CHEMOTHERAPY

ANTIVIRAL AGENTS

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VIRUSES, WHAT ARE THEY?

- **Viruses are dependent 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

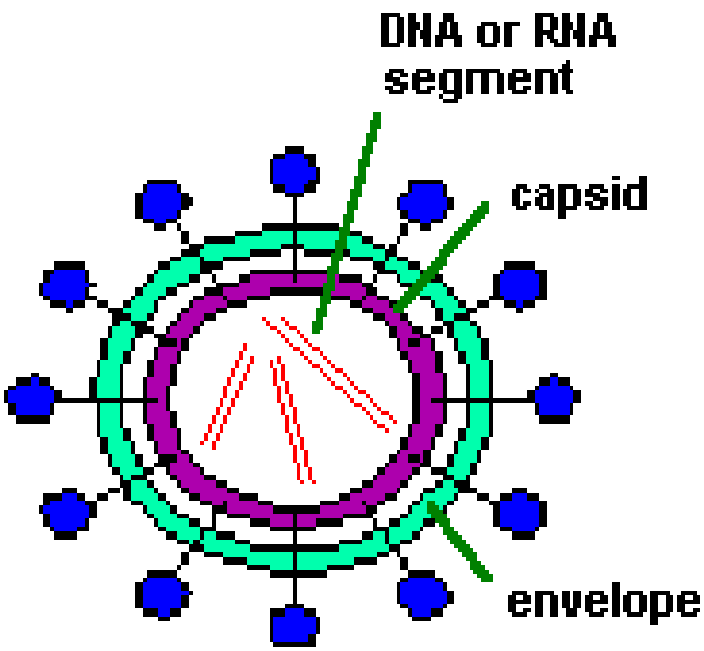


Diagram of a Virion

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**

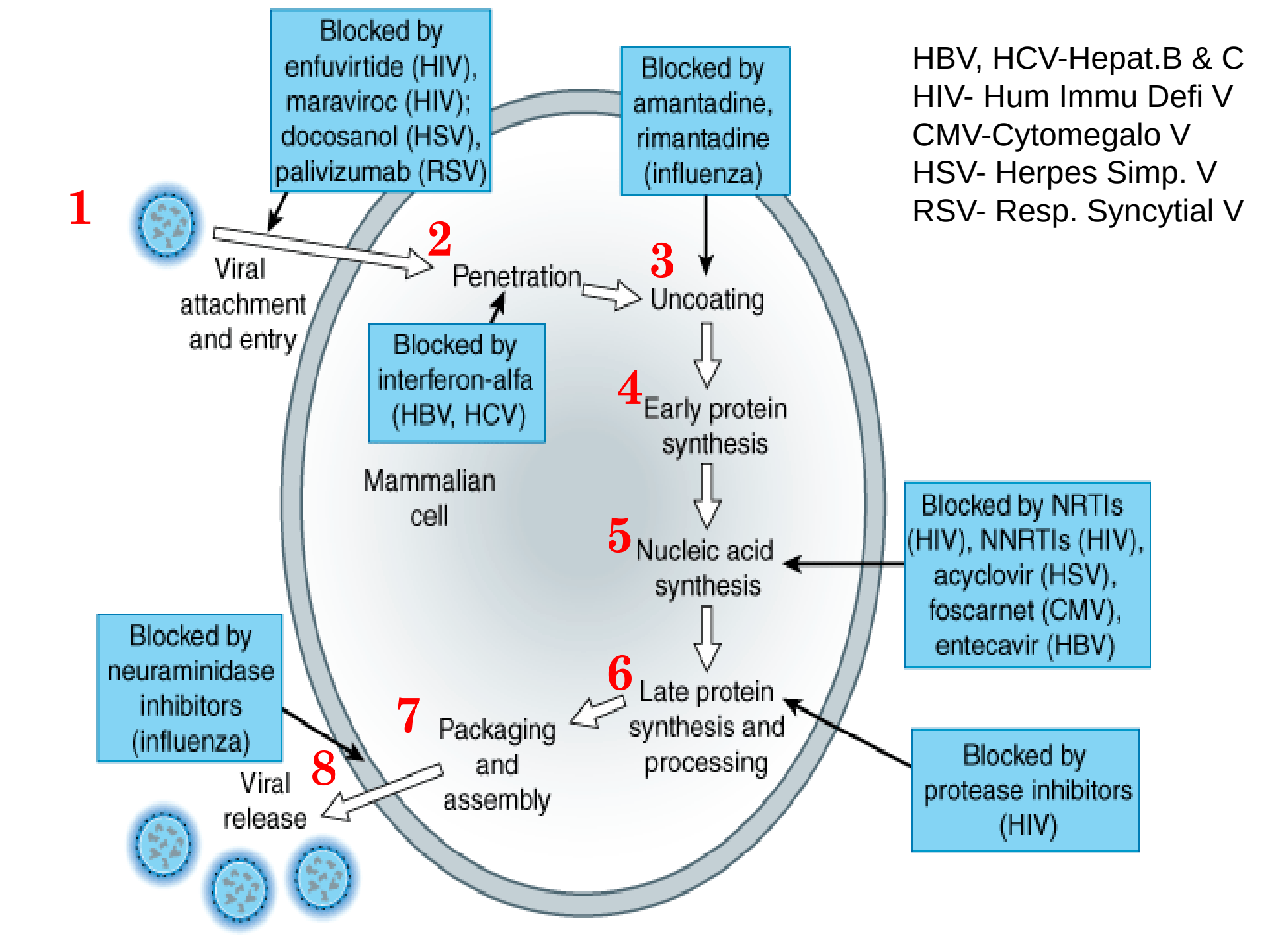
The Life Cycle of Viruses

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;

