# ANTIVIRAL AGENTS

- 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 bodys immune system
- Other viruses cause serious and even fatal disease & require aggressive therapy

# Principles of antiviral therapy

- **Viruses are obligate intracellular parasites**
- They do not have a metabolic machinery of their own – use host enzymes
- Difficulty in obtaining **selective toxicity** against viruses

# 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

- **Antiviral therapy is challenging:**

1. Rapid **replication** of viruses makes it difficult to develop effective antiviral
2. Viruses can rapidly **mutate – drug resistant viral mutants**
3. They are active only against replicating viruses and **do not affect latent virus**

# Structure of viruses

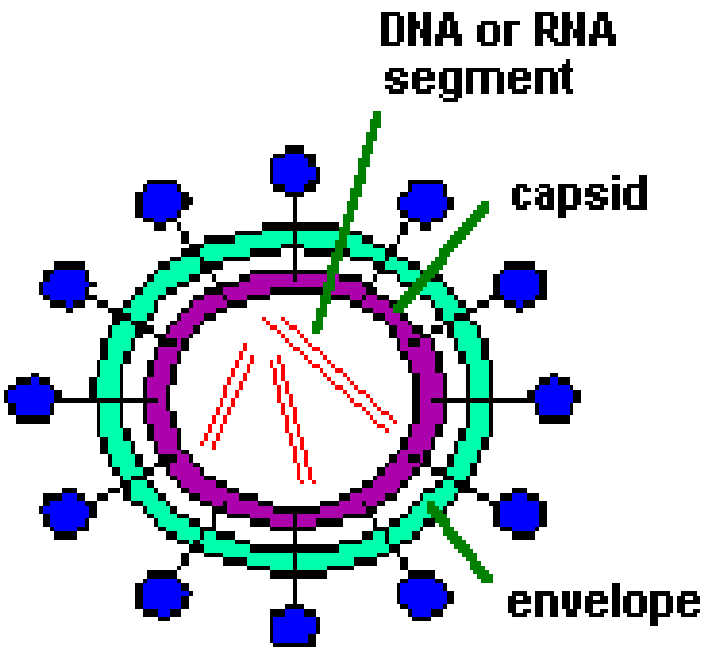



Diagram of a Virion

Virus particles (virions) consist of following parts:

Nucleic acid core:

- DNA or RNA

Contain virus-specific enzymes

Surrounded by “capsid”

An outer lipid “envelope”

