आईएफटीएम विश्वविद्यालय, मुरादाबाद, उत्तर प्रदेश

IFTM University, Moradabad, Uttar Pradesh

NAAC ACCREDITED

E-Content

IFTM University, Moradabad

Unit-III (III)
Antiviral drugs

A **virus** is a submicroscopic infectious agent that replicates only inside the living cells of an organism
Viruses infect all life forms, from animals and plants to microorganisms, including bacteria and archaea

When infected, a host cell is often forced to rapidly produce thousands of copies of the original virus. When not inside an infected cell or in the process of infecting a cell, viruses exist in the form of independent particles, or ***virions***, consisting of
(i) the genetic material, i.e., long molecules of DNA or RNA that encode the structure of the proteins by which the virus acts;
(ii) a protein coat, the *capsid*, which surrounds and protects the genetic material; and in some cases
(iii) an outside envelope of lipids.

The shapes of these virus particles range from simple helical and icosahedral forms to more complex structures. Most virus species have virions too small to be seen with an optical microscope and are one-hundredth the size of most bacteria.

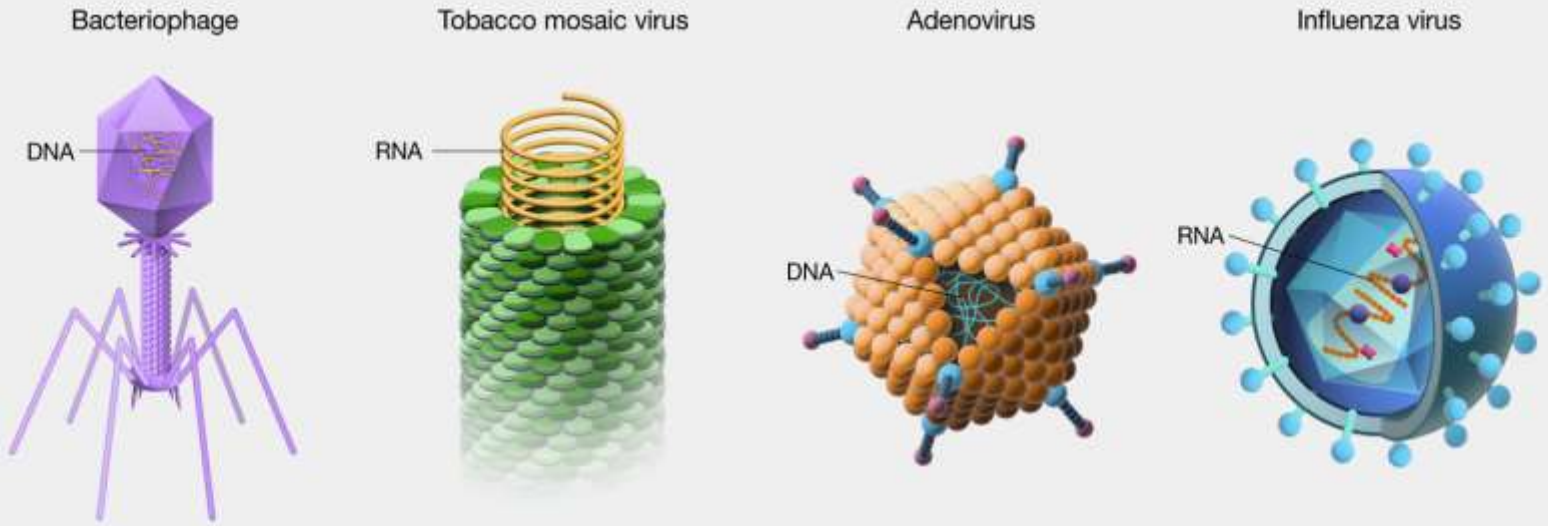
Viruses spread in many ways. One transmission pathway is through disease-bearing organisms known as vectors: for example, viruses are often transmitted from plant to plant by insects that feed on plant sap, such as aphids; and **viruses in animals can be carried by blood-sucking insects. Many viruses, including influenza viruses, SARS-CoV-2, chickenpox, smallpox, and measles, spread in the air by coughing and sneezing.**

A virus is an infectious microbe consisting of a segment of nucleic acid (either DNA or RNA) surrounded by a protein coat. A virus cannot replicate alone; instead, it must infect cells and use components of the host cell to make copies of itself.

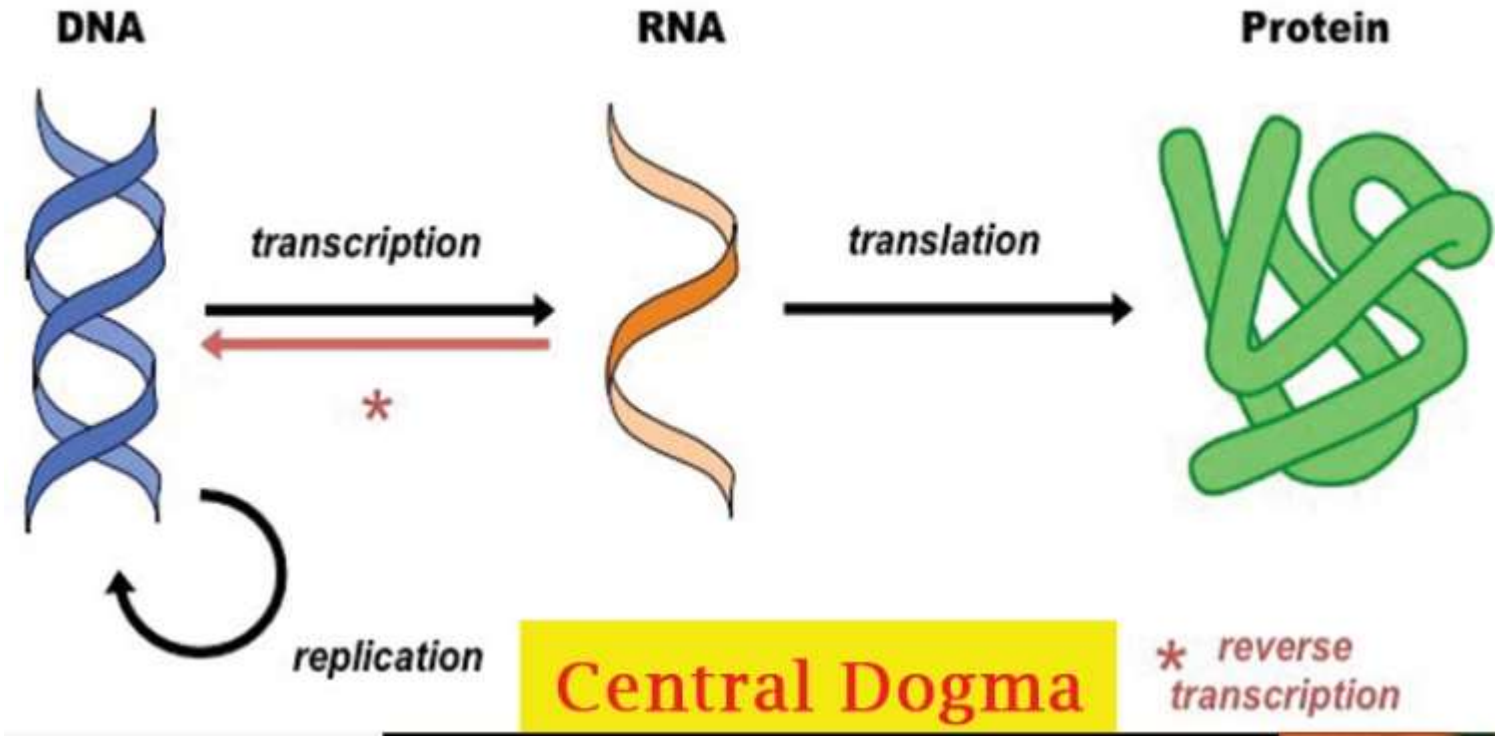
Often, a virus ends up killing the host cell in the process, causing damage to the host organism.

Well-known examples of viruses causing human disease include AIDS, COVID-19, measles and smallpox.

Examples of viruses



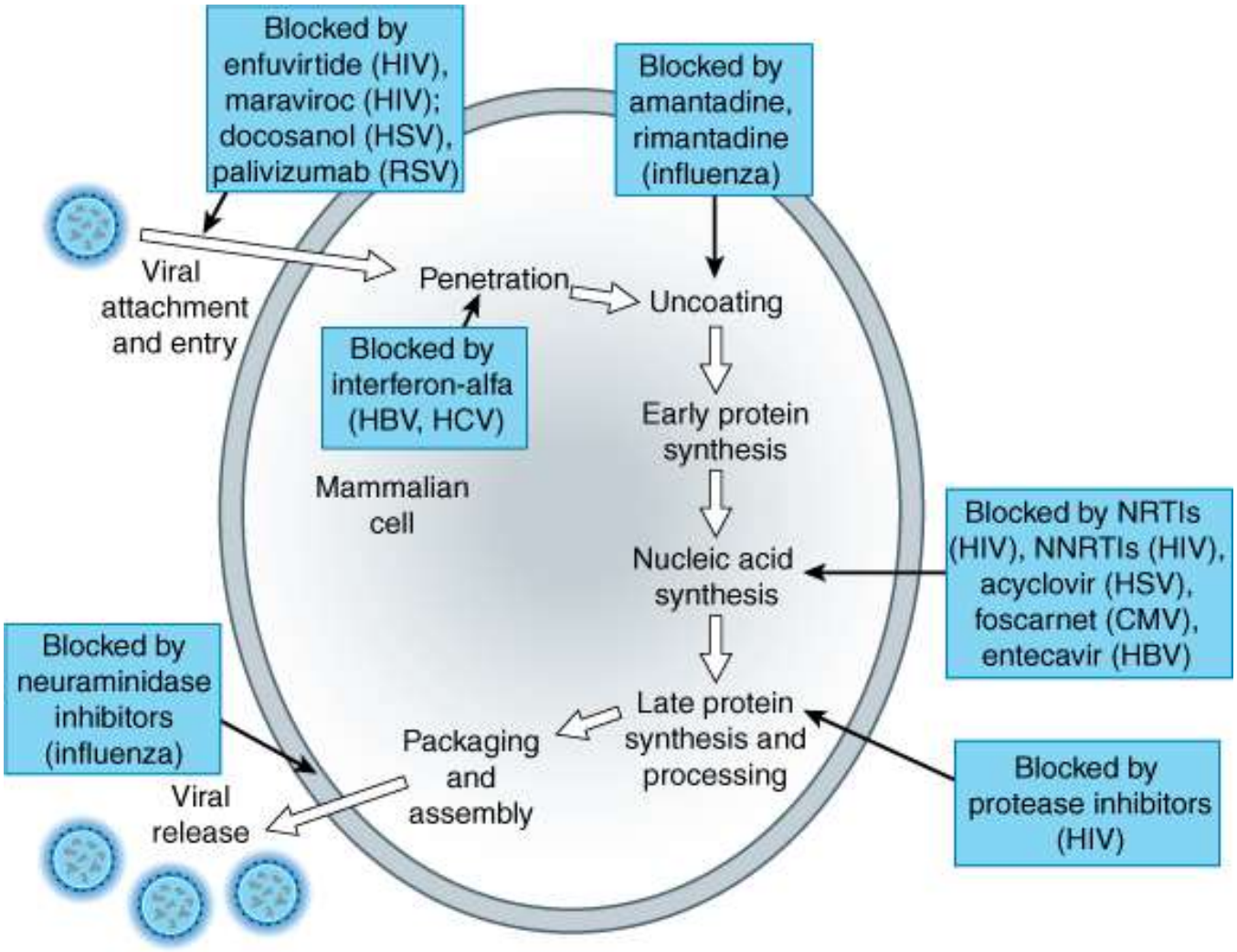
Transcription Vs Translation



CLASSIFICATION OF ANTIVIRAL DRUGS	
The viral growth cycle	**Selective inhibitors**
1) Attachment ***2) Penetration***	-Antiviral antibodies (gamma globulin)
3) Uncoating	**-Amantadine**, rimantadine -Interferons
4) Early translation (early mRNA and protein synthesis)	fomivirsen
5) Transcription (viral genome replication)	***Inhibitors of DNA-polymerase*** **-Acyclovir -Gancyclovir** -Famcyclovir -Cidofovir **-Vidarabine** -Idoxuridine -Trifluridine **-Foscarnet** ***Inhibitors of RNA-dependent DNA-polymerase (reverse transcriptase)*** **-Zidovudine** -Didanosine -Stavudine -Zalcitabine -Lamivudine -Foscarnet

6) Late translation (late mRNA an protein synthesis)	**-Ribavirin** **-Interferons**
7) Posttranslational modifications (proteolytic cleavage)	***Protease inhibitors*** **-Saquinavir** -Indinavir -Ritonavir
8) Assembly (packaging of viral nucleic acids)	-Interferons -Rifampin
9) Release (virion is released from cell)	-Antiviral antibodies -Cytotoxic T lymphocytes

The major sites of antiviral drug action.

