Antivirals

Pharmacology 3

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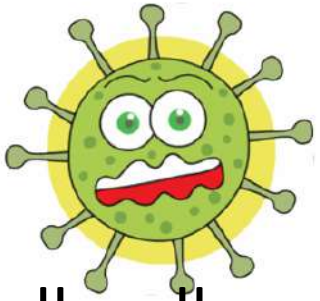
Overview

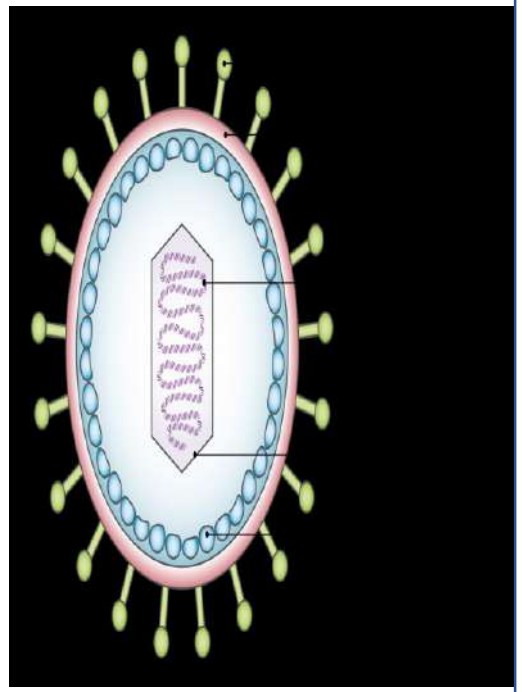


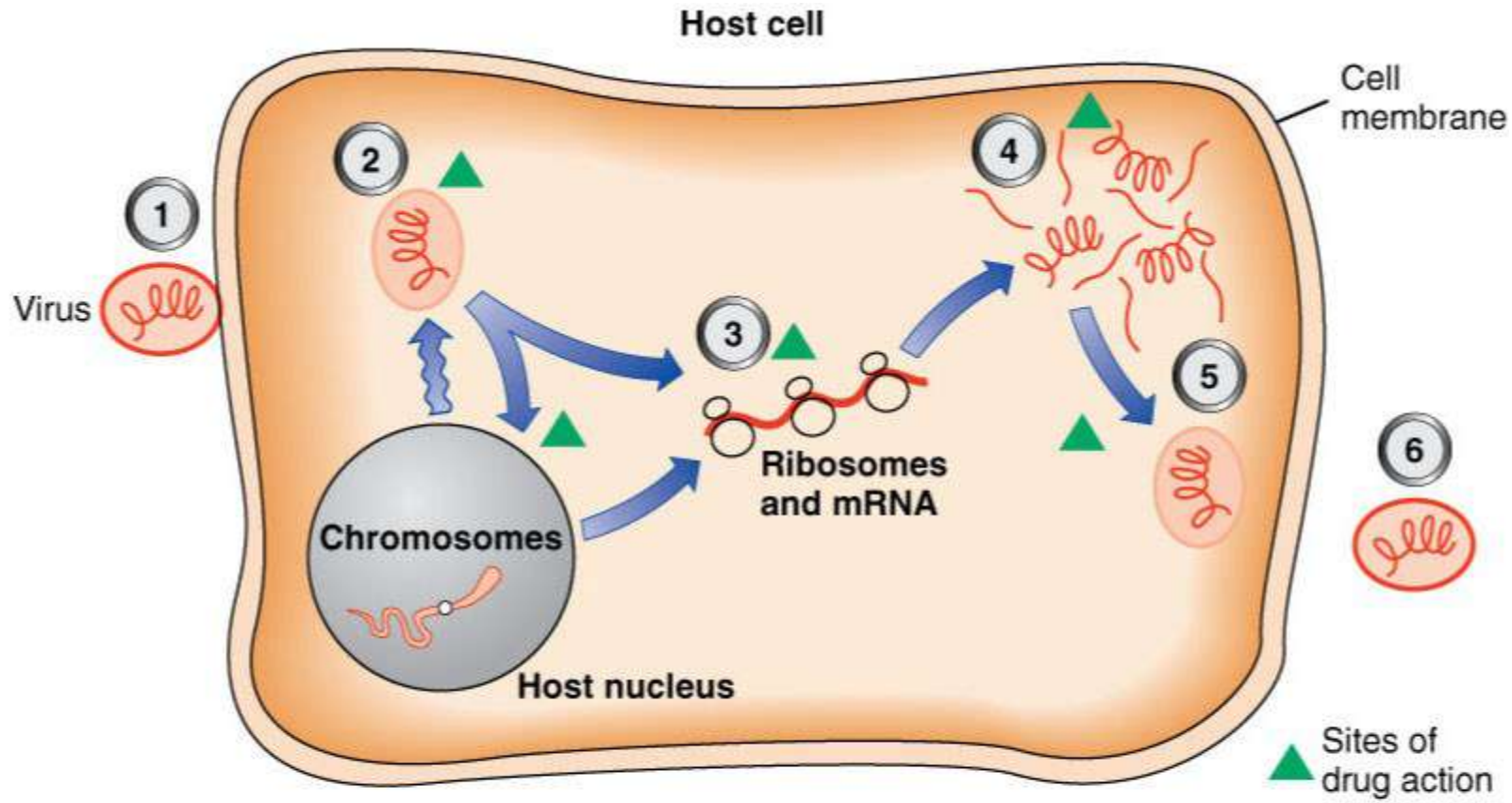
- Viruses are obligate intracellular parasites. They lack both a cell wall and a cell membrane, and they do not carry out metabolic processes.

- A virus cannot replicate on its own

- It must attach to and enter a host cell

- It then uses the host cell's energy to synthesize protein, DNA, and RNA





1. Attachment to host cell
2. Uncoating of virus, and entry of viral nucleic acid into host cell nucleus
3. Control of DNA, RNA, and/or protein production
4. Production of viral subunits
5. Assembly of virions
6. Release of virions

(Modified from Brody TM, Larner J, Minneman KP: Human pharmacology: molecular to clinical, *ed 3, St Louis, 1998, Mosby.)*

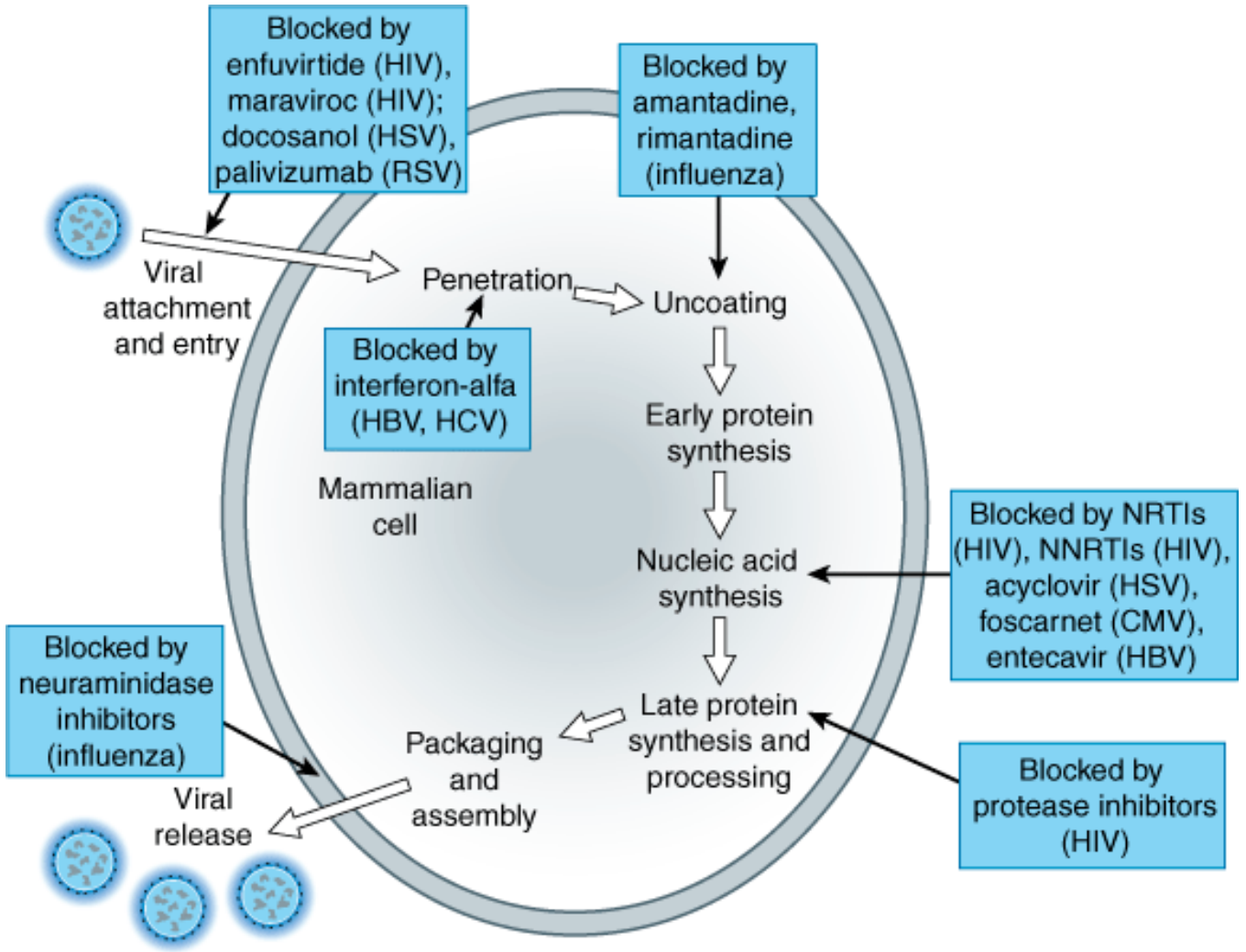
Fig. 39-1. Virus replication. Some viruses integrate into host chromosome with development of latency.

- **Stages of viral replication**

(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) synthesis of early regulatory proteins, eg, nucleic acid polymerases.
(5) synthesis of new viral RNA or DNA
(6) integration into the nuclear genome
(7) synthesis of late, structural proteins
(8) assembly(maturation) of viral particles.
(9) release from the cell.

Antiviral agents can potentially target any of these steps.

The major sites of antiviral drug action.



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

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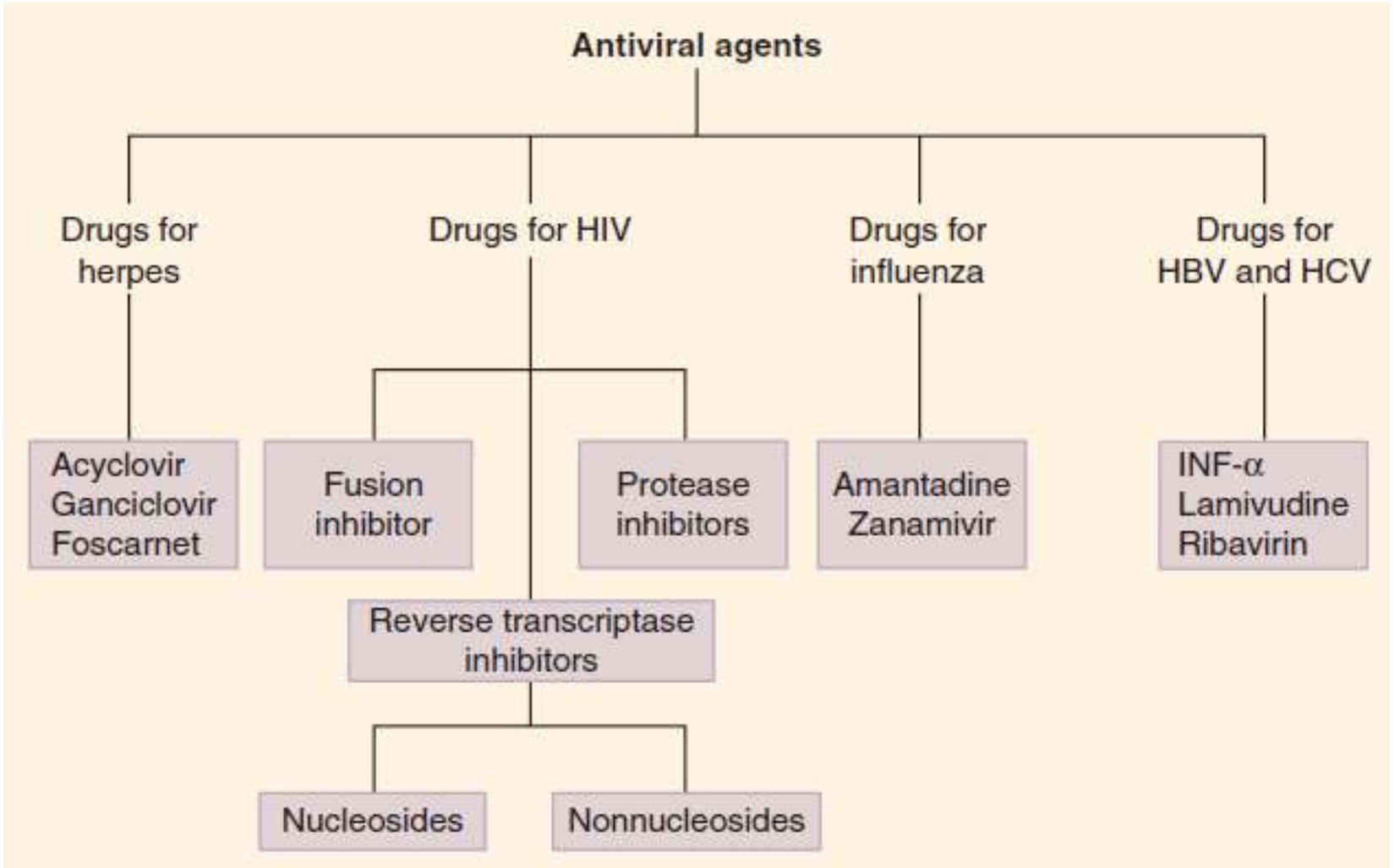

Antiviral agents
Drugs for herpes
Drugs for HIV
Drugs for influenza
Drugs for HBV and HCV
Acyclovir
Ganciclovir
Foscarnet
Fusion inhibitor
Protease inhibitors
Amantadine
Zanamivir
INF-α
Lamivudine
Ribavirin
Reverse transcriptase inhibitors
Nucleosides
Nonnucleosides

Key characteristics of antiviral drugs

- **Able to enter the cells infected with virus.**
- **Interfere with** viral nucleic acid **synthesis and/or regulation.**
- Some drugs **interfere with ability of virus to bind to cells.**
- Some drugs **stimulate the body's immune system.**

- **Best responses** to antiviral drugs are in **patients with competent immune systems.**

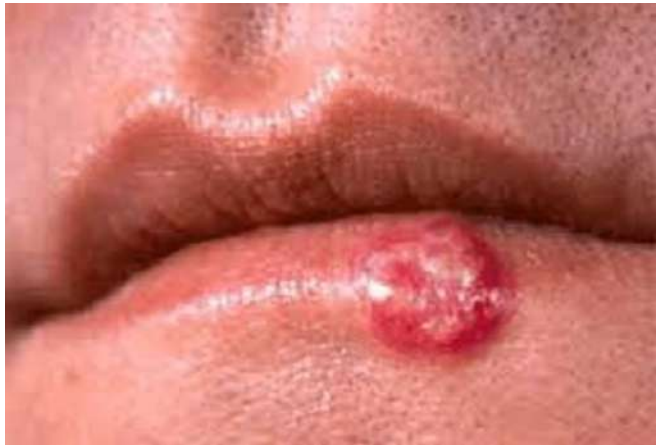
- A **healthy immune system works synergistically with the drug** to eliminate or suppress viral activity.

Herpes virus Infections

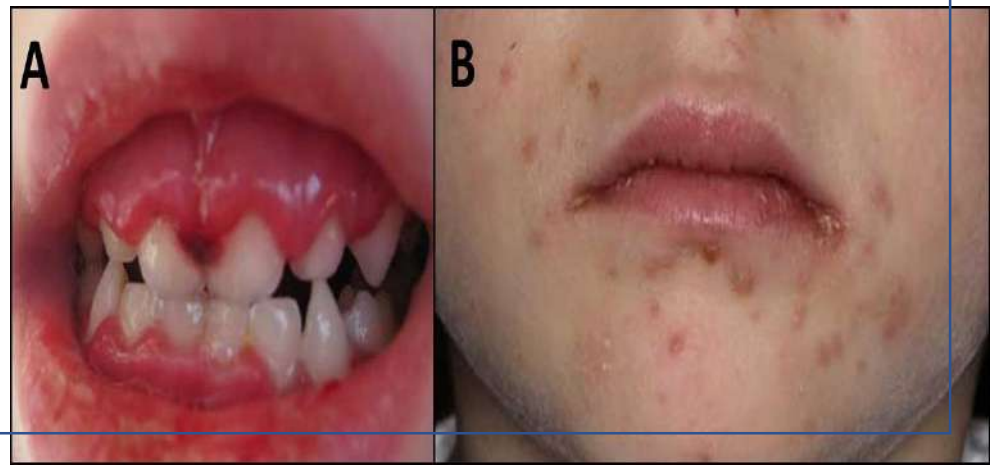
Herpes viruses:

- Varicella-zoster viruse (VZV) :chicken pox جدري الماء and shingles
- HSV-1 cause oral herpes (which can include symptoms known as "cold sores").
- HSV-2 is a sexually transmitted infection that causes genital herpes.
- Cytomegalovirus (CMV)

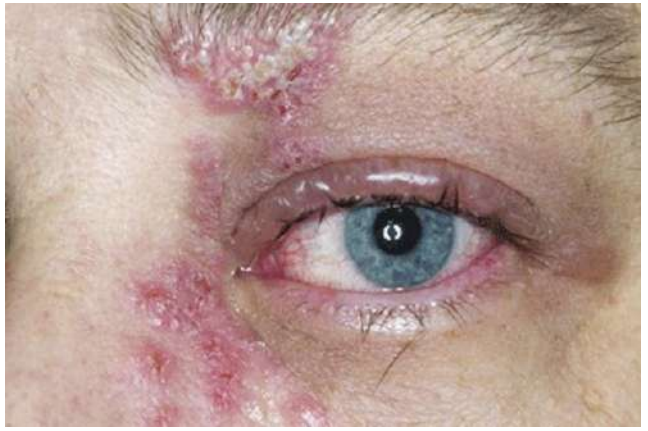
Recurrent Herpes Simplex Labialis

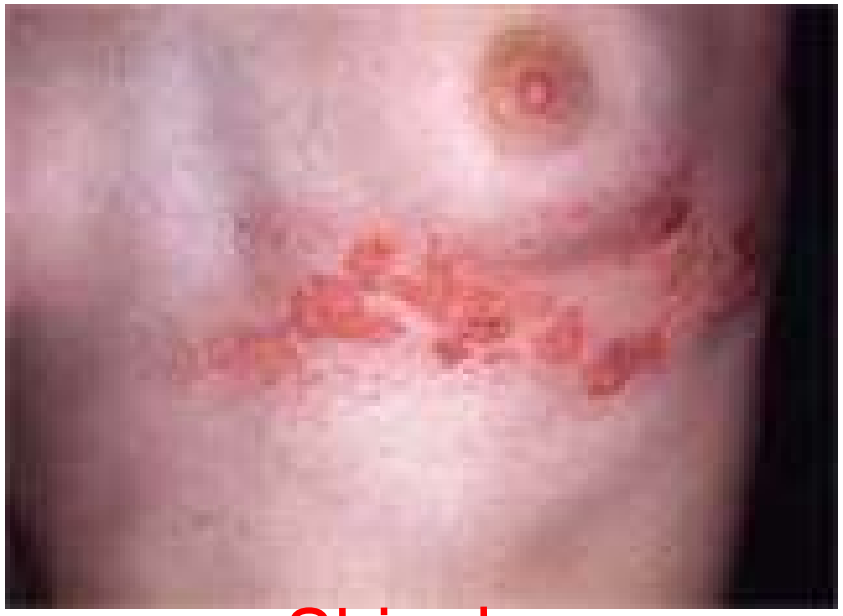


Acute primary herpetic gingivostomatitis (APHG).



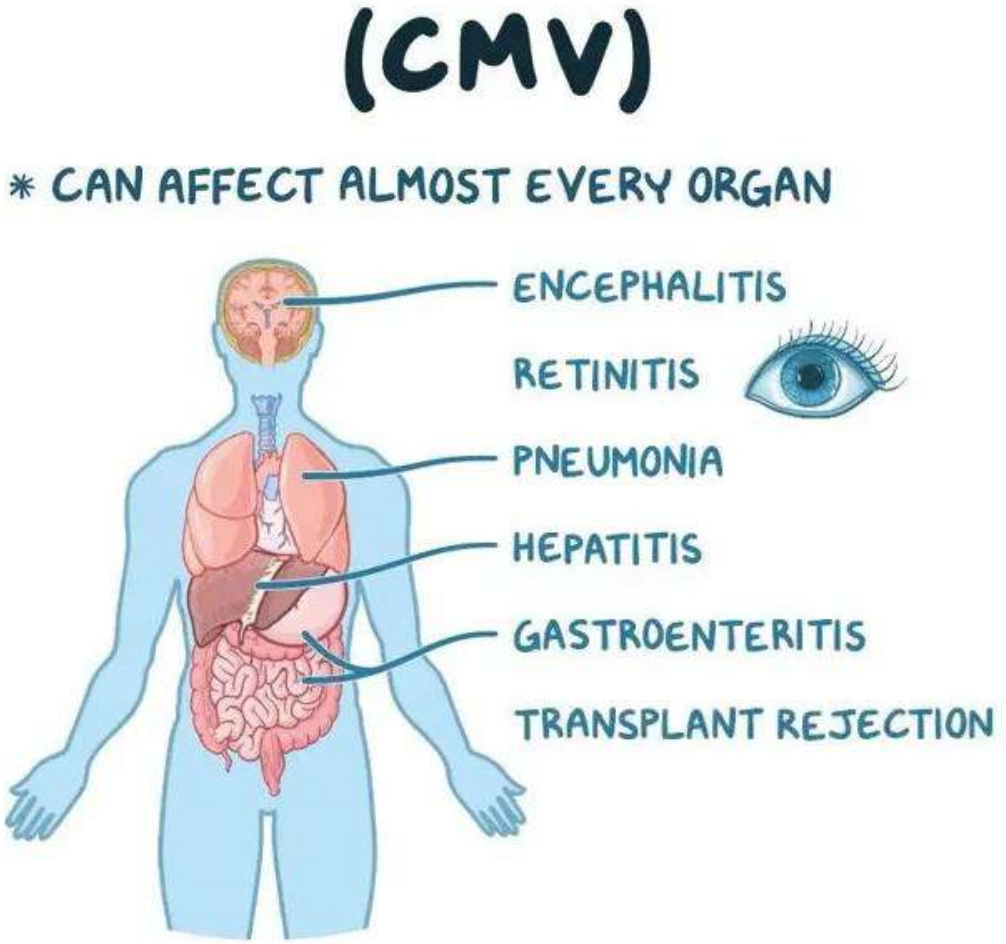
Ophthalmic shingles





Shingles

Chickenpox



TREATMENT OF HERPESVIRUS INFECTIONS

➢Acyclovir

- is the prototypic antiherpetic therapeutic agent .
- acyclovir stops the replication of herpes viral DNA (Inhibits DNA polymerase).
- **HSV types 1 & 2, VZV** & some Epstein-Barr virus infections are sensitive to acyclovir.
- Acyclovir is used to treat infections caused by herpes viruses, such as genital herpes, cold sores, shingles, and chickenpox.

- The most common use of acyclovir is in therapy for genital herpes infections.

Acyclovir is administered by IV, oral, or topical routes.

- High doses effective for adults (shingles) herpes zoster and children (chickenpox) **if begun within 24 hours of rash.**
- Intravenous acyclovir is the treatment of choice for:

1. Herpes simplex encephalitis
2. Neonatal HSV infection
3. Serious HSV or VZV infections
4. In immunocompromised patients with VZV infection, intravenous acyclovir reduces the incidence of cutaneous and visceral dissemination.

- ADEs depends on the route of administration:
  - **Oral administration:** NVD and headache
  - **Topical administration:** local irritation

TREATMENT OF HERPESVIRUS INFECTIONS

➢Ganciclovir : is an analog of acyclovir that has **greater activity against CMV.**

- It is used for:

1. the treatment CMV retinitis in immunocompromised patients
2. CMV prophylaxis in transplant patients.

- Ganciclovir is carcinogenic as well as embryotoxic and teratogenic in experimental animals

TREATMENT OF RESPIRATORY VIRAL INFECTIONS

- **Viral respiratory tract infections** for which treatments exist include those of:

1. influenza A and B
2. respiratory syncytial virus (RSV) (Respiratory syncytial virus (RSV) causes infection of the lungs and respiratory tract. It's so common that most children have been infected with the virus by age 2. it can also infect adults)

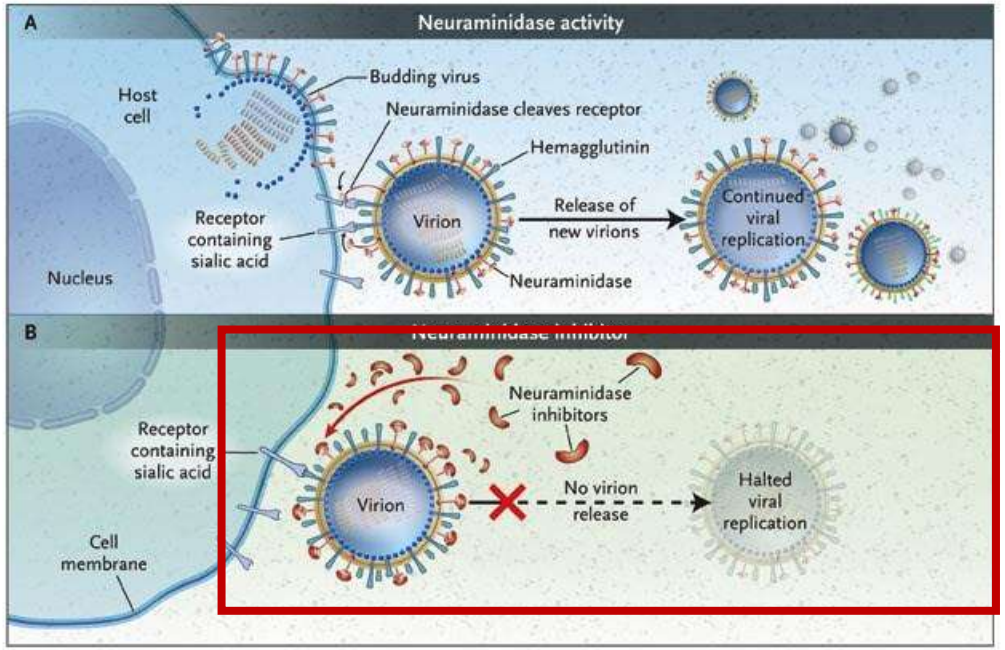
- **Influenza is caused by RNA viruses.**

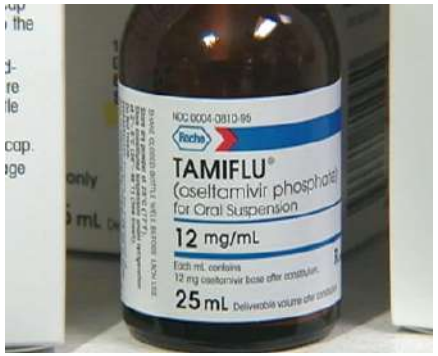
- **Influenza virus strains are classified** by their core proteins (ie, A, B, or C), species of origin (eg, avian, swine), and geographic site of isolation

TREATMENT OF RESPIRATORY VIRAL INFECTIONS

Sialic acid analogues
Agents: **Oseltamivir** & **Zanamivir**
Active against both **type A & Type B influenza viruses**

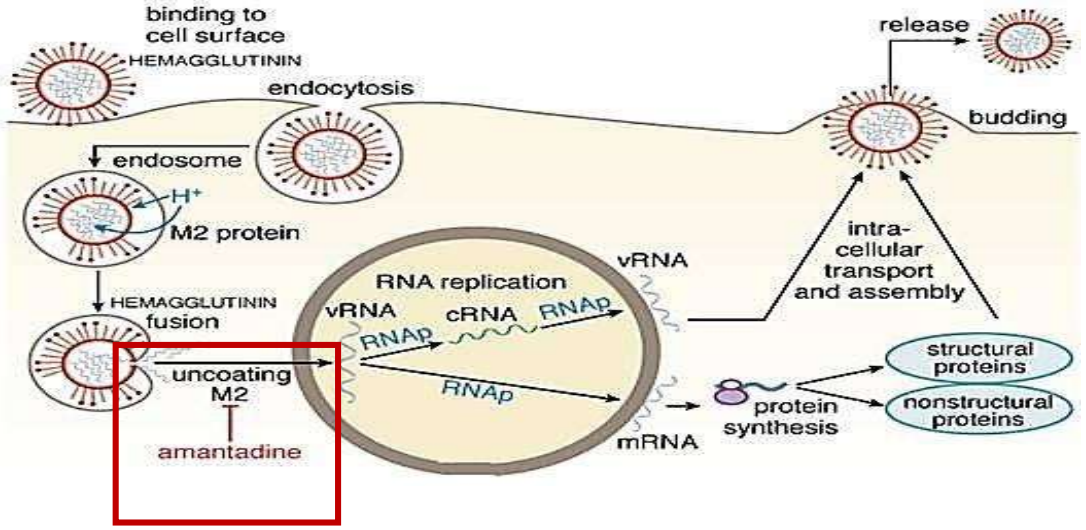
MOA: *Oseltamivir* and *zanamivir* selectively inhibit neuraminidase, thereby preventing the release of new virions and their spread from cell to cell.
Early administration is crucial (within the first 24 to 48hrs after the onset of the infection)





TREATMENT OF RESPIRATORY VIRAL INFECTIONS

- **Amantadine and Rimantadine**
- Are limited to influenza A infections.
- **Mechanism of action:** *Amantadine* and *rimantadine* interfere with the function of the viral M2 protein, possibly blocking uncoating of the virus particle and preventing viral release within infected cells
- are **<u>effective for the prevention and treatment of influenza A virus infections</u>**



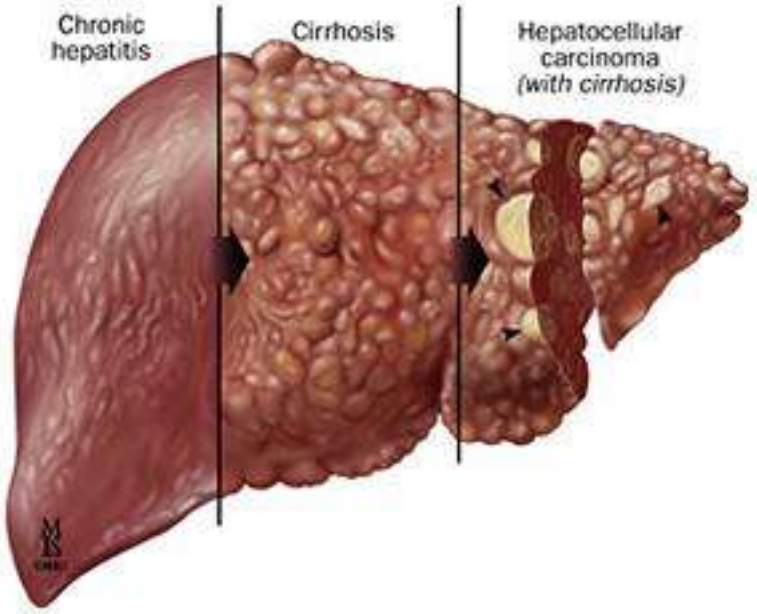
- *Amantadine* distributes throughout the body and readily penetrates into the central nervous system (CNS)

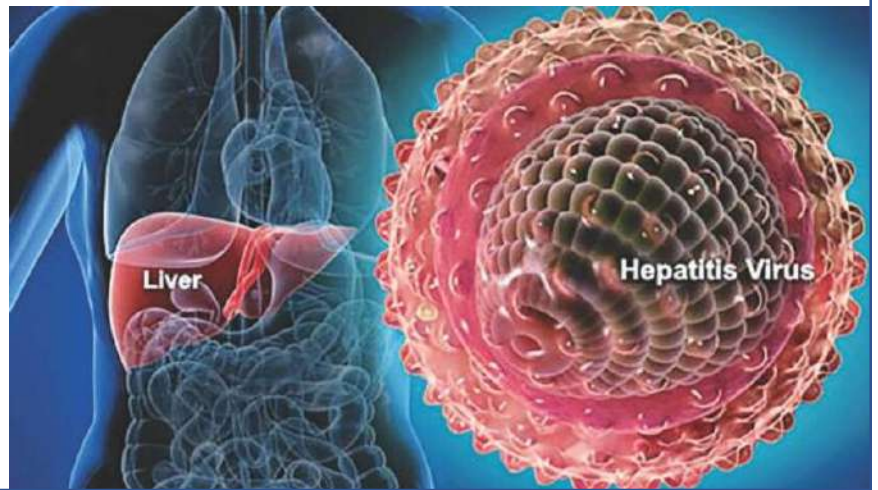
viral Hepatitis

- The hepatitis viruses thus far identified (A, B, C, D, and E) each have a pathogenesis specifically involving replication in and destruction of hepatocytes.
- Of this group, hepatitis B (a DNA virus)

and hepatitis C (an RNA virus) are the most common causes of chronic hepatitis,

cirrhosis, and hepatocellular carcinoma and are the only hepatic viral infections for which therapy is currently available.





TREATMENT OF HEPATIC VIRAL INFECTIONS

- **Most cases of acute hepatitis are due to viral infections**
- hepatitis **B and hepatitis C** are the most common causes of **chronic hepatitis, cirrhosis, and hepatocellular carcinoma**
- Chronic hepatitis **B** is usually treated with interferon alfa. Oral therapy includes lamivudine, adefovir, enetecavir, or telbivudine
- Treatment of chronic **hepatitis C**, the preferred treatment is the combination of **interferon-α plus ribavirin**

Interferon alfa

- Interferons are host cytokines that exert complex antiviral, immunomodulatory, and antiproliferative activities
- **Synthesized by recombinant DNA technology**
- **Interferon (IFN)-alfa appears to function by:**
  1. Induction of intracellular signals resulting in **inhibition of viral penetration, translation, transcription, protein processing, maturation, and release**
  2. Enhanced **phagocytic activity of macrophages**
  3. Augmentation of the proliferation and survival of cytotoxic T cells.

  Not active orally. Administered SC or IM

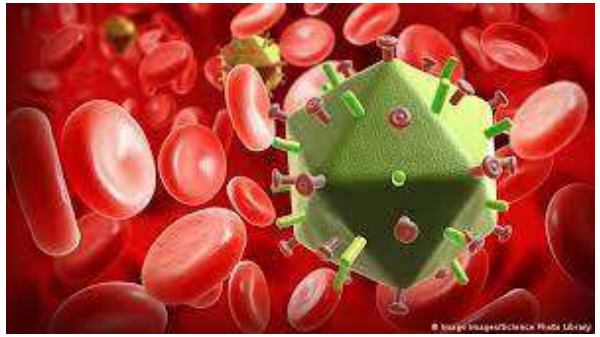
Lamivudine

- Cytosine analog that must be phosphorylated by host cellular enzymes to the triphosphate (active) form
- **MOA:** Competitively inhibits **HBV DNA polymerase** at concentrations that have negligible effects on host DNA polymerase.
- ADEs: well tolerated with rare occurrences of headache and dizziness

Antiviral Drugs (Against HIV)

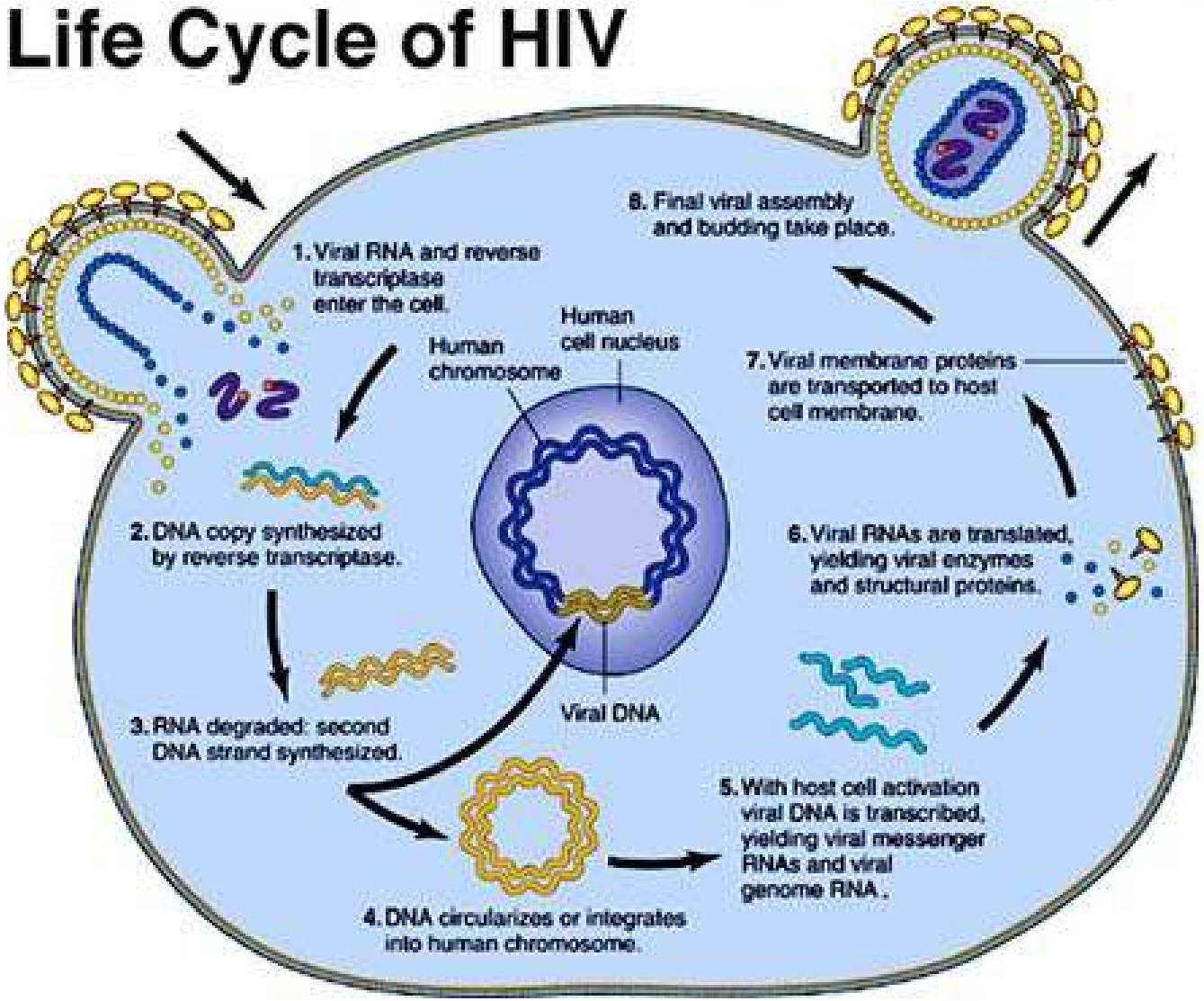
- RNA retroviruses “HIV”

  contain an enzyme(reverse transcriptase) making a DNA copy of viral RNA which then enter the nucleus and is integrated into host DNA (genes) and direct the generation of new viruses.



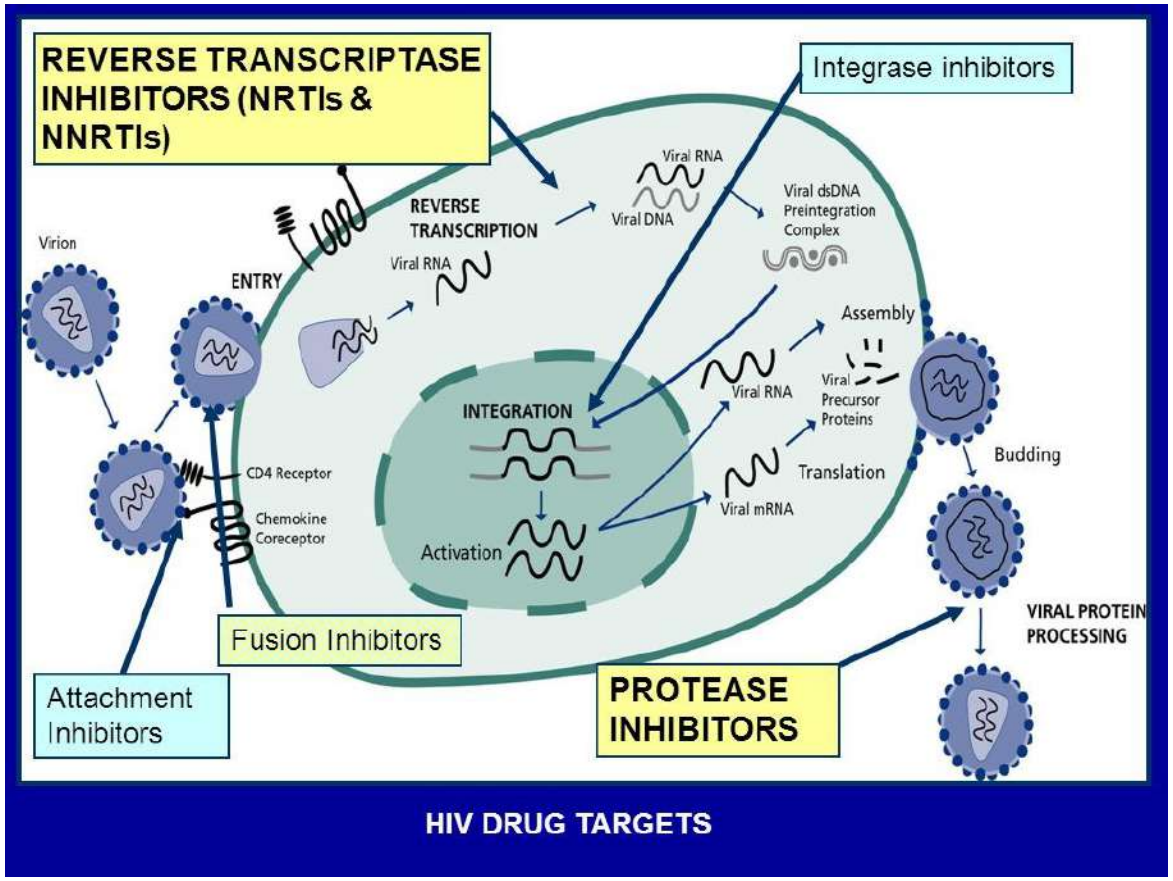
Byer/Shainberg/Galliano *Dimensions Of Human Sexuality*, 5e. Copyright © 1999. The McGraw-Hill Companies, Inc. All Rights Reserved.

Life Cycle of HIV



Inhibitors of HIV Replication

- A: Nucleoside reverse transcriptase inhibitors(NRTI).
- B: Non- nucleoside reverse transcriptase inhibitors(NNRTI).
- C: Protease inhibitors(PI).
- D:Integrase inhibitors
- E: Entry inhibitors



- TT of AIDS with antivirals:

  i. Delay in onset of the disease and death.

  ii. Improvement in markers of TT outcome as CD4-positive T lymphocyte

1 or 2 agents have been associated with:

- ❑ High rate of disease progression.
- ❑ Viral resistance.

❖ Three or more drugs are now used, usually:

2NRTIs + one PI or one NNRTI.

Antiretroviral Drugs

<u>HAART - Highly active antiretroviral therapy</u>

- Includes **at least three medications**
  - “cocktails”
- These **medications work in different ways to reduce the viral load**

Anti-AIDs Combination

1)avoiding the use of two agents of the same nucleoside analog.

2) avoiding overlapping toxicities.

3) patient factors, such as disease symptoms and concurrent illnesses.

4) impact of drug interactions.

5) ease of adherence to the regimen.

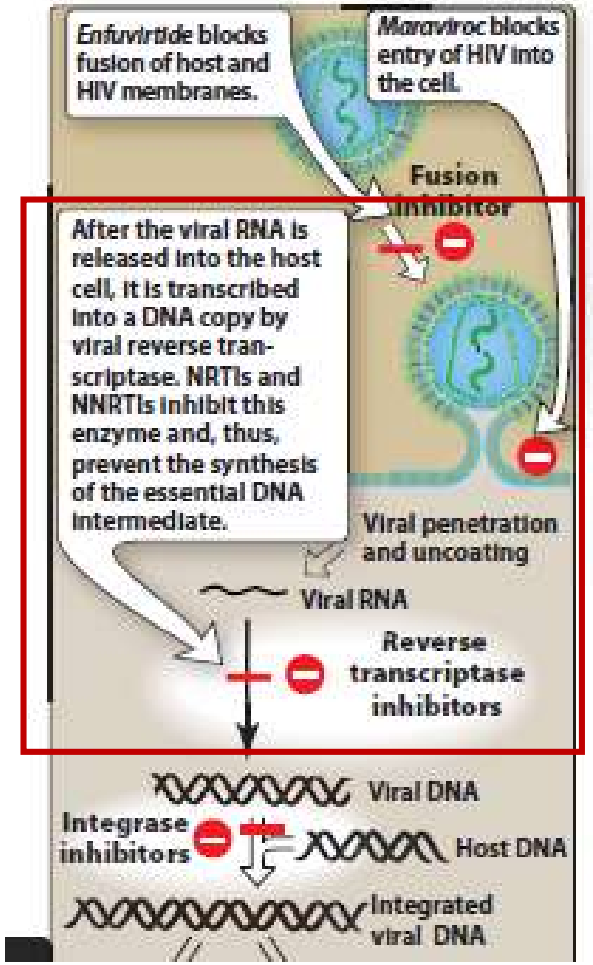
The goals of therapy are to maximally and durably suppress HIV RNA replication, to restore and preserve immunologic function, to reduce HIV-related morbidity and mortality, and to improve quality of life.

NRTIs

- They are activated intracellularly by cellular kinase to the triphosphate forms which:

1. Competitively inhibit RT.
2. Incorporated into HIV DNA → chain termination

- More selective to RT than cellular polymerase



NRTIs

Drug	Elimination	Main ADRs
Zidovudine(T)	H&R	BM suppression
Zalcitabine(C)	R	Neuropathy and stomatitis

NNRTIs

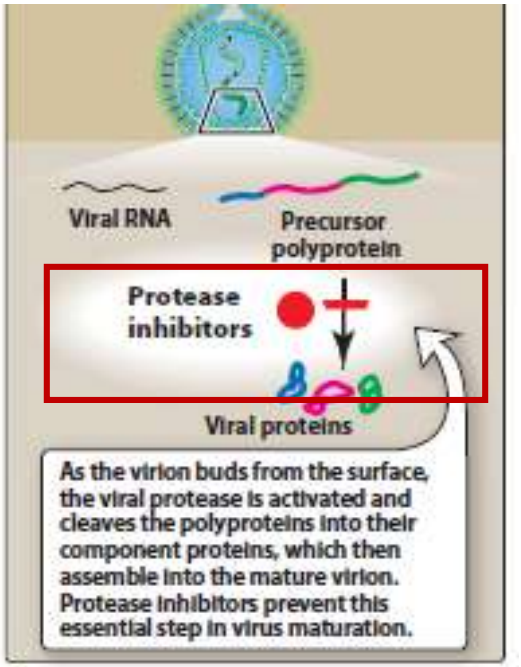
- They are potent inhibitors of HIV-1 RT.
- They do not need intracellular phosphorylation
- RT mutation produces cross resistance to all NNRTIs.

NNRTIs

Drug	Main ADRs
Nevirapine* (tab)	Skin rash & hepatitis
Delavirdine(tab)	Skin rash

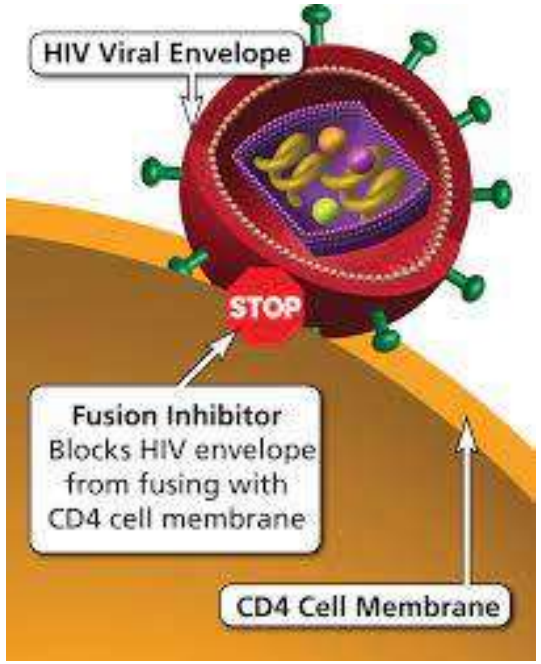
PIs

- Reversible inhibitors of HIV1 & 2 protease
- They do not need intracellular activation
- Marked resistance develops easily, if they are used alone.
- Combination with NRTIs → additive effect and decrease resistance
- Example: Ritonavir (caps)



Antiretroviral Drugs

- **<u>Fusion inhibitors</u>**
  - Inhibit viral fusion, preventing viral replication
  - Example: enfuvirtide



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