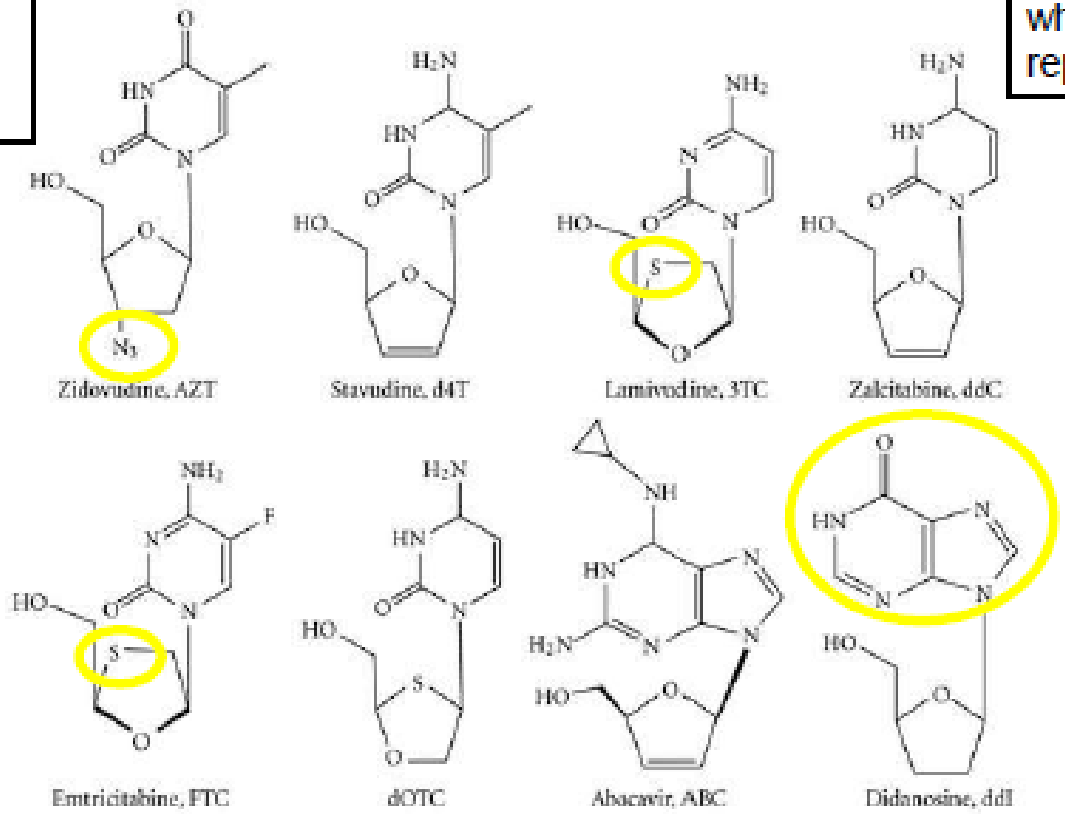




Nucleoside reverse transcriptase inhibitors (NRTI)