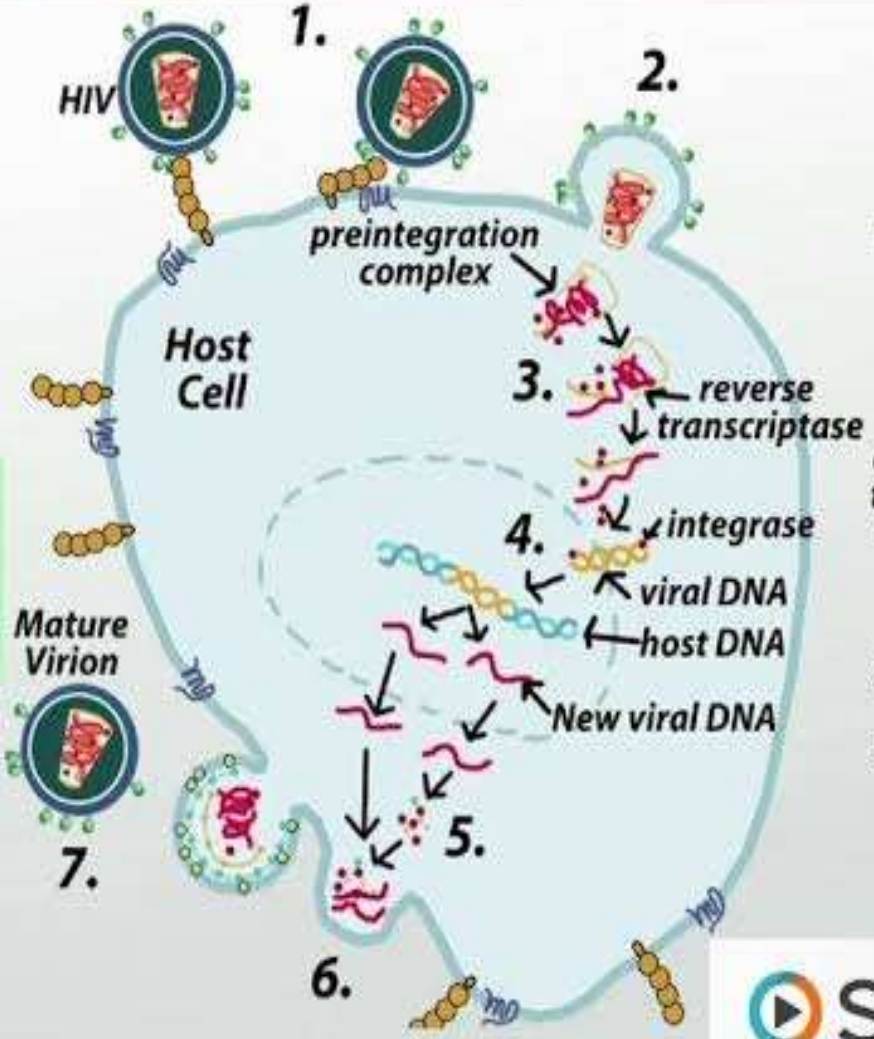


Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Classification

I . Anti-viral drugs classified based on chemical structures		
1	**Purine Analogues:**	Acyclovir,Valacyclovir,Ganciclovir,Abacavir,Famciclovir,Valganciclovir, Adefovir,penciclovir.
2	**Pyrimidine Analogues**	Idoxuridine, Trifluridine, Telbivudine, Cidofovir.
3	**Thiosemicarbazone**	Methisazone
4	**Adamantane amines**	Amantadine, Rimantadine, Docosanol,Somantidine.
5	**Immunomodulators:**	Interferons, Palivizumab, Imiquimod
6	**Miscellaneous**	Foscarnet sodium, Ribavirin
II.Classified based on enzyme inhibition		
1	**Inhibitor of DNA polymerase**	Idoxuridine, Trifluridine,Vidarabine,Acyclovir.
2	**Reverse-transcriptase Inhibitors:**	Zidovudine,Stavudine,Zalcitabine,Didanosine,Lamivudine, Abacavir
3	**Nucleoside anti-metabolite**	Ribavirin
4	**Non-nucleosideReversetranscriptase Inhibitors:**	Nevirapine,efavirenz,Delaviridine
5	**HIV-Protease Inhibitors:**	Amprenavir, Atazanavir, Darunavir,Saqunavir, Ritonavir, Nelfinavir, Lopinavir.
6	**Integrase Inhibitors**	Zintevir

REVERSE TRANSCRIPTASE INHIBITORS



1. Fusion of HIV to the host cell surface

2. HIV RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell

3. Viral DNA is formed by reverse transcription

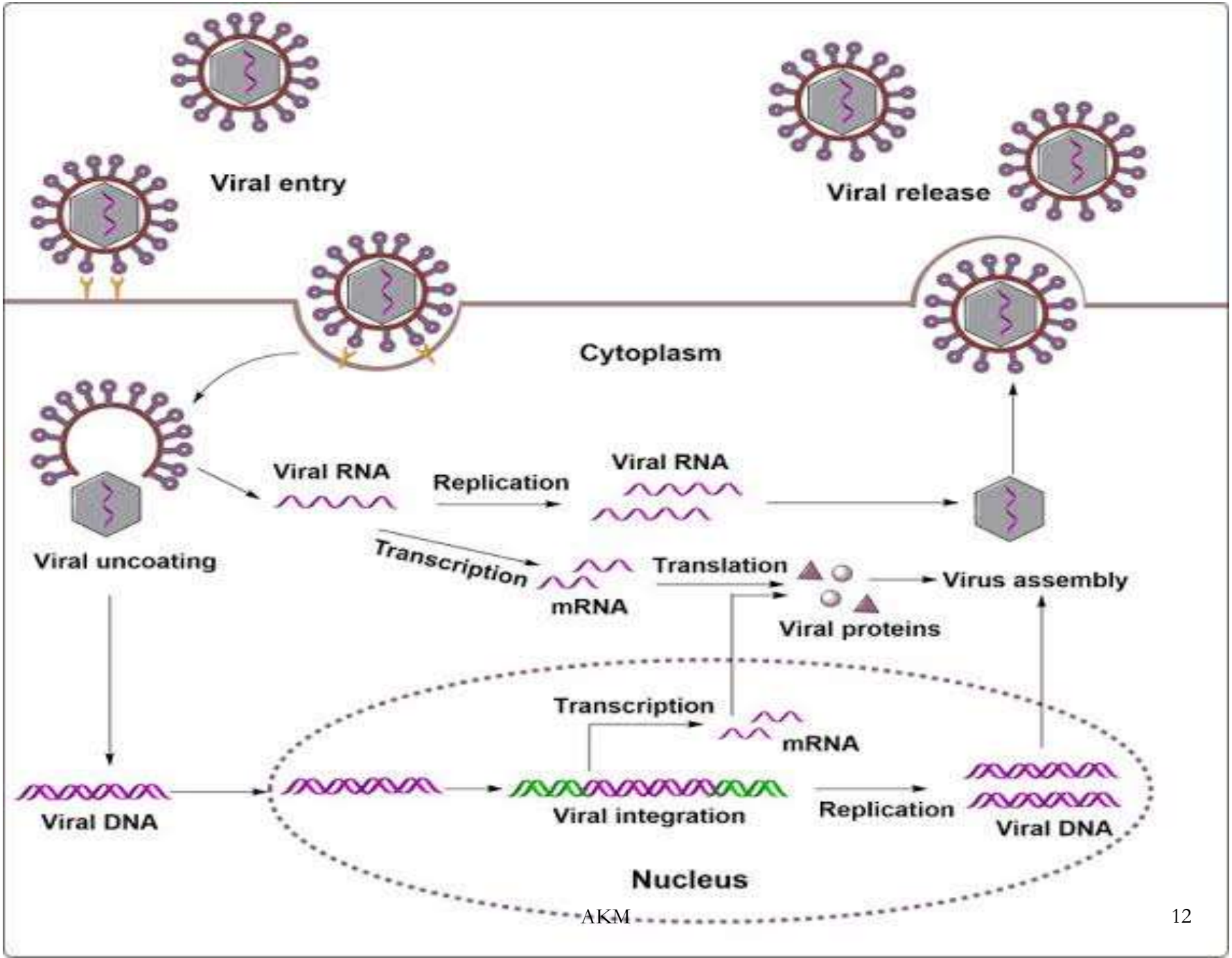
4 Viral DNA is transported across the nucleus and integrates into the host DNA

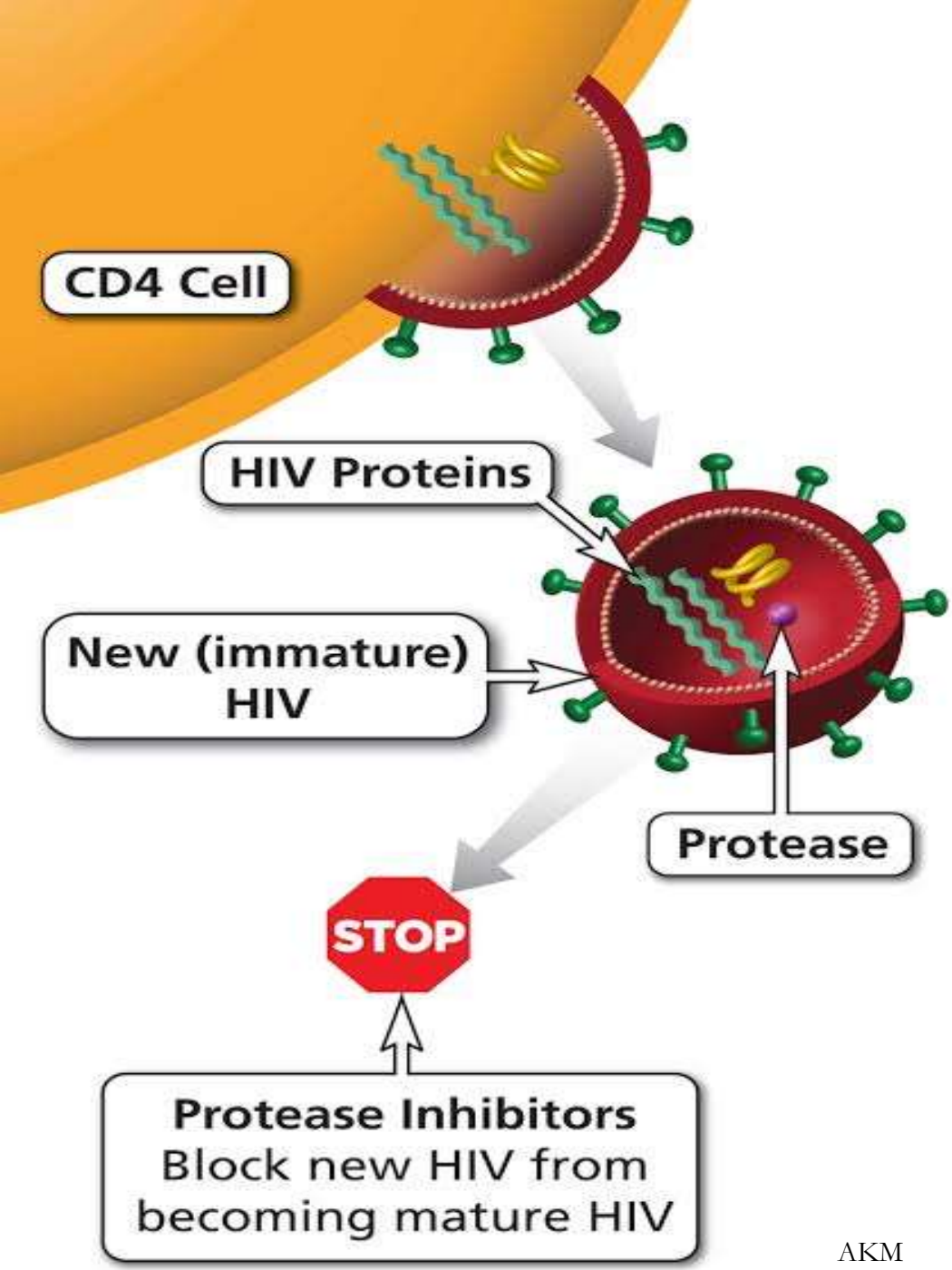
5. New viral RNA is used as genomic RN and to make viral proteins