# The Life Cycle of Viruses

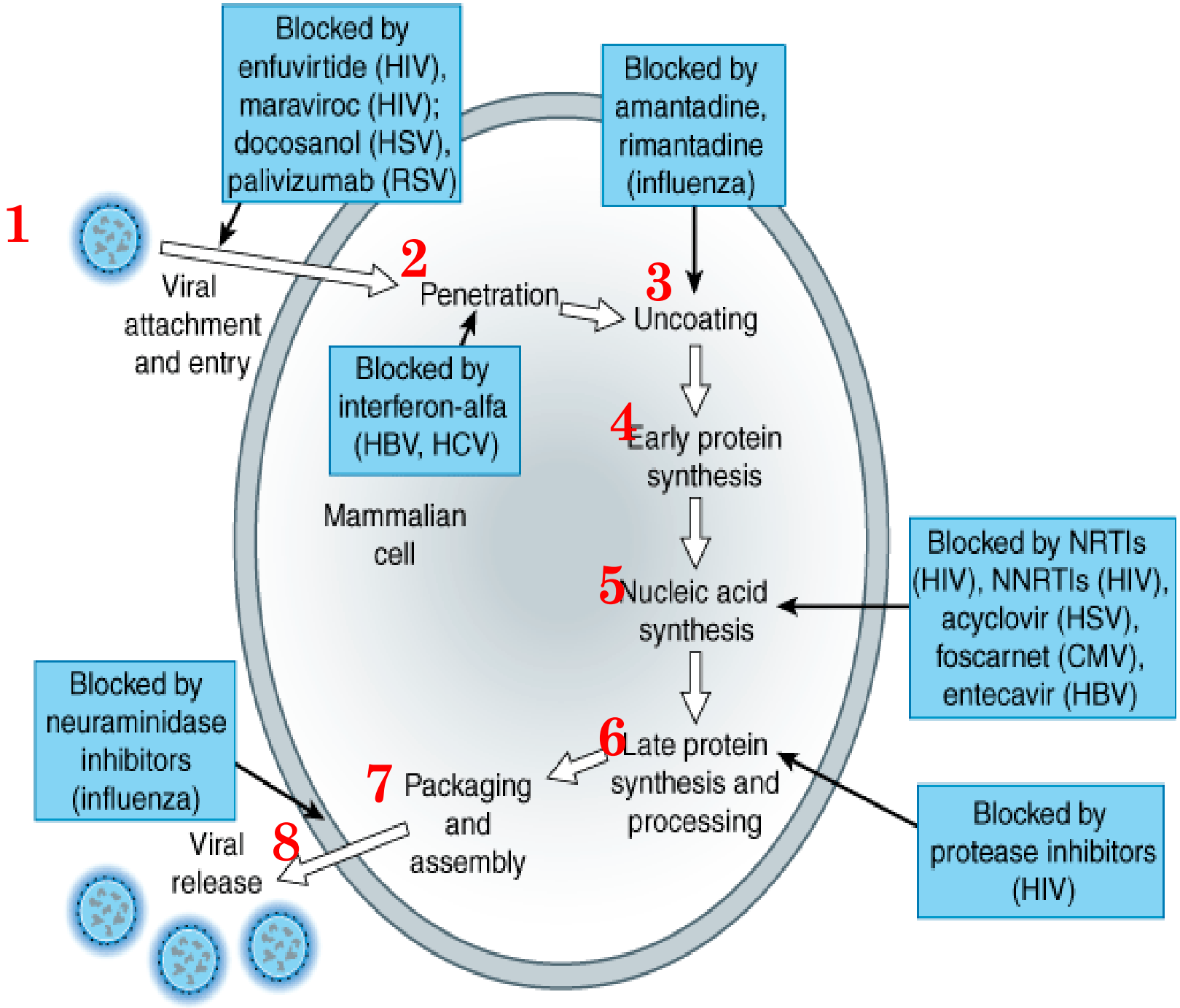
1. **Attachment** of the virus to receptors on cell surface
2. **Entry** of the virus through the host cell membrane
3. **Uncoating** of viral nucleic acid
4. **Replication**

   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
Viral attachment and entry
