Viruses, what are they?

- Viruses are obligate intracellular parasites, i.e. they utilize:
- Host metabolic enzymes
- Host ribosome for protein synthesis
- They cannot make anything on their own, they use the cell's materials to build themselves

Structure of viruses

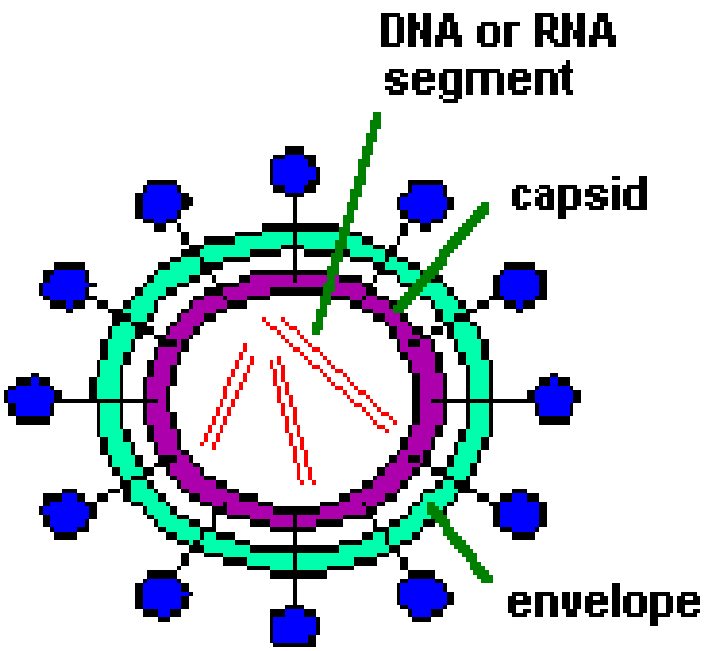


Diagram of a Virion

Virus particles (virions) consist of following parts:

- Nucleic acid core: DNA or RNA
- Often contain virus-specific enzymes
- Surrounded by protein: “capsid”
- sometimes an outer lipid “envelope”

VIRUS STRUCTURE

Genetic Material
Viruses can have one of two kinds of genetic material, DNA or RNA. The latter are named retroviruses.

Membrane Envelope and Capsid
a layer of fatty acids coats many viruses. It is usually derived from the membrane of the host cell.



Ligands
proteins that stick out of the surface of the virus. They act as a key to recognize the cell to be infected and invade it.

Classification of Viruses

DNA viruses

- **Contain an DNA genome.**
- **Virus replication:**
  - **DNA polymerase**
- **Examples:**
  - **Herpes Virus**
  - **Hepatitis B virus**
  - **Epstein-Barr virus**

RNA Viruses

- **Contain an RNA genome.**
- **Virus replication:**
  - **RNA-dependent RNA polymerase**
  - **Reverse transcriptase (Retroviruses)**
- **Examples:**
  - **Rubella virus**
  - **Dengue fever virus**
  - **Hepatitis A virus**
  - **Hepatitis C virus**
  - **HIV**
  - **Influenza virus**

The Life Cycle of Viruses

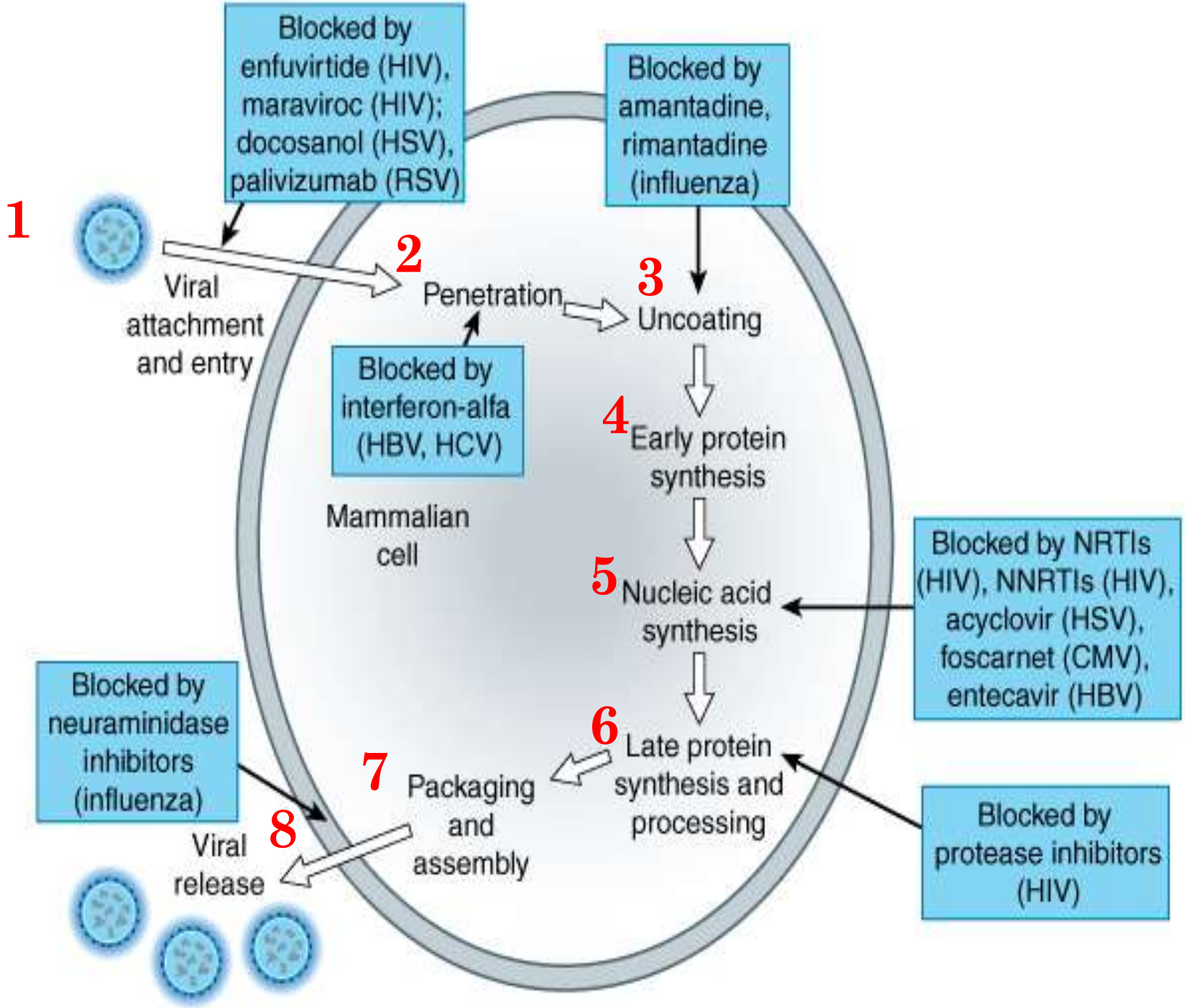
1. **Attachment** of the virus to receptors on the host cell surface;
2. **Entry** of the virus through the host cell membrane;
3. **Uncoating** of viral nucleic acid;
4. **Replication**

   Synthesis of **early regulatory proteins**, eg, nucleic acid polymerases;