6. New viral RNA and protein move to the cell surface and a new, immature, HIV forms

7. The virus matures by protease releasing individual HIV proteins

Study.com


Viral entry
Viral release
Cytoplasm
Viral RNA
Replication
Viral RNA
Viral uncoating
Transcription
mRNA
Translation
Virus assembly
Viral proteins
Transcription
mRNA
Viral DNA
Viral integration
Replication
Viral DNA
Nucleus

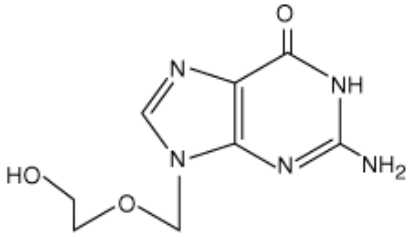

CD4 Cell
HIV Proteins
New (immature) HIV
Protease
STOP
Protease Inhibitors
Block new HIV from becoming mature HIV

Antiviral agents are drugs approved by the Food and Drug Administration (FDA) for the treatment or control of viral infections. Available antiviral agents mainly target stages in the viral life cycle.

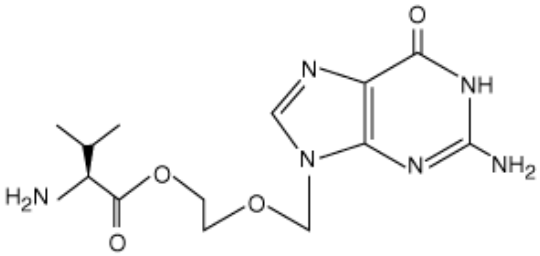
The target stages in the viral life cycle are; viral attachment to host cell, uncoating, synthesis of viral mRNA, translation of mRNA, replication of viral RNA and DNA, maturation of new viral proteins, budding, release of newly synthesized virus, and free virus in body fluids.

Chemical structures of some antiviral nucleoside and nucleotide analogs

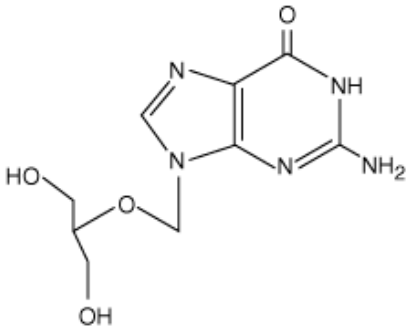
A. Antiherpes agents



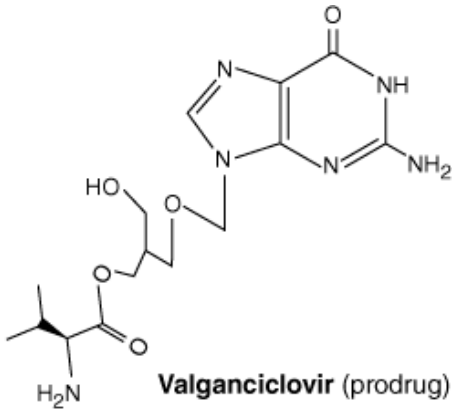
Acyclovir



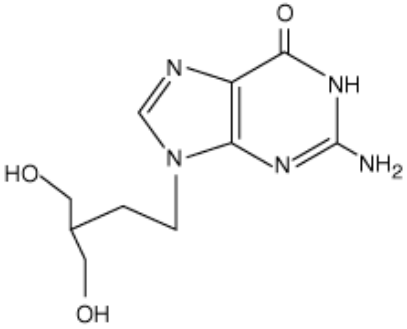
Valacyclovir (prodrug)



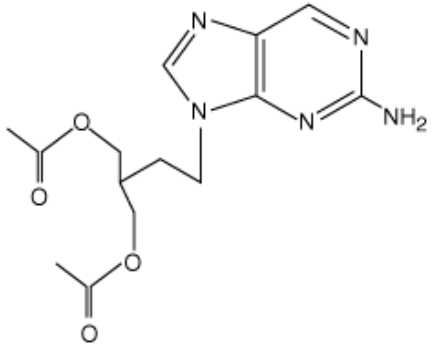
Ganciclovir



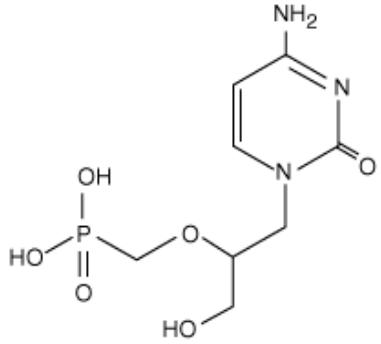
Valganciclovir (prodrug)



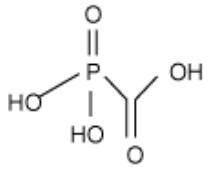
Penciclovir



Famciclovir (prodrug)



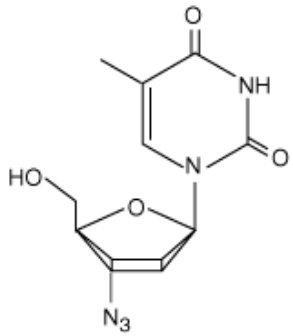
Cidofovir



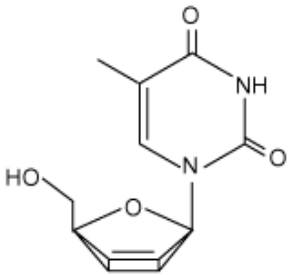
Foscarnet

Chemical structures of some antiviral nucleoside and nucleotide analogs

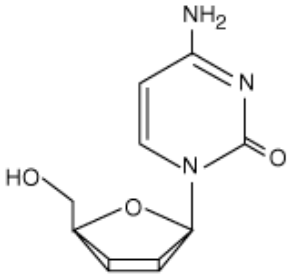
B. Anti-HIV NRTI agents



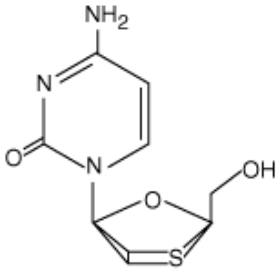
Zidovudine (AZT)



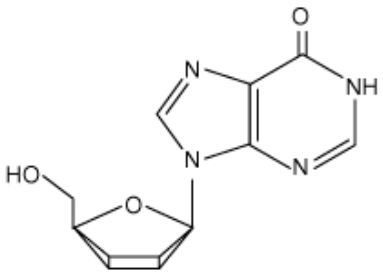
Stavudine (d4T)



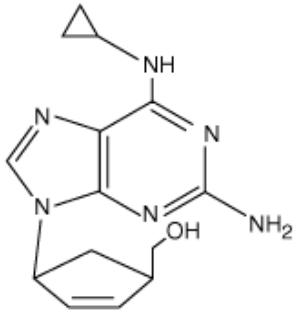
Zalcitabine (ddC)



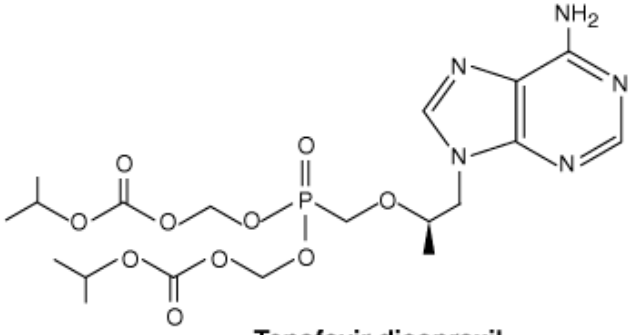
Lamivudine (3TC)



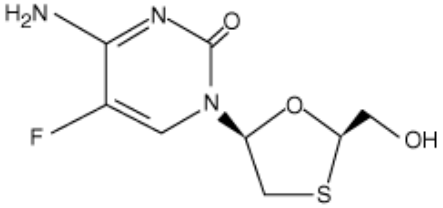
Didanosine (ddI)