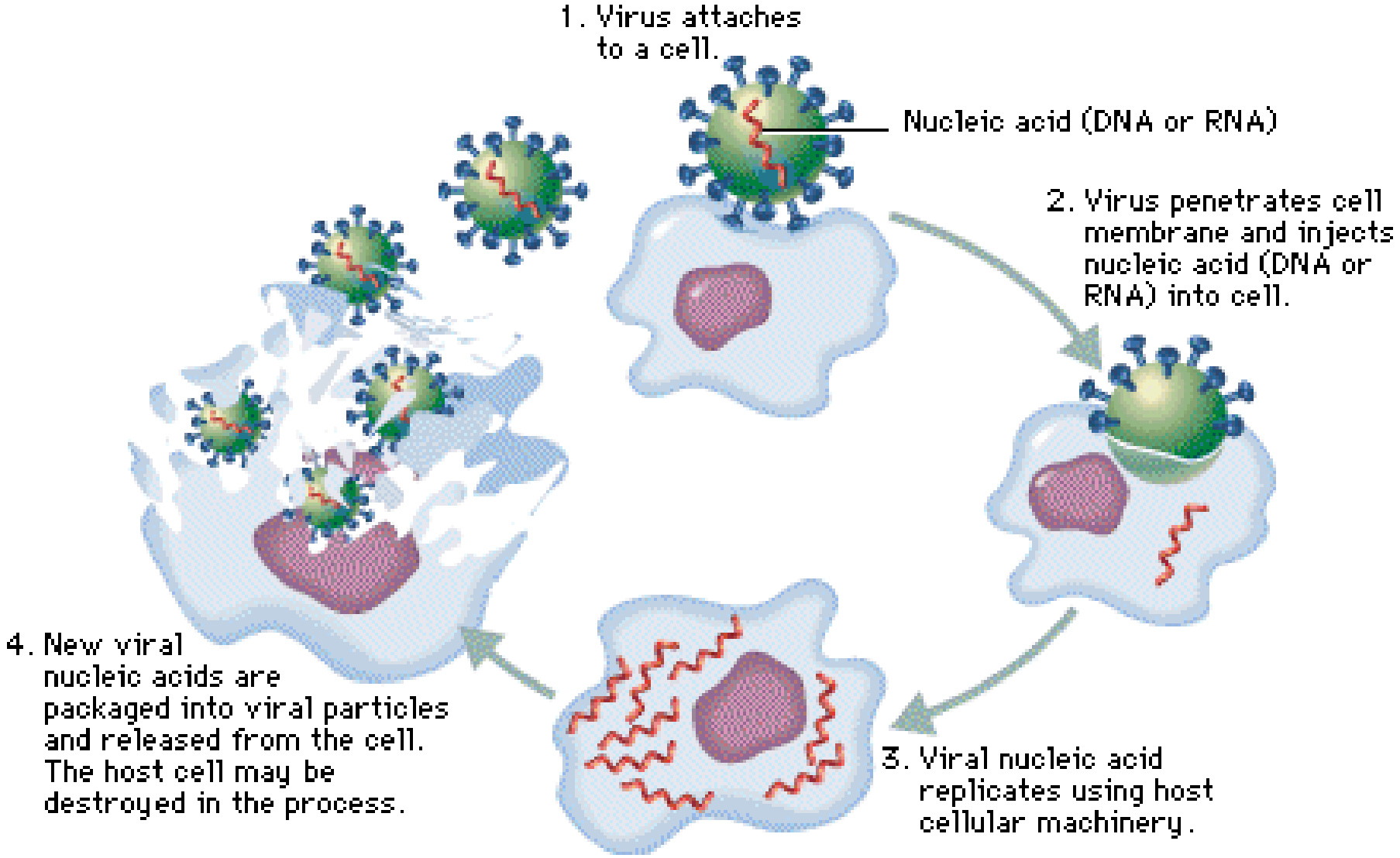
   Synthesis of new viral **RNA or DNA**;

   Synthesis of **late, structural proteins;**
5. **Assembly** (maturation) of viral particles;
6. **Release** from the cell



HBV, HCV-Hepat.B & C
HIV- Hum Immu Defi V
CMV-Cytomegalo V
HSV- Herpes Simp. V
RSV- Resp. Syncytial V

Virus Replication



The virus uses the cell mechanism to replicate itself

- 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 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

Antiviral Drugs

- Vaccines are often used to build up immunity before a viral infection occurs.
- Common viral infections such as the influenza, mumps, or chicken pox are usually overcome by the body's immune system.
- To be effective, antiviral agents must either block viral entry into or exit from the cell or be active inside the host cell.

- Antiviral drugs work by:

1. Altering the cell's genetic material so that the virus cannot use it to multiply, i.e. acyclovir (inhibiting Viral enzymes, Host expression of viral proteins & Assembly of viral proteins)

2. Preventing new virus formed from leaving the cell, i.e. amatadine.

- **Antiviral therapy challenging.**

  1. Rapid **replication** of viruses makes it difficult to develop effective antiviral.
  2. Viruses can rapidly **mutate** and drug becomes ineffective.
  3. Difficulty for drug to find virus **without injuring** normal cells.(**Nonselective** inhibitors of virus **replication** may interfere with host cell function and result in toxicity.)

Antiviral drugs share the common property of being virustatic; they are active only against replicating viruses and do not affect latent virus.