   Synthesis of new viral **RNA or DNA**;

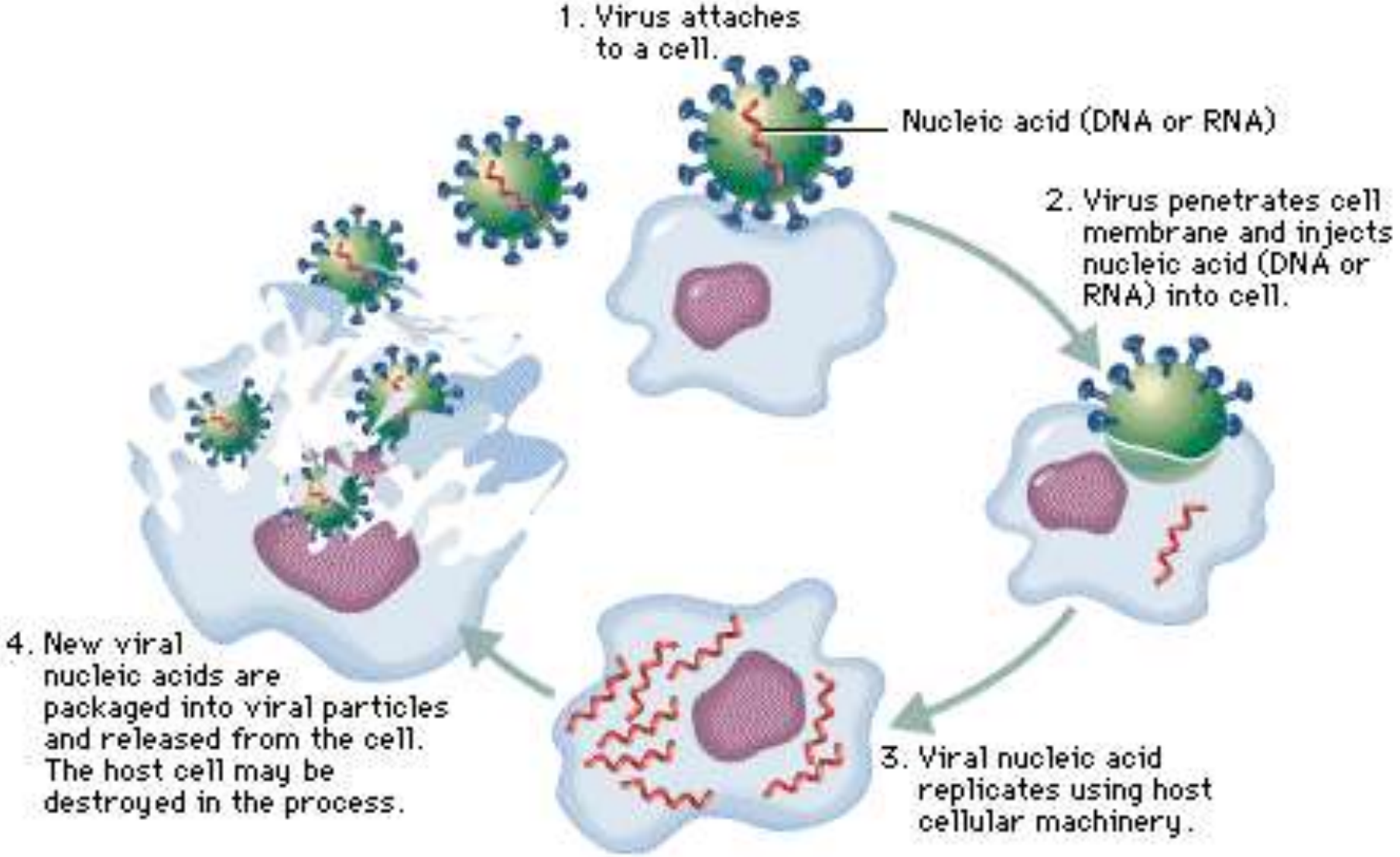
   Synthesis of **late, structural proteins;**

5. **Assembly** (maturation) of viral particles;
6. **Release** from the cell


Blocked by enfuvirtide (HIV), maraviroc (HIV); docosanol (HSV), palivizumab (RSV)
Blocked by amantadine, rimantadine (influenza)
1
2
3
Viral attachment and entry
Penetration
Uncoating
Blocked by interferon-alfa (HBV, HCV)
4
Early protein synthesis
Mammalian cell
5
Nucleic acid synthesis
Blocked by NRTIs (HIV), NNRTIs (HIV), acyclovir (HSV), foscarnet (CMV), entecavir (HBV)
Blocked by neuraminidase inhibitors (influenza)
6
Late protein synthesis and processing
7
Packaging and assembly
8
Viral release
Blocked by protease inhibitors (HIV)

- Many viruses infect a specific host cell
- Many viral infections are self-limiting and require no medical treatment—ex. Rhinoviruses that cause common cold.
- Common viral infections such as the influenza, mumps, or chicken pox are usually overcome by the body's immune system.
- Other viruses cause serious and even fatal disease & require aggressive therapy—ex. HIV that causes AIDS.

Virus Replication



The virus uses the cell mechanism to replicate itself

Virus Groups of Clinical Importance

Virus Genera	Nucleic Acid	Clinical Illness
Adenovirus	DNA	URTIs, Eye infections
Hepadnaviridae	DNA	Hepatitis B, Cancer (?)
Herpesvirus	DNA	Genital herpes, Varicella, IM, Encephalitis, Retinitis
Papillomavirus	DNA	Papilloma, Cancer
Parvovirus	DNA	Erythema infectiosum
Arenavirus	RNA	Lymphocytic choriomeningitis
Bunyavirus	RNA	Encephalitis
Coronavirus	RNA	URTIs
Influenzavirus	RNA	Influenza
Paramyxovirus	RNA	Measles, URTIs
Picornavirus	RNA	Poliomyelitis, diarrhea, URTIs
Retrovirus	RNA	Leukemia, AIDS
Rhabdovirus	RNA	Rabies
Togavirus	RNA	Rubella, Yellow fever

Anti-viral drugs

- Viruses have no cell wall and made up of nucleic acid components
- Viruses containing envelope – antigenic in nature
- Viruses are obligate intracellular parasite
- They do not have a metabolic machinery of their own – uses host enzymes
- Certain viruses multiply in the cytoplasm but others do in the nucleus
- Most multiplication take place before diagnosis is made

Anti-Viral drugs

- 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.
- Anti-viral agents inhibits active replication so the viral growth resumes after drug removal.
- Current anti-viral agents do not eliminate non-replicating or latent virus
- Effective host immune response remains essential for the recovery from the viral infection
- Clinical efficacy depends on achieving inhibitory conc. at the site of infection within the infected cells

Anti-viral drugs

Stages of viral replication

- Cell entry – attachment
  - penetration
- Uncoating
- Transcription of viral genome
- Translation
- Assembly of virion components
- Release

Anti-viral drugs

Anti-herpes virus agents

- Acyclovir / Valacyclovir
- Famciclovir / Penciclovir
- Ganciclovir / Cidofovir
- Foscarnet
- Trifluridine / Idoxuridine / Vidarabine

Anti-viral drugs

Acyclovir & Congeners :