Abacavir



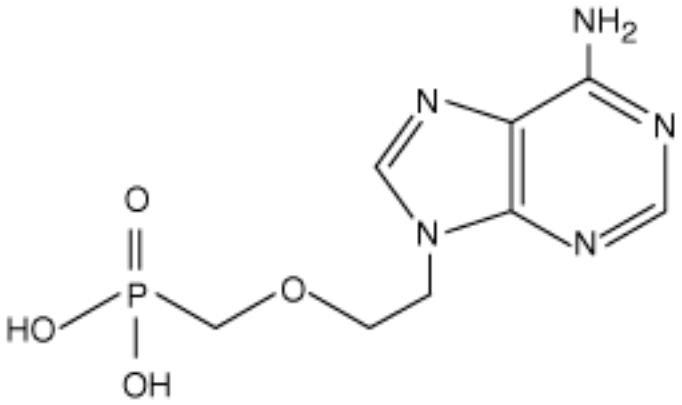
Tenofovir disoproxil



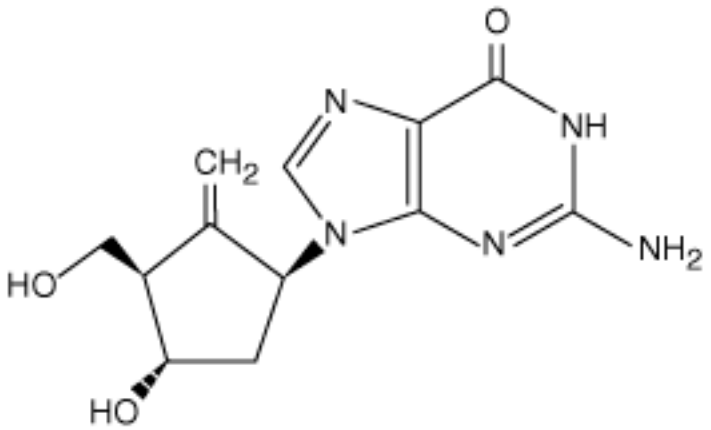
Emtricitabine

Chemical structures of some antiviral nucleoside and nucleotide analogs

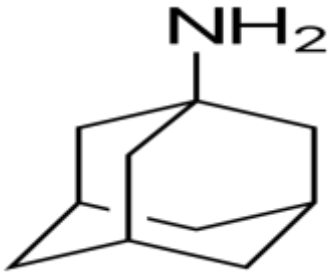
C. Anti-HBV agents



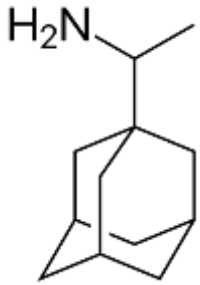
Adefovir



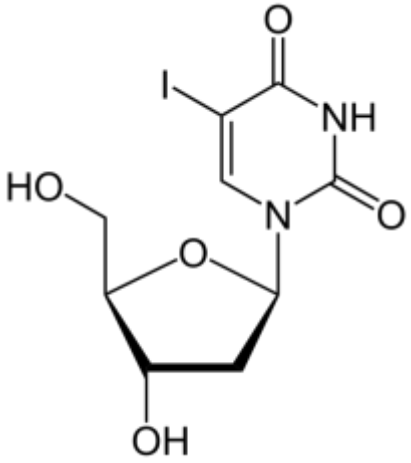
Entecavir



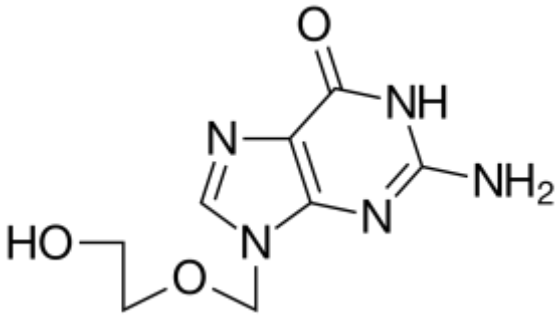
Amantadine



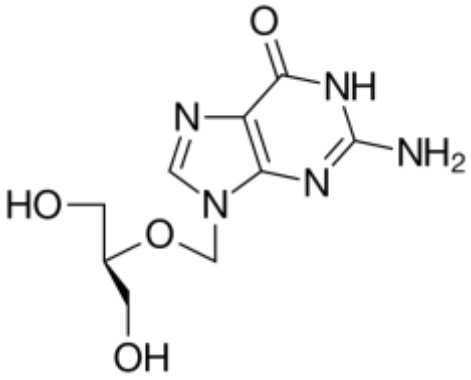
Rimantadine



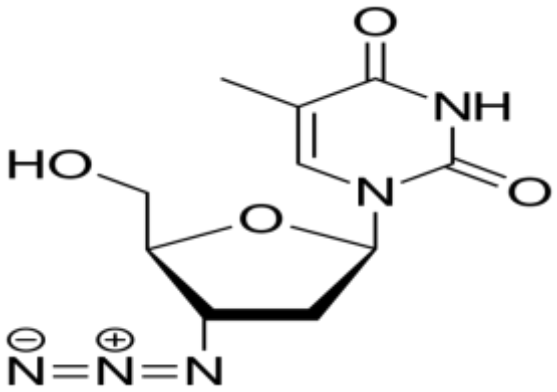
Idoxuridine



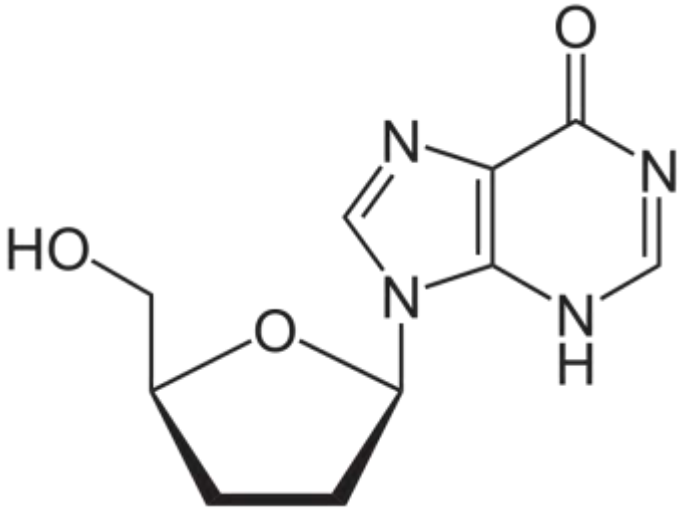
Acyclovir



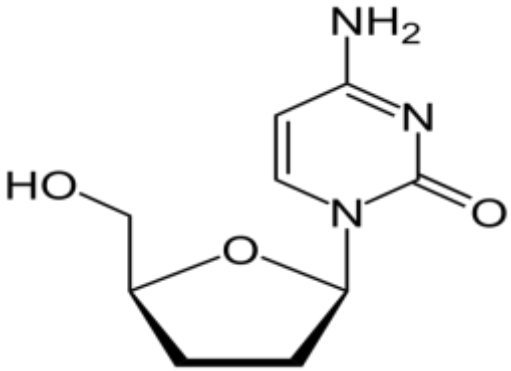
Gancyclovir



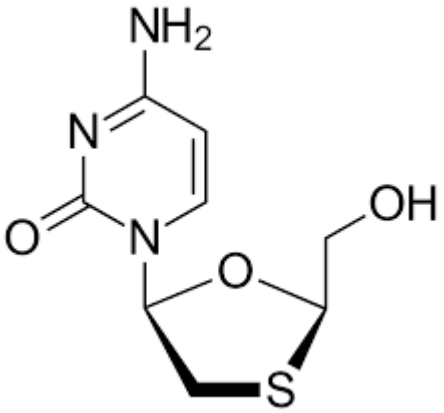
Zidovudine



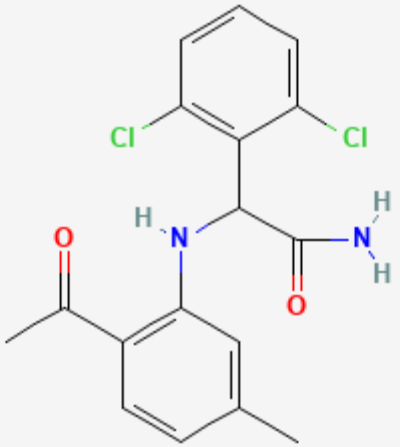
didanosine



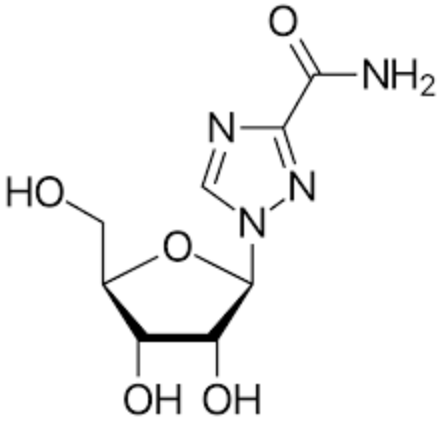
zalcitabine



lamivudine

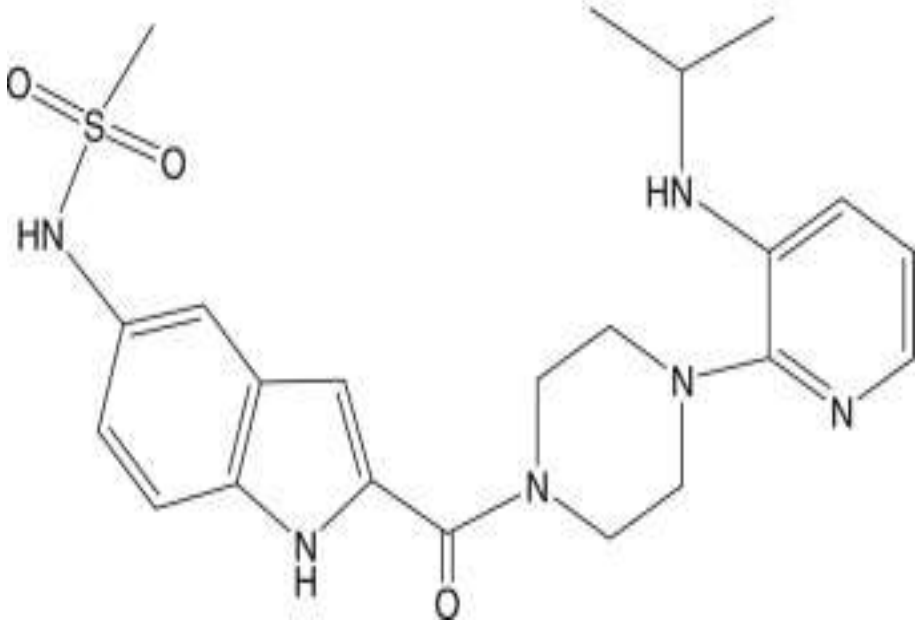


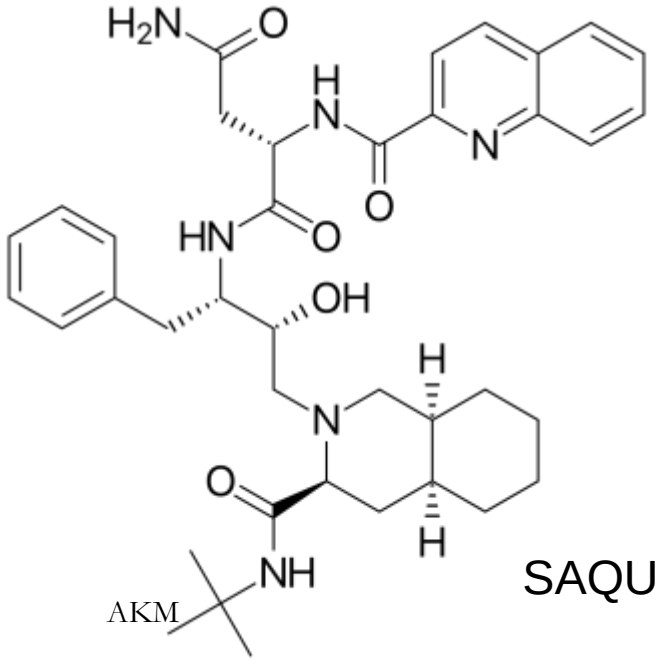
Loviride



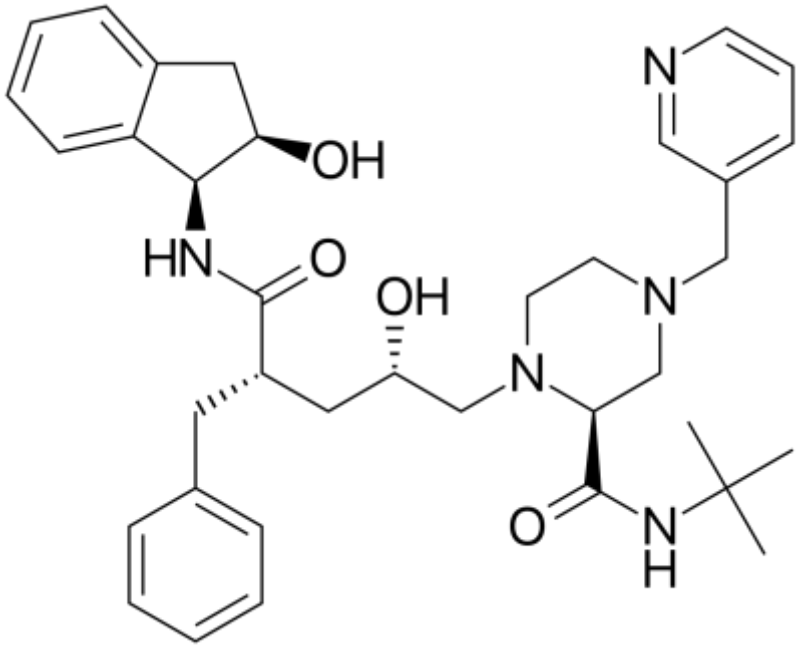
RIBAVIRIN

Delavirdine

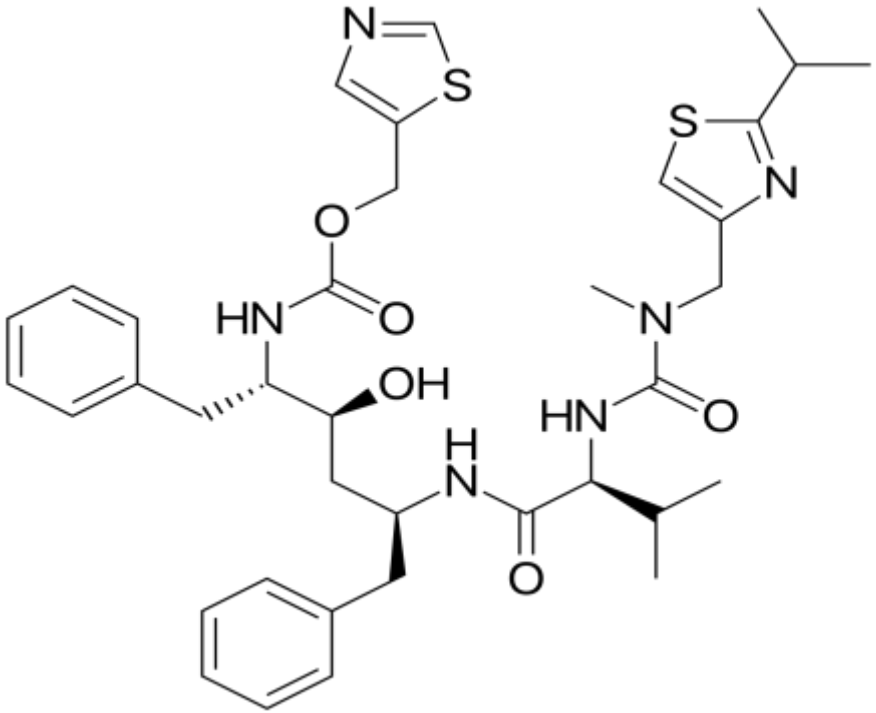




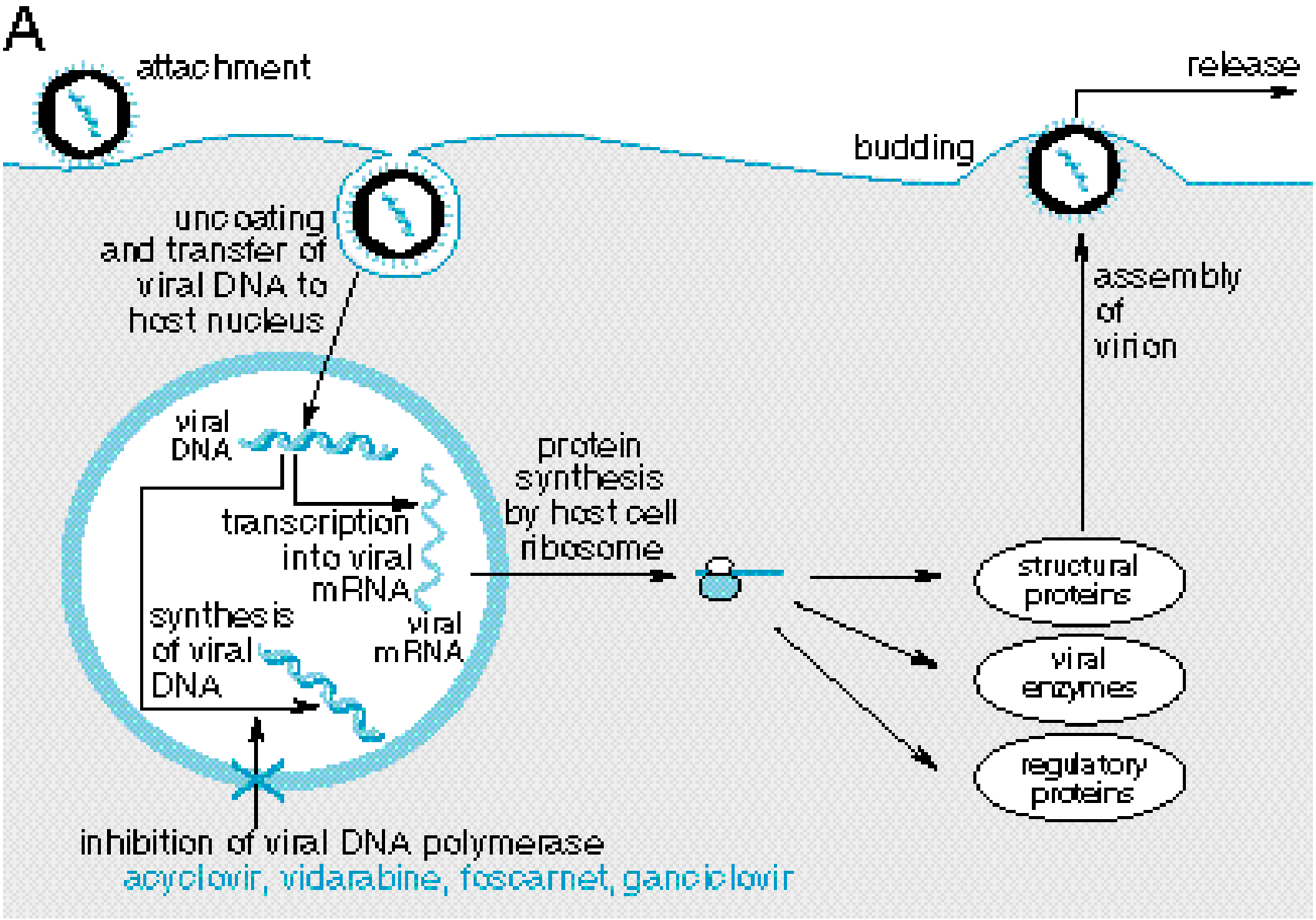
SAQUINAVIR



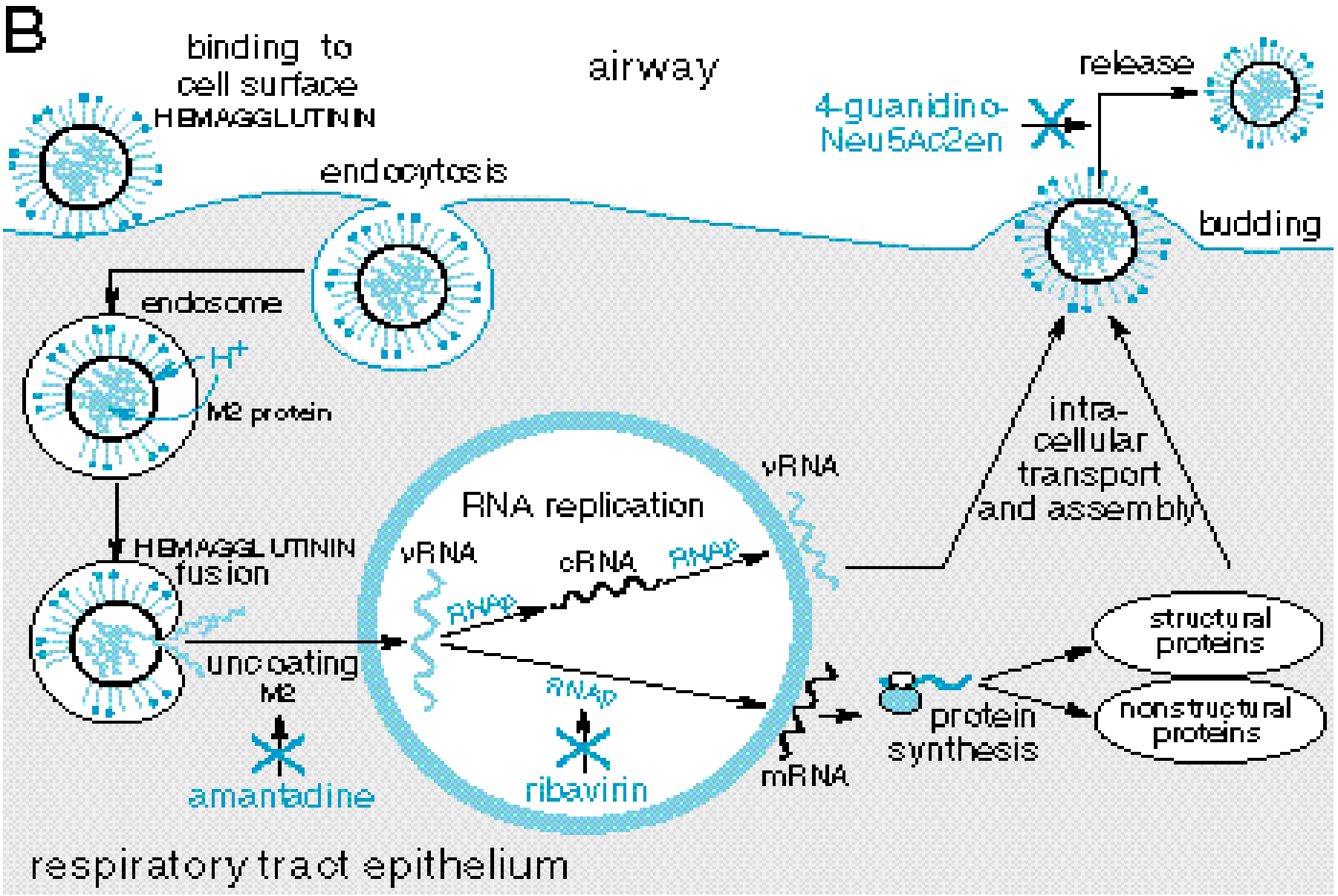