Penetration
3
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)

- Antiviral drugs work by:

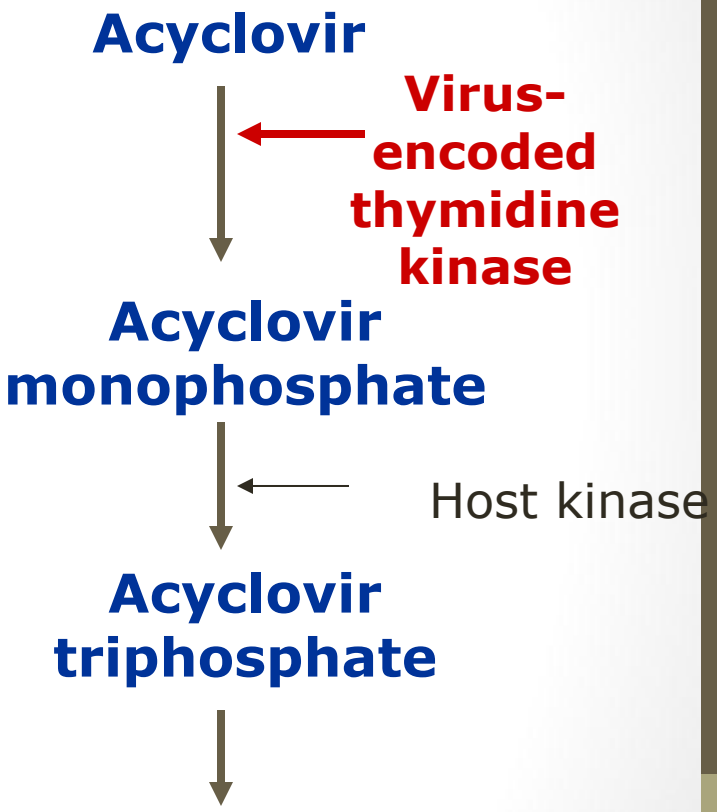
1. Altering the cells genetic material so that the virus cannot use it to multiply, i.e. acyclovir (inhibiting Viral enzymes, Host expression of viral proteins & Assembly of viral proteins)