- **Valacyclovir is a prodrug of Acyclovir with better bioavailability.**
- **Famciclovir is hydrolyzed to Penciclovir and has greatest bioavailability.**
- **Penciclovir is used only topically whereas Famciclovir can be administered orally.**

Anti-Viral drugs

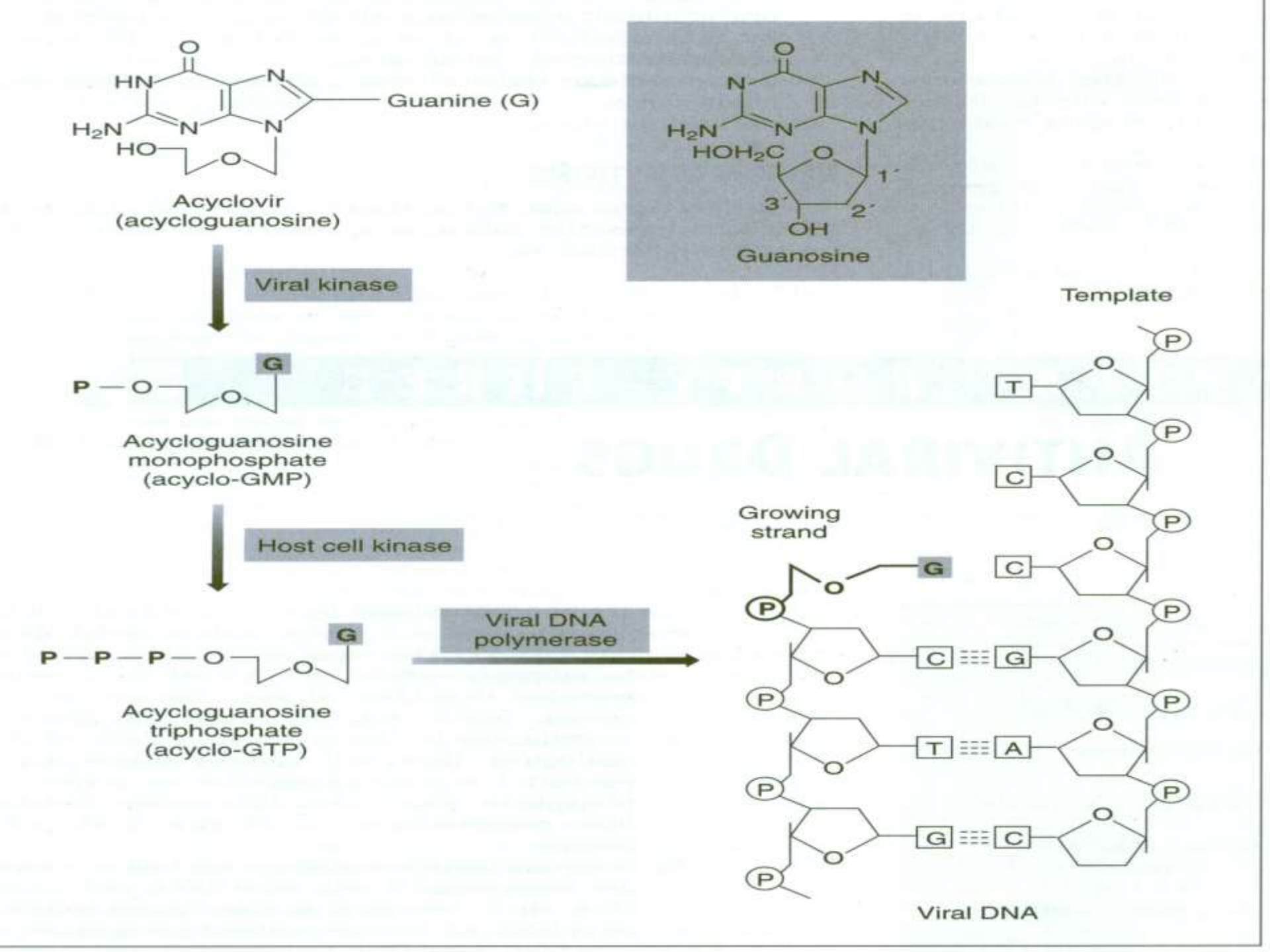
PHARMACOLOGY OF ACYCLOVIR AND CONGENERS

- **Acyclovir, Valacyclovir, Ganciclovir, Famciclovir, Penciclovir all are guanine nucleoside analogs.**

Anti-viral drugs

Mechanism of action of Acyclovir and congeners

- 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
- Acyclovir is thus selectively activated in cells infected with herpes virus.
- Uninfected cells do not phosphorylate acyclovir.


Guanine (G)
Acyclovir
(acycloguanosine)
Guanosine
Viral kinase
Acycloguanosine
monophosphate
(acyclo-GMP)
Host cell kinase
Acycloguanosine
triphosphate
(acyclo-GTP)
Viral DNA
polymerase
Template
Growing
strand
Viral DNA

Anti-Viral drugs

Antiviral spectrum :

- Acyclovir: HSV-1, HSV-2, VZV, Shingles.
- Ganciclovir / Cidofovir : CMV
- Famciclovir : Herpes genitalis and shingles
- Foscarnet : HSV, VZV, CMV, HIV
- Penciclovir : Herpes labialis
- Trifluridine : Herpetic keratoconjunctivitis

Anti-Viral drugs

Pharmacokinetics of Acyclovir :

- Oral bioavailability ~ 20-30%
- Distribution in all body tissues including CNS
- Renal excretion: > 80%
- Half lives: 2-5 hours
- Administration: Topical, Oral , IV

Anti-viral drugs

Adverse effects of Acyclovir / Ganciclovir

- **Nausea, vomiting and diarrhea**
- **Nephrotoxicity - crystalluria, haematuria, renal insufficiency**
- **Myelosuppression – Neutropenia and thrombocytopenia – Ganciclovir**

Anti-viral drugs

Therapeutic uses :

Acyclovir is the drug of choice for:

- **HSV Genital infections**
- **HSV encephalitis**
- **HSV infections in immunocompromised patient**

Ganciclovir is the drug of choice for:

- **CMV retinitis in immunocompromised patient**
- **Prevention of CMV disease in transplant patients**

Anti-viral drugs

Cidofovir :

- It is approved for the treatment of CMV retinitis in immunocompromised patients
- It is a nucleotide analog of cytosine – no phosphorylation required.
- It inhibits viral DNA synthesis
- Available for IV, Intravitreal inj, topical
- Nephrotoxicity is a major disadvantage.

Anti-viral drugs

PHARMACOLOGY OF VIDARABINE

- Vidarabine is a nucleoside analog. (adenosine)

Antiviral spectrum of Vidarabine :

HSV-1, HSV-2 and VZV.

Its use is limited to HSV keratitis only

Anti-viral drugs

Vidarabine

- The drug is converted to its triphosphate analog which inhibits viral DNA-polymerase.
- Oral bioavailability ~ 2%
- Administration: Ophthalmic ointment
- Used in HSV keratoconjunctivitis in immunocompromised patient.
- Anemia and SIADH are adverse effects.

Anti-viral drugs

PHARMACOLOGY OF TRIFLURIDINE

- Trifluridine is a Pyrimidine nucleoside analogs - inhibits viral DNA synthesis.