INDINAVIR



RITONAVIR



Replicative cycles of herpes simplex virus, an example of a DNA virus, and the probable sites of action of antiviral agents.



Replicative cycles of influenza, an example of an RNA virus, and the loci for effects of antiviral agents.

ANTIVIRAL DRUGS: GENERAL FEATURES

- Many antiviral drugs are ***purine or pyrimidine analogs.***

-Many antiviral drugs are **prodrugs.**
They must be **phosphorylated by viral or cellular enzymes** in order to become active.

- Antiviral drugs typically have a restricted spectrum of antiviral activity and inhibit a specific viral protein, most often an **enzyme** involved in viral nucleic acid synthesis.

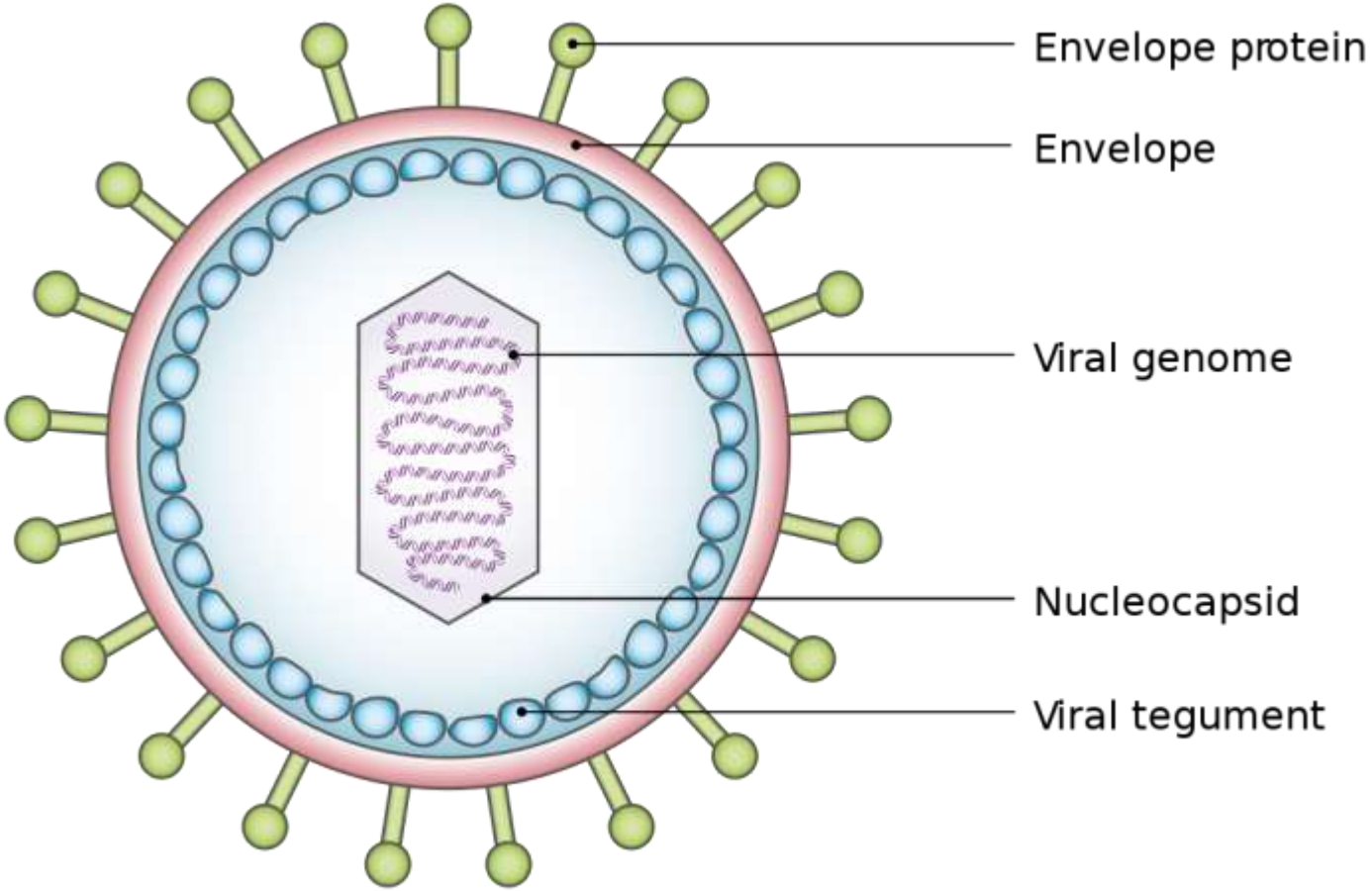
- **Single nucleotide changes leading to critical amino acid substitutions in a target protein often are sufficient to cause *antiviral drug resistance*.**

- Current agents inhibit active replication ***but do not eliminate nonreplicating or latent viruses*** so that viral growth may resume after drug removal. Effective host immune response remain essential for recovery from infection.