Agents To Treat Herpes Simplex Virus (HSV) & Varicella-zoster Virus (VZV) Infections

Oral Agents

Acyclovir

Valacyclovir

Famciclovir

Topical Agents

Acyclovir

Docosanol

Penciclovir

Ophthalmic

Trifluridine

Intravenous

Acyclovir

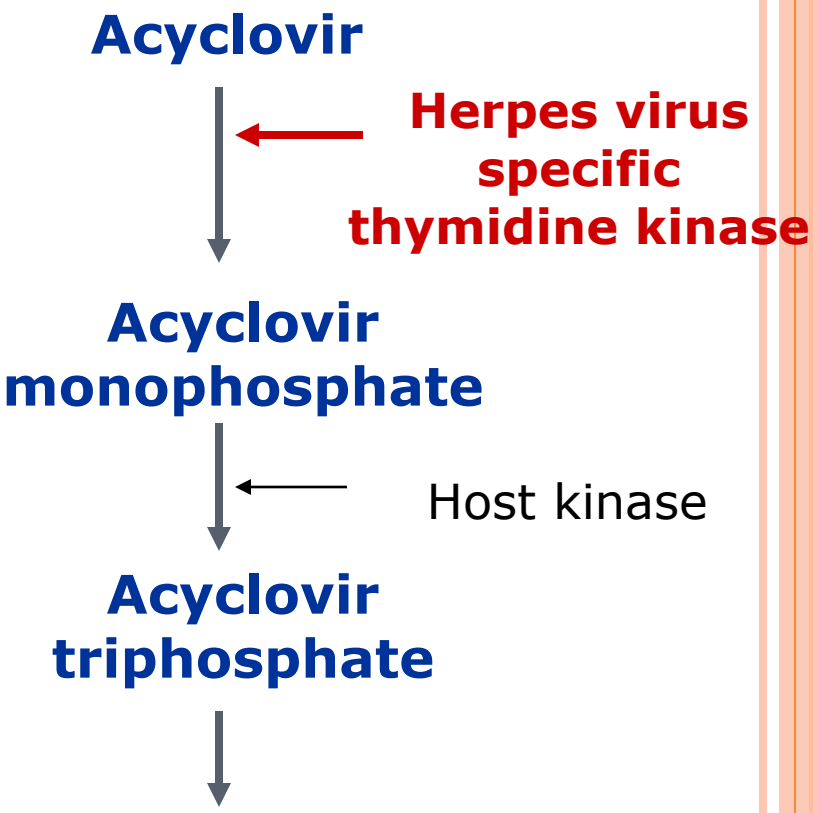
- Herpes simplex viruses (HSV)—cause repeated, blister-like lesions on the skin, genitals, mucosal surfaces.

- Some remain latent; activated by physical or emotional stress
- HSV-type 1—non genital

- HSV type 2—genital infections

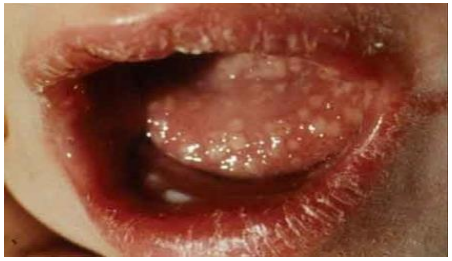
Acyclovir

- Valacyclovir is a prodrug, with better availability
- Acyclovir is Guanosine analog
- mostly taken up by the virus infected cells and has low toxicity for host cells.



1. Incorporated into DNA and terminates synthesis
2. Inhibition of herpes virus DNA polymerase

Acyclovir. Clinical Use



- Herpes simplex
- Herpes zoster
- Chickenpox
- Epstain-Barr virus

IV, oral, topical.

Can be used during pregnancy

- Adverse Reactions:
  - Well tolerated
  - Toxic effect occur in patients with renal failure.

Other Topical drugs for HSV

- Orolabial herpes
  - Penciclovir
    - similar to acyclovir
    - Application site reactions
  - Docosanol
    - Active against a broad range of lipid-envelop viruses
    - MOA: interferes with viral fusion to host cell
- HSV Keratoconjuctivitis
  - Trifluridine Active against acyclovir resistant strains
    - Also active against vaccinia virus and smallpox

Agents used to Treat Cytomegalovirus (CMV) Infections

Ganciclovir

Valganciclovir

Foscarnet

Cidofovir

Fomivirsen

- CMV infections occur in advanced immunosuppression, typically due to reactivation of latent infection.
- Dissemination results in end-organ disease: retinitis, colitis, esophagitis, CNS disease, and pneumonitis.

GANCICLOVIR

Valganciclovir (a prodrug)