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

# Inhibition of Viral Nucleic acid

# Acyclovir

- Acyclovir is a Guanosine analogue
- Active primarily against HSV1,2 and VZV
- No activity against CMV
- Valacyclovir is a prodrug, with better availability
- 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

# Other Topical drugs for HSV

- **Penciclovir**
  - Similar to acyclovir
  - Treatment of recurrent orolabial herpes simplex
- **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

# Ganciclovir

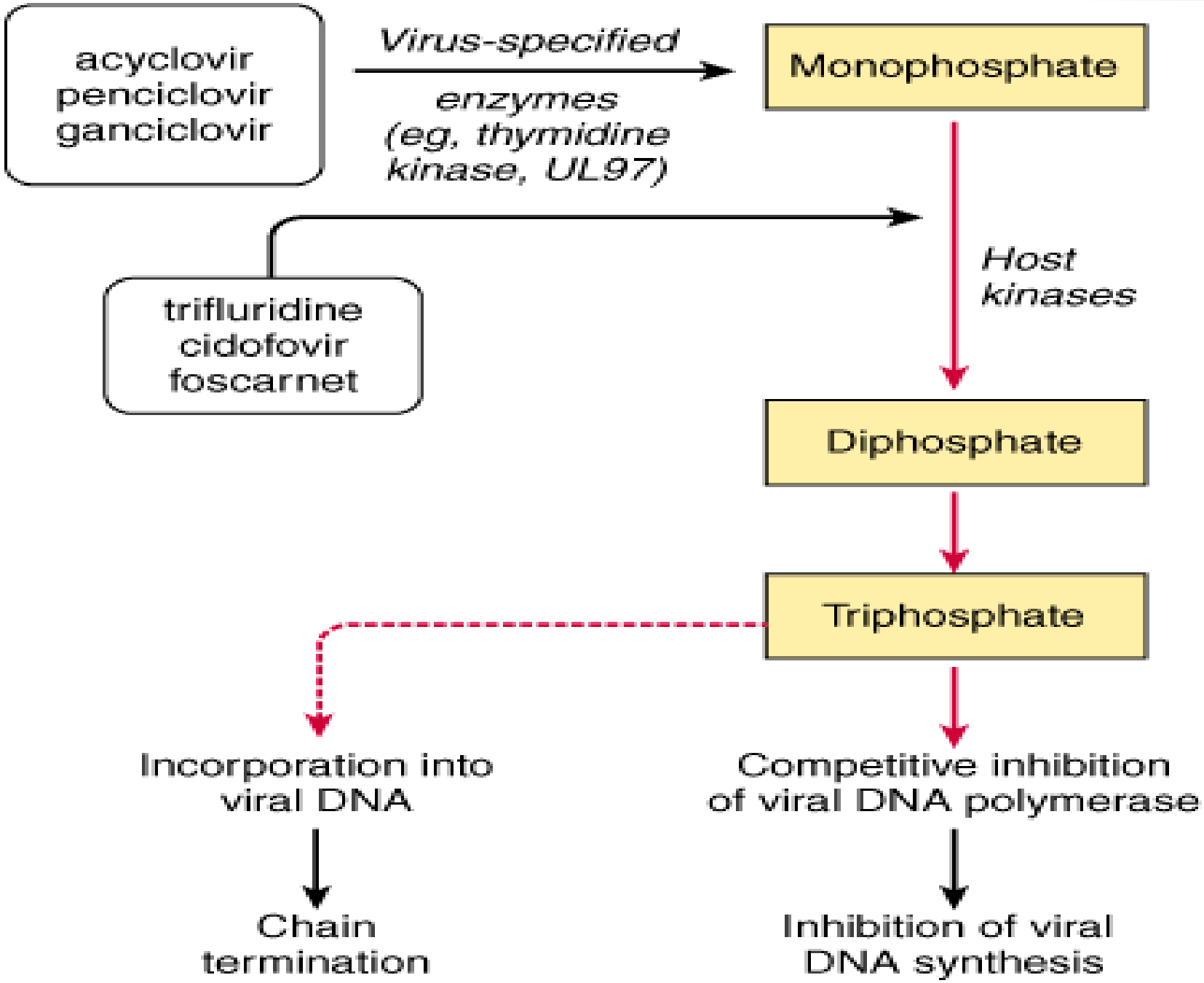
- Mechanism like Acyclovir
- Active against all Herpes viruses & CMV
- Activated by a CMV-encoded phosphokinase
- Low oral bioavailability given I.V.
- Most common adverse reaction: bone marrow suppression (leukopenia, thrombocytopenia ) and CNS effects (headache, psychosis, convulsions).
- 1/3 of patients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