Antiviral spectrum Trifluridine :

- HSV-1, HSV-2 and VZV.
- Use is limited to Topical - Ocular HSV Keratitis

Anti-viral drugs

PHARMACOLOGY OF FOSCARNET

- Foscarnet is an inorganic pyrophosphate analog
- It directly inhibits viral DNA and RNA - polymerase and viral inverse transcriptase (it does not require phosphorylation for antiviral activity)

Anti-viral drugs

Foscarnet

- HSV-1, HSV-2, VZV, CMV and HIV.
- Oral bioavailability ~ 10-20%
- Distribution to all tissues including CNS
- Administration: IV

Anti-viral drugs

Adverse effects of Foscarnet

- Hypocalcemia and hypomagnesemia (due to chelation of the drug with divalent cations) are common.
- Neurotoxicity (headache, hallucinations, seizures)
- Nephrotoxicity (acute tubular nephrosis, interstitial nephritis)

Anti-viral drugs

Therapeutic uses of Foscarnet

- ***It is an alternative drug for***
- HSV infections (acyclovir resistant / immunocompromised patient)
- CMV retinitis (ganciclovir resistant / immunocompromised patient)

Anti-viral drugs

Respiratory viral infections

Influenza –

- Amantadine / Rimantadine
- Oseltamivir / Zanamavir
  (Neuraminidase inhibitors)

RSV bronchiolitis –

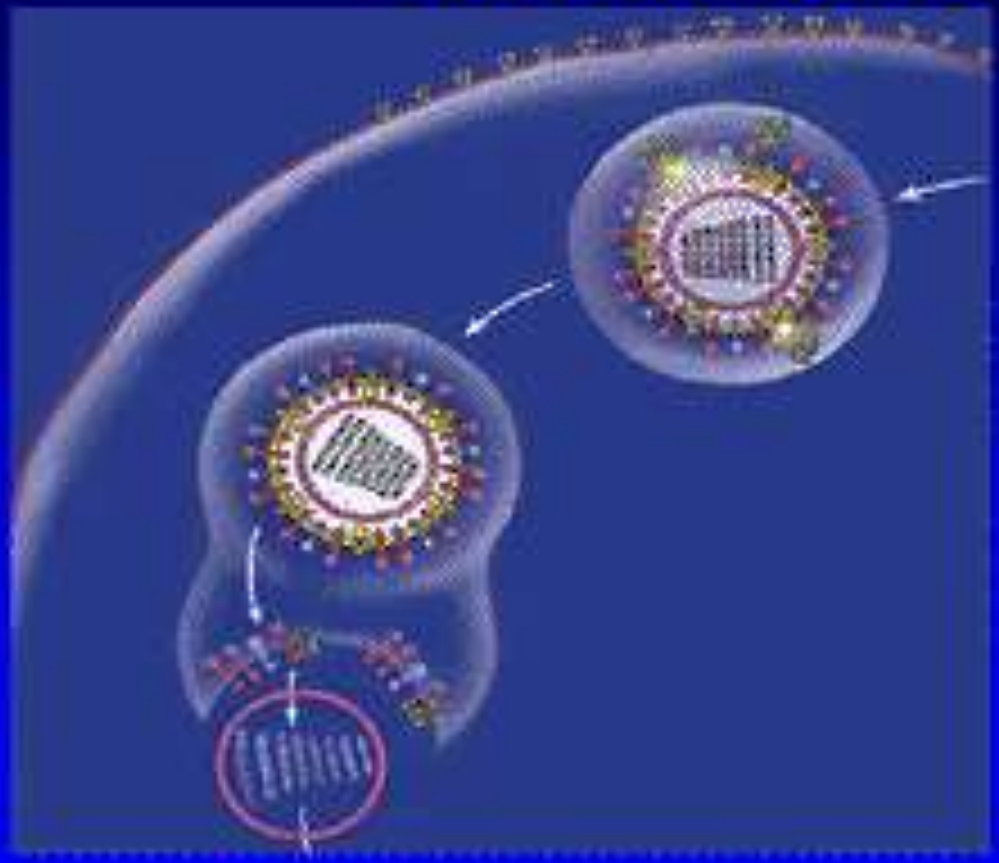
- Ribavirin

Anti-viral drugs

Amantadine and Rimantadine : Influenza

- Prevention & Treatment of influenza A
- **Inhibition of viral uncoating** by inhibiting the viral membrane protein M2
- Influenza A virus
- Amantadine has anti-parkinsonian effects.

Amantadine and Rimantadine: Mechanism of Action



- Blocks M2 protein channel (type A only)
- Disrupts hydrogen transport, viral uncoating in host cell and therefore viral RNA transcription

Anti-viral drugs

Pharmacokinetics of Amantadine

- Oral bioavailability ~ 50-90%
- Amantadine cross extensively BBB whereas Rimantadine does not cross extensively .
- Administration: Oral

Anti-viral drugs

Neuraminidase inhibitors : Influenza

Oseltamivir / Zanamavir

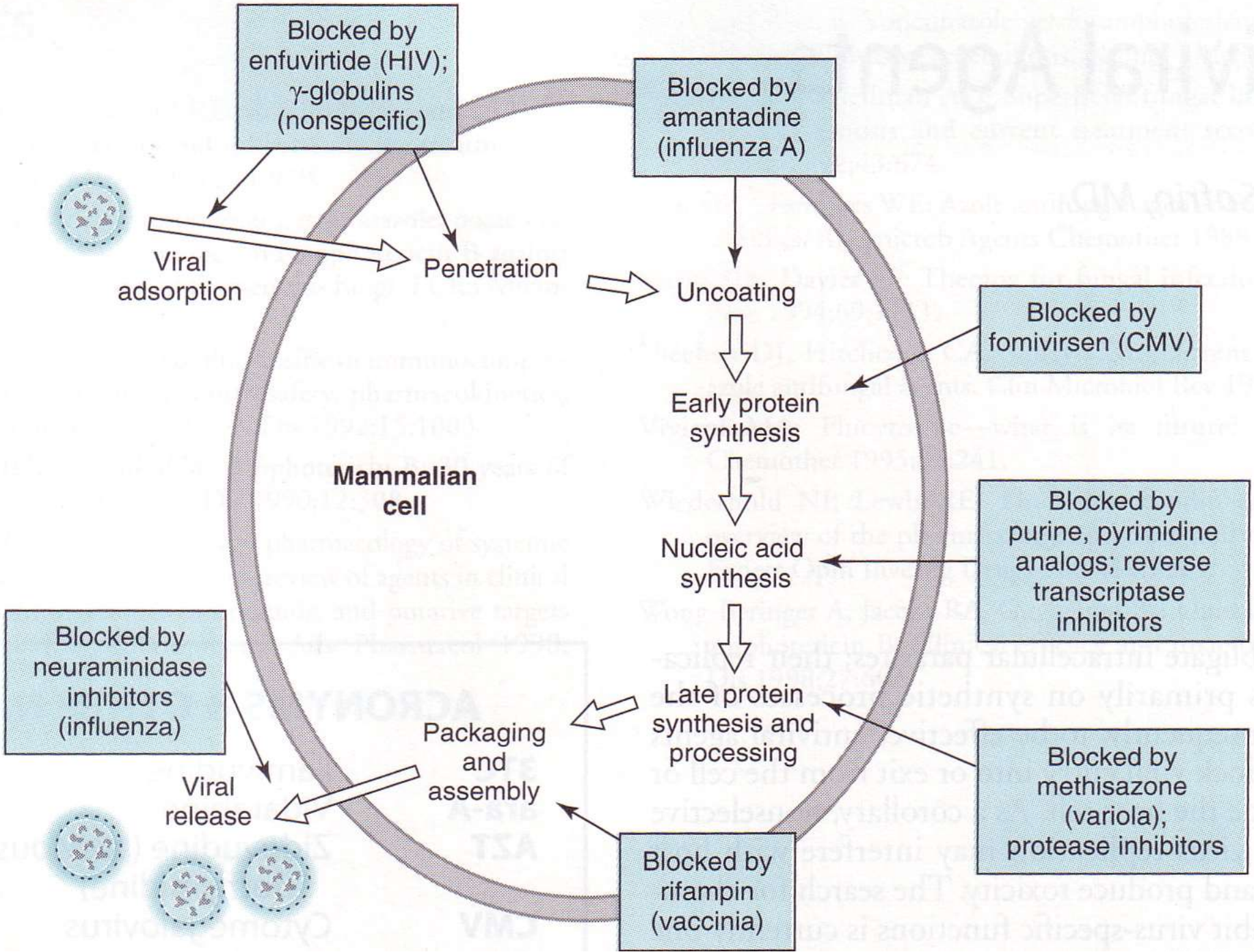
- **Influenza** contains an enzyme *neuraminidase* which is essential for the replication of the virus.
- ***Neuraminidase inhibitors*** prevent the release of new virions and their spread from cell to cell.