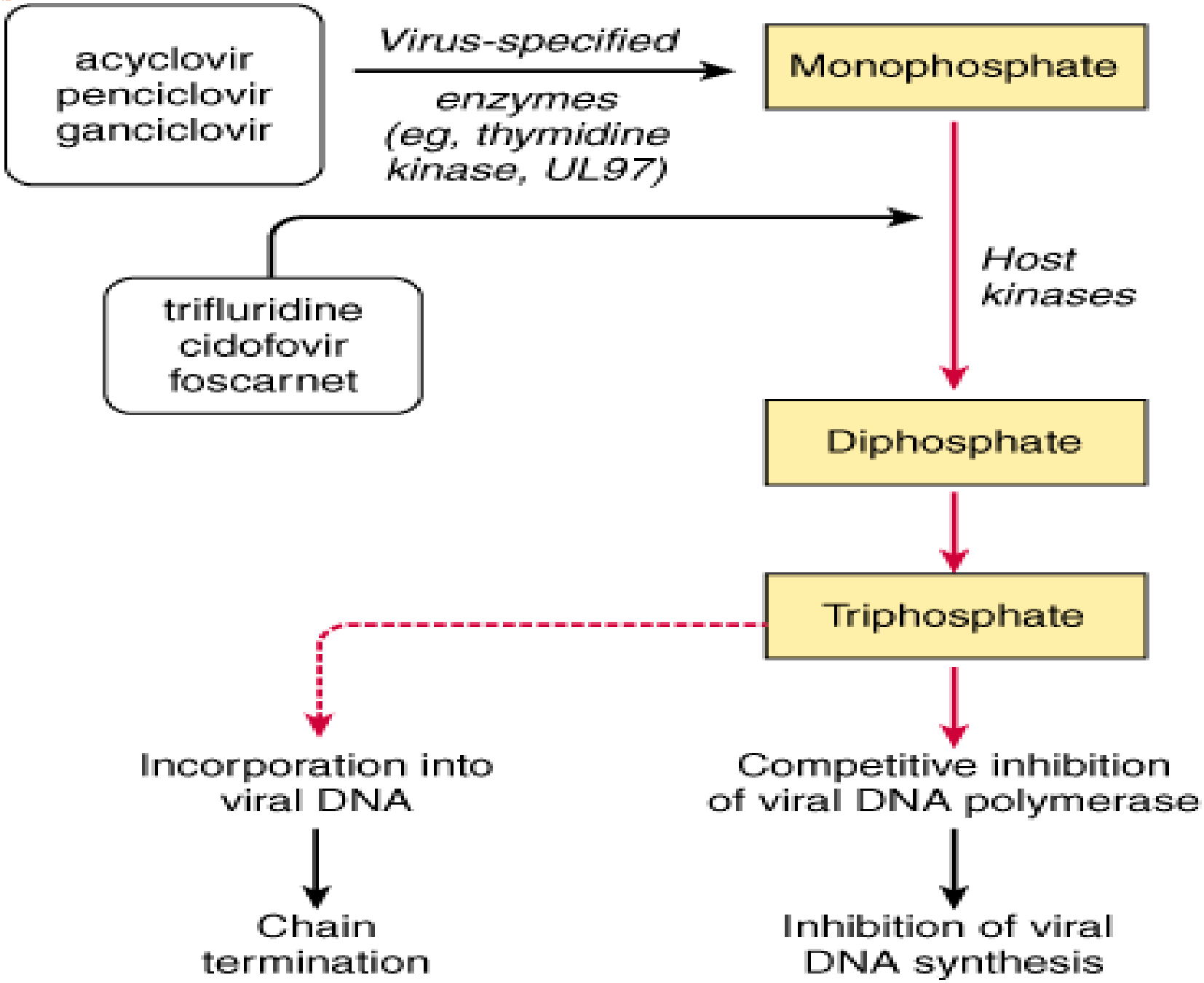
- Mechanism like Acyclovir
- Active against all Herpes viruses & CMV
- Low oral bioavailability given I.V.
- Most common A/E: bone marrow suppression (leukopenia, thrombocytopenia) and CNS effects (headache, psychosis, convulsions).
- 1/3 of patients have to stop because of adverse effects

FOSCARNET

- An inorganic pyrophosphate analog
- does not have to be phosphorylated
- Active against Herpes (I, II, Varicella , CMV), including those resistant to Acyclovir and Ganciclovir.
- IV only
- Direct inhibition of DNA polymerase and RT
- A/E: Nephrotoxicity , electrolyte abnormalities, CNS toxicity
- Foscarnet should only be given during pregnancy when benefit outweighs risk.

Cidofovir

- Incorporation into viral DNA chain results in reductions of the rate of viral DNA synthesis
- A/E: nephrotoxicity
- Must be administered with high-dose probenecid & adequate hydration


acyclovir
penciclovir
ganciclovir
Virus-specified
enzymes
(eg, thymidine
kinase, UL97)
Monophosphate
trifluridine
cidofovir
foscarnet
Host
kinases
Diphosphate
Triphosphate
Incorporation into
viral DNA
Chain
termination
Competitive inhibition
of viral DNA polymerase
Inhibition of viral
DNA synthesis

Antihepatitis Agents

Treatment of Viral Hepatitis A

- **There is no specific hepatitis A treatment.** Fortunately, the disease usually gets better on its own. Most people who get hepatitis A recover in several weeks or months.
- Persons acutely infected with HAV should avoid alcohol and other hepatotoxic medications until they have fully recovered.

Viral Hepatitis B

- **Acute hepatitis B infection does not usually require antiviral drug treatment. Early antiviral treatment may only be required in patients, with a very aggressive "fulminant hepatitis" or who are immunocompromised.**

For people with chronic hepatitis B, antiviral drug therapy used to slow down liver damage and prevent complications (cirrhosis and liver cancer).

Alpha interferon

Pegylated alpha interferon

Lamivudine

INTERFERONs

- A family of small antiviral proteins produced as earliest response of body to viral infections
- Both DNA and RNA viruses induce interferon but RNA viruses tend to induce higher levels.
- currently grouped into : IFN-α, IFN-β, and IFN-γ.
- **α** and **β** are produced by all body cells in response to various stimuli: viruses, bacteria, parasites and tumor cells
- **γ** produced by T-lymphocytes and natural killer cells, has less anti-viral activity.
-

- Administered Intralesionally, S.C, and I.V
- Distribution in all body tissues, except CNS and eye.
- Pegylated interferons are modified interferons with improved pharmacokinetic properties

Interferon Alfa

Acts by :

- Binding to membrane receptors on cell surface
- induction host cell enzymes that inhibit viral RNA translation and cause degradation of viral mRNA and tRNA
- May also inhibit viral penetration, uncoating, mRNA synthesis, and translation, and virion assembly and release

- Enhancement of phagocytic activity of macrophages,
- Augmentation of the proliferation and survival of cytotoxic T cells.