- Antiviral drugs may have *antiviral synergistic effects* when given concomitantly (i.e. gancyclovir and foscarnet, zidovudine and didanosine, zidovudine and protease inhibitors, etc.). In other cases ***toxic synergistic effects*** preclude concurrent administration of two antiviral drugs (i.e. zidovudine and acyclovir, zidovudine and gancyclovir, etc.)

- Clinical efficacy of antiviral drugs depends on achieving ***inhibitory concentrations within infected cells.*** Therefore a clear relationship between blood concentration and clinical response have not been established for most antiviral agents.

virus layers



PHARMACOLOGY OF AMANTADINE AND CONGENERS

Chemistry

-**Amantadine** and rimantadine are tricyclic amines.

Mechanism of action

-***Inhibition of viral uncoating*** by:

a) Blockade of the viral membrane matrix protein M2, which function as an ion channel. This channel is required for the **fusion** of the viral membrane with the cell membrane.

b) **Rising the pH of the endosome** (an acidic pH inside the endosome is required for viral uncoating)

Antiviral spectrum and resistance

-Influenza A virus (not B and C virus)

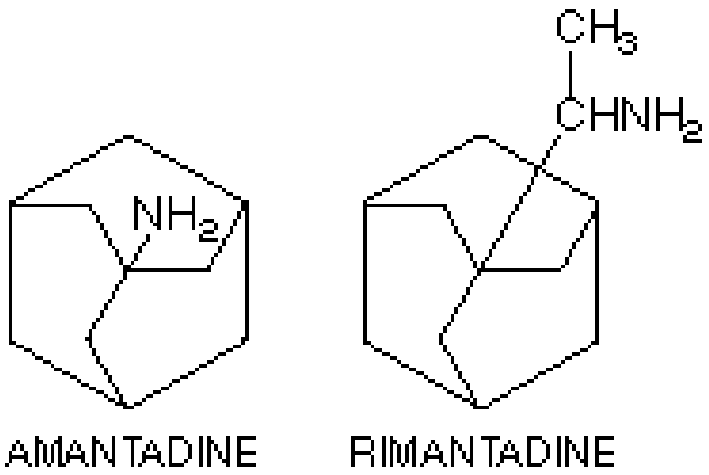
-Resistant variants are selected rapidly during treatment (approximately in 30% of treated patients)

Other effects

-Amantadine has antiparkinsonian effects. The mechanism of action is not clear but it may be related to:

a) the antimuscarinic properties of the drug

b) the stimulation of the synthesis and release of dopamine (and other catecholamines)



AMANTADINE RIMANTADINE

Pharmacokinetics and administration (amantadine)

-F(oral): 50-90%
-Distribution in all body tissues including CNS
-Renal excretion: > 90%
-Half lives: » 16 hours
-Administration: oral

Adverse effects

-Anorexia, nausea and vomiting ,stypsis, xerostomia, urinary retention.
-Nervousness ,insomnia, lightheadedness, difficulty concentrating, ataxia
-Delirium, hallucinations, seizures (with high doses)
-Teratogenic effects in animals

Therapeutic uses

-Treatment of influenza A (treatment within the first 48 hours after the exposure reduces the duration of symptoms and speeds functional recovery)
-Prevention of influenza A (70-90% protective). The
drugs do not impair the immune response to influenza A vaccine.

PHARMACOLOGY OF ACYCLOVIR AND CONGENERS

Chemistry

-**Acyclovir, gancyclovir**, famcyclovir, pemcyclovir all are guanine nucleoside analogs.

Mechanism of action

-**All drugs are phosphorylated by a viral thymidine-kinase, then metabolized by host cell kinases to nucleotide analogs.**

-The analog inhibits viral DNA-polymerase

-Only actively replicating viruses are inhibited

Antiviral spectrum and resistance

-Acyclovir: HSV-1, HSV-2, VZV.

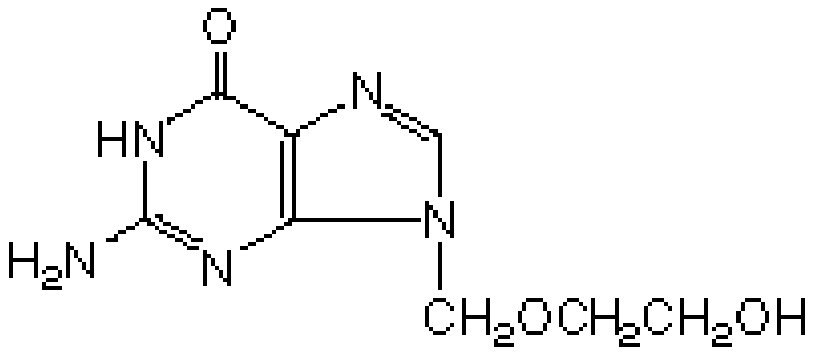
-Gancyclovir: HSV-1, HSV-2, VZV, EBV, CMV.

-Viral resistance may occur and may be due to:

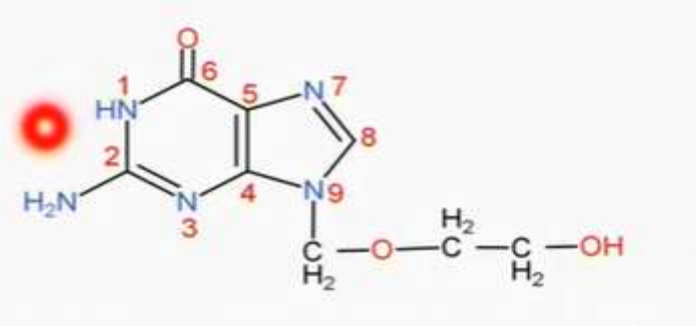
a) decreased production of thymidine kinase

b) altered thymidine kinase substrate specificity

c) altered viral DNA polymerase


O
HN
N
N
H_2N
N
$CH_2OCH_2CH_2OH$

ACYCLOVIR


O
1
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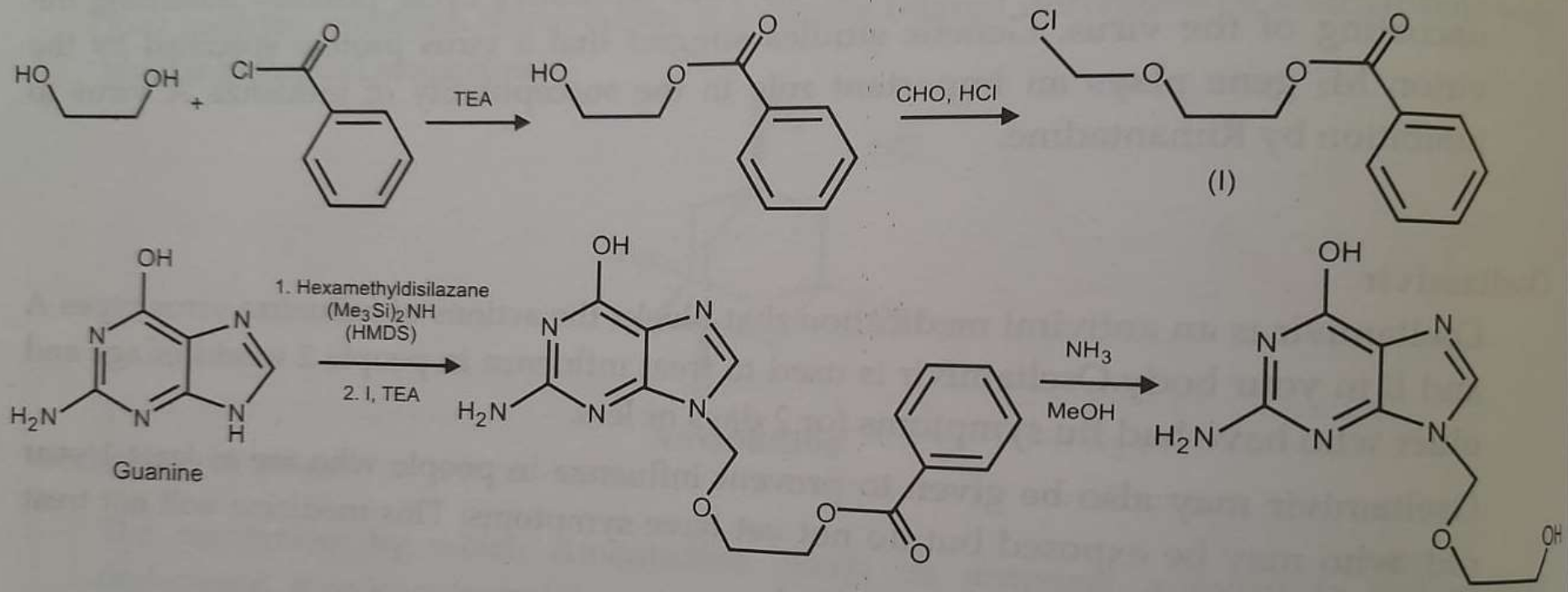
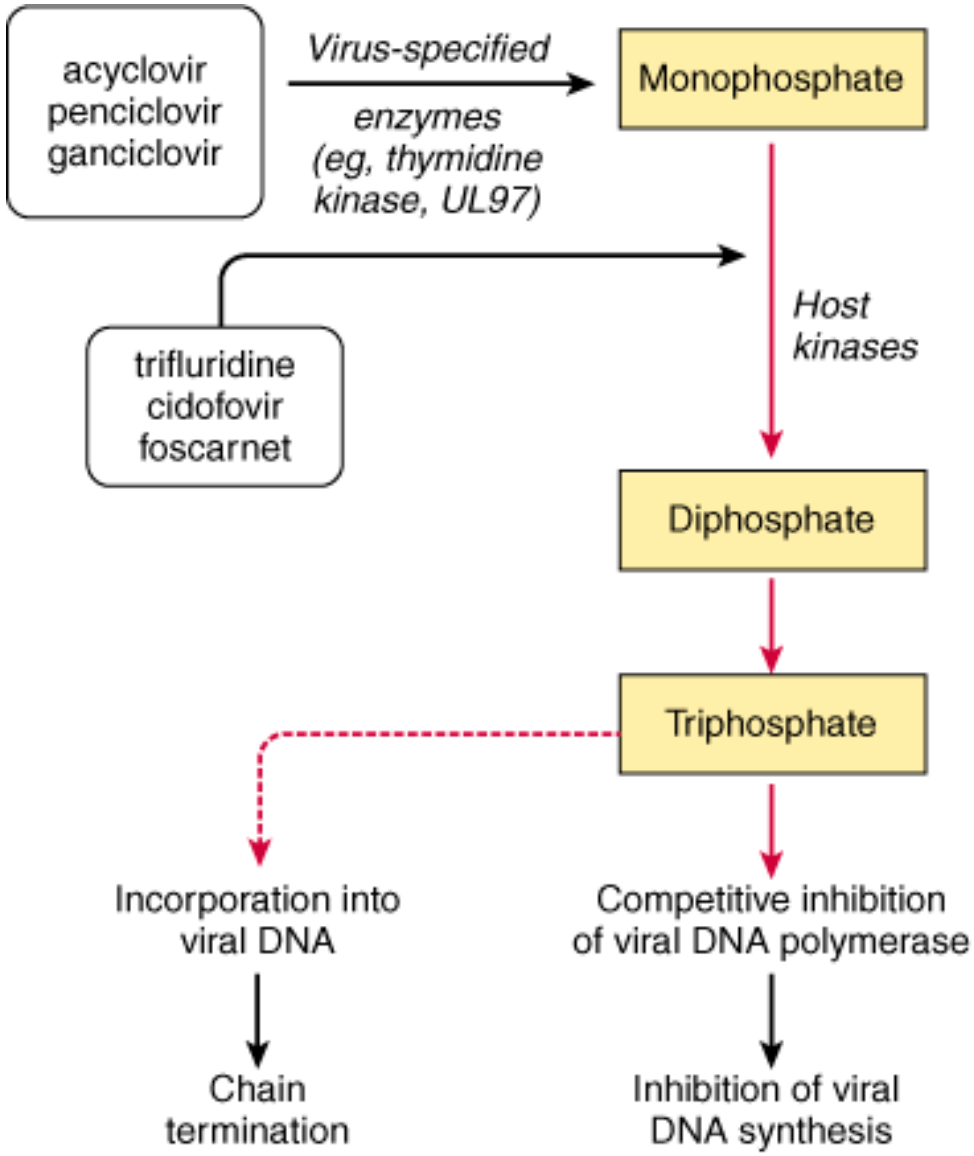
9.7 SYNTHESIS OF ACYCLOVIR