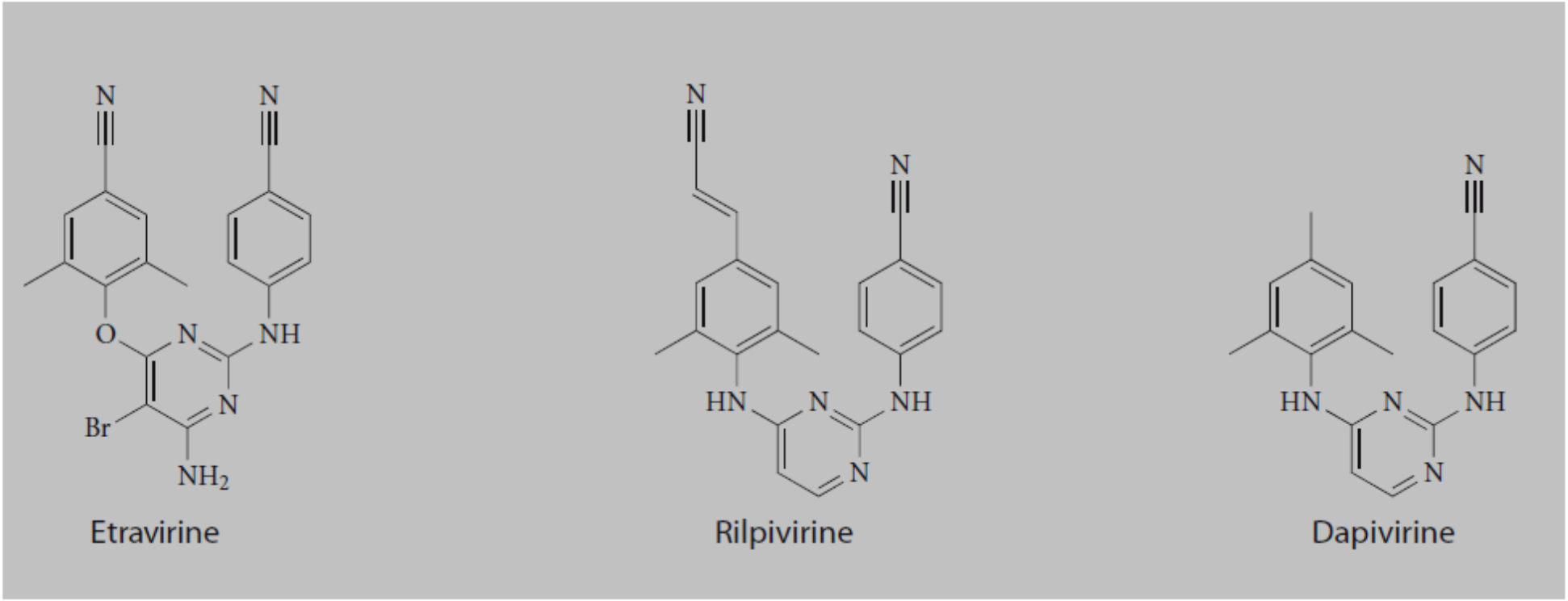
Zidovudine:
sugar 3′-hydroxyl group
has been replaced by an azido group

lamivudine and **emtricitabine:**
analogues of deoxycytidine where the 3′ carbon has been replaced by sulphur.



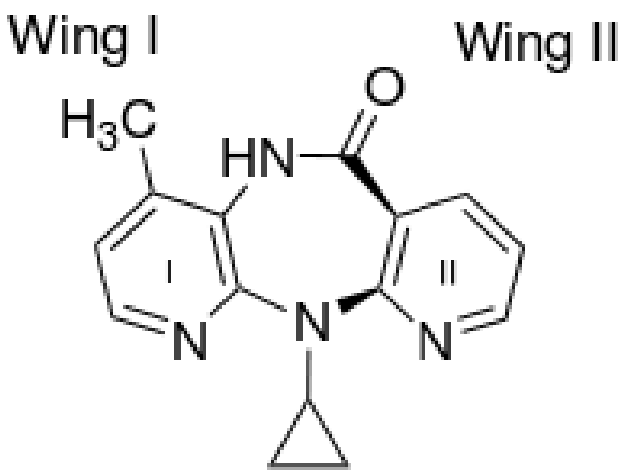
Didanosine:
nucleic acid base present is inosine base

Non-nucleoside reverse transcriptase inhibitors



- must be hydrophobic
- bind to an allosteric binding site that is adjacent to the substrate (nucleoside) binding site.
- binding locks the adjacent substrate binding site into an inactive conformation.
- improved specificity for reverse transcriptase over DNA polymerases resulting in less toxicity
- unfortunately, rapid resistance is developed

Nevirapine



Nevirapine

- Nevirapine has a rigid butterfly-like conformation that makes it chiral. One 'wing' interacts through hydrophobic and van der Waals interactions with aromatic residues in the binding site, while the other wing interacts with aliphatic residues.