Anti-viral drugs

Neuraminidase inhibitors : Influenza

Oseltamivir / Zanamavir

- These are effective against both types of influenza A and B.
- Do not interfere with immune response to influenza A vaccine.
- Can be used for both prophylaxis and acute treatment.

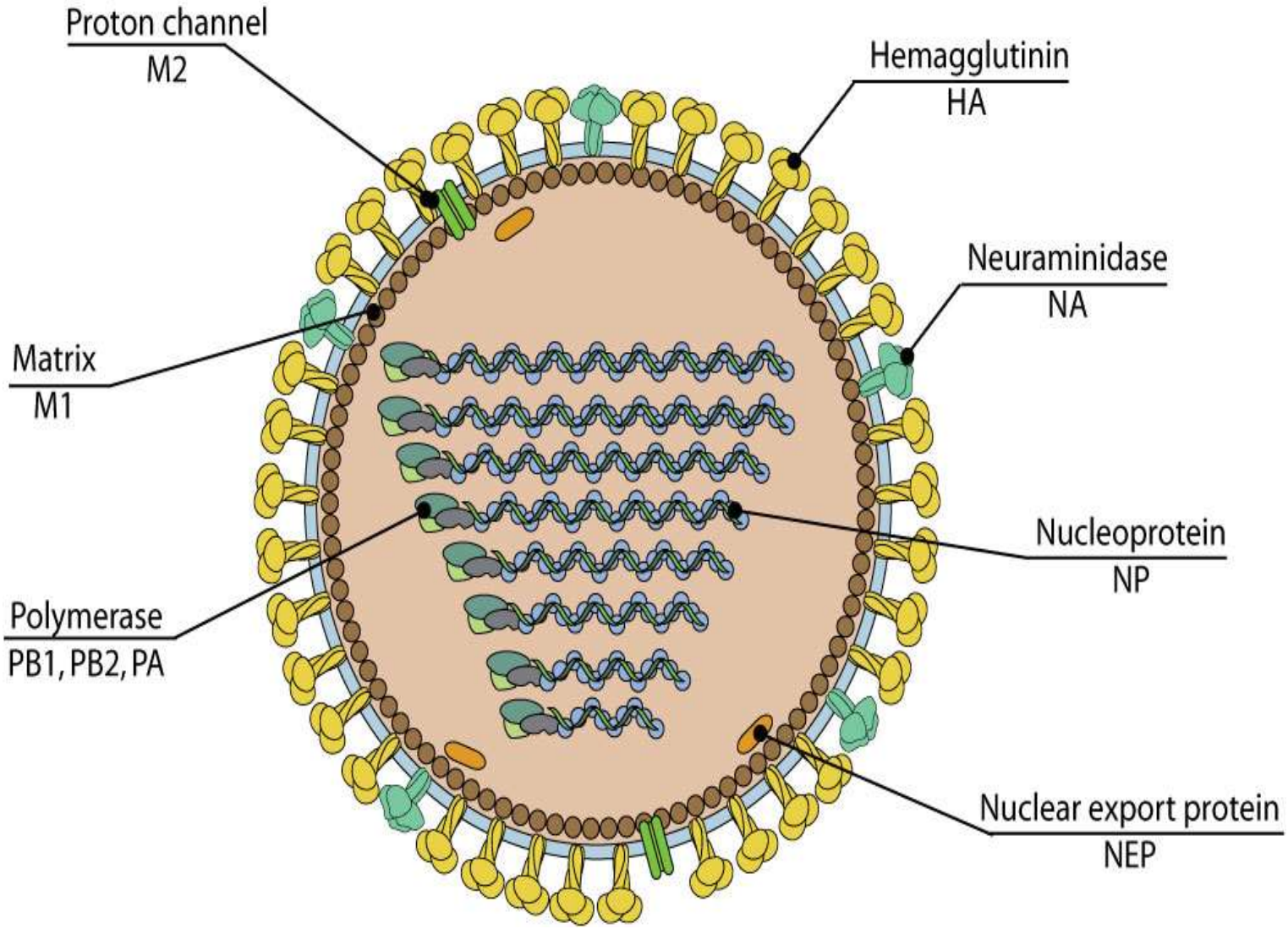

Blocked by enfuvirtide (HIV); γ-globulins (nonspecific)
Blocked by amantadine (influenza A)
Viral adsorption
Penetration
Uncoating
Blocked by fomivirsen (CMV)
Early protein synthesis
Mammalian cell
Nucleic acid synthesis
Blocked by purine, pyrimidine analogs; reverse transcriptase inhibitors
Blocked by neuraminidase inhibitors (influenza)
Late protein synthesis and processing
Packaging and assembly
Viral release
Blocked by methisazone (variola); protease inhibitors
Blocked by rifampin (vaccinia)

Anti-viral drugs

Neuraminidase inhibitors : Influenza

Oseltamivir / Zanamavir

- Oseltamivir is orally administered.
- Zanamavir is given intranasal.
- Risk of bronchospasm with zanamavir


Proton channel
M2
Hemagglutinin
HA
Neuraminidase
NA
Matrix
M1
Nucleoprotein
NP
Polymerase
PB1, PB2, PA
Nuclear export protein
NEP

Anti-viral drugs

PHARMACOLOGY OF RIBAVIRIN

- **Ribavirin** is a guanosine analog.
- ***Inhibition of RNA polymerase***

Antiviral spectrum : DNA and RNA viruses are susceptible, including influenza, parainfluenza viruses, **RSV,** Lassa virus

Anti-viral drugs

Ribavirin : RSV

- Distribution in all body tissues, except CNS
- Administration : Oral, IV, Inhalational in RSV.
- Anemia and jaundice are adverse effects
- Not advised in pregnancy.

