

Antiviral Agents

Dr J Haylor,
Medicine 2025

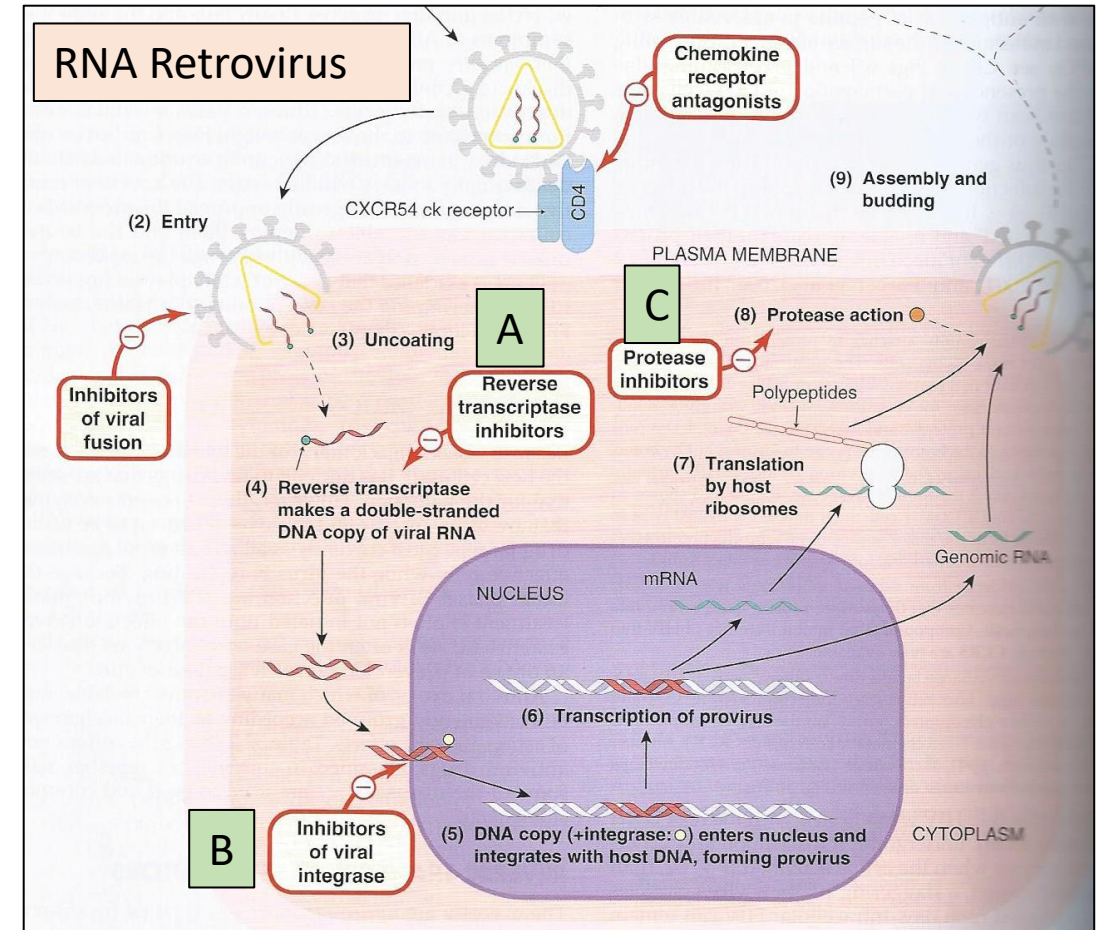
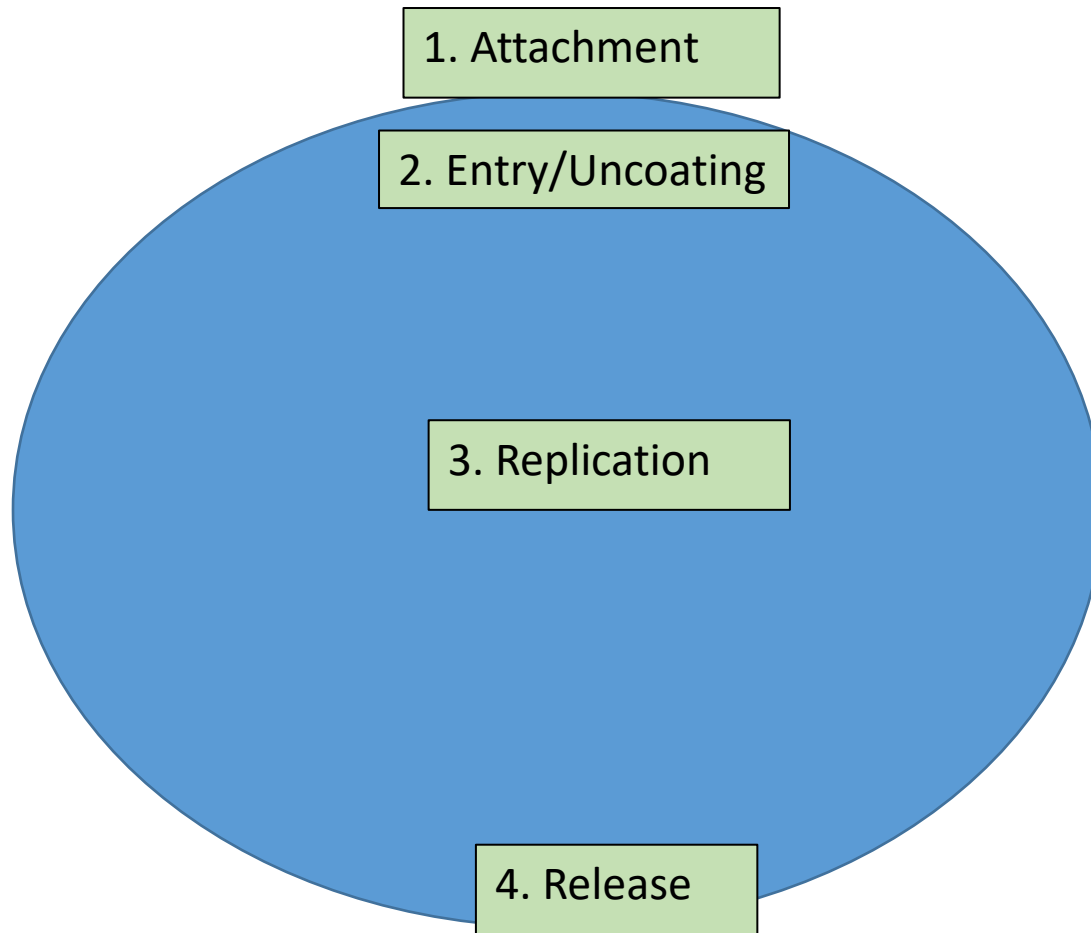
Learning Outcomes

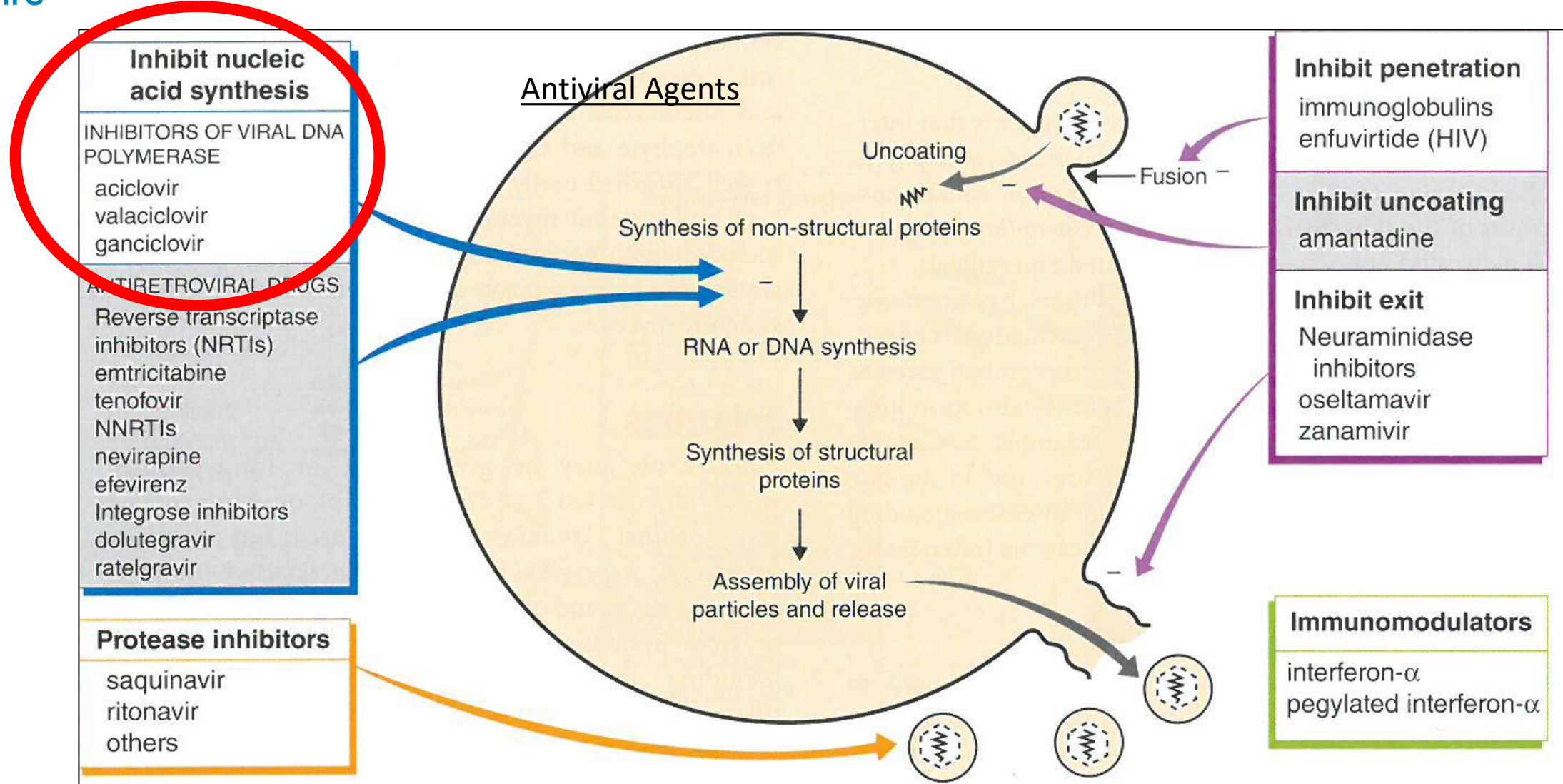
To understand the pharmacological basis for the therapeutic use and adverse effects of antiviral drugs.

1 – Herpes, influenza, hepatitis C.

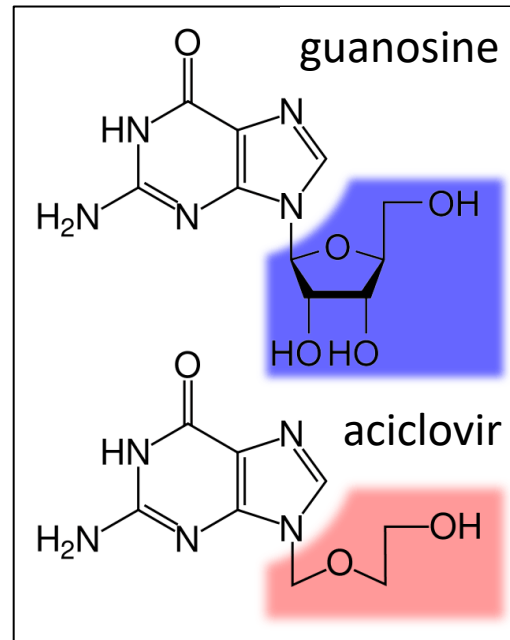
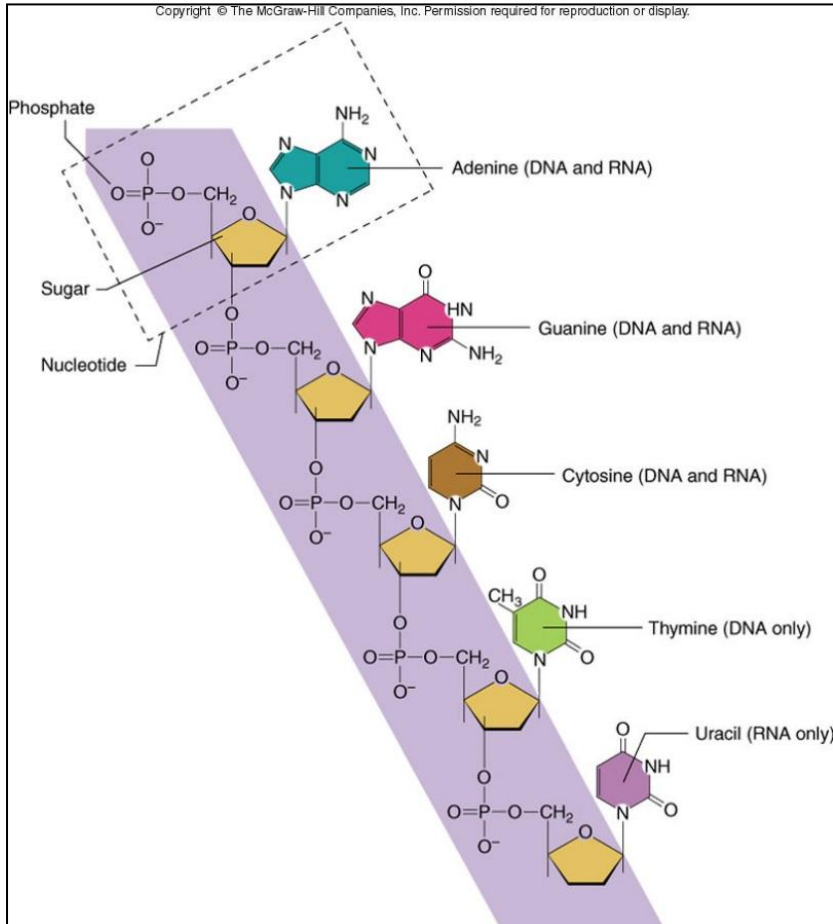
2 - HIV/AIDS

Cellular Targets for Antiviral Drugs



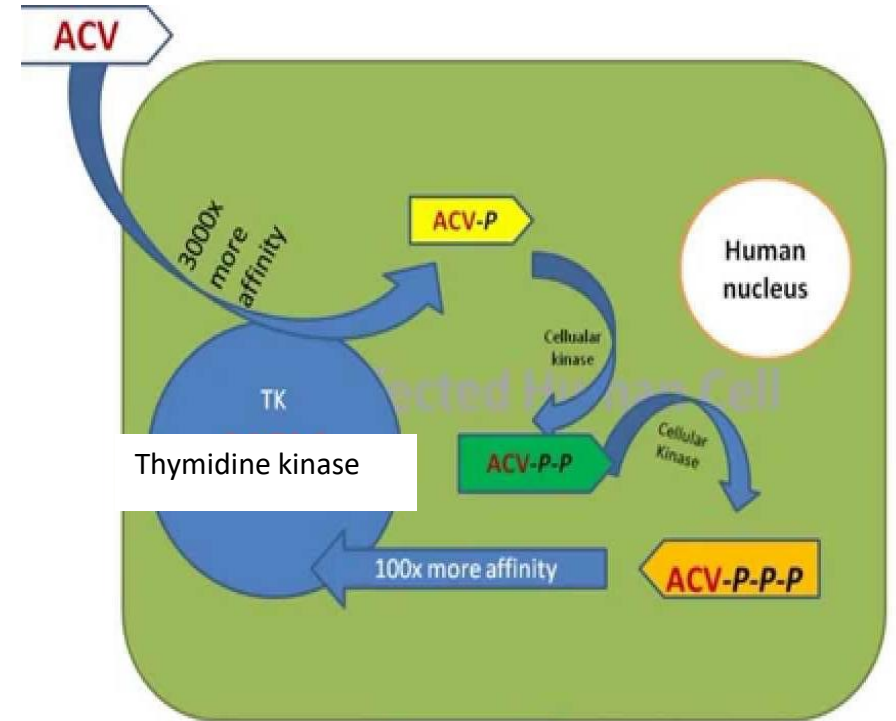


DNA Polymerase Inhibitors



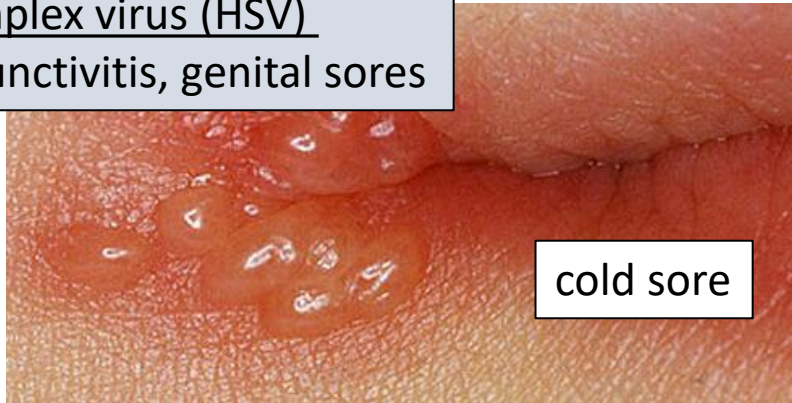
Analogue of the nucleoside guanosine

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

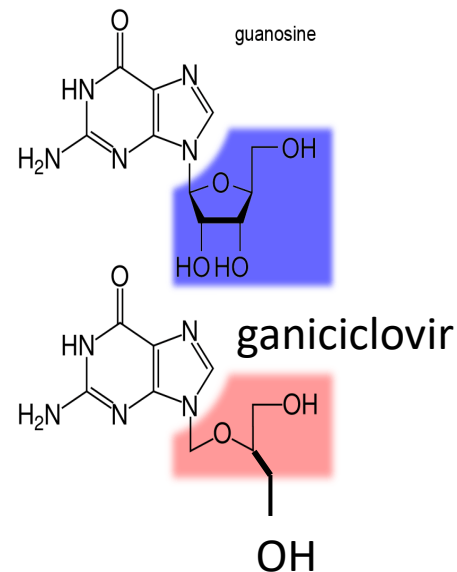
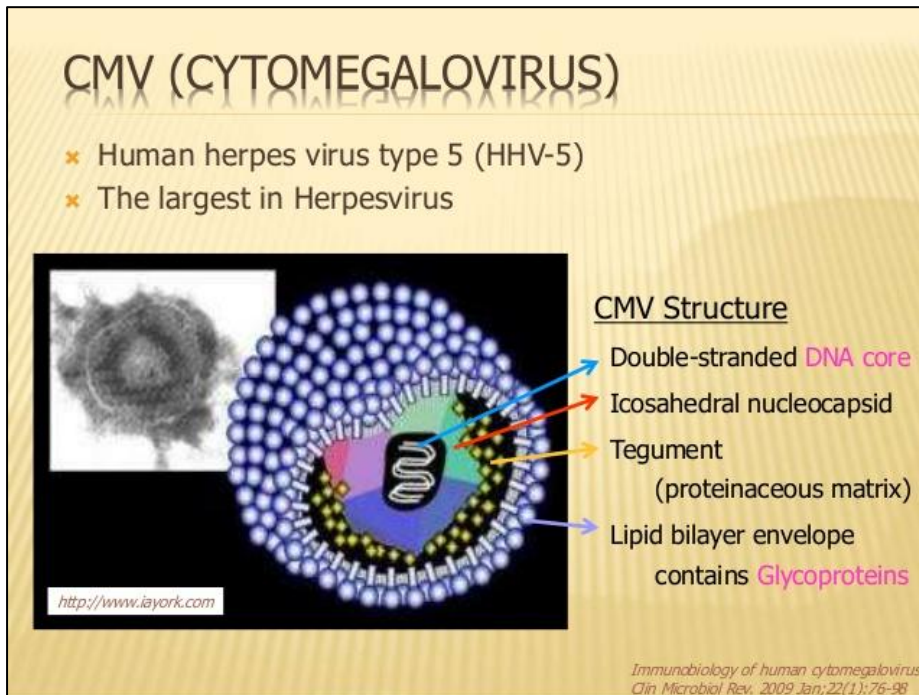
Valaciclovir – prodrug of aciclovir

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

Famciclovir – prodrug of penciclovir

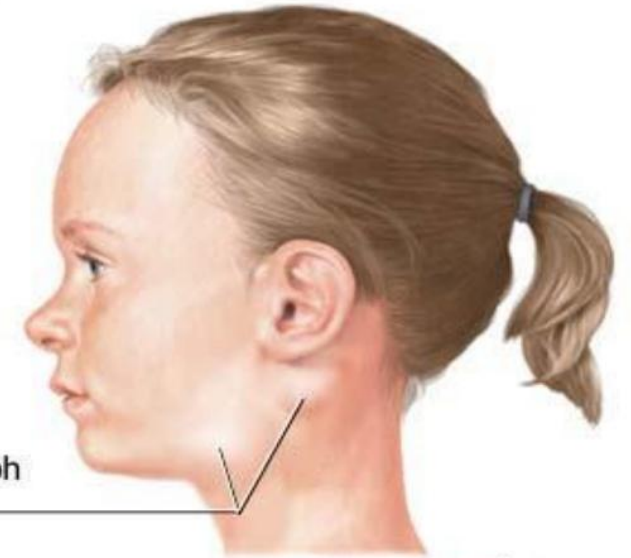
Ganaciclovir

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



Mononucleosis causes:

- Fever
- Fatigue
- Sore throat
- Swollen lymph glands



Dr.T.V.Rao MD

 ADAM

Ganaciclovir, 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

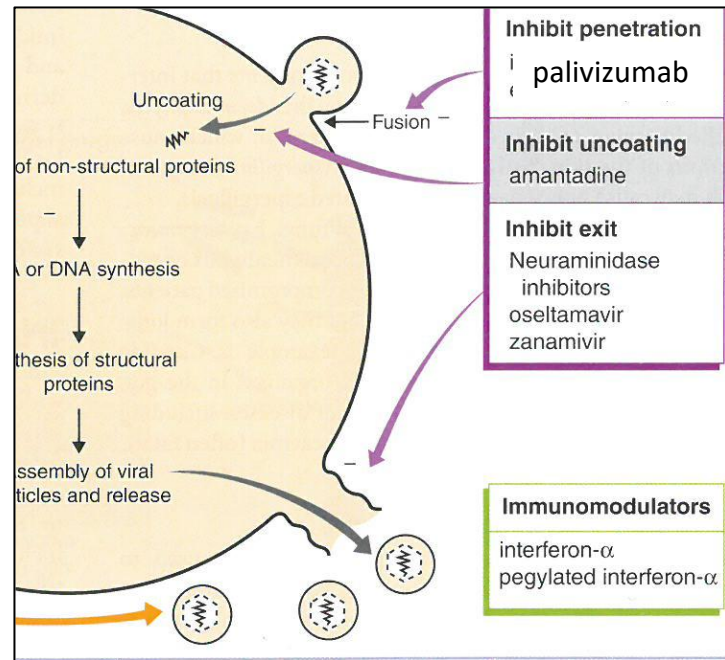
Palivizumab (1998)

Nirsevimab (2022)

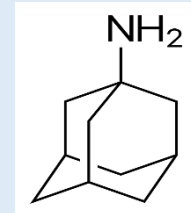
Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infection in infants.

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

Single 6 monthly injection
- reduces hospitalisation by 50%



Amantadine

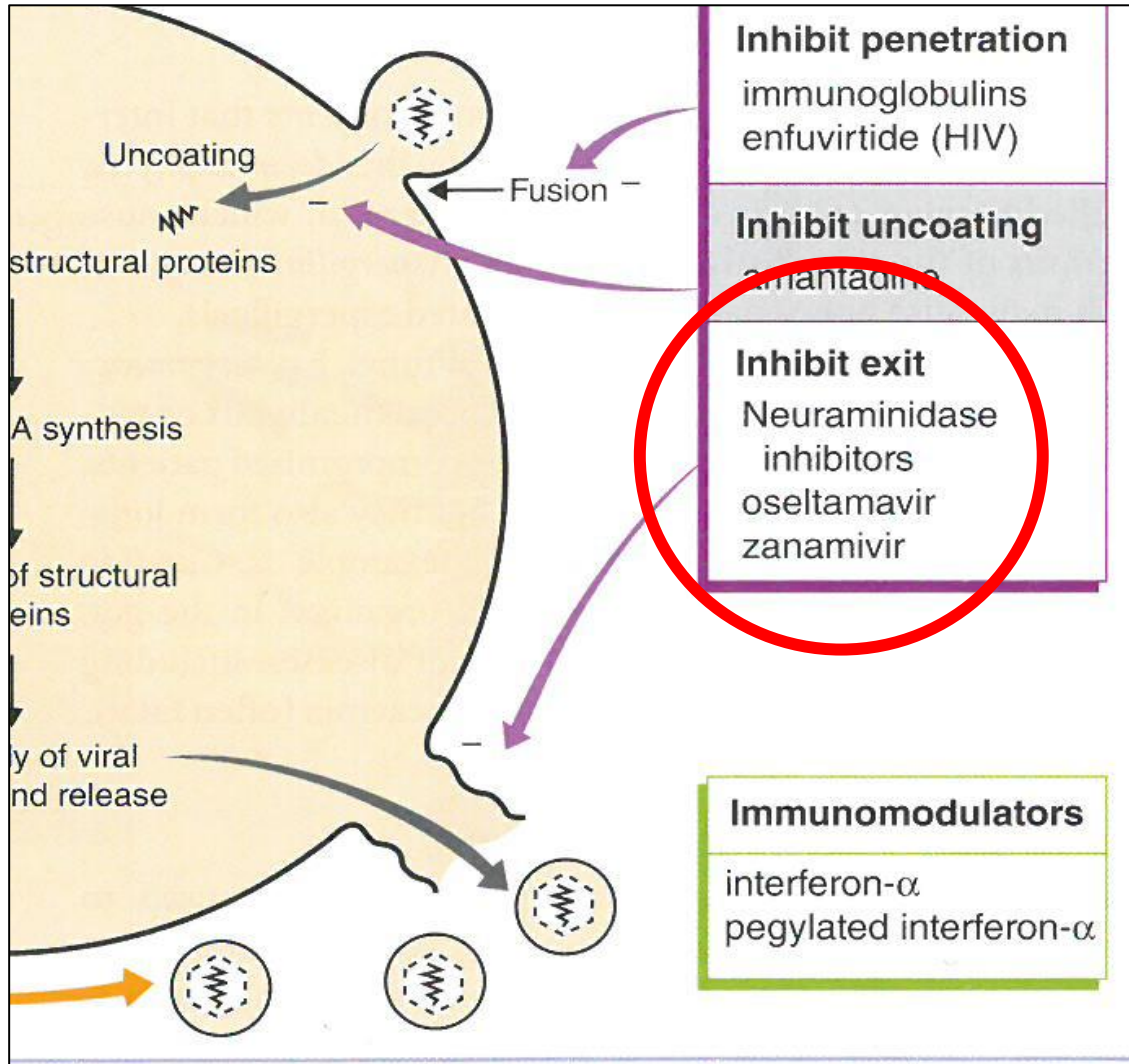


Following endocytosis the influenza virus is localised in acidic vacuoles. Acidification starts the process of viral replication by releasing ribonucleoproteins.

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



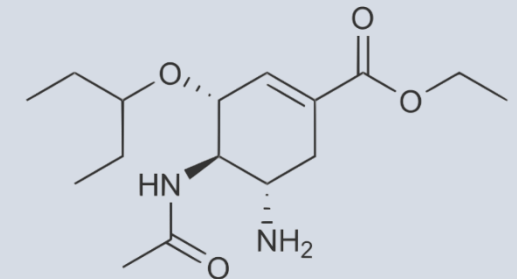
Neuroaminidase Inhibitors

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.

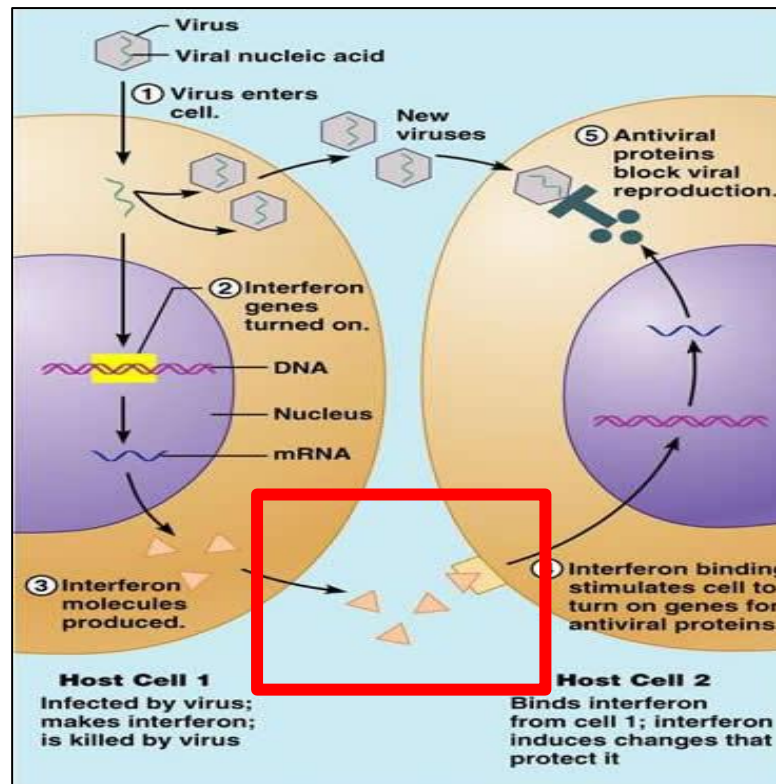
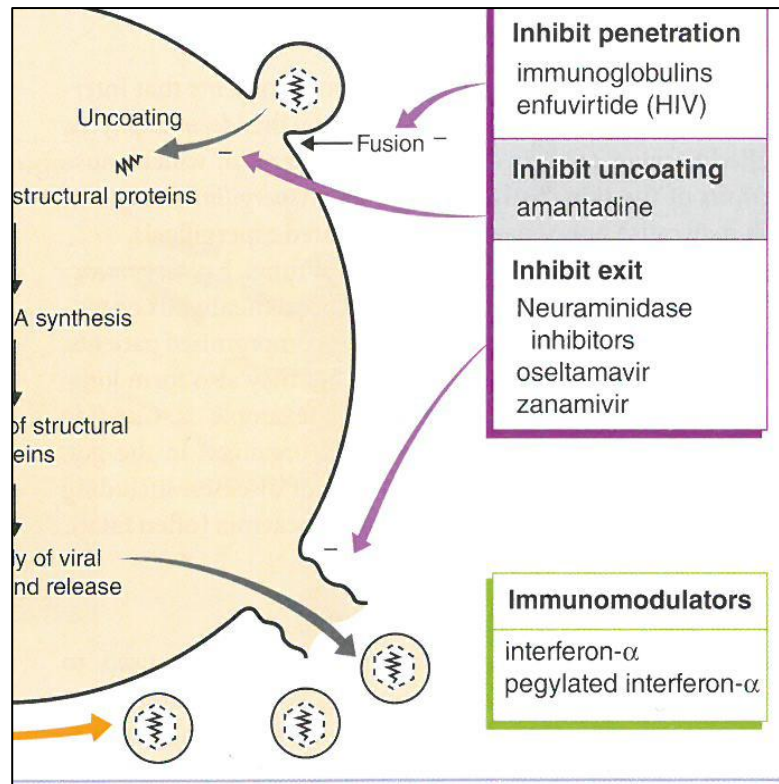


Star anise



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.

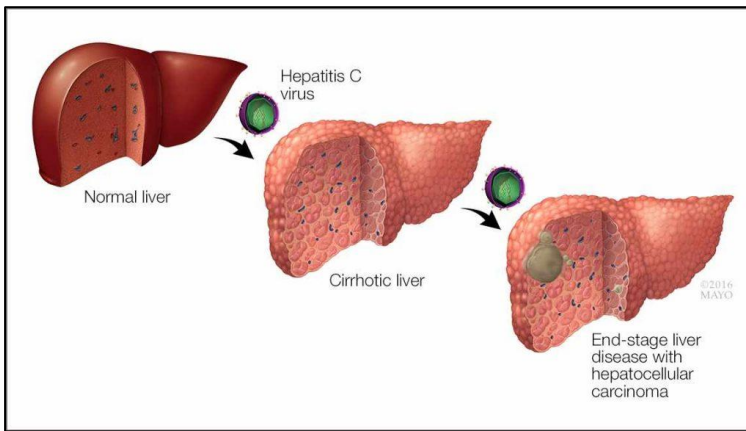
Important use in hepatitis B/C as well as HIV infection.

Hepatitis C

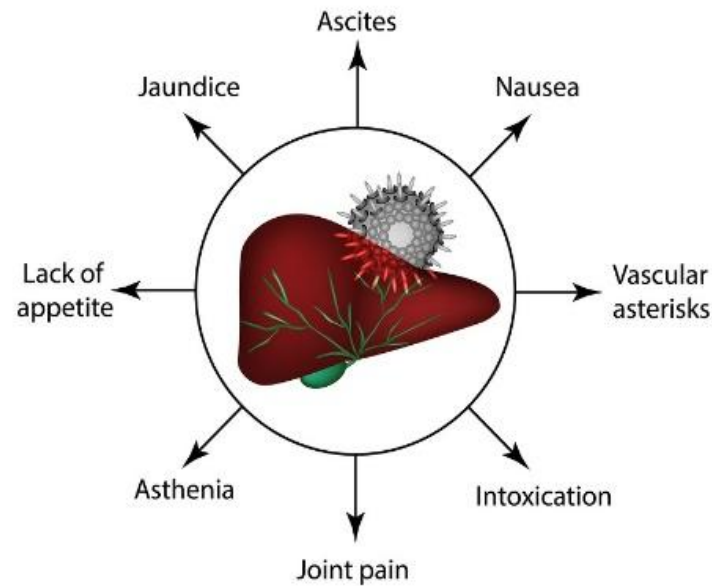
Hepatitis C

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)