- are generally hydrophobic molecules that bind to an allosteric binding site which is hydrophobic in nature. Since the allosteric binding site is separate from the substrate binding site, the NNRTIs are non-competitive, reversible inhibitors

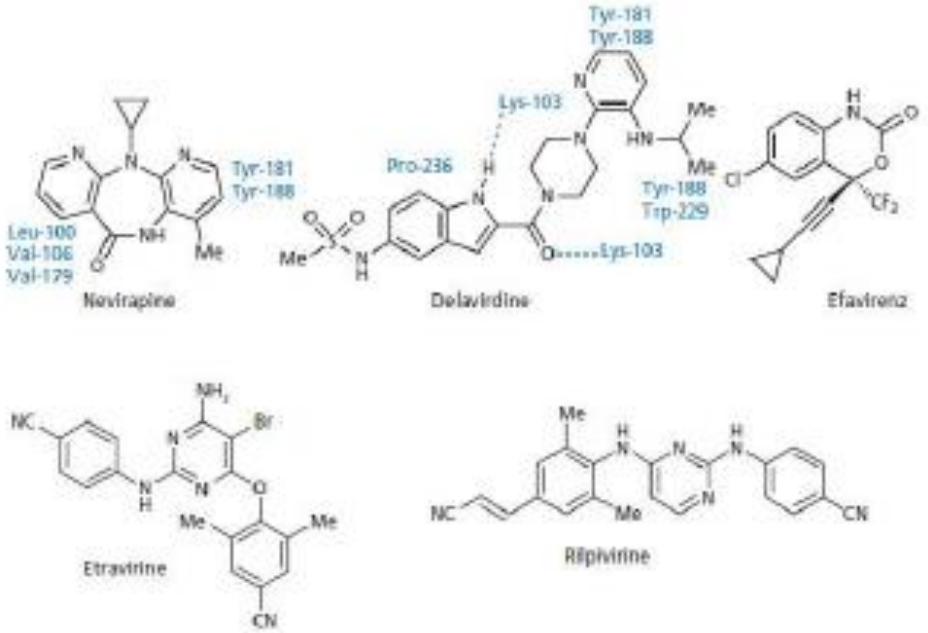


FIGURE 20.14 Non-nucleoside reverse transcriptase inhibitors in clinical use (interactions with amino acids in the binding site are shown in blue).

Metabolism of Nevirapine

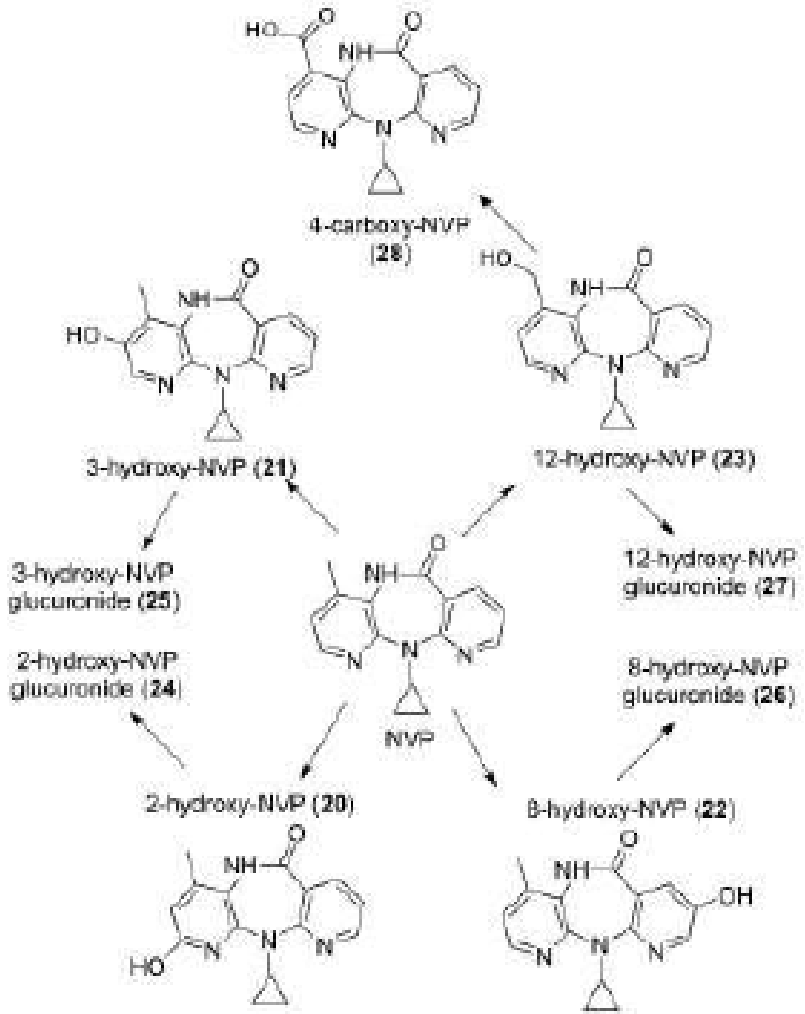
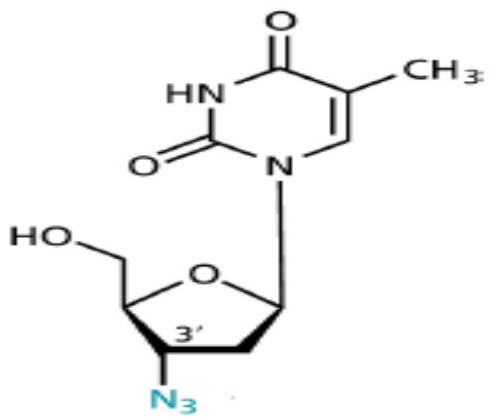


