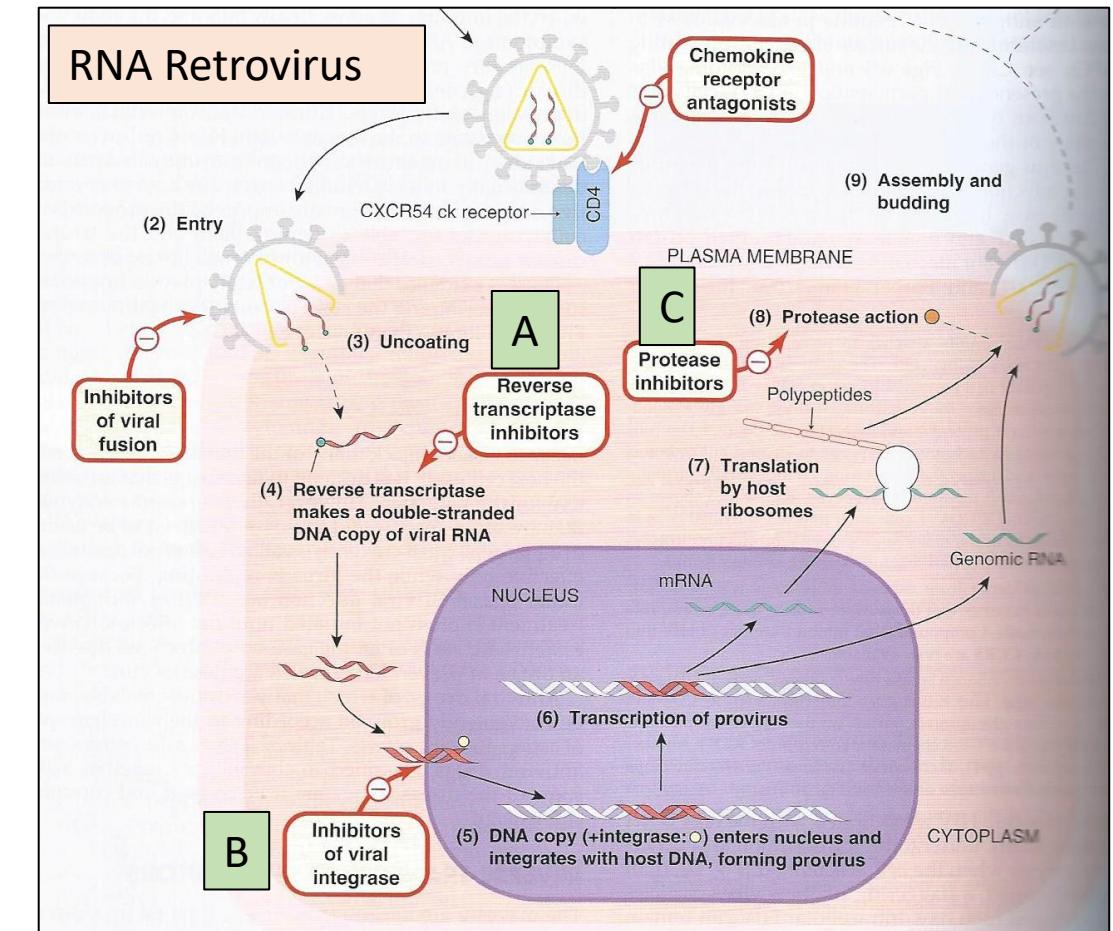
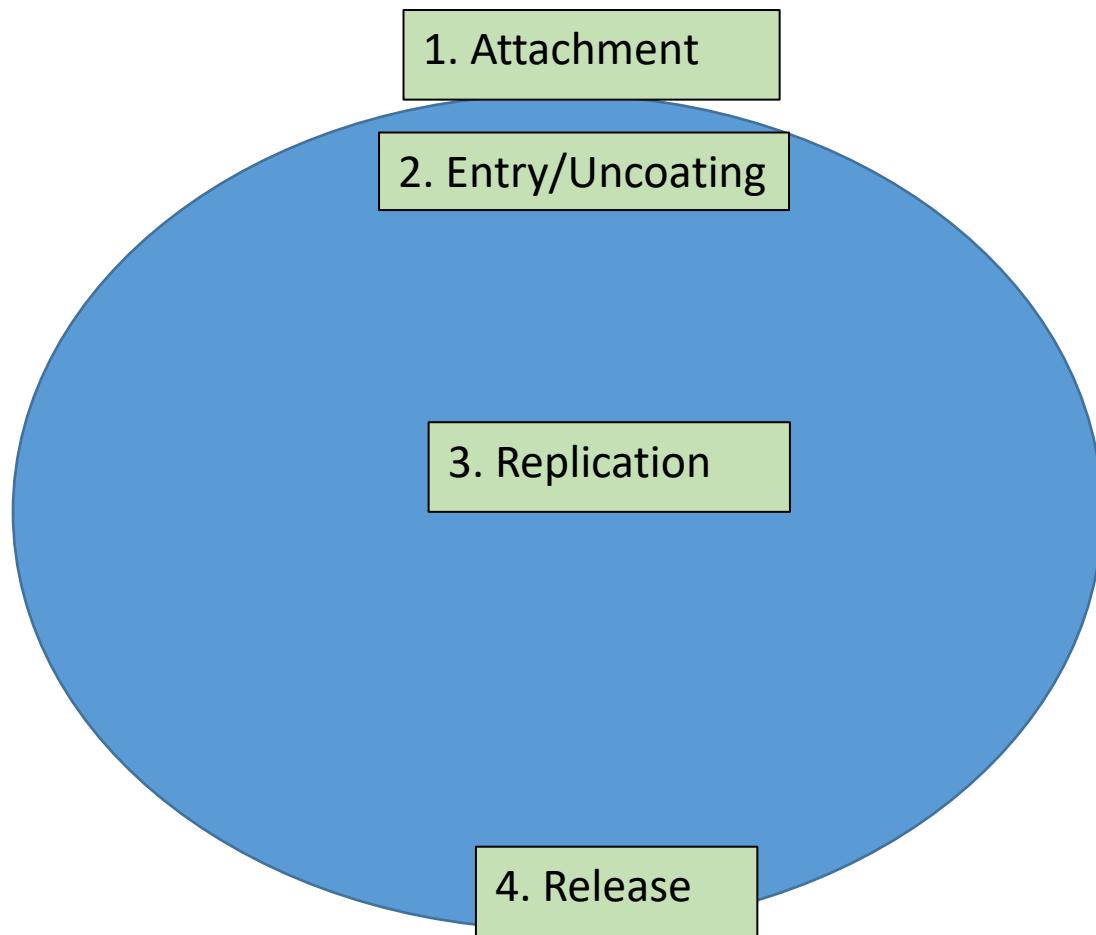


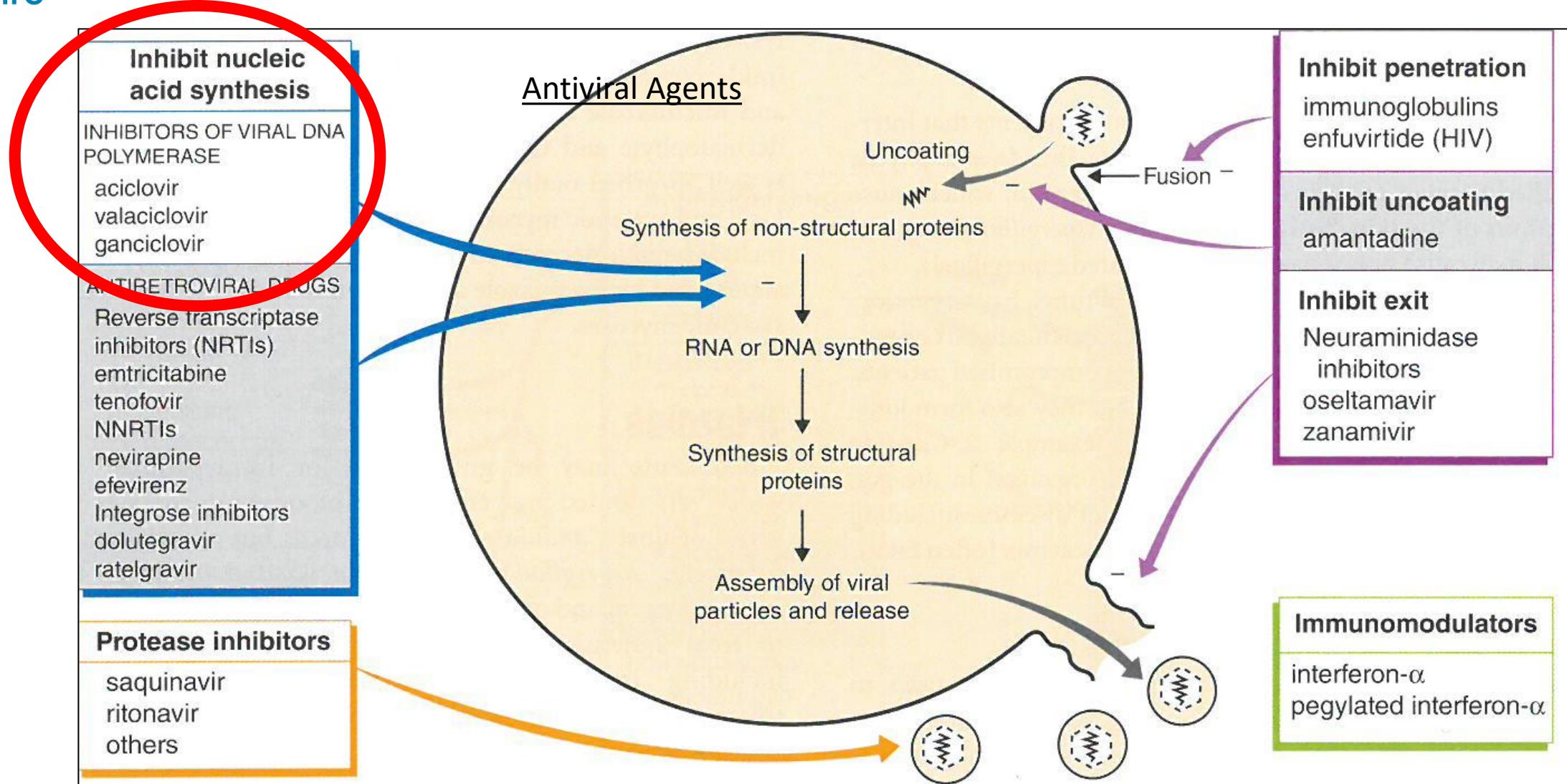
## Learning Outcomes

To understand the pharmacological basis for the therapeutic use and adverse effects of antiviral drugs.