Anti-viral drugs

Therapeutic uses Ribavirin

Ribavirin is the drug of choice for:

- RSV bronchiolitis and pneumonia in hospitalized children (given by aerosol)
- Lassa fever

Ribavirin is an alternative drug for:

- Influenza, parainfluenza, measles virus infection in immunocompromised patients

Anti-viral drugs

Hepatic Viral infections :

- Interferons
- Lamivudine – cytosine analog – HBV
- Entecavir – guanosine analog – HBV – lamivudine resistance strains
- Ribavirin – Hepatitis C (with interferons)

Anti-viral drugs

Interferons

Interferons (IFNs) are natural proteins produced by the cells of the immune systems in response to challenges by foreign agents such as viruses, bacteria, parasites and tumor cells.

- Antiviral, immune modulating and anti-proliferative actions
- Three classes of interferons – **α , β, γ**

Anti-viral drugs

Interferons

- **α and β interferons** are produced by all the cells in response to *viral infections*
- **γ interferons** are produced only by T lymphocyte and NK cells in response to cytokines – *immune regulating effects*
- γ has less anti-viral activity compared to α and β interferons

Anti-viral drugs

Mechanism of action of Interferons :

- **Induction** of the following enzymes:

1) a protein kinase which inhibits protein synthesis

2) an oligo-adenylate synthase which leads to degradation of viral mRNA

3) a phosphodiesterase which inhibit t-RNA

The action of these enzymes leads to an **inhibition of translation**

Anti-viral drugs

Antiviral spectrum : Interferon α

- Includes HBV, HCV and HPV.
- Anti-proliferative actions may inhibit the growth of certain cancers - like Kaposi sarcoma and hairy cell leukemia.

Anti-viral drugs

Pharmacokinetics : Interferons

- Oral bioavailability: < 1%
- Administered Intralesionally, S.C, and I.V
- Distribution in all body tissues, except CNS and eye.
- Half lives: 1-4 hours

Anti-viral drugs

Adverse effects of Interferons

- Acute flu-like syndrome (fever, headache)
- Bone marrow suppression (granulocytopenia, thrombocytopenia)
- Neurotoxicity (confusion, seizures)
- Cardiotoxicity - arrhythmia
- Impairment of fertility

Anti-viral drugs

Therapeutic uses Interferons

- Chronic hepatitis B and C (complete disappearance is seen in 30%).
- HZV infection in cancer patients (to prevent the dissemination of the infection)
- CMV infections in renal transplant patients
- Condylomata acuminata (given by intralesional injection). Complete clearance is seen ~ 50%.
- Hairy cell leukemia (in combination with zidovudine)
- AIDS related Kaposi's sarcoma

Antiretroviral Agents

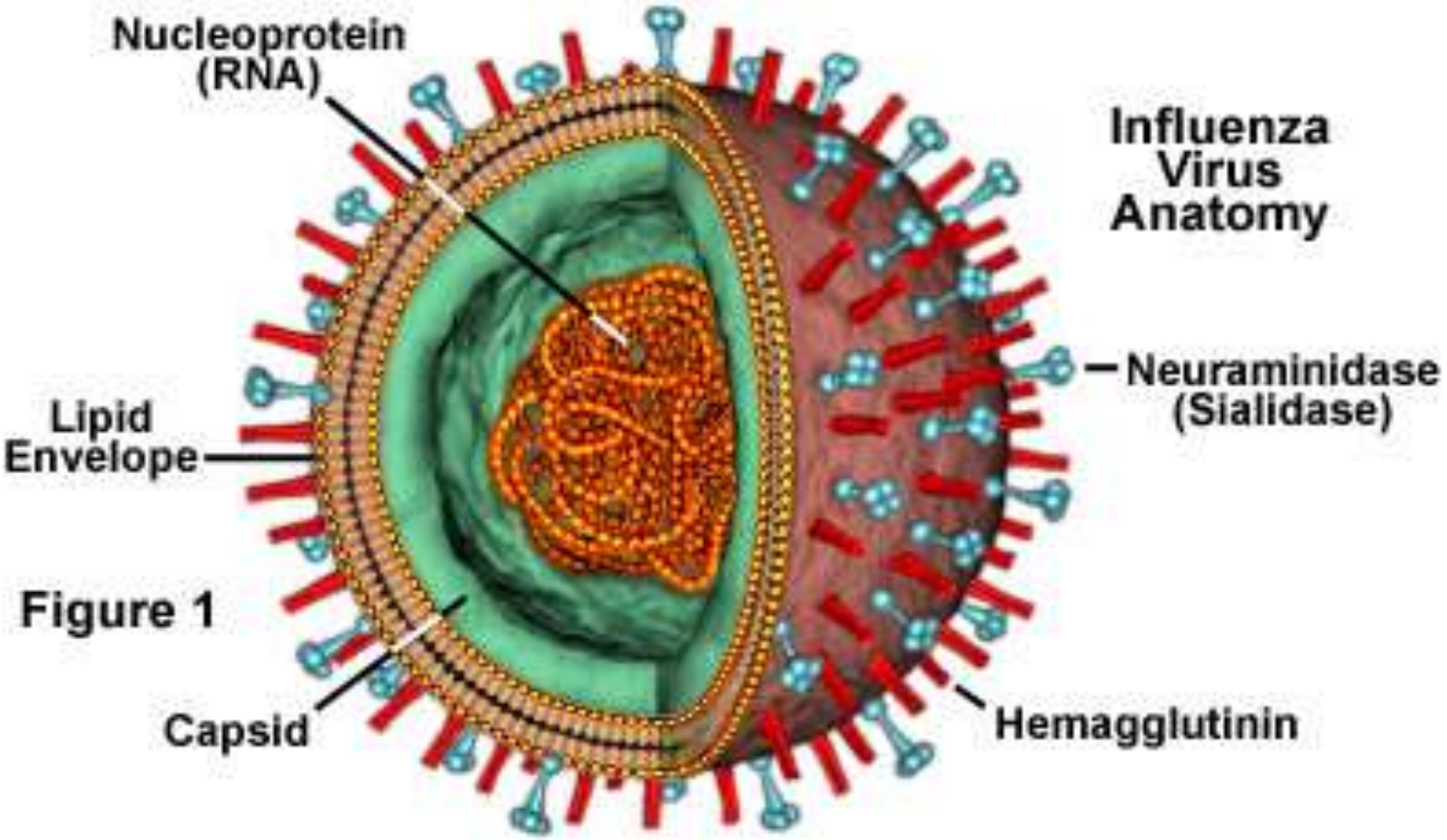
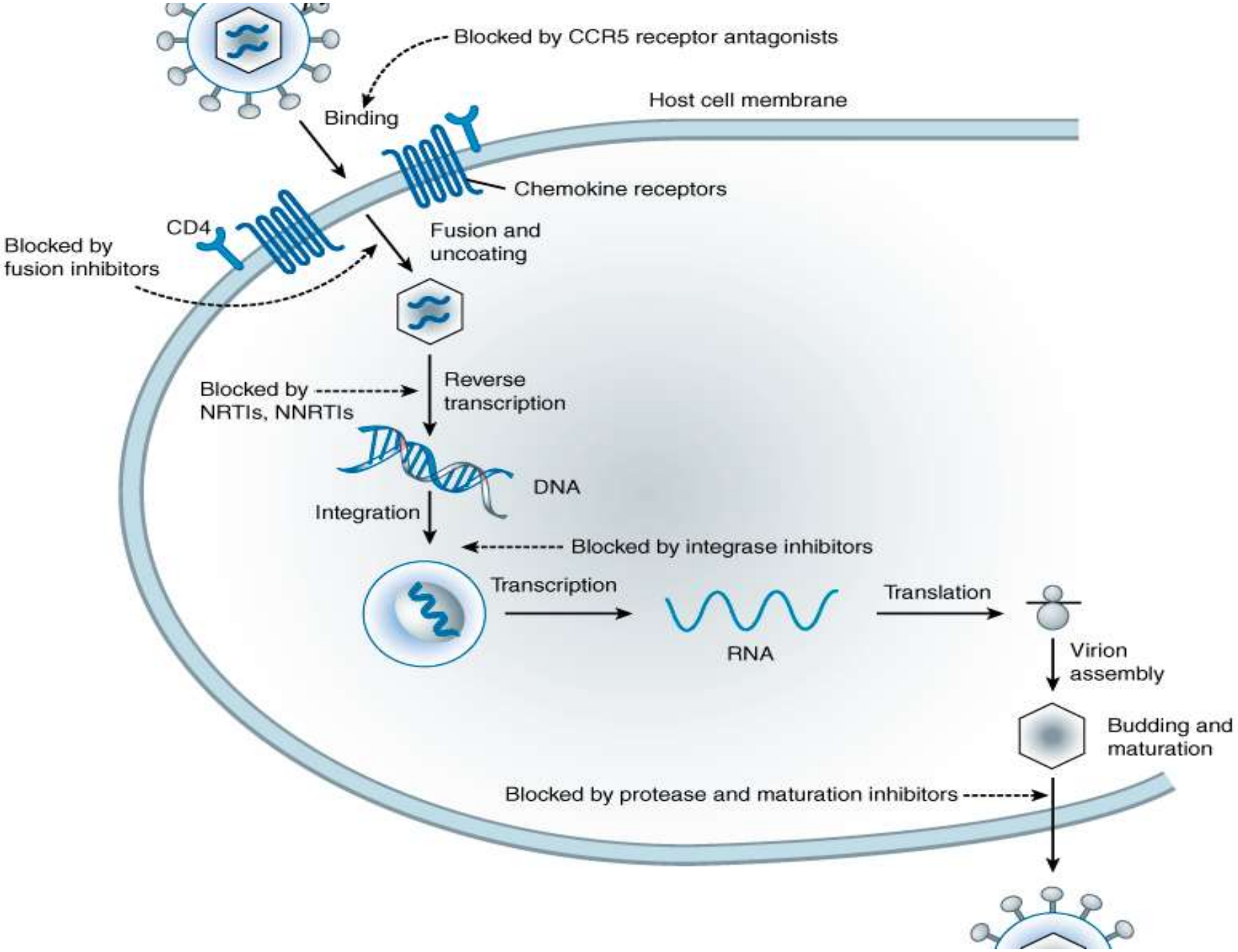