# Cidofovir

- A nucleoside analogue of cytosine
- 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

# Foscarnet

- A non-nucleoside inhibitor
- An inorganic pyrophosphate analogue
- 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
- A/E: Nephrotoxicity , electrolyte abnormalities, CNS toxicity
- Foscarnet should only be given during pregnancy when benefit outweighs risk


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

# *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
- 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

# *Lamivudine*

- A potent nucleoside analogue
- Inhibits HBV DNA polymerase and both types (1 and 2) of HIV reverse transcriptase
- It is prodrug-needs to be phosphorylated
- Adverse Effects:
  - CNS: paresthesias and peripheral neuropathies
  - Pancreatitis
  - neutropenia

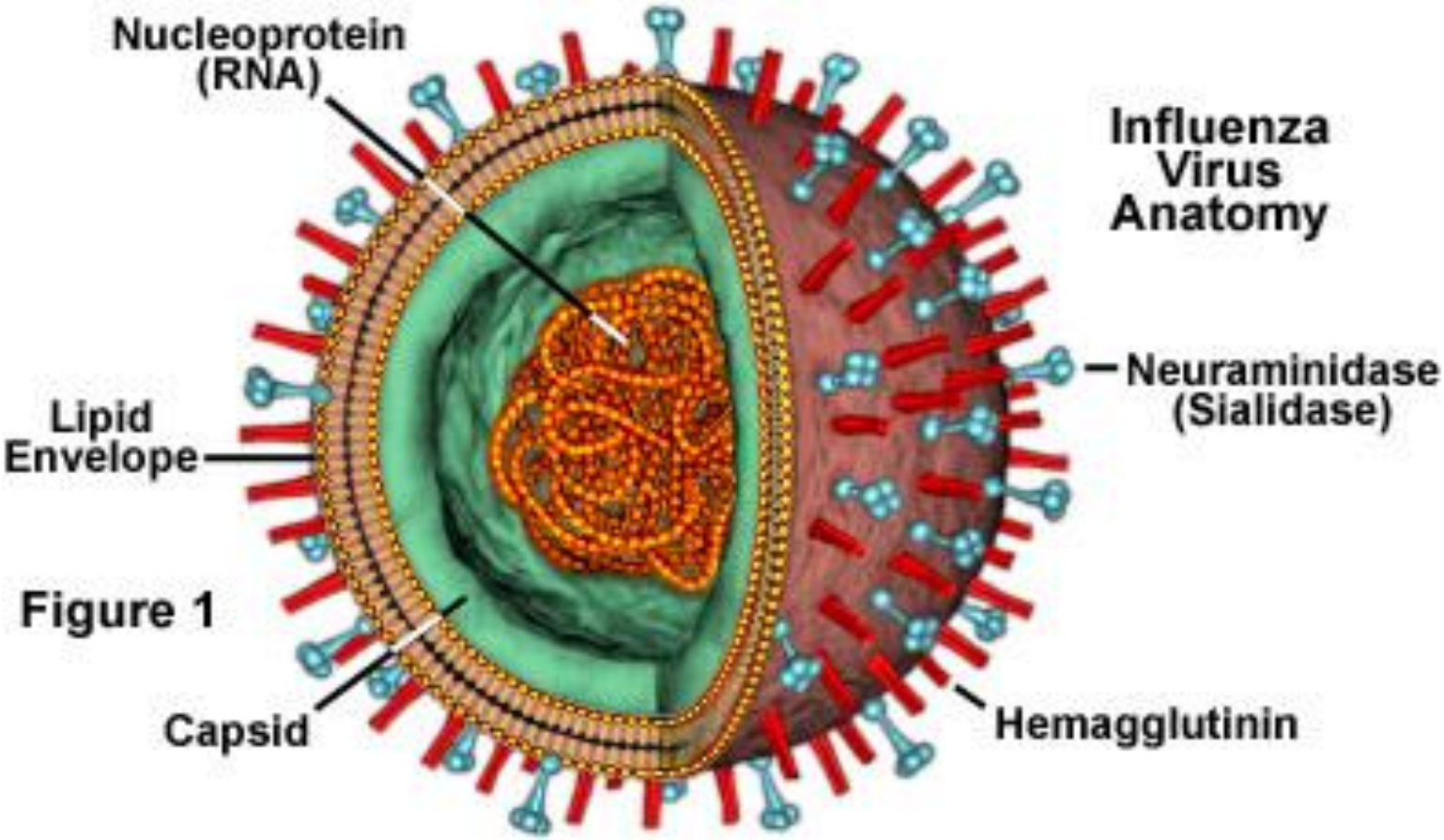
# *Treatment of Chronic Viral Hepatitis C*