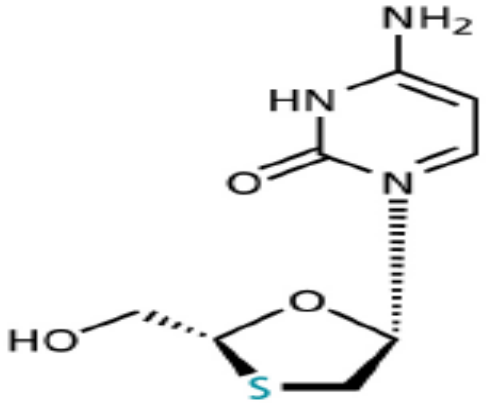
FIGURE 11 – Main metabolic routes of nevirapine.

HIV combination therapy (HAART)

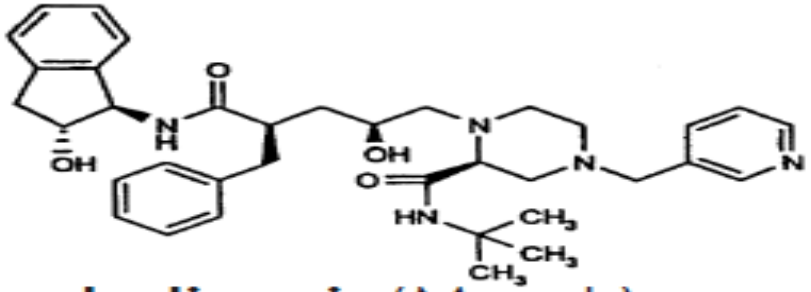
Highly Active AntiRetroviral Therapy



Zidovudine or azidothymidine (AZT)