Figure 1

- **Retroviruses are enveloped, single stranded RNA viruses that replicate through a DNA intermediate using Reverse Transcriptase.**

- **This enzyme converts the RNA genome into DNA, which then integrates into the host chromosomal DNA by the enzyme Integrase.**

- **This large and diverse family includes members that are oncogenic, are associated with a variety of immune system disorders, and cause degenerative and neurological syndromes.**


Blocked by CCR5 receptor antagonists
Binding
Host cell membrane
Chemokine receptors
CD4
Fusion and uncoating
Blocked by fusion inhibitors
Blocked by NRTIs, NNRTIs
Reverse transcription
DNA
Integration
Blocked by integrase inhibitors
Transcription
RNA
Translation
Virion assembly
Budding and maturation
Blocked by protease and maturation inhibitors

Current classes of antiretroviral drugs include:

Three main enzymatic targets:

- **Reverse Transcriptase,**
- **Protease,**
- **Integrase**

six drug classes

1. **Nucleoside Reverse Transcriptase Inhibitors (NRTIs)**
2. **Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**
3. **Protease inhibitors (PIs)**
4. **Entery inhibitors**
5. **CCR5 receptor antagonists**
6. **Integrase inhibitors**

Current ARV Medications

NRTI

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

NNRTI

- Efavirenz
- Etravirine
- Nevirapine

PI

- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

Fusion Inhibitor

- Enfuvirtide
-

CCR5 Antagonist

- Maraviroc

Integrase Inhibitor

- Raltegravir

Fixed-dose Combinations

- Zidovudine/ lamivudine
- Zidovudine/lamivudine/abacavir
- Abacavir/lamivudine
- Emtricitabine/tenofovir
- Efavirenz/emtricitabine /tenofovir

HIV Drug Regimens

- Always combine multiple agents.
- Usually 2 NRTIs along with:
  - A PI enhanced with a low dose of a second PI,
  - An NNRTI
  - An integrase inhibitor
  - An entery inhibitor

HAART

- Taking 3 or more antiretroviral drugs at the same time vastly reduces the rate at which resistance develops, the approach is known as **highly active antiretroviral therapy**, or **HAART.**

HIV Drug Toxicity

- HIV drugs have side effects that are either drug or drug class specific (but distinguishing them from effects of prolonged infection are challenging)
- Severe, life-threatening, and essentially irreversible

HIV Drug Resistance

- HIV mutates readily
- If virus replicates in presence of drug, mutations that allow faster replication (drug resistance) will be selected
- Selection of drug resistance mutations will allow higher levels of viremia and progression of immunologic disease unless drugs changed and replication again controlled
- Drug resistance can be transmitted

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

- These were the first type of drug available to treat HIV infection .
- NRTIs interfere with the action of an HIV protein called reverse transcriptase, which the virus needs to make new copies of itself.
- Most regimens contain at least two of these drugs

(Reverse transcriptase changes viral RNA to DNA)

- Act by competitive inhibition of HIV reverse transcriptase; incorporation into the growing viral DNA chain results in premature chain termination due to inhibition of binding with the incoming nucleotide .
- Require intracytoplasmic activation via phosphorylation by cellular enzymes to the triphosphate form.

NRTIs Common Adverse Effects

- Zidovudine
- N/V, fatigue, bone marrow suppression

- Didanosine, Zalcitabine Stavudine:
- peripheral neuropathy, pancreatitis

- Abacavir : N/V/D, perioral paresthesias, hypersensitivity

- Tenofovir , Lamivudine : (generally well-tolerated) N/Vvomiting, flatulence

- All NRTIs may be associated with mitochondrial toxicity, lactic acidosis with fatty liver may occur, which can be fatal.
- Zidovudine and Stavudine : dyslipidemia and insulin resistance.
- Increased risk of myocardial infarction in : Abacavir or Didanosine.