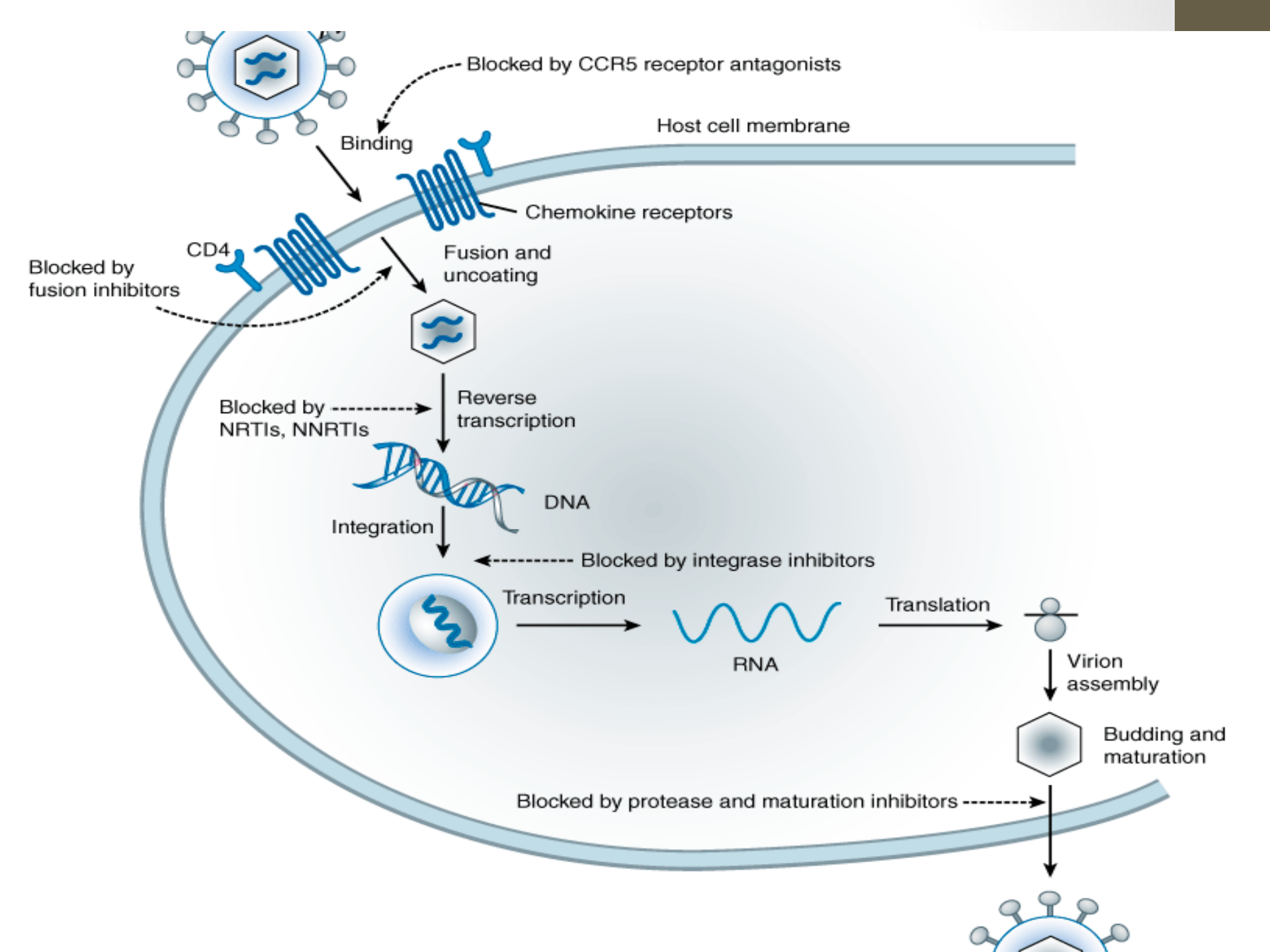
- ***Interferon alpha***
- ***Pegylated interferon alpha***
- ***Ribavirin***

# Ribavirin

- Guanosine analogue
- Mechanism: Phosphorylated to triphosphate by host enzymes
- Inhibits RNA-dependent RNA polymerase, viral RNA synthesis, and viral replication
- Ribavirin aerosol is used clinically to treat pneumonitis caused by RSV in infants
- A/E: Hemolytic anemia, Conjunctival and bronchial irritation

# Antiretroviral Agents




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

**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. **Entry 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

# Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

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

Act by competitive inhibition of HIV reverse transcriptase


All NRTIs may be associated with

mitochondrial toxicity, lactic acidosis with fatty liver

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
- Binding site of NNRTIS is near to but distinct from that of NRTIS
- **Do not** require phosphorylation to be active

# 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

- **A/E:**
- **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

- Inhibitors of the human CCR5 receptor
- 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 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**