Lamivudine



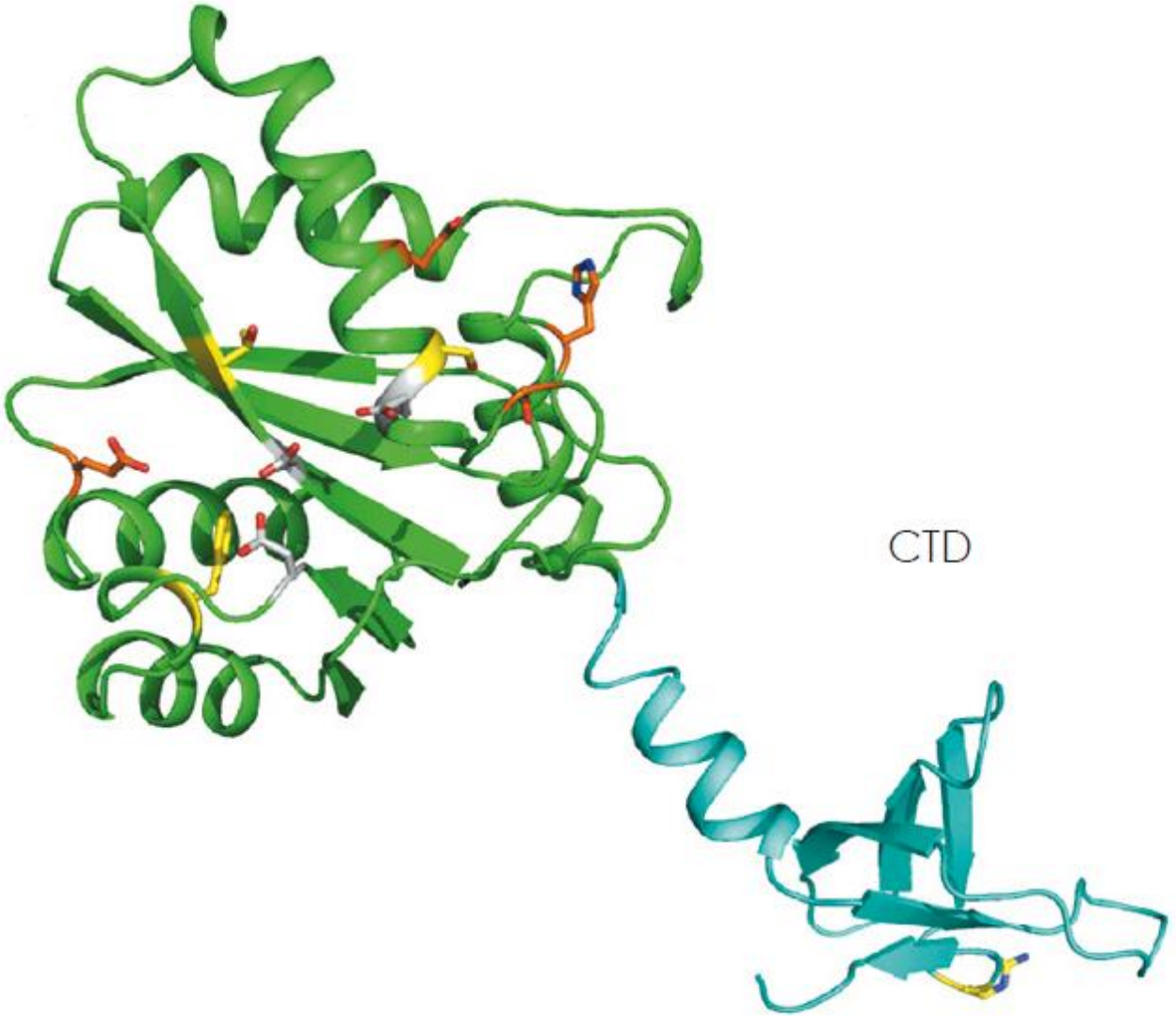
Indinavir (Merck)

Atripla ([Efavirenz + Emtricitabine + Tenofovir disoproxil fumarate (TDF)] Gilead/Bristol-Myers Squibb) is a single-tablet regimen approved for the treatment of HIV-1 infection.

It is a co-formulation of the marketed HIV non-nucleoside reverse transcriptase inhibitor (NNRTI) Sustiva (efavirenz; Bristol-Myers Squibb) and two nucleos(t)ide reverse transcriptase inhibitors (NRTIs):

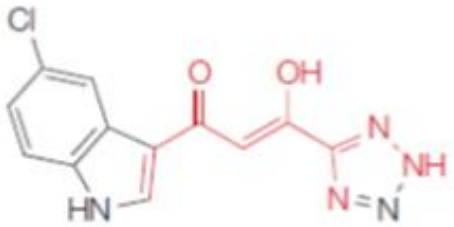
Emtriva (emtricitabine; Gilead) and Viread (TDF; Gilead).

The HIV Integrase

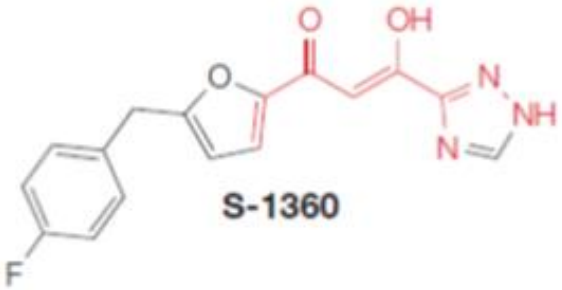


Diketoaryl (DKA) and DKA-strand-transfer selective inhibitors

Diketo aryls (Shionogi)