Clinical Use

- Chronic hepatitis B and C
- Herpes viruses
- Influenza viruses
- Some types of cancer: Kidney cancer, Malignant melanoma, Lymphomas, Leukemia
- AIDS-related Kaposi's sarcoma.

Side effects:

- Flu-like symptoms (within few hours after administration)
- Neurotoxicity (depression, seizures).
- Myelosuppression (neutropenia)
- elevation of hepatic enzymes.
- Mild hair loss

C/I: Hepatic failure, Autoimmune diseases, Pregnancy

OTHER TREATMENT OF HEPATITIS B VIRUS INFECTION

Competitively inhibit HBV DNA polymerase to result in chain termination after incorporation into the viral DNA.

Adefovir dipivoxil

Entecavir

Lamivudine

Telbivudine

Tenofovir

Lamivudine

- Lamivudine is a potent nucleoside analog
- Lamivudine inhibits HBV DNA polymerase and both types (1 and 2) of HIV reverse transcriptase.
- It is prodrug. It is needs to be phosphorylated to its triphosphate form before it is active.
- Clinical Use:

  Chronic hepatitis B HIV

- Adverse Effects:
  - CNS: paresthesias and peripheral neuropathies
  - Pancreatitis

Treatment of Chronic Viral Hepatitis C

- *Interferon alpha*
- *Pegylated interferon alpha*
- *Ribavirin*

Ribavirin

- Guanosine analog
- Mechanism: Phosphorylated to triphosphate by host enzymes, and inhibits RNA-dependent RNA polymerase, viral RNA synthesis, and viral replication.
- A/E: Hemolytic anemia, Conjunctival and bronchial irritation

Antiretroviral Agents

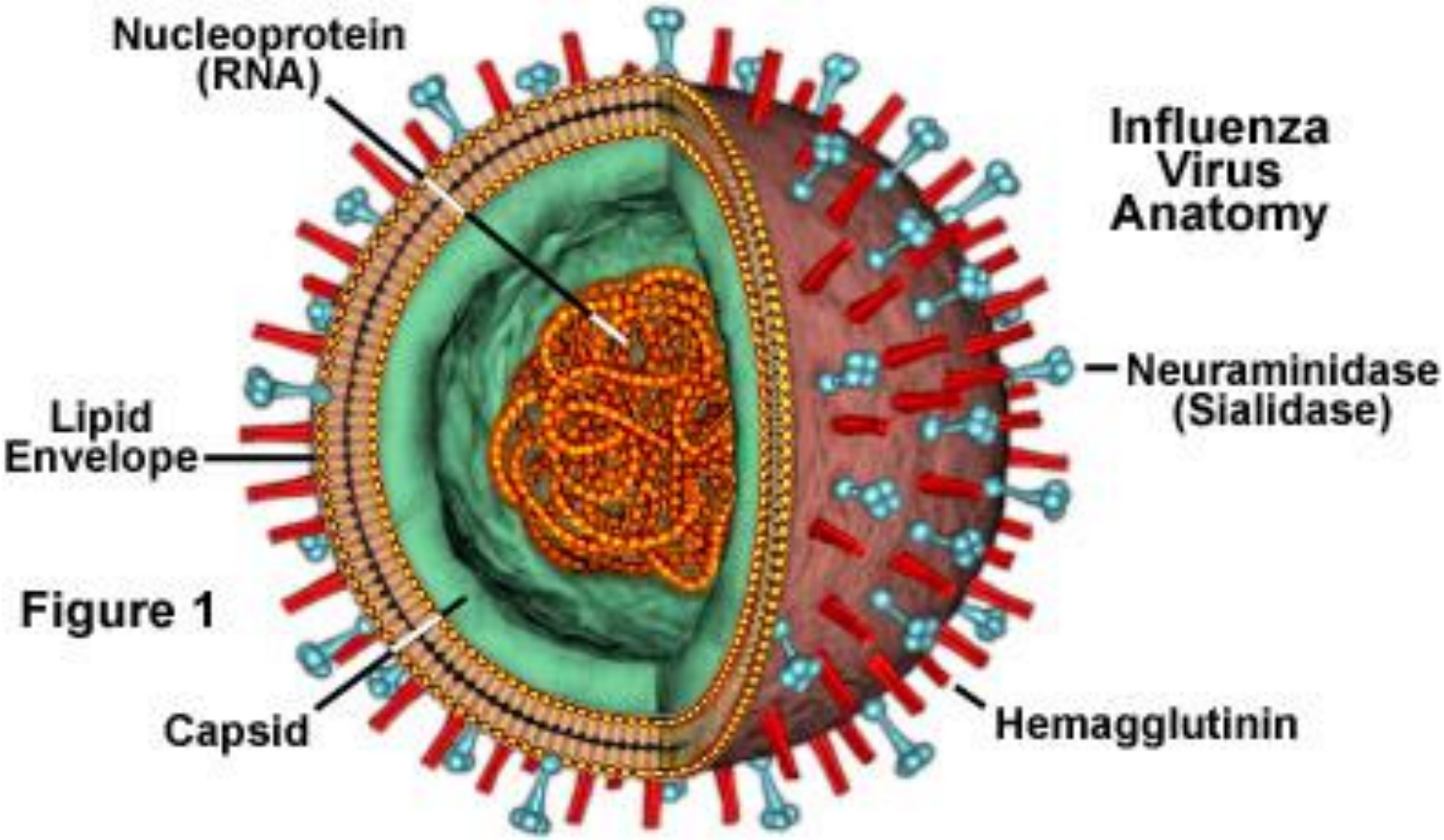
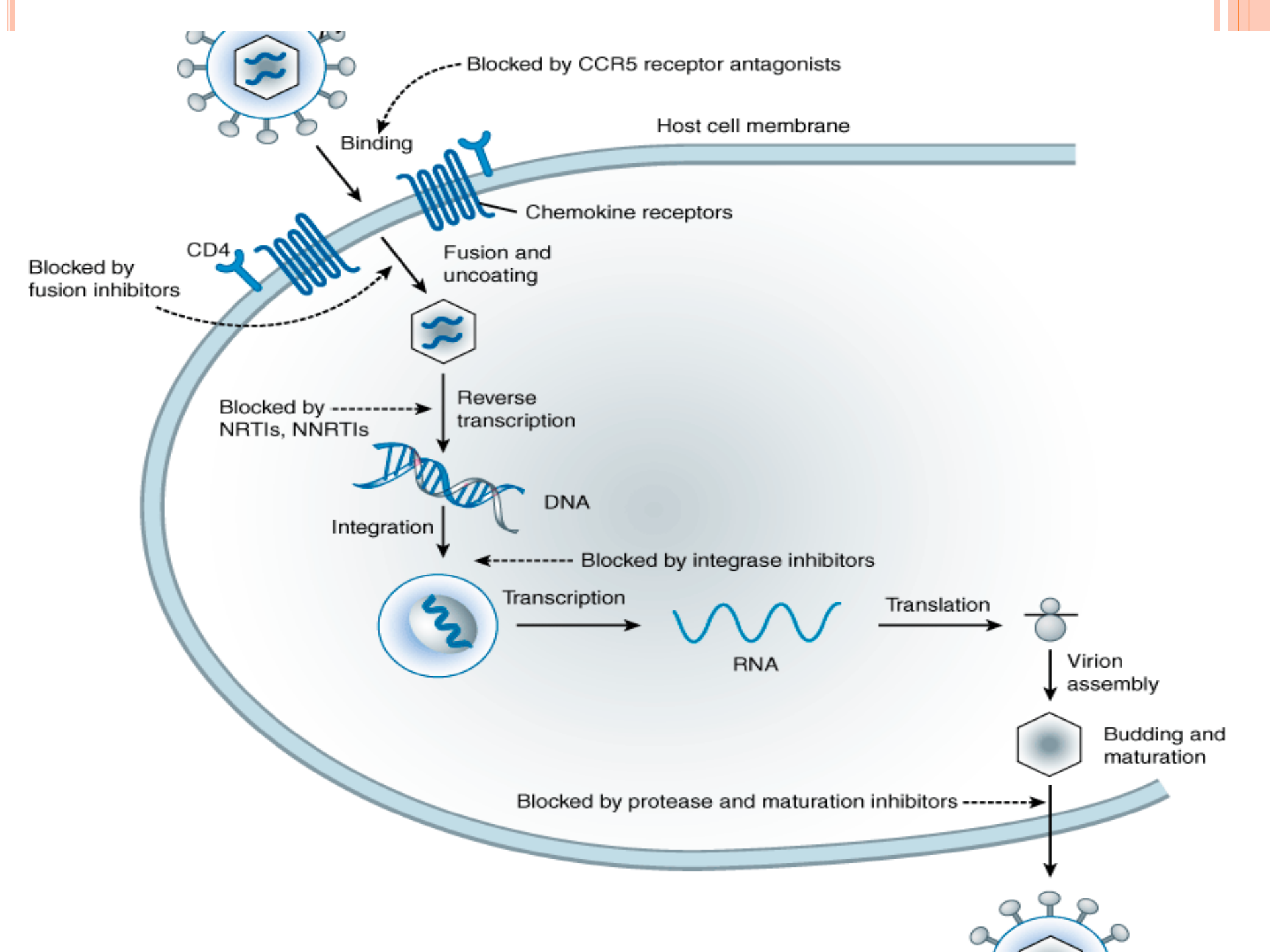