Mechanism of action of antiherpes agents (**Acyclovir, gancyclovir**, famcyclovir, pemcyclovir)



Pharmacokinetics and administration

-F(oral): acyclovir 20-30%; gancyclovir < 10%
-Distribution in all body tissues including CNS (CSF/plasma ratio » 0.5)
-Renal excretion: > 80%
-Half lives: 2-5 hours
-Administration: topical, oral (acyclovir), IV (acyclovir, gancyclovir)

Adverse effects

-Nausea and vomiting ,diarrhea (acyclovir PO)
-Neurotoxicity (1-5% of patients) (headache, tremor, behavioral changes, delirium, seizures, coma) (acylovir and gancyclovir, high doses IV)
-Nephrotoxicity (crystalluria, hematuria, renal insufficiency (acyclovir, high doses IV)
-Mielosuppression (neutropenia, thrombocytopenia) (gancyclovir)
-Teratogenic effects in animals

Therapeutic uses

Acyclovir is the drug of choice for:
-Genital HSV infections
-HSV encephalitis
-HSV infections in immunocompromised patient *Gancyclovir is the drug of choice for:*
-CMV retinitis in immunocompromised patient
-Prevention of CMV disease in transplant patients

PHARMACOLOGY OF IDOXURIDINE AND TRIFLURIDINE

Chemistry

-Idoxuridine and trifluridine are pyrimidine nucleoside analogs.

Mechanism of action

-The drugs are converted by cellular enzymes to their triphosphate analogs which inhibits viral (and, to a lesser extent, human**) DNA synthesis**.

Antiviral spectrum and resistance

-Antiviral spectrum includes HSV-1, HSV-2 and VZV.

-Prolonged treatment can select drug-resistant mutants.

Administration

-topically administered (eye, oral, genital mucosae)

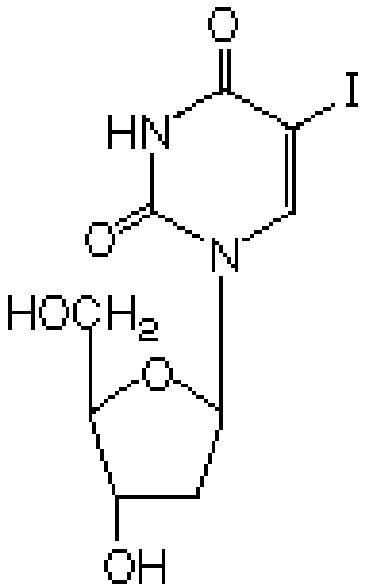
Adverse effects

-Pain, pruritus, edema involving the eye or lids.

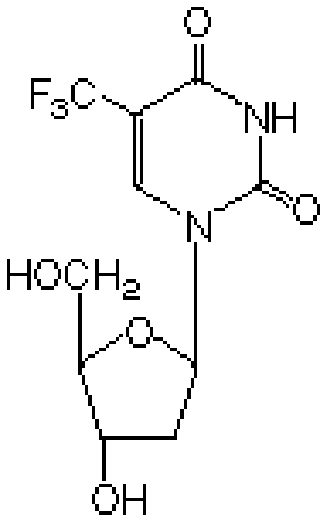
-Allergic reactions (rare)

Therapeutic uses

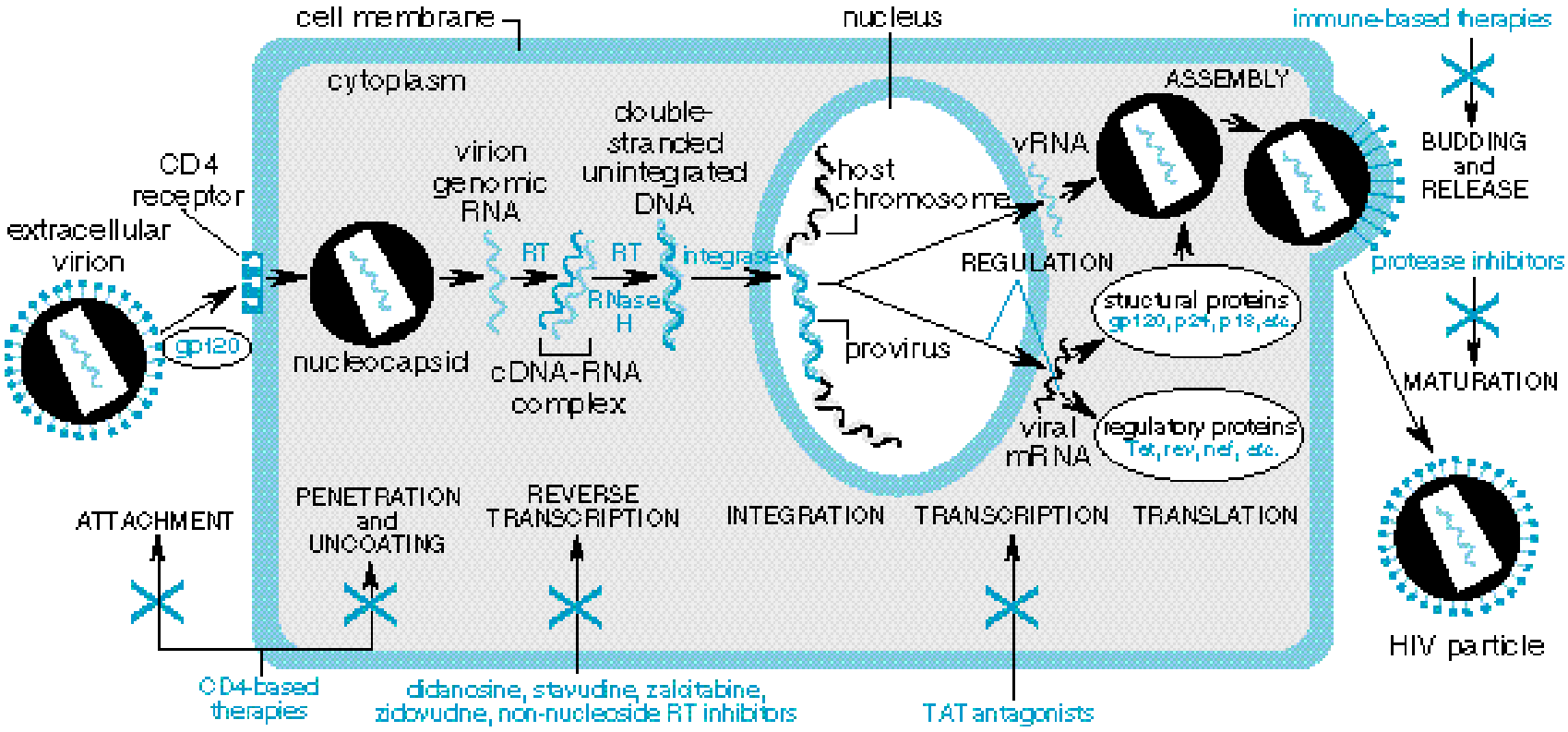
-Ocular, oral, genital HSV infections



IDOXURIDINE



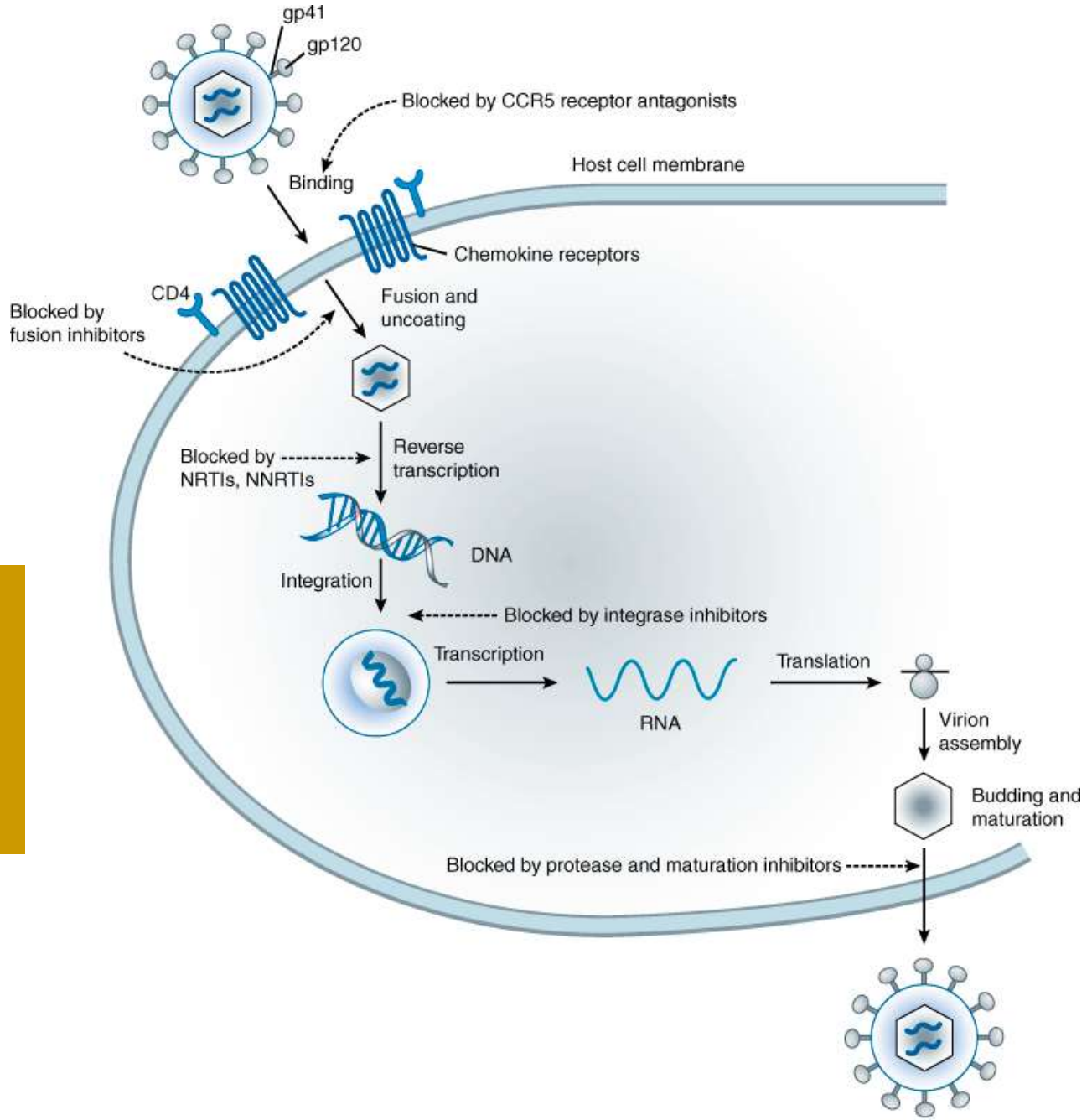
TRIFLURIDINE



Replicative cycle of HIV-1, an example of a retrovirus, showing the sites of action of antiviral agents.

Various antiviral agents are shown in blue. Key: RT, reverse transcriptase; cDNA, complementary DNA; mRNA, messenger RNA; Tat, a protein that regulates viral transcription and affects the rate of replication; RNaseH, ribonuclease H; gp120, envelope glycoprotein.