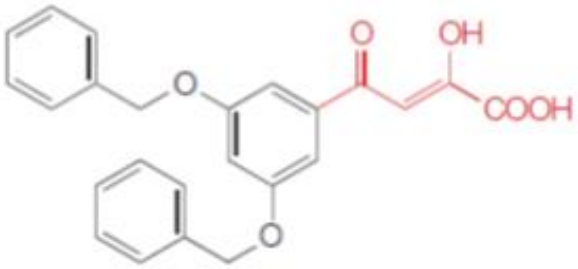


5CITEP

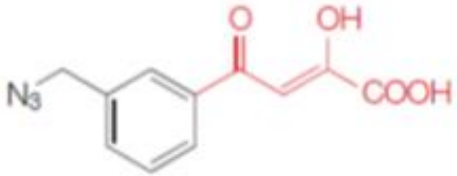


S-1360

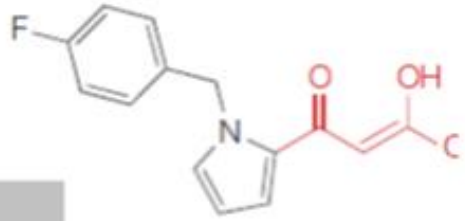
Diketo acids



L-708,906

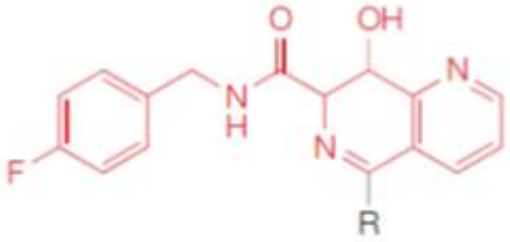


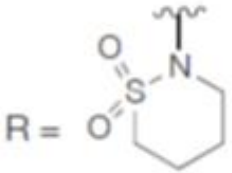
MA-DKA



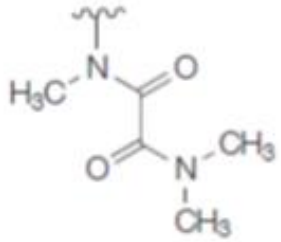
L-731,988

Naphthyridine carboxamides (Merck)

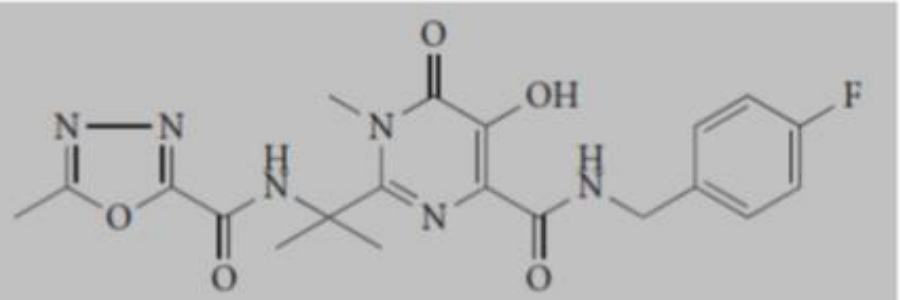




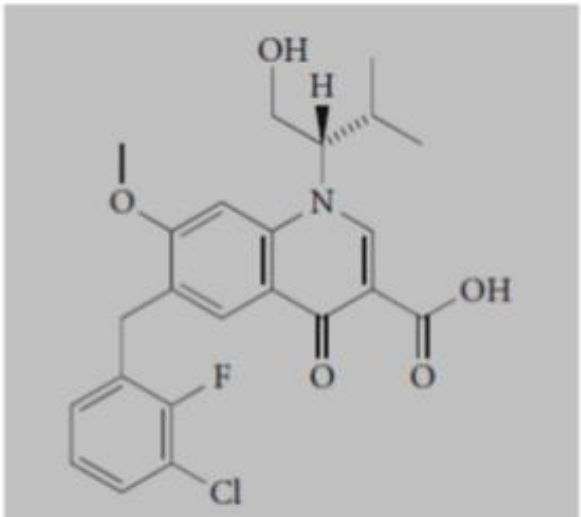
L-870,810



L-870,812



Raltegravir (MK-0518)



Elvitegravir (GS-9137, JTK-303)

These drugs are used in cases of resistance to HAART treatment.