Protease Inhibitors

- Prevent the processing of viral proteins into functional conformations, resulting in the production of immature, noninfectious viral particles .
- Do not need intracellular activation.

Atazanavir

Indinavir

Lopinavir

Nelfinavir

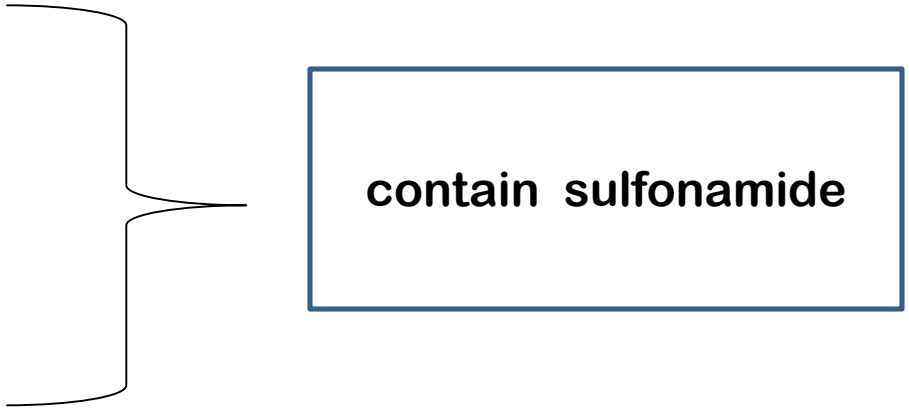
Saquinavir

Ritonavir

Darunavir

Fosamprenavir

Tipranavir



PI Class Side Effects

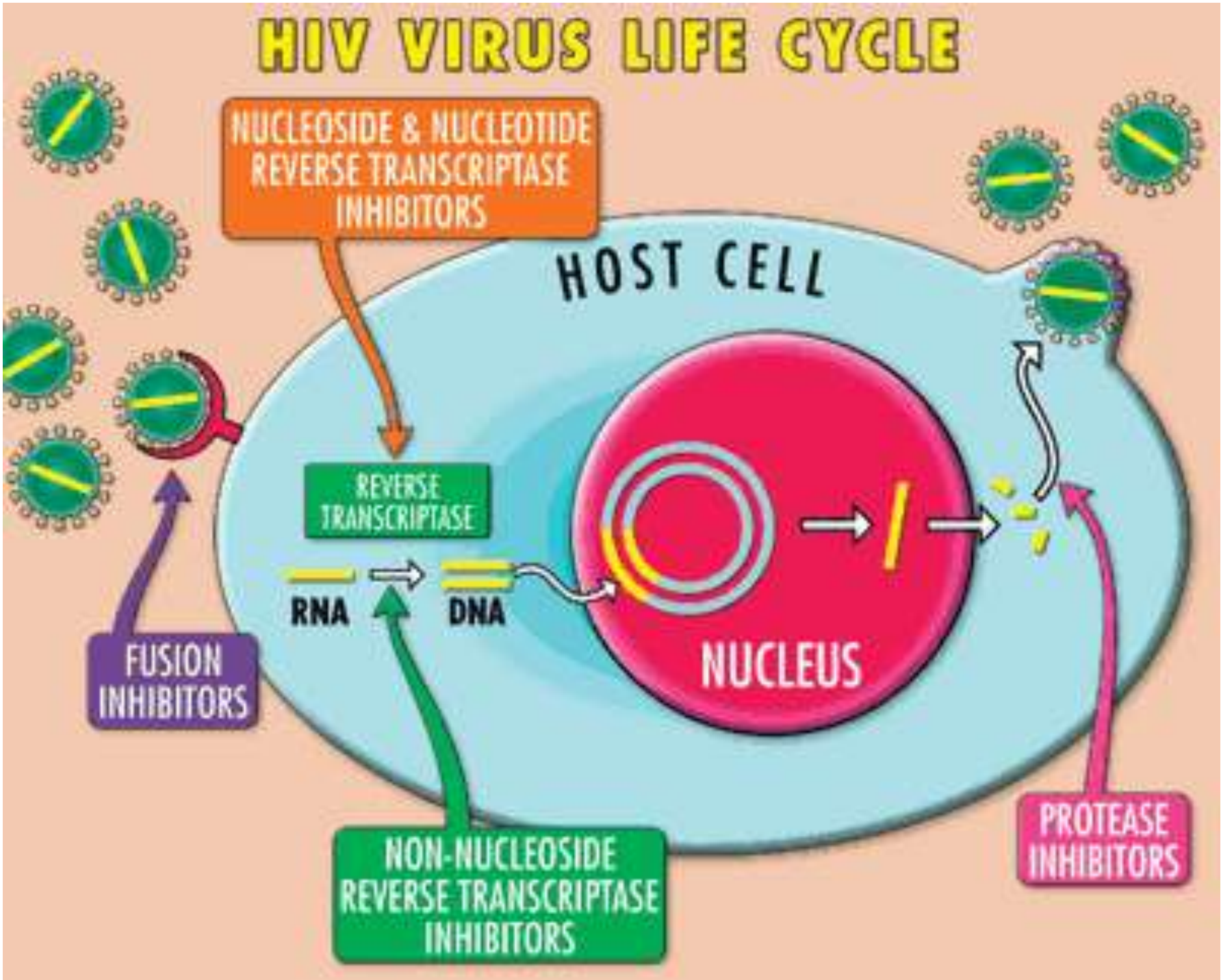
- Metabolic Disorders
  - Hepatotoxicity
  - Hyperglycemia, insulin resistance
  - Lipid abnormalities (increases in triglyceride and LDL levels)
  - Fat redistribution
- Bone Disorders
- GI Intolerance

INTEGRASE INHIBITORS

Bind integrase, a viral enzyme essential to the replication of HIV, Inhibits strand transfer, the final step of the provirus integration, thus interfering with the integration of reverse-transcribed HIV DNA into the chromosomes of host cells.

Raltegravir

A/E: Nausea, Headache, Diarrhea


HIV VIRUS LIFE CYCLE
NUCLEOSIDE & NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS
HOST CELL
REVERSE TRANSCRIPTASE
RNA
DNA
NUCLEUS
FUSION INHIBITORS
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
PROTEASE INHIBITORS

Virus	Diseases	Drug(s) of choice	Alternative drugs
FLU A	Influenza	Amantadine	Rimantadine
RSV	Pneumonia, bronchiolitis	Ribavirin (aerosol)	
HSV	Genital herpes	Acyclovir	Foscarnet
	Keratitis Conjunctivitis	Trifluridine	Idoxuridine Vidarabine
	Encephalitis	Acyclovir	
	Neonatal HSV infection	Acyclovir	Vidarabine
	Herpes infections in immuno-compromised host	Acyclovir	Foscarnet

VZV	In normal host	No therapy	
	In immunocompro-mised host, or during pregnancy	Acyclovir	Foscarnet
CMV	Retinitis	Ganciclovir	Foscarnet
HIV	AIDS HIV antibody positive with CD4 count < 500/mm^3	Zidovudine ± protease inhibitors	Didanosine, Stavudine
HBV **HCV**	Hepatitis B, C	Interferons	