# ANTI-INFLUENZA AGENTS

# Classes of Influenza Antiviral Drugs

## M2 ion channel inhibitors

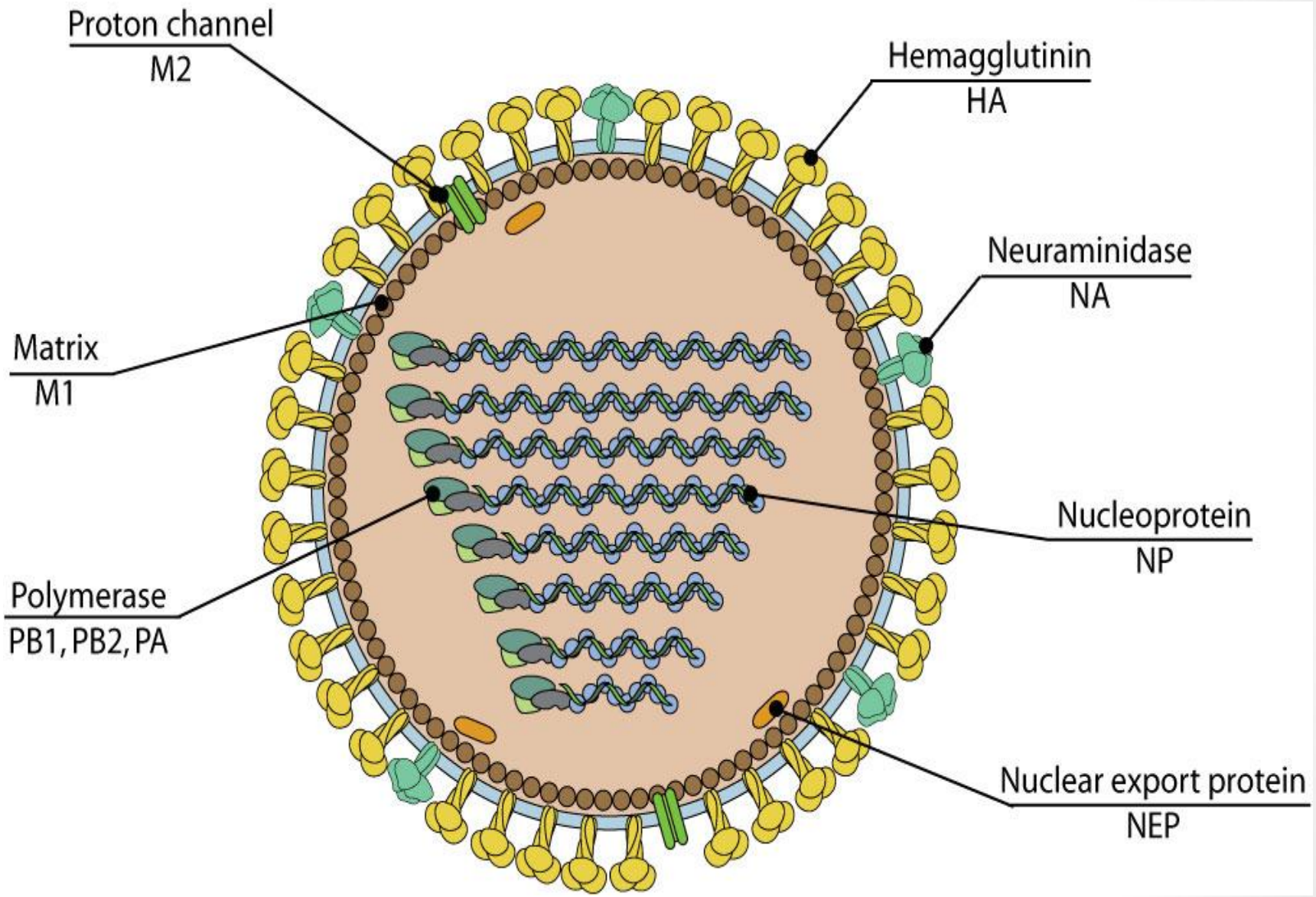
**Amantadine**

**Rimantadine**

## Neuraminidase inhibitors

**Oseltamivir**

**Zanamivir**


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

# 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.

- 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.

# 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.

# 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.