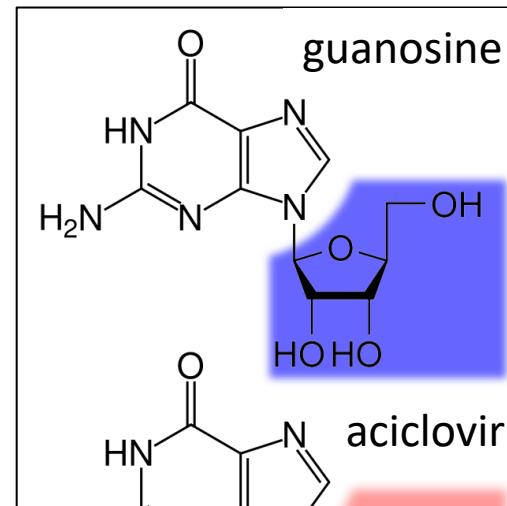
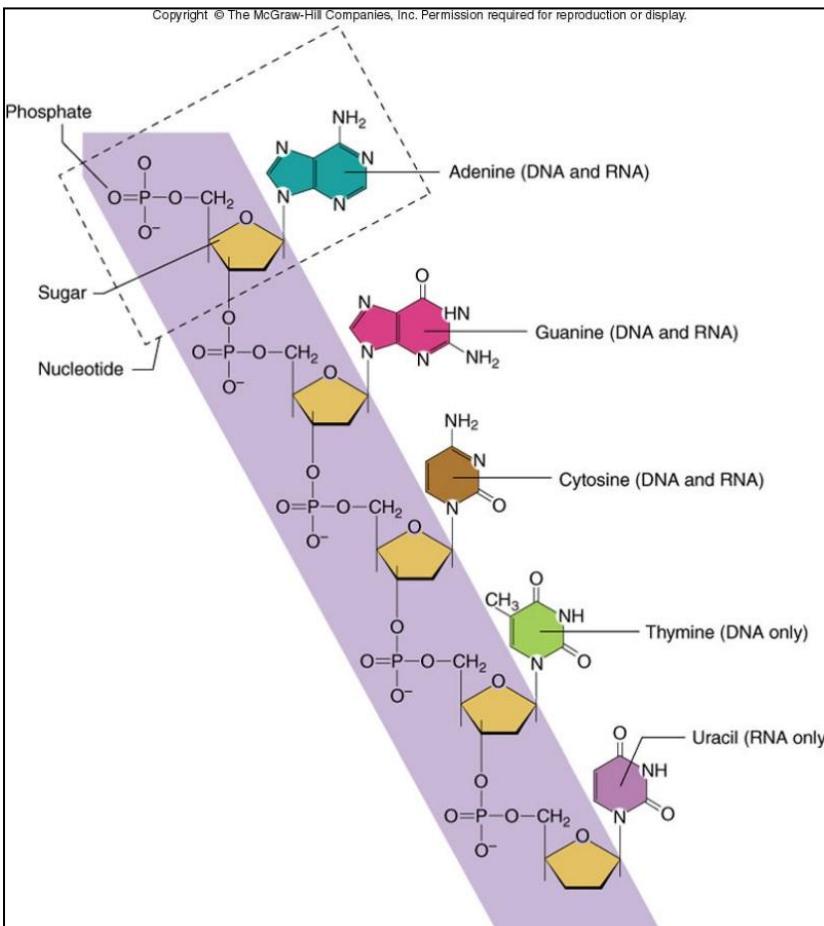
- 1 – Herpes, influenza, hepatitis C.**
- 2 - HIV/AIDS**

# Cellular Targets for Antiviral Drugs



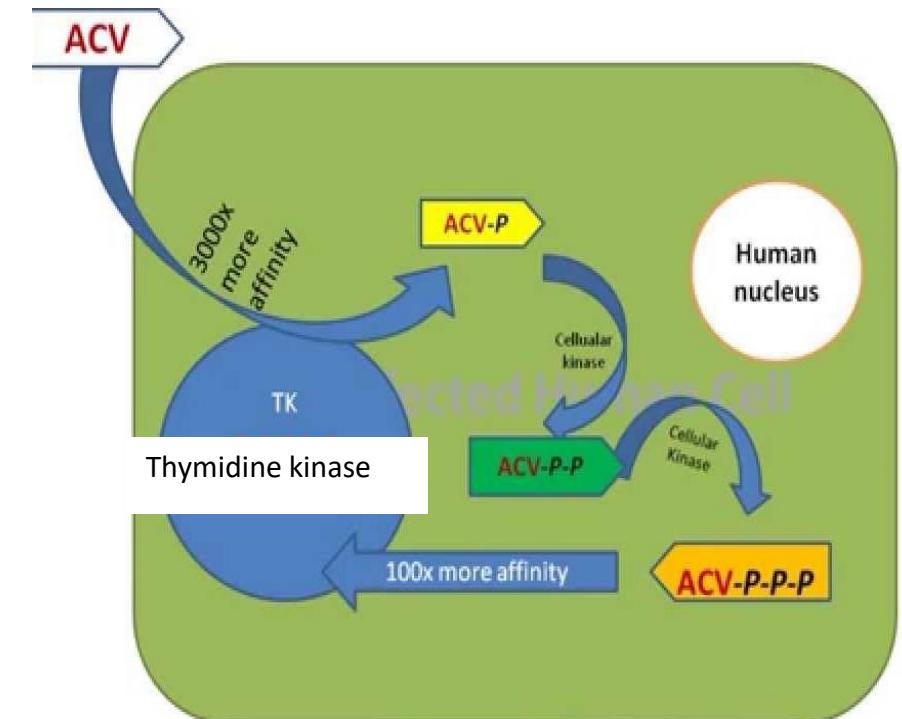


# DNA Polymerase Inhibitors



Analogue of the nucleoside  
guanosine

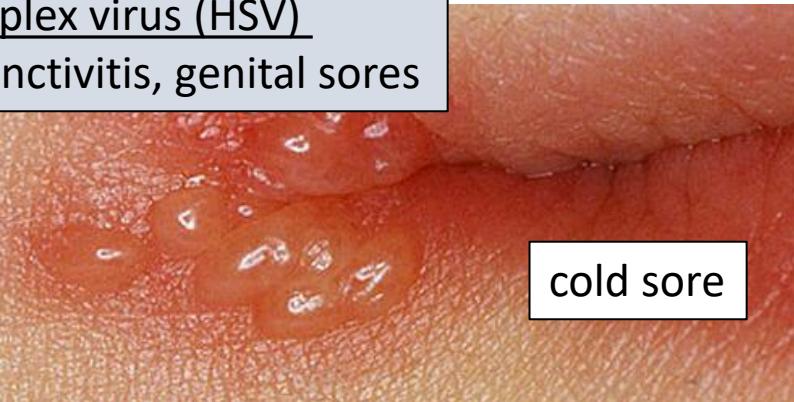
## Two step activation of ACICLOVIR



# Aciclovir

## Herpes simplex virus (HSV)

cold sores, conjunctivitis, genital sores



## Varicella zoster virus (VZV)

chickenpox and shingles



Prevents viral reproduction - suppress symptoms and reduce time of healing.

### Pharmacokinetics:

Topical – mouth, eye, genitals (aciclovir/penciclovir)

Oral - poor water solubility & oral absorption, bioavailability (20%)

Systemic treatment required for neonates/immunocompromised

Injection - IV for high dose.

### Adverse effects

1. Nausea, diarrhoea, vomiting
2. Safe in pregnancy, but excreted in breast milk
3. Rapid IV infusion - reversible kidney failure as crystals of drug precipitate especially if dehydrated or with renal impairment.

### Analogues

**Valaciclovir** – prodrug of aciclovir

**Penciclovir** is similar to aciclovir but active triphosphate retained for longer in cell.

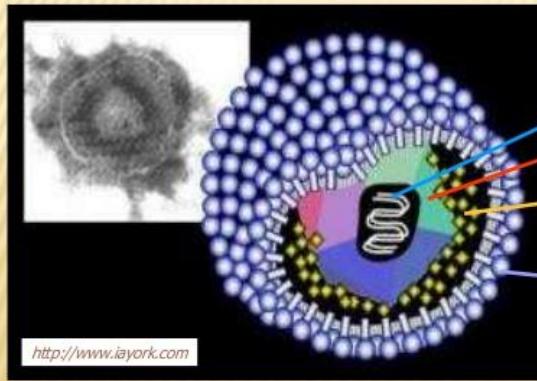
**Famciclovir** – prodrug of penciclovir

# Ganiclovir

**Cytomegalovirus (CMV) includes human herpes virus -5 (HHV-5) which produces a latent infection in salivary glands and may induce pneumonia**

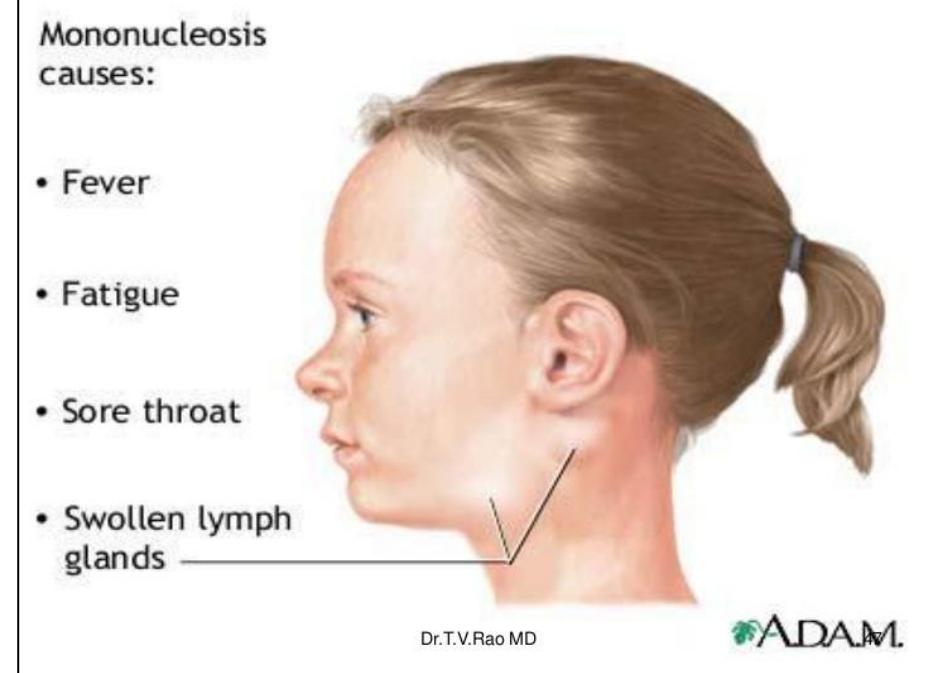
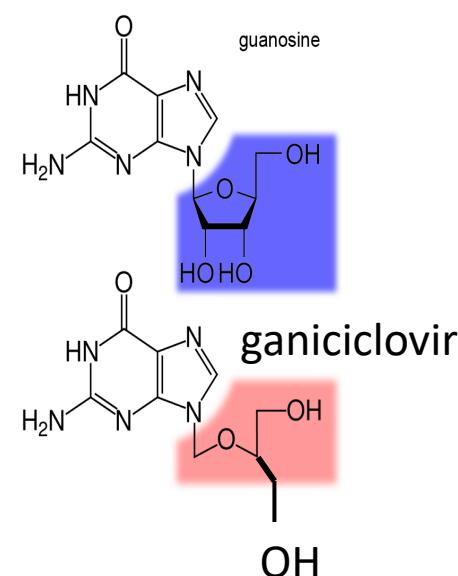
### CMV (CYTOMEGALOVIRUS)