Figure 1

- **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
Host cell membrane
Binding
Chemokine receptors
CD4
Fusion and uncoating
Blocked by fusion inhibitors
Reverse transcription
Blocked by NRTIs, NNRTIs
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.


NRTI

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.

Non nucleoside Reverse Transcriptase Inhibitors (NNRTI)

- Bind directly to HIV reverse transcriptase, prevents viral RNA from conversion to the viral DNA that infects healthy cells, by causing conformational changes in the enzyme.
- The binding site of NNRTIS is near to but distinct from that of NRTIS.
- Do not require phosphorylation to be active.

Drug resistance develops quickly if NNRTIs are administered as monotherapy and therefore NNRTIs are always given as part of combination therapy, (HAART).

Delavirdine

Efavirenz

Nevirapine

NNRTI's: Adverse Effects

Side effects are worst during the first 1 to 2 weeks of therapy.

NNRTI agents are associated with varying levels of GI intolerance and skin rash.

- **elevated LFT**
- **CNS effects (e.g. sedation, insomnia, dizziness, confusion)**

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

Lopinavir

Saquinavir

Indinavir

Nelfinavir

Ritonavir

Darunavir

Fosamprenavir

Tipranavir

contain sulfonamide

PI Class Side Effects

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

Entry Inhibitors

Binds to the viral envelope glycoprotein, preventing the conformational changes required for the fusion of the viral and cellular membranes

Enfuvirtide

By subcutaneous injection

- Toxicity
  - Injection site reactions
  - Nausea, diarrhea, fatigue, hypersensitivity

CCR5 RECEPTOR ANTAGONISTS

- They are inhibitors of the human CCR5 receptor, a receptor that is found on several host defense cells (T-cells and killer cells). The act of the CCR5 antagonist binding to the CCR5 receptor is thought to alter the conformational state of the CCR5 receptor.