Life cycle of HIV



PHARMACOLOGY OF ZIDOVUDINE

Chemistry

-Zidovudine is a thymine nucleoside analog (deoxythymidine)

Mechanism of action

-The drug is phosphorylated by cellular thymidine kinase to the corresponding nucleotide analog

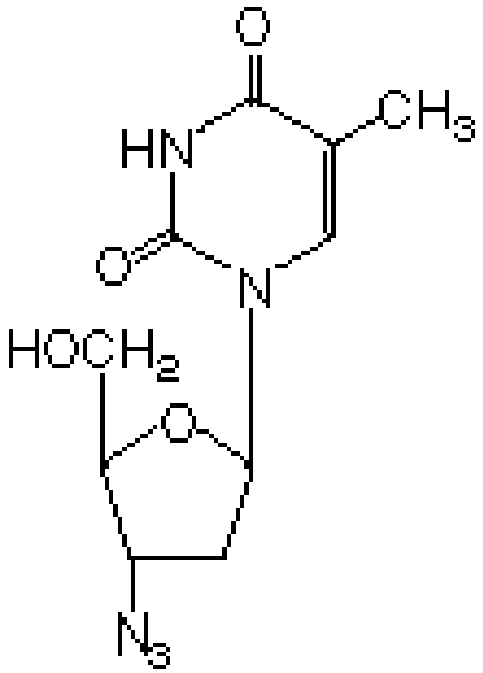
-The analog inhibits the RNA dependent DNA-polymerase (inverse transcriptase) so blocking DNA synthesis

-Viral DNA-polymerases are more sensitive to this inhibition than are mammalian polymerases

Antiviral spectrum and resistance

-Antiviral spectrum includes HIV-1, HIV-2, HTLV-1 and other retroviruses.

-Highly resistant mutants have been recovered from many AIDS patients treated for more than 6 months.



ZIDOVUDINE

Pharmacokinetics

-F(oral): » 65%
-Distribution in all body tissues including CNS (CSF/plasma ratio » 0.5)
-Biotransformation: » 85% (glucuronidation)
-Renal excretion: » 15%
-Half life: » 1 hour

Adverse effects

-Severe anemia and leukopenia, due to bone marrow suppression (30% of patients need transfusions)
-Malaise, fever, fatigue, headache, nausea and vomiting, diarrhea, insomnia, agitation (mainly during first few weeks)
-Myopathy (10% of patients after long term use)
-Encephalopathy (confusion, tremulousness), seizures (with high doses, can be fatal)
-Hepatic steatosis, lactic acidosis (can be fatal)
[toxicity is increased by concomitant use of drugs which inhibit glucuronidation (e.g fluconazole, cimetidine) or are extensively gucuronosylconjugated (e.g. benzodiazepines)]

Therapeutic uses

-Initial drug of choice in AIDS patients with CD4 counts less than 500/mm$^{3.}$ (the drug initially reduces morbidity and mortality, but the effect is transient)
-In asymptomatic HIV-infected individuals the drug slow the rate of progression of AIDS.

PHARMACOLOGY OF OTHER DEOXYNUCLEOSIDES USED IN AIDS

Chemistry

-Didanosine is a purine deoxynucleoside .

-Zalcitabine and stavudine are pyrimidine deoxynucleosides.

Mechanism of action

-The drug are phosphorylated by cellular kinases to the corresponding nucleotide analogs.

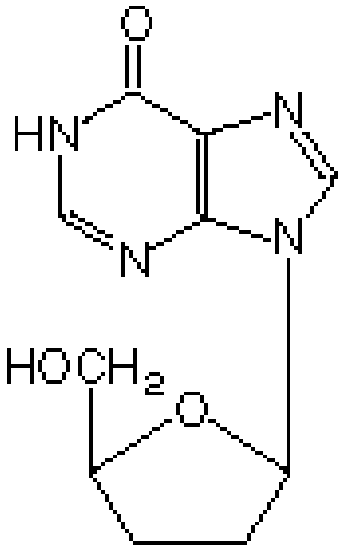
-The analog inhibits the RNA dependent DNA-polymerase (inverse transcriptase) so blocking DNA synthesis

-Viral DNA-polymerases are more sensitive to this inhibition than are mammalian polymerases

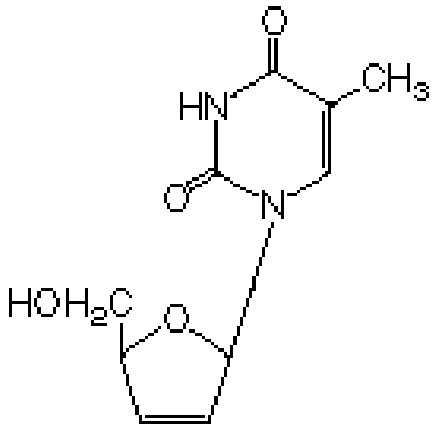
Antiviral spectrum and resistance

-The drugs are active against HIV-1 and HIV-2, including ***most zidovudine resistant strains***.

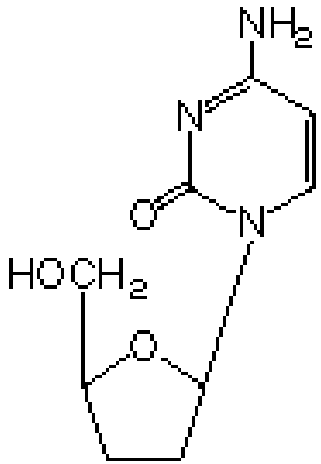
-Resistant mutants have been recovered from treated patients.



DIDANOSINE



STAVUDINE



ZALCITABINE

Pharmacokinetics

-F(oral): variable (didanosine »40%; zalcitabine >80%)
-Distribution in all body tissues including CNS
-Renal excretion: 40-75%
-Half lives: 1-3 hours

Adverse effects

-Painful peripheral neuropathy (up to 30% of patients)
-Pancreatitis (can be fatal)
-Headache, insomnia, agitation, seizures (didanosine)
-Arthralgia, fever, rash
-Stomatitis, esophageal ulceration (zalcitabine)
-Hepatic steatosis, lactic acidosis (can be fatal)

Therapeutic uses

-Advanced HIV infection in patients who are intolerant of or deteriorating on zidovudine.

PHARMACOLOGY OF HIV PROTEASE INHIBITORS

Chemistry

-Atazanavir, Darunavir, Fosamprenavir, Lopinavir, Nelfinavir, Tipranavir, **Saquinavir,** Ritonavir and **Indinavir** are structural analogs of HIV protease

Mechanism of action

-HIV protease is an aspartic endopeptidase that cleaves viral polypeptide products to form structural proteins of the virion core and essential viral enzymes (i.e reverse transcriptase, integrase, etc.)

-***By inhibiting HIV protease the drugs block the maturation of the virus*** and therefore are active in both acutely and chronically infected cells

-The drugs are highly specific inhibitors of HIV protease and do not affect human endopeptidases

Antiviral spectrum and resistance

-The drugs are active against HIV-1 and HIV-2, including ***most strains resistant to nucleoside analogs*** -Resistant mutants have emerged during therapy.

-Some cross-resistance occurs among HIV protease inhibitors, but not with other antiviral drugs.

Pharmacokinetics and administration

-F(oral): 4-10% (due to extensive first pass-effect)
-Distribution in all body tissues, except CNS
-Biotransformation: extensive, by the mixed function oxidase system, in intestinal wall and liver.
-Administration: PO

Adverse effects

-Nausea and vomiting, diarrhea, abdominal pain
-Stomatitis, glossitis, gastritis, hemorrhoids, pancreatitis (rare)
-Elevated hepatic aminotransferase levels, hepatitis, jaundice (rare)
-Skin rashes, urticaria
-Stevens-Johnson syndrome (very rare)
-Anemia, leukopenia, thrombocytopenia (rare)

Drug interactions

-Drugs which inhibit the hepatic mixed function oxidase system may increase plasma concentrations of HIV protease inhibitors.

Therapeutic uses

-Advanced HIV infection (in combination with deoxynucleoside antiretroviral drugs)

INTERFERONS

A natural substance that helps the body's immune system fight infection and other diseases, such as cancer. Interferons are made in the body by white blood cells and other cells, but they can also be made in the laboratory to use as treatments for different diseases.

PHARMACOLOGY OF INTERFERONS

Chemistry

-Interferons are inducible endogenous cytokines (glycoproteins)

-Three major classes of human interferons (IFN) are:

IFN-alpha (human leukocyte IFN), induced by viruses

IFN-beta (human fibroblast IFN), induced by viruses

IFN-gamma (human immune IFN), induced by antigens

Mechanism of antiviral action

-Binding to specific receptors of the host cells

-Induction of the following main enzymes:

1) a protein kinase which inhibits protein synthesis

2) an oligoadenylate synthase which leads to degradation of viral mRNA

3) a phosphodiesterase which can inhibit tRNA

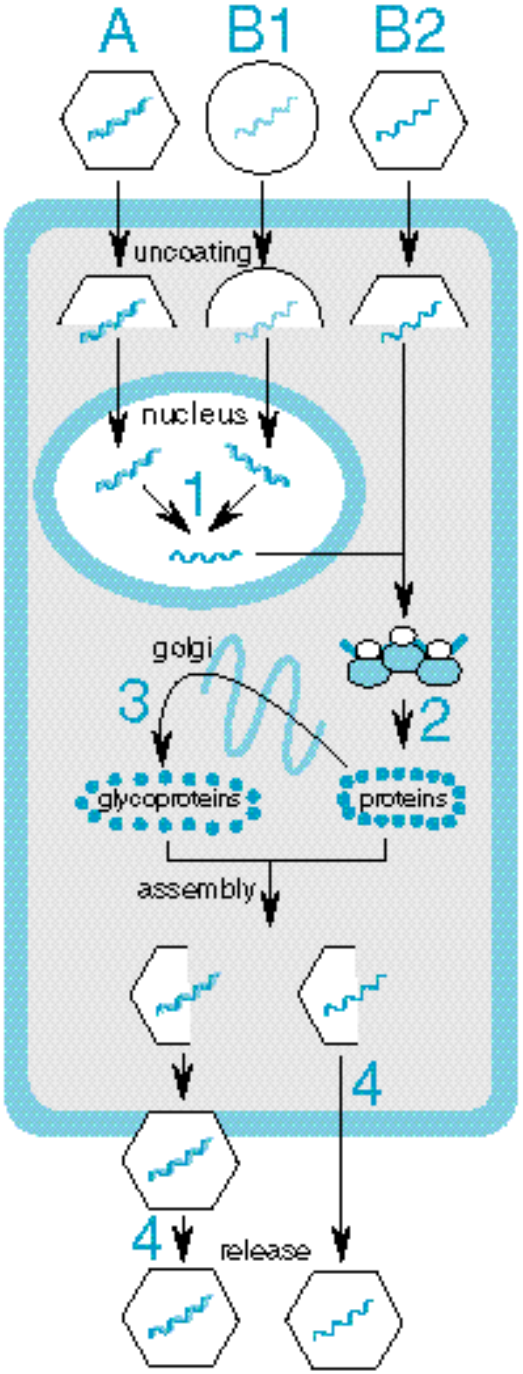
-The action of these enzymes leads to **an inhibition of translation** (late viral RNA and protein synthesis)

Antiviral spectrum

-Antiviral spectrum includes HBV, HCV, HDV, HSV, VZV, CMV and human papillomavirus (HPV).

Other effects

-Interferons possess immunomodulating and antiproliferative actions and may inhibit the growth of certain cancer cells.



Viruses

A. DNA

B. RNA

1. orthomyxoviruses and retroviruses
2. picornaviruses and most RNA viruses

IFN Effects

1. transcription inhibition

activates Mx protein
blocks mRNA synthesis

2. translation inhibition

activates methylase —>
blocks mRNA cap methylation

activates 2'5' oligoadenylate synthetase —> 2'5'A —> inhibits mRNA splicing and activates RNaseL —> cleaves viral RNA

activates protein kinase P1 —> blocks eIF-2α function —> inhibits initiation of mRNA translation

activates phosphodiesterase —> blocks tRNA function

3. protein processing inhibition

glycosyltransferase —> blocks protein glycosylation

4. virus maturation inhibition

glycosyltransferase —>blocks glycoprotein maturation

causes membrane changes —> blocks budding