- ✖ Human herpes virus type 5 (HHV-5)
- ✖ The largest in Herpesvirus



<http://www.layork.com>

*Immunobiology of human cytomegalovirus  
Clin Microbiol Rev. 2009 Jan;22(1):76-98.*



Ganiclovir, activated by phosphorylation. HHV-5 infection serious in infants and immunocompromised patients.  
Adverse effects – bone marrow depression

# Viral Entry into Host cell

## Antibodies

### **Human Immunoglobulins**

Hepatitis A, measles rubella

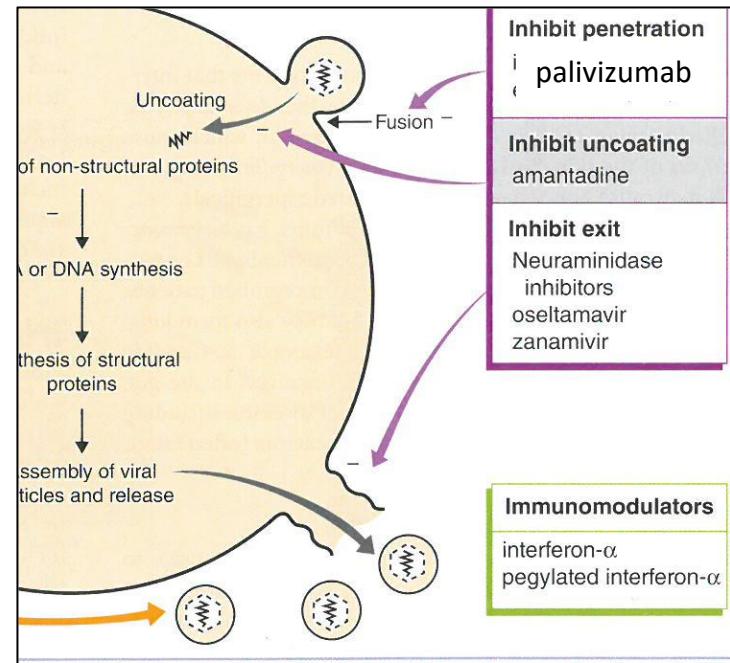
Palivizumab (1998)

### **Nirsevimab (2022)**

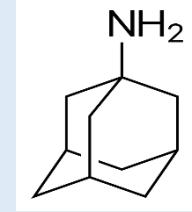
Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infection in infants.

Humanised monoclonal Mab to a fusion protein on the surface of the RSV virus.

Single 6 monthly injection  
- reduces hospitalisation by 50%



## **Amantadine**

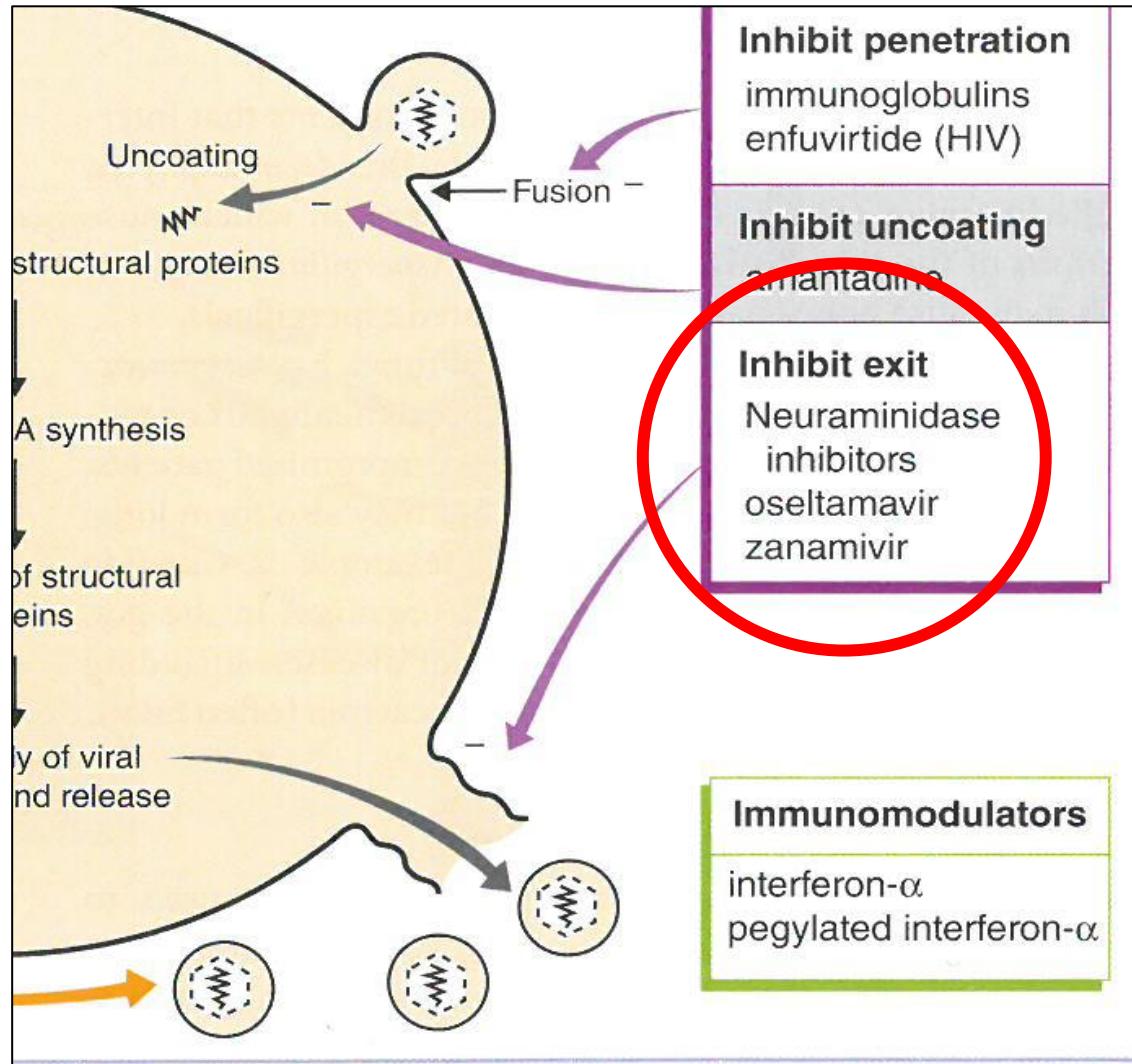


Following endocytosis the influenza virus is localised in acidic vacuoles. Acidification starts the process of viral replication by releasing ribonucleoproteins.

Amantadine blocks the matrix 2 channel for hydrogen ions - inhibits the flow of hydrogen ions reducing the acidification process.

\* Little used – vaccination preferred.

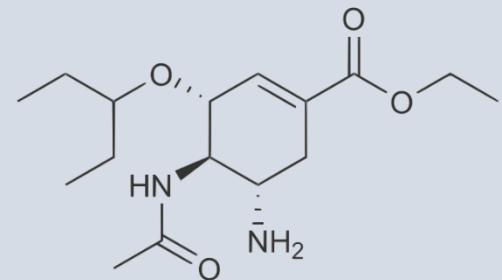
# Viral Exit from Host cell



## Neuroaminidase Inhibitors

Influenza virus

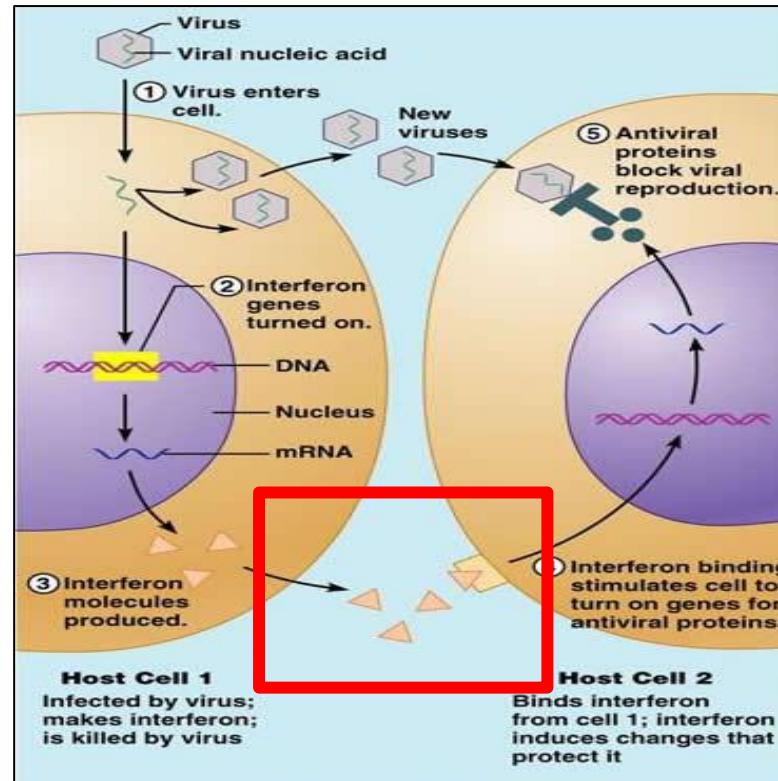
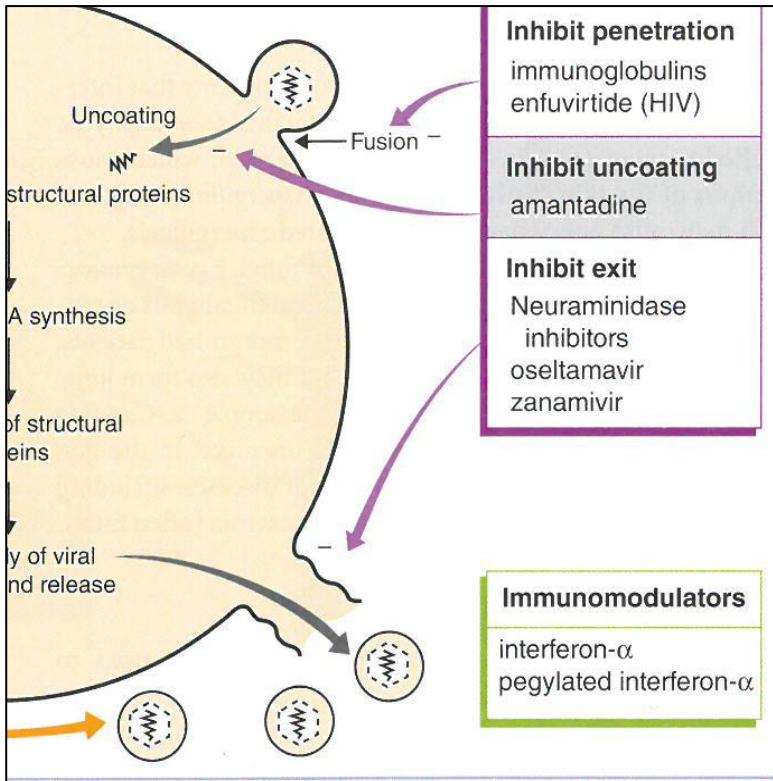
New virions must exit the cell by budding from cell membrane. This requires the enzyme neuroaminidase to cleave link between viral coat and membrane sialic acids.



Star anise

**Oseltamivir**  
(Tamiflu)

# Immunomodulators



## Peginterferon 2 alpha

Interferons induced following viral infection reduce protein synthesis, degrade RNA, induce apoptosis

Recombinant interferons are cytokines which have been pegylated by the addition of polyethylene glycol to increase their molecular size and duration of effect.

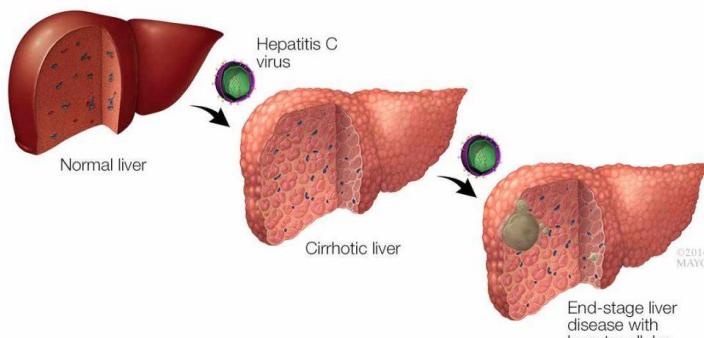
Important use in hepatitis B/C as well as HIV infection

# Hepatitis C

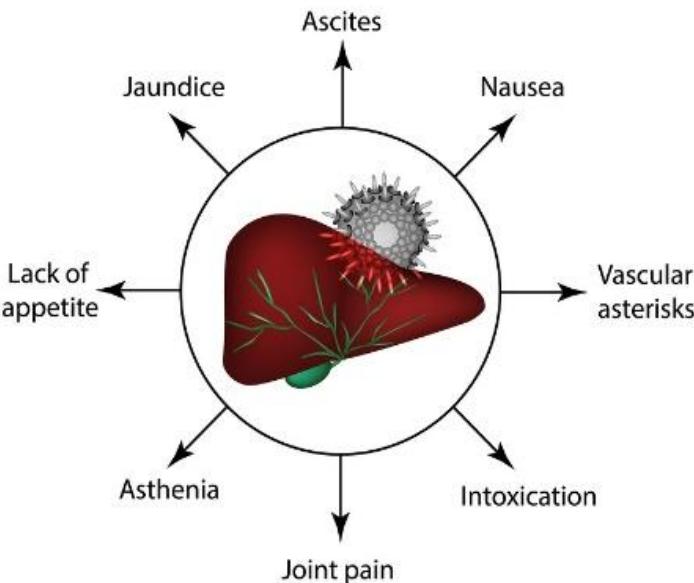
## Hepatitis C

Small, enveloped single strand RNA virus

**No 1 cause of liver cancer and requirement for liver transplant**



## SYMPTOMS OF HEPATITIS C



## Directly Acting Anti-Viral Agents

Viral replication proteins

NS5A (RNA binding protein)

NS5B (RNA polymerase)

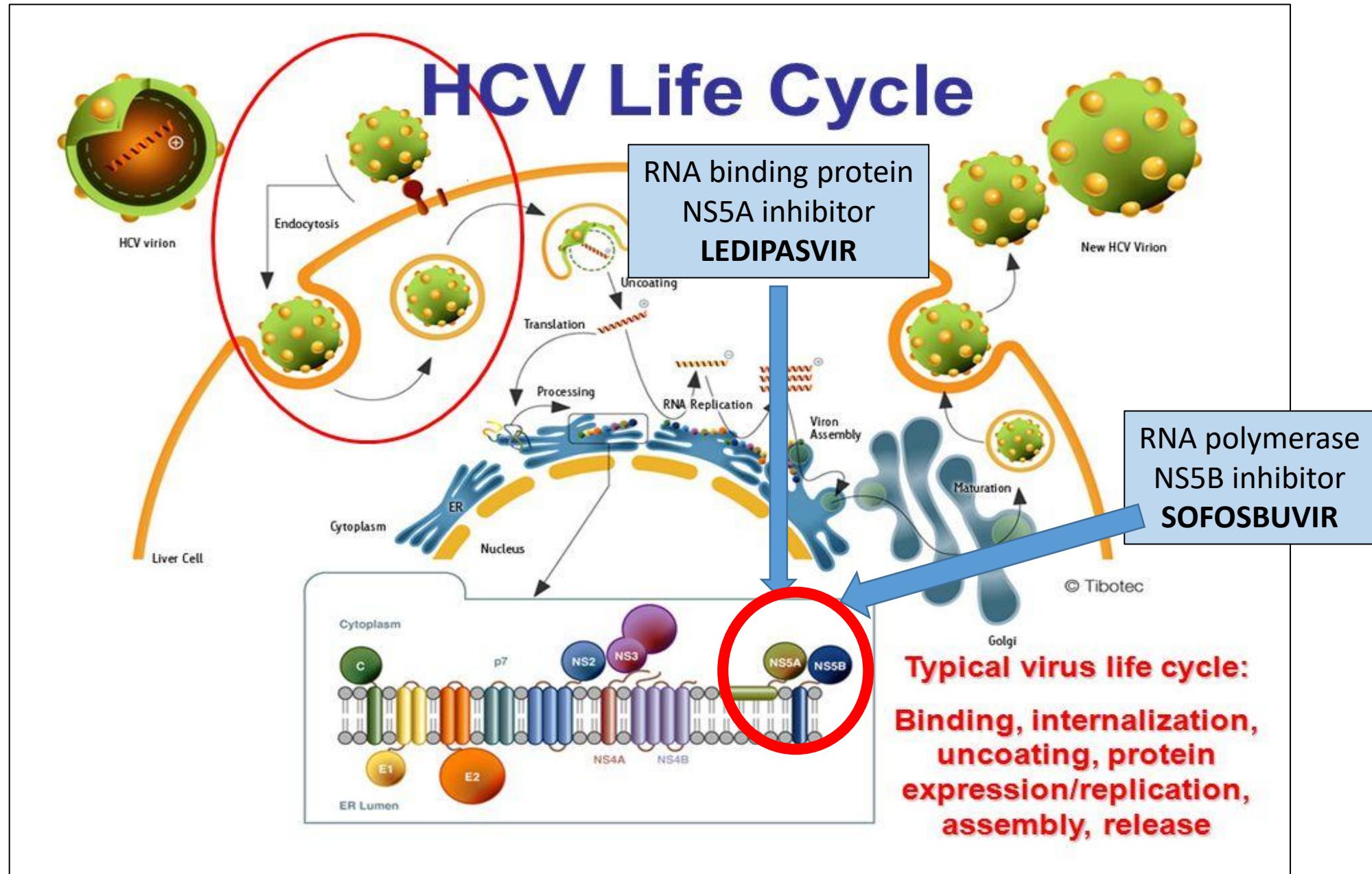
## Dual Combination (Harvoni, Gilead)

**Ledipasvir (NS5A inhibitor)**

**+ Sofosbuvir (NS5B inhibitor)**

Once daily oral treatment, 3-month course  
(99% cure, cost?)

Adverse effects (reactivate hep B, bradycardia)  
Replacing interferon-based therapies



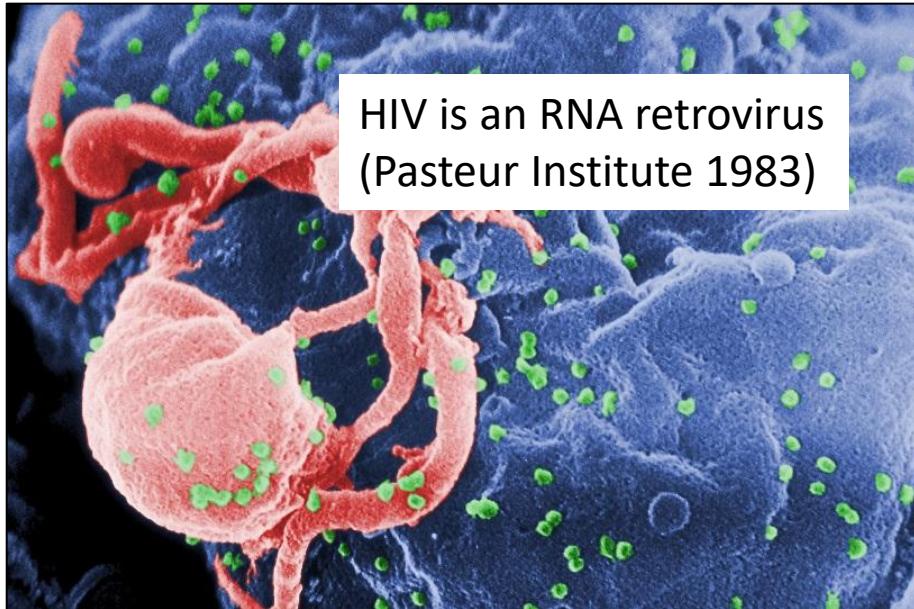


A close-up, colorized electron micrograph of several HIV-1 virus particles. The particles are spherical and covered in numerous small, spike-like proteins. They are set against a background of various other cellular structures, some appearing pinkish-red and others blue.

To understand the pharmacological basis for  
the therapeutic use and adverse effects of antiviral drugs.

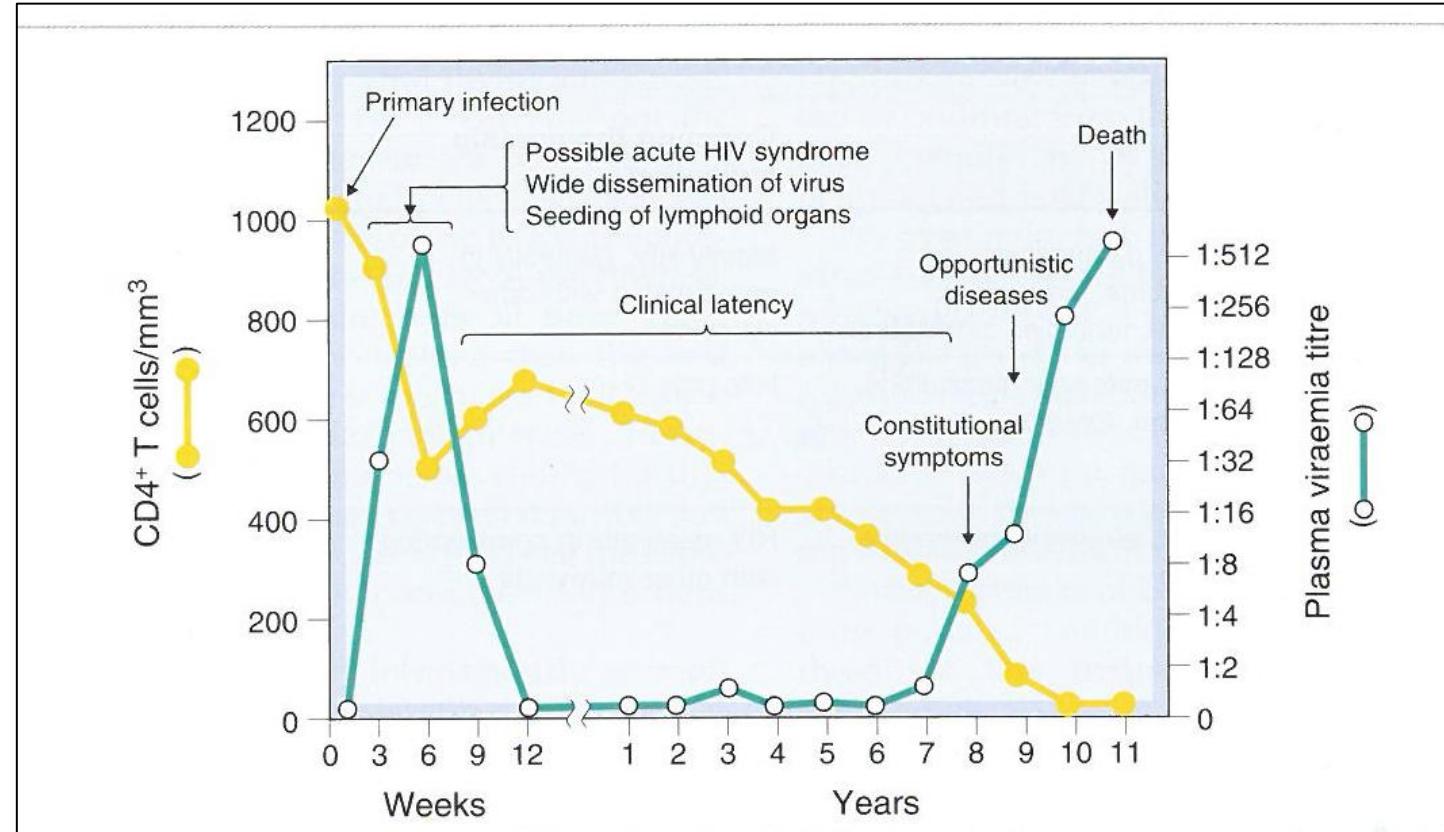
## HIV infection

# Human Immunodeficiency Virus (HIV)



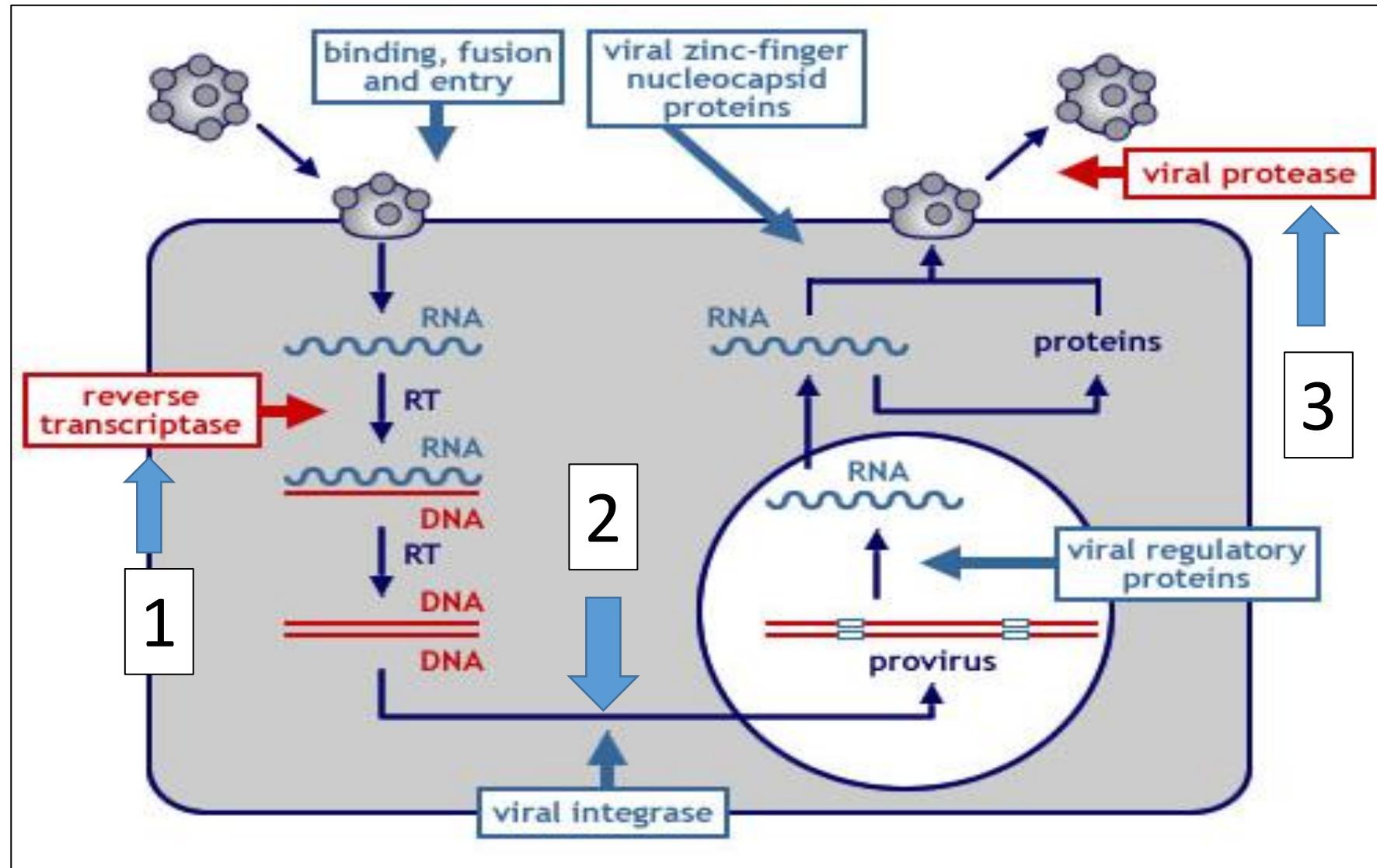
2024

40 million have AIDS  
2/3 in sub-Saharan Africa  
1.3 million newly infected each year  
30 million access to retroviral drugs  
(90 million infected/42 million died)

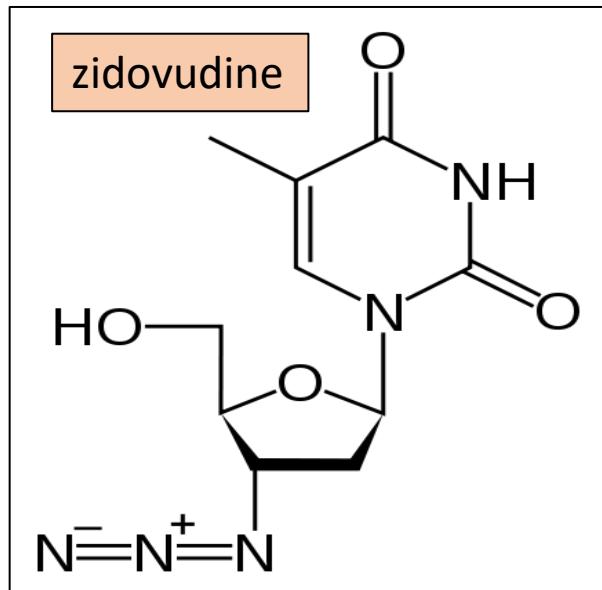
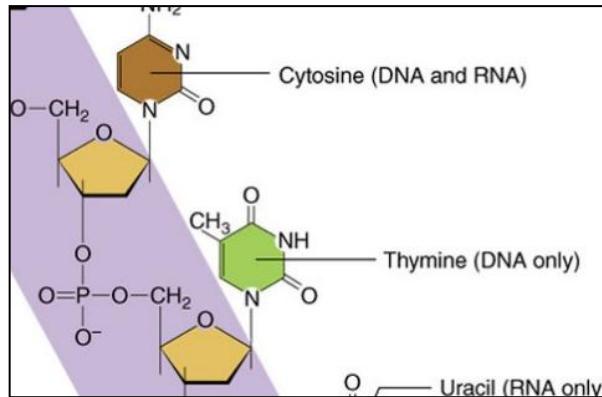


Rang & Dale Pharmacology fig 52.4 p647

# Antiviral Drugs for HIV (RNA Retrovirus)



# Reverse Transcriptase Inhibitors (NRTI): NUCLEOSIDES



## **Zidovudine (azidothymidine AZT 1986)**

**1st treatment approved for HIV**

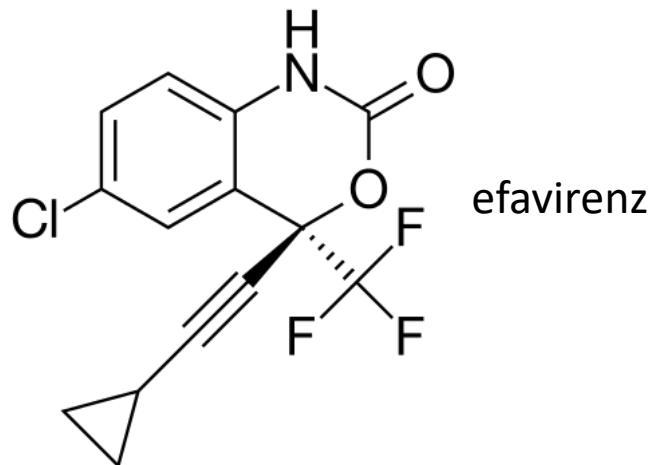
**– restoration of T-cell immunity, weight gain, prolonged life**

- Activated to triphosphate form by cellular phosphatases
- Competitive substrate - reverse transcriptase affinity (100x DNA polymerase)
- Thymidine analogue - lacks OH on deoxyribose required for phosphodiester bonding with the next nucleotide. Prevents extension of the DNA chain
- HIV virus lacks ability to repair its broken DNA strands
- Can also inhibit the extension of host DNA giving common side effects gastric upset, heartburn, headache, loss of sleep, loss of body weight

–

**NRTI used in combination Lamivudine (cytidine analogue)**

## Reverse Transcriptase Inhibitors (NnRTI): NON-NUCLEOSIDE



### Enzyme Inhibitor

bind to allosteric site adjacent to active site of RT enzyme

NOT a nucleoside analogue

Only inhibits HIV-1

### Efavirenz

#### Adverse effects

neurological/psychiatric take at bedtime,  
5HT2 agonist (depression/anxiety)

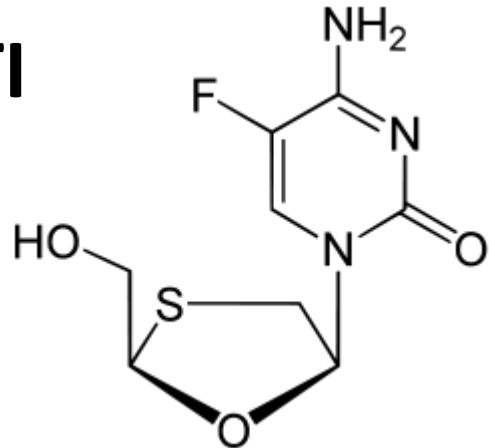
# Pre-exposure Prophylaxis (PrEP)

## (high risk groups)

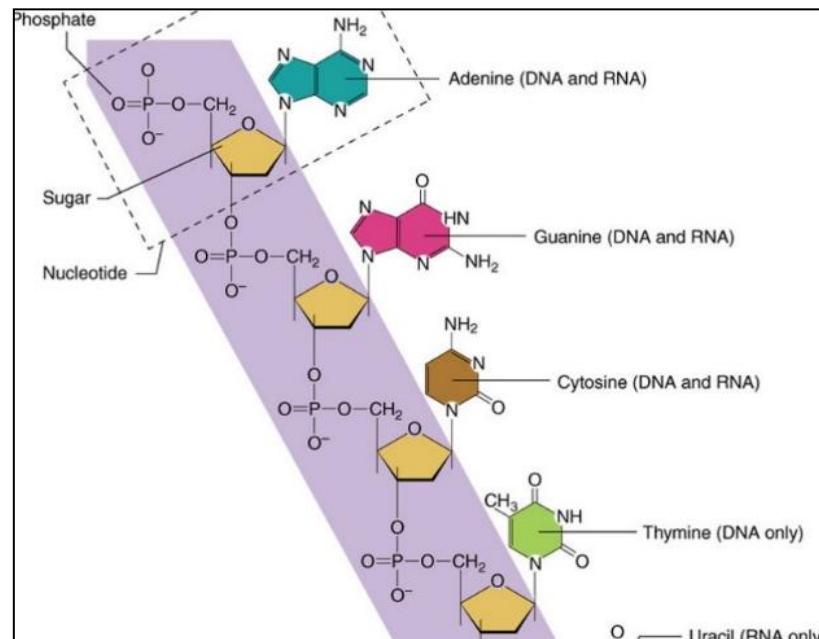
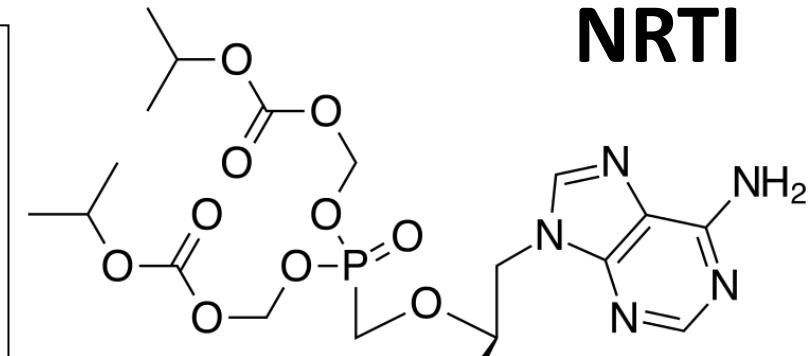
1. Gay or bisexual men who either have had anal sex without a condom or been diagnosed with an STD in the past 6 months
2. Heterosexual men or women who do not regularly use condoms during sex with partners of unknown HIV status who are substantial risk
3. Injection of illicit drugs in the last month with sharing of equipment
4. Discordant heterosexual and homosexual partners where one partner is HIV-positive and the other HIV-negative

**Potential treatment issues over adherence**

# PrEP Therapy

**NRTI**

**Emtricitabine**  
cytidine analogue

**NRTI**

**Tenofovir disoproxil**

(defective adenine nucleotide)  
prodrug

Patients see HIV reduction benefit after 72 h but the medicine must be taken for thirty days after a high-risk sexual event to ensure HIV transmission levels are optimally reduced.

**Truvada** (Gilead) - emtricitabine + tenofovir disoproxil [generic PreP available]

**Descovy** (Gilead) – emtricitabine + tenofovir alafenamide

# Highly Active Antiretroviral Therapy (HAART)

Modern HIV therapy requires at least 3 drugs with a different ARV mechanism of action

Treatment should reduce the viral load to undetectable levels within 3 months CD4 T cell recovery maybe poor

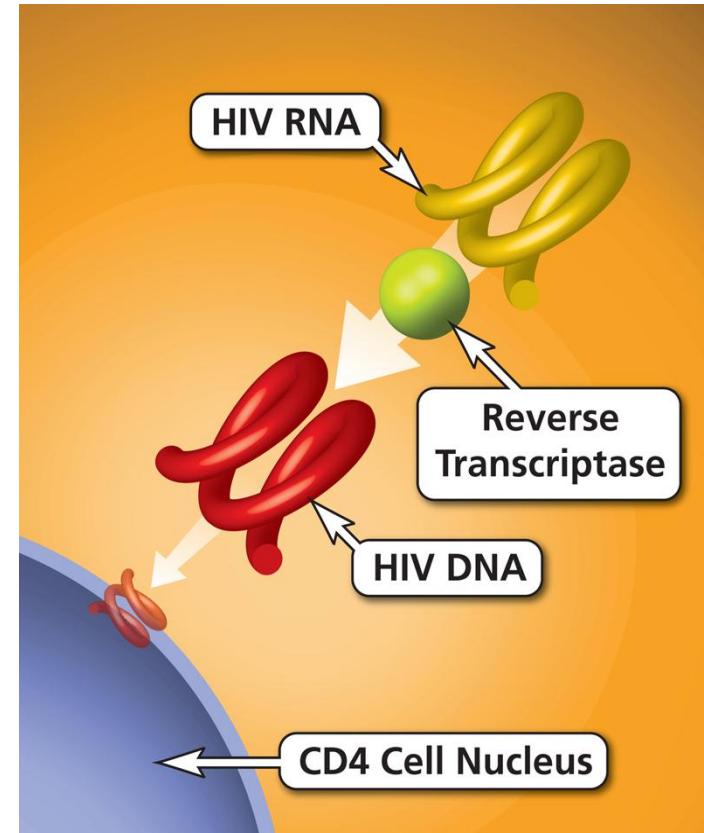
Immunocompromised patients required to reduce viral load, (increase CD4 T-cells)

## Preferred initial regimen

(WHO 2013)

tenofovir

+ lamivudine (or emtricitabine)  
+ efavirenz



## Atripla

Efavirenz 600mg

Emtricitabine 300mg

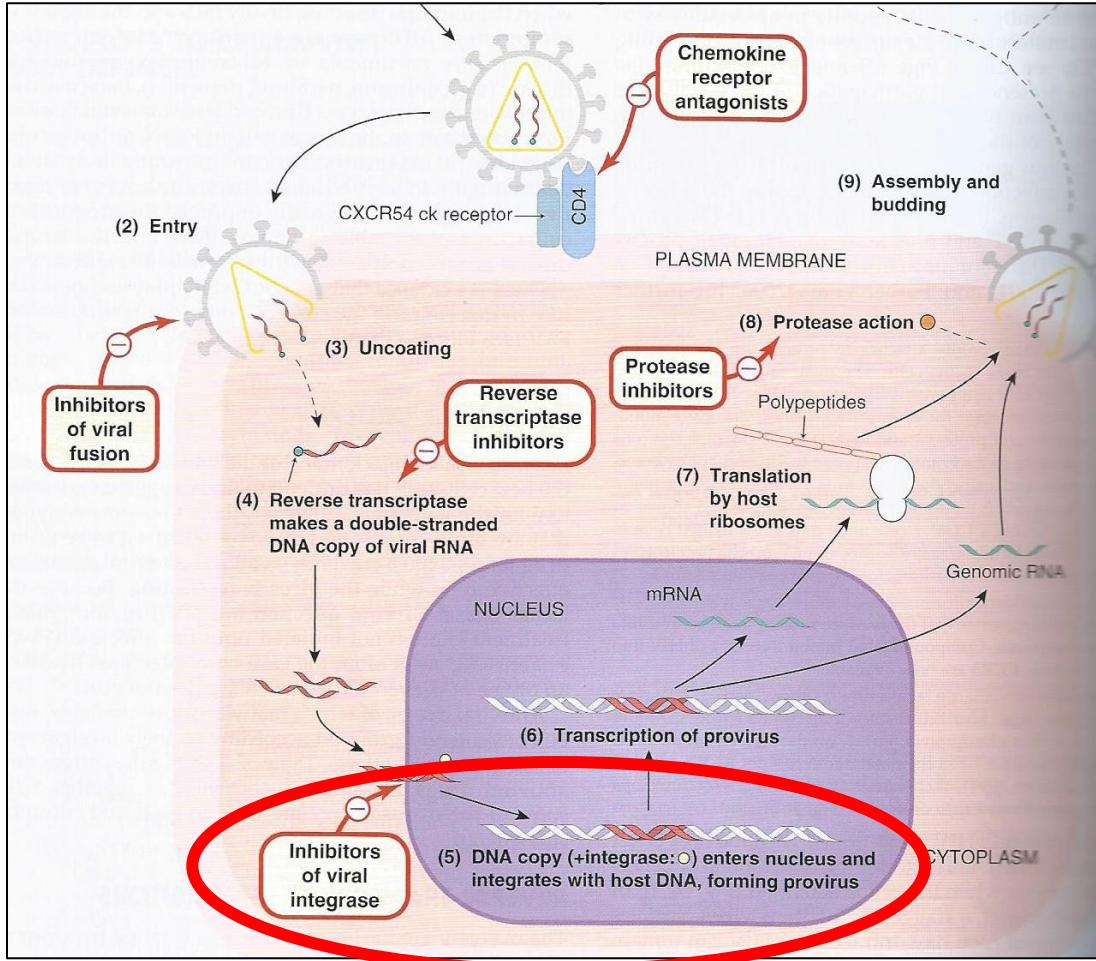
Tenofovir disoproxil 300mg



Combined once a day fixed dose combinations improves adherence

Atripla taken at night to avoid central side effects including depression/hallucination

## 2. Integrase Inhibitors



### Integrase

A viral enzyme which inserts the viral genome into the DNA of the host cell through a series of cutting and joining procedures

**raltegravir (2007), dolutegravir (2012)**

Adverse effects

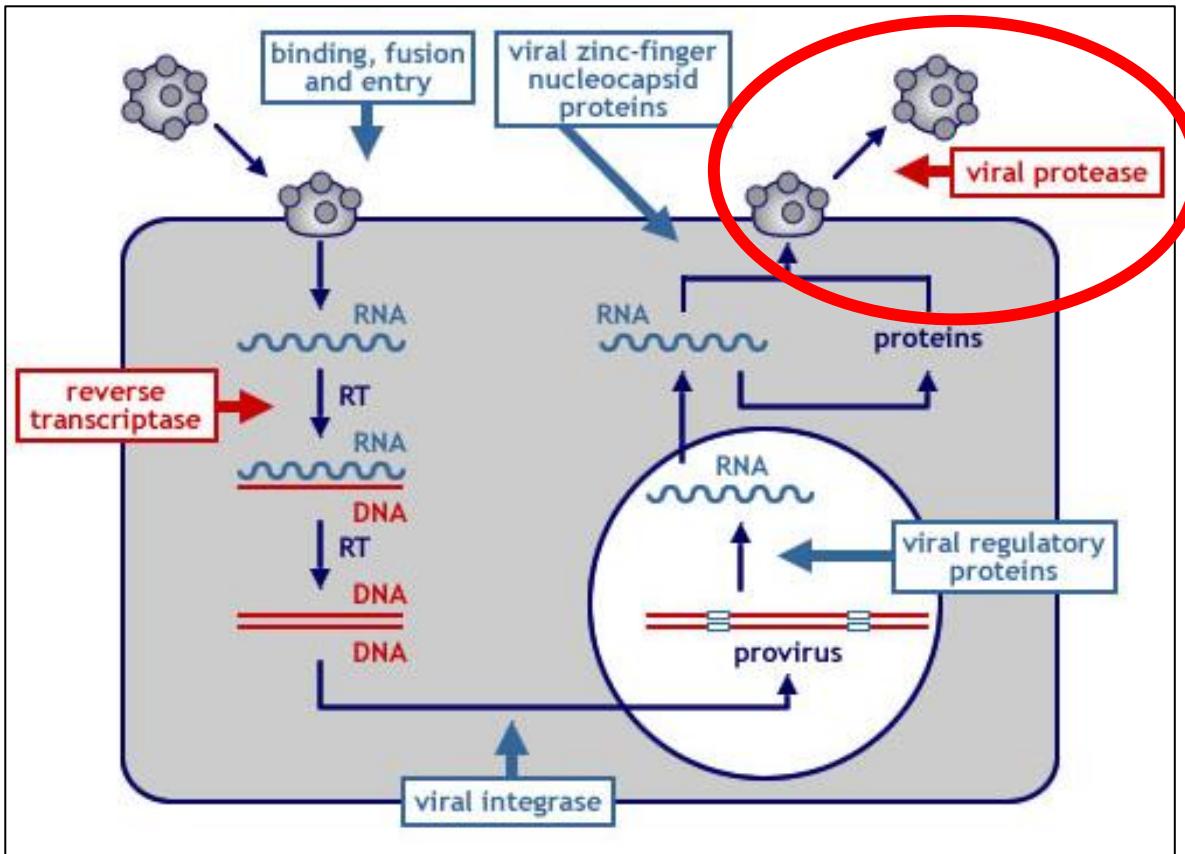
rashes are common, can be severe  
(muscle pain/mouth ulceration/angioedema)

Risk factors

myopathy, hepatitis infection B/C, depression

**HIV infection treated in combination with other drugs**

### 3. HIV Protease Inhibitor



**Viral Protease :** Viral mRNA's produce inert polyproteins translated into mature functional proteins by a viral specific protease.

#### HIV Protease Inhibitor : Saquinavir

- Protease inhibition prevents maturation of the virions resulting in the production of non-infectious particles.
- HIV protease inhibitors inhibit both HIV-1 and HIV-2

#### Adverse effects

liver failure/cardiac arrhythmias. GI tract effects common.

# Pharmacokinetic Inhibitor

## Ritonavir

Inhibits major drug metabolising enzymes -  
**CYP3A4 & CYP2D6**

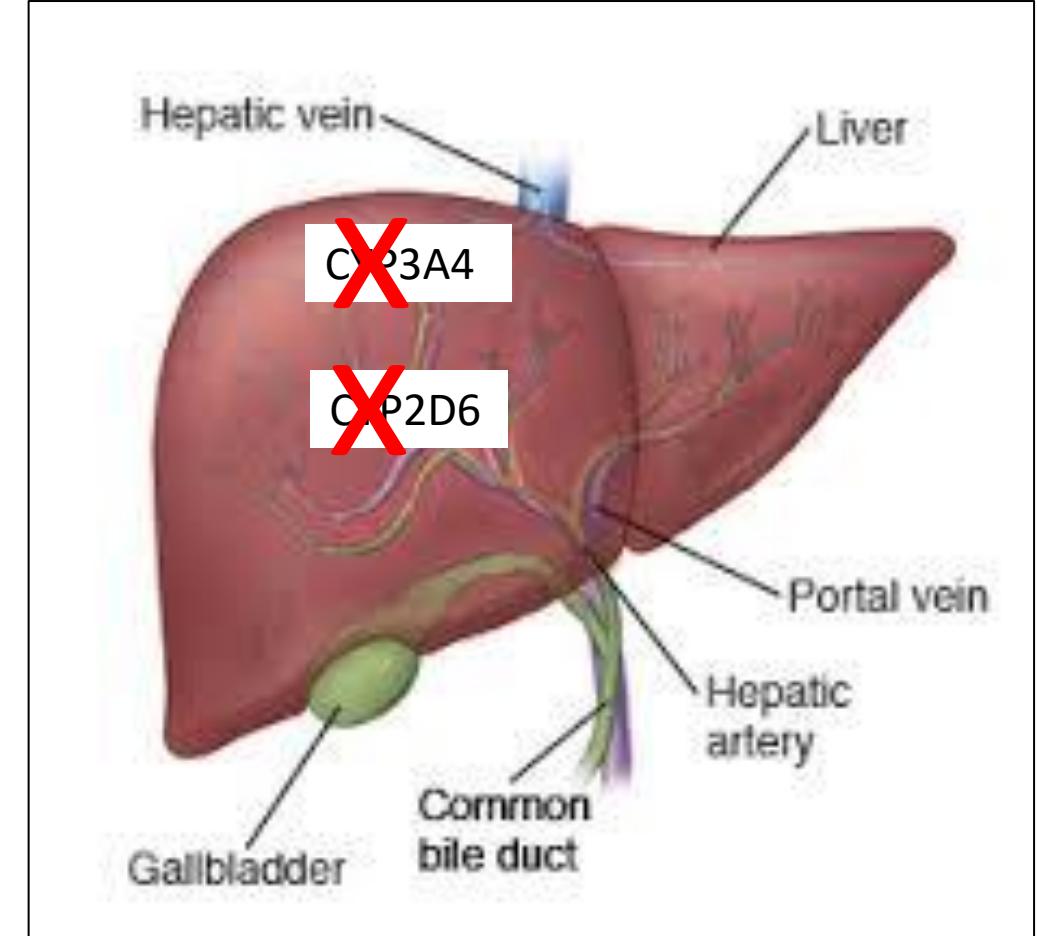
Induces CYP1A2

New use in low dose (100mg)

elevate plasma levels of other protease  
inhibitors such as saquinavir.

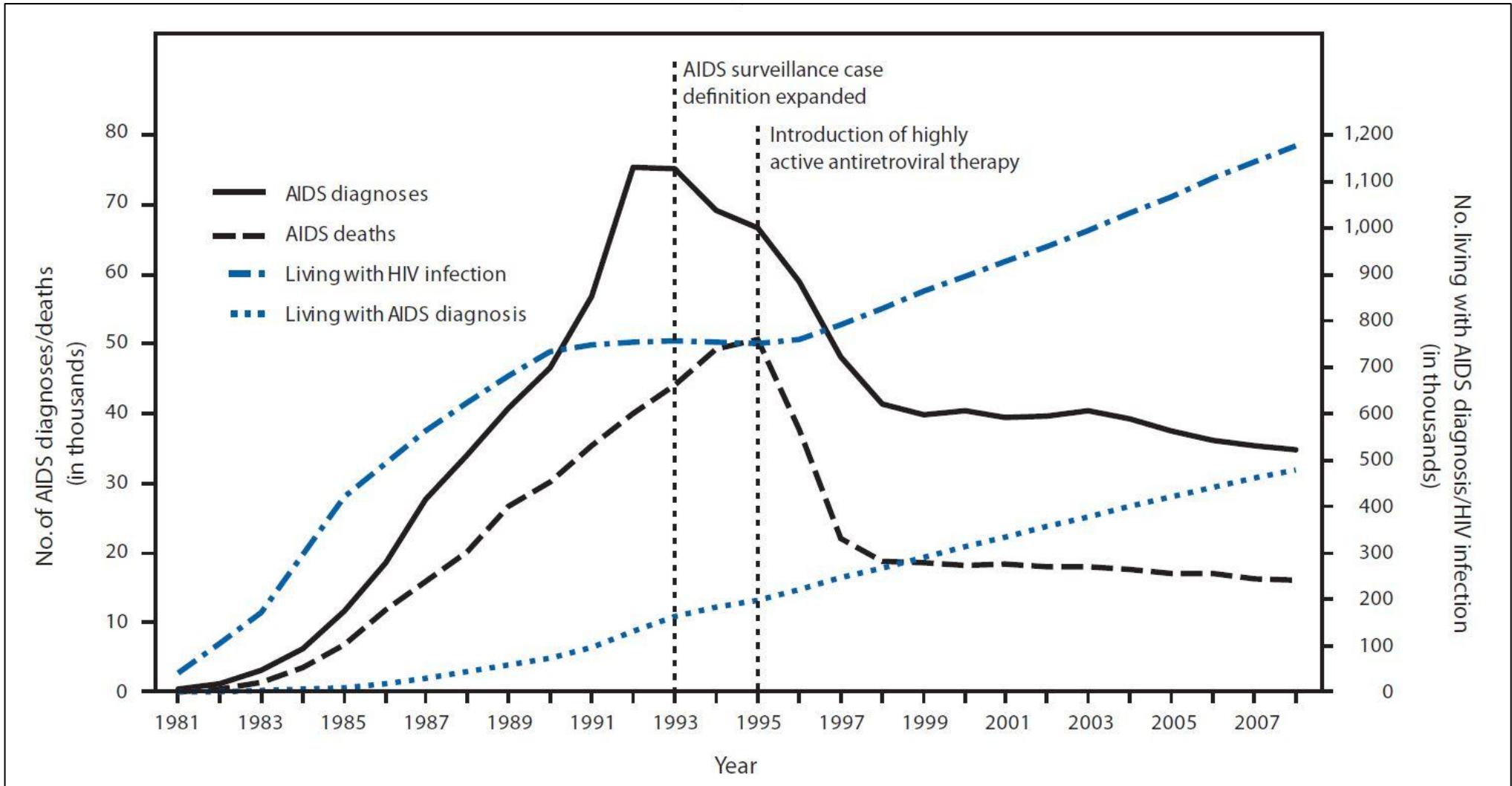
Combination tablet

**lopinavir with ritonavir**

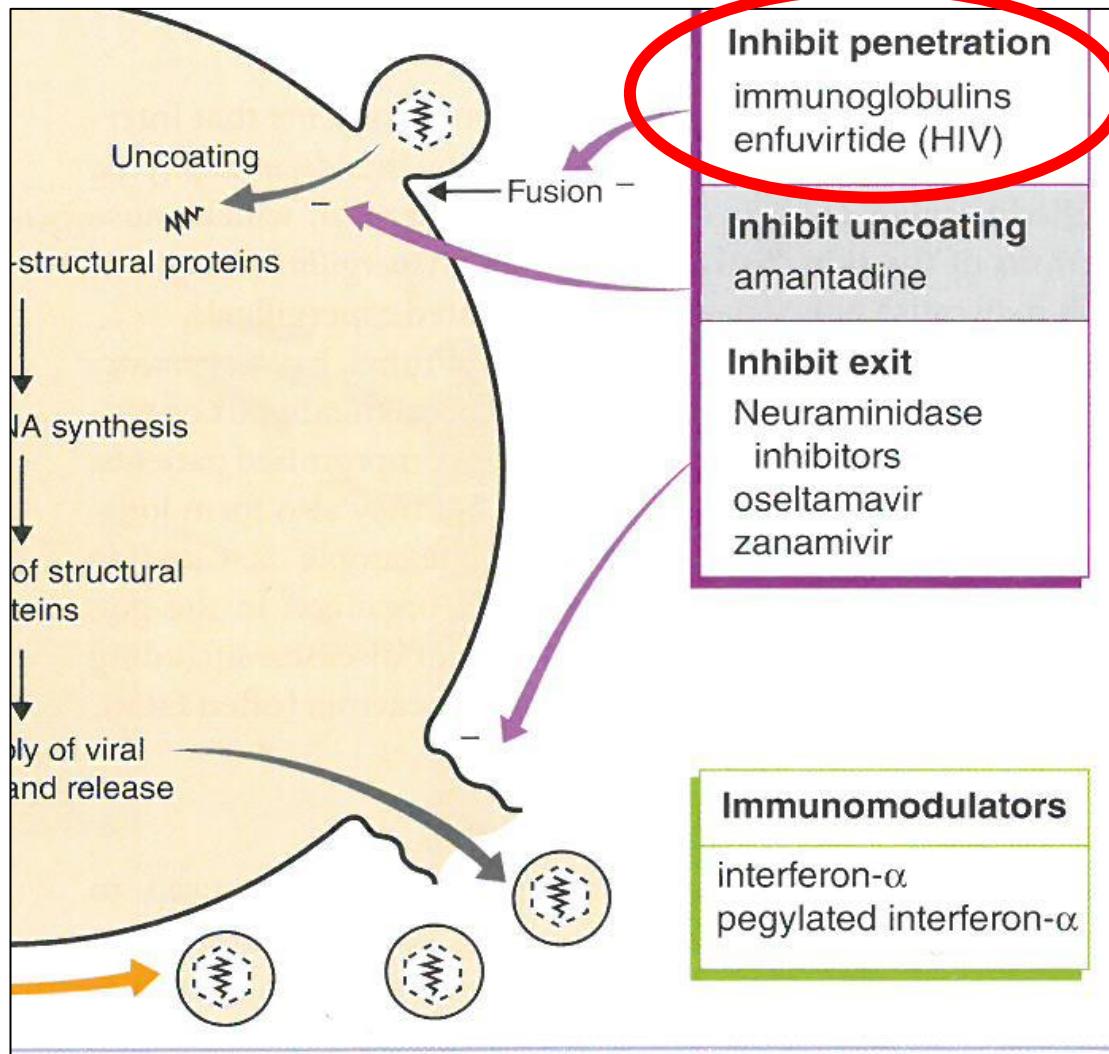


# Success of HIV antiretroviral therapy

**Antiviral drug treatment is converting a fatal disease into a chronic illness with normal life expectancy**



# HIV Viral Entry into Host cell



## HIV Fusion Inhibitor

**Enfuvirtide (2003)**

36 amino acid peptide

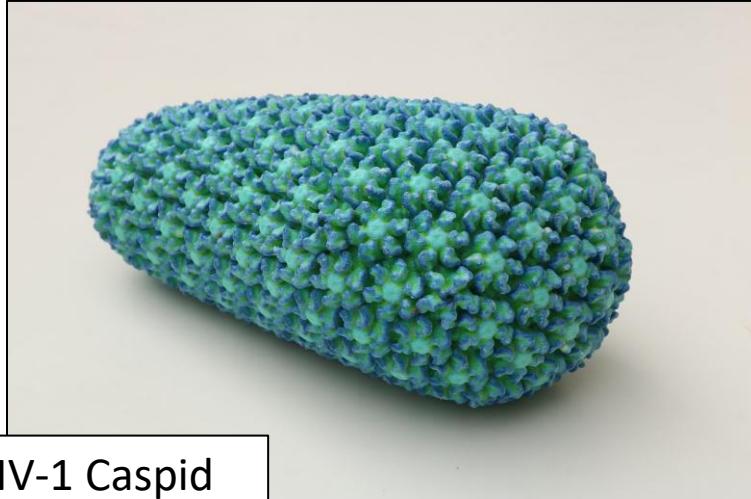
Mimics the domain (gp41) of the HIV viral membrane (gp41) involved in fusion with the host cell.

Binds to host cell preventing the formation of an entry pore for the capsid of the virus

Subcutaneous injection

Salvage use in multi-drug resistant HIV

# Capsid Inhibitor - Lenacapavir



HIV-1 Capsid



6 monthly SC injection

## **CASPID**

Conical protein shell (24kD protein polymer) which encases the viral genome/enzymes within the mature viral particle

## **LENACAPAVIR**

Capsid inhibitor – stabilises capsid structure,  
prevents capsid disassembly

6 monthly injection, initial cost - \$28,000/year

Indication –Prep & resistant organisms

\* Now available to low-middle income countries \$40 a year  
UK - Limited at moment – trials for Prep in women

# Can HIV be Cured?

(can you live free from HIV infection in the absence of antiretroviral drugs)

**Berlin Patient**



Timothy Brown

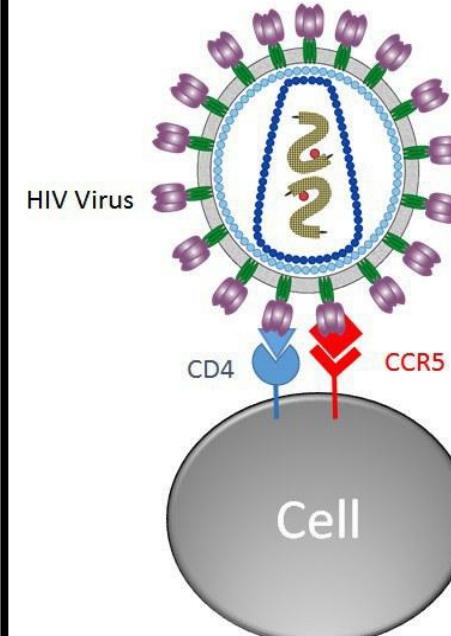
**Berlin Patient**

Acute myeloid leukaemia -  
two stem cell transplants  
from CCR5-delta 32 donor.  
Free from HIV infection  
without retroviral therapy  
for 10 years

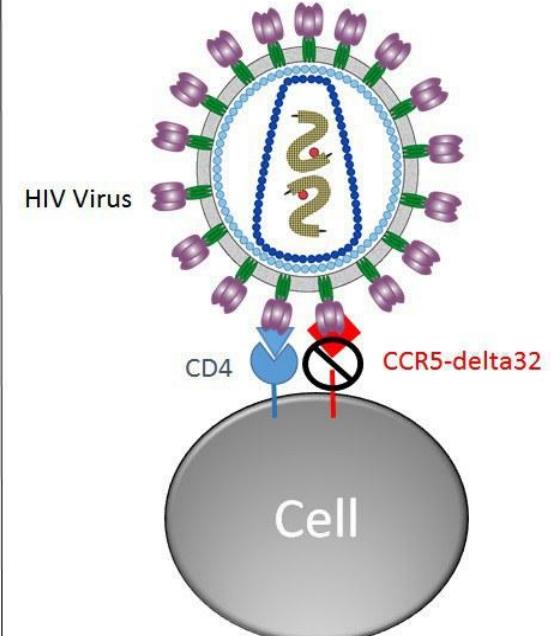
**London Patient**

Bone marrow transplant  
from HIV resistant patient  
of same blood group for  
treatment of Hodgkin's  
lymphoma

**Infection**



**NO Infection**



# Important Antiviral Drugs

## General

- Aciclovir
- Ganiciclovir
- Nirsevimab
- Oseltamivir
- Peginterferon 2 alpha \*

## HIV

- Zidovudine
- Efavirenz
- Emtricitabine
- Tenofovir
- Dolutegravir
- Saquinavir
- Ritonavir
- Enfuvirtide