Maraviroc

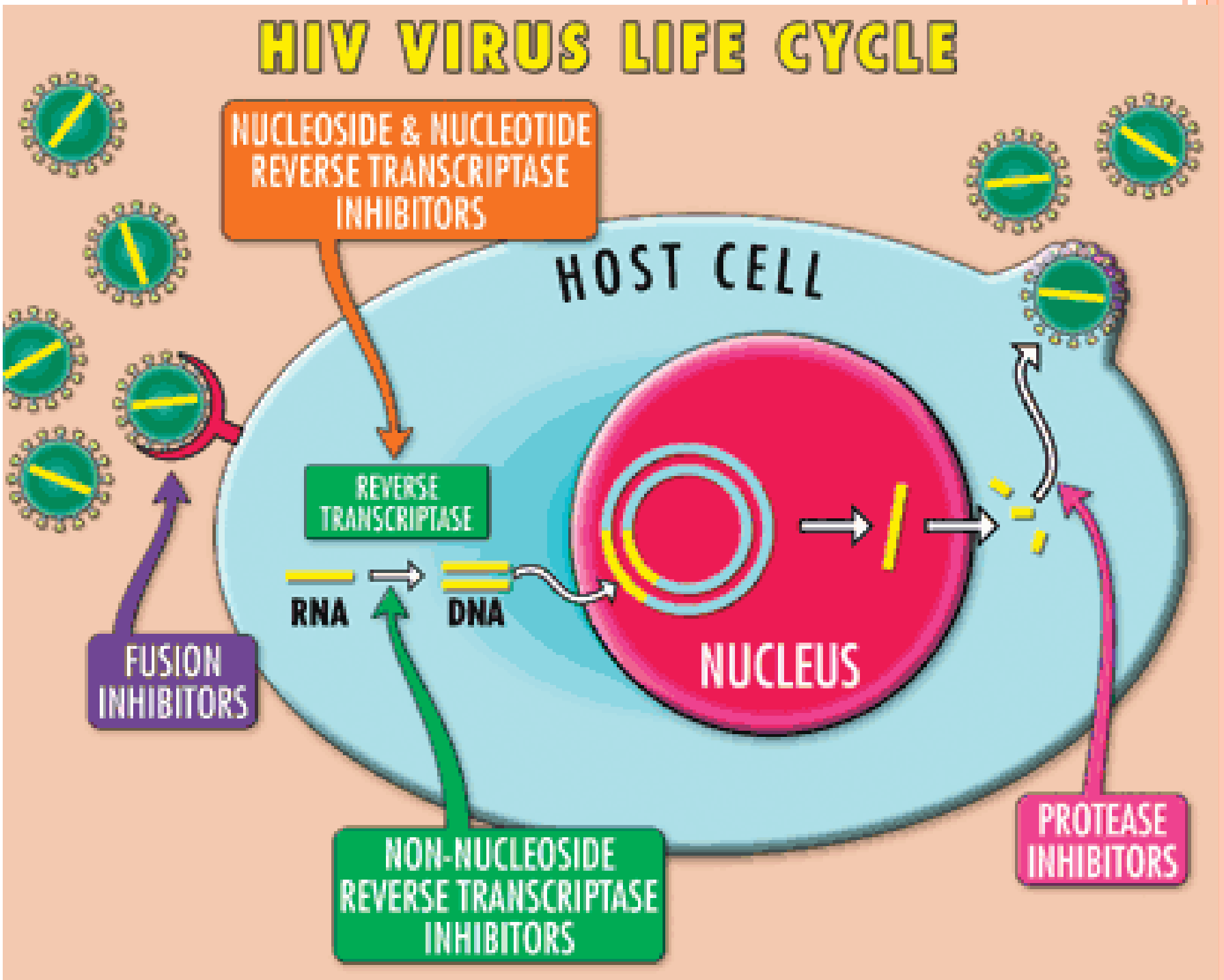
- A/E: Abdominal pain, Upper respiratory tract infections, Cough, Hepatotoxicity, Musculoskeletal symptoms, Rash

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

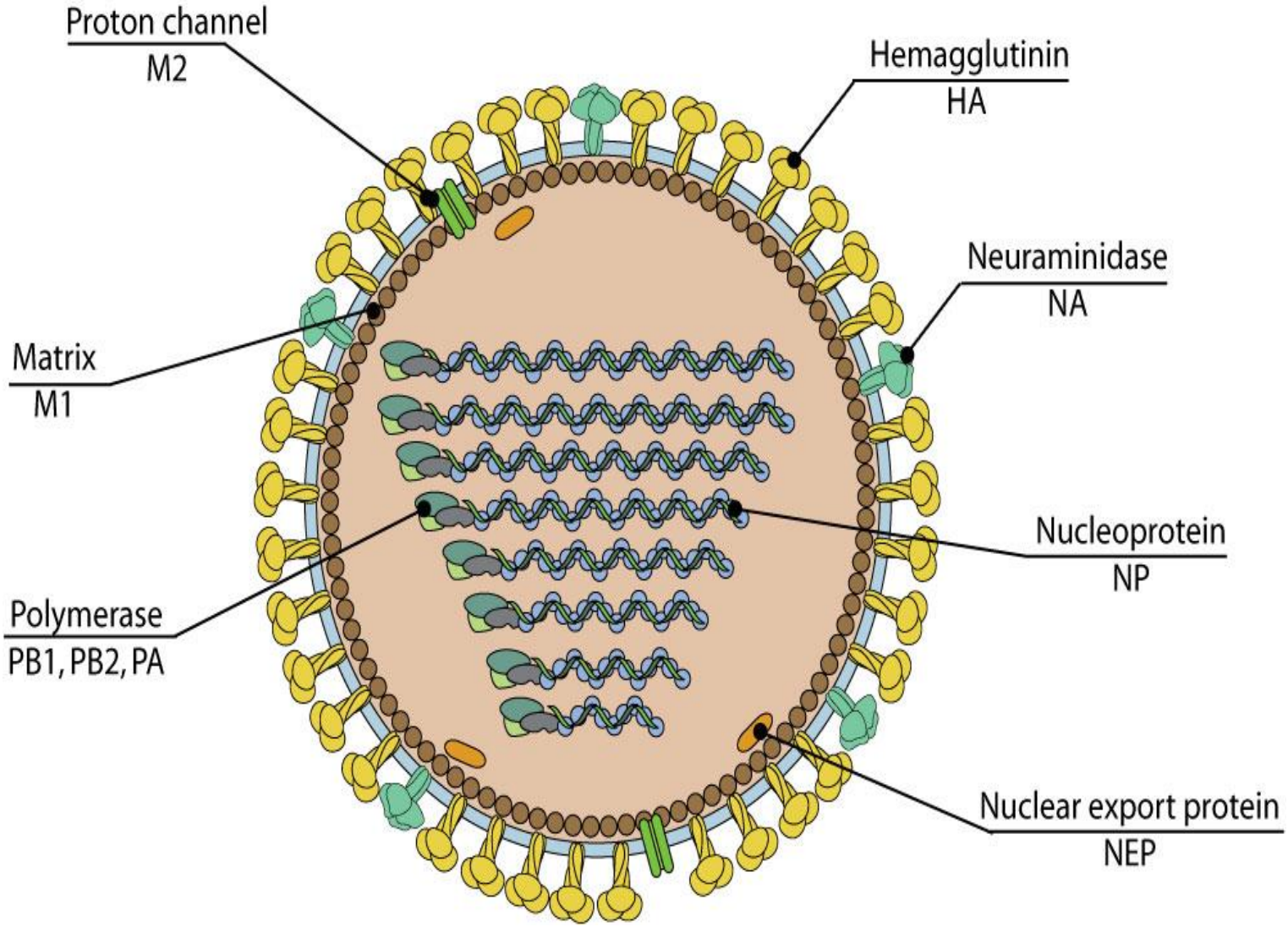

HIV VIRUS LIFE CYCLE
NUCLEOSIDE & NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS
HOST CELL
REVERSE TRANSCRIPTASE
RNA
DNA
NUCLEUS
FUSION INHIBITORS
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
PROTEASE INHIBITORS

ANTI-INFLUENZA AGENTS

- Influenza virus strains are classified by :
  - Their core proteins (i.e., A, B, or C),
  - Species of origin (eg, avian, swine),
  - Geographic site of isolation.

Influenza A

- Is the only strain that causes pandemics.
- Is classified into 16 H (hemagglutinin) and 9 N (neuraminidase) known subtypes based on surface proteins.
- Can infect a variety of animal hosts.
- Avian influenza subtypes are highly species-specific, but they can also on rare occasions crossed the species barrier to infect humans and cats.


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

- Viruses of the H5 and H7 subtypes (eg, H5N1, H7N7, and H7N3) may:
  - Rapidly mutate within poultry
  - Have recently expanded their host range to cause both avian and human disease.

H5N1 virus

- First caused human infection (including severe disease and death) in 1997 and has become endemic in some areas since 2003. It is feared that the virus will become transmissible from person to person rather than solely from poultry to human.

Classes of Influenza Antiviral Drugs

M2 ion channel inhibitors

Amantadine

Rimantadine

Neuraminidase inhibitors

Oseltamivir

Zanamivir

Amantadine & Rimantadine

- Block the M2 ion channel of the virus particle and inhibit Uncoating of the viral RNA within infected host cells, thus preventing its replication.
- Activity: influenza A only.
- Rimantadine is 4 to 10 times more active than amantadine in vitro.
- A/E

GI disturbance, nervousness, insomnia.

- The marked increase in the prevalence of resistance to both agents in clinical isolates over the last decade, in influenza A H1N1 as well as H3N2, has limited the usefulness of these agents for either the treatment or the prevention of influenza.

Oseltamivir & Zanamivir

- Neuraminidase inhibitors, 1999
- Chemically related, but have different routes of administration

- Interfere with release of influenza virus from infected to new host cells.
- Competitively and reversibly interact with the active enzyme site to inhibit neuraminidase activity and destroy the receptors found on normal host cells recognized by viral hemagglutinin.

- Activity: both influenza A and influenza B viruses.
- Early administration is crucial because replication of influenza virus peaks at 24–72 hours after the onset of illness.
- Oseltamivir is FDA-approved for patients 1 year and older, whereas zanamivir is approved in patients 7 years or older.

Oseltamivir

- Administered orally
- Prodrug that is activated by hepatic esterases
- Widely distributed throughout the body.
- A/E: N/V/D, Abd. Pain, Headache, Fatigue, Rash.
- Rates of resistance to oseltamivir among H1N1 viruses have risen abruptly and dramatically worldwide. It may be associated with point mutations in the viral hemagglutinin or neuraminidase genes.

Zanamivir

- Administered by inhalation.
- 10 to 20 % of the active compound reaches the lungs, and the remainder is deposited in the oropharynx.
- A/E: cough, bronchospasm, reversible decrease in pulmonary function, and transient nasal and throat discomfort.

Resistance

Resistance to any antiviral drug must be anticipated :

- **viruses replicate so efficiently**
- **have modest to high mutation frequencies**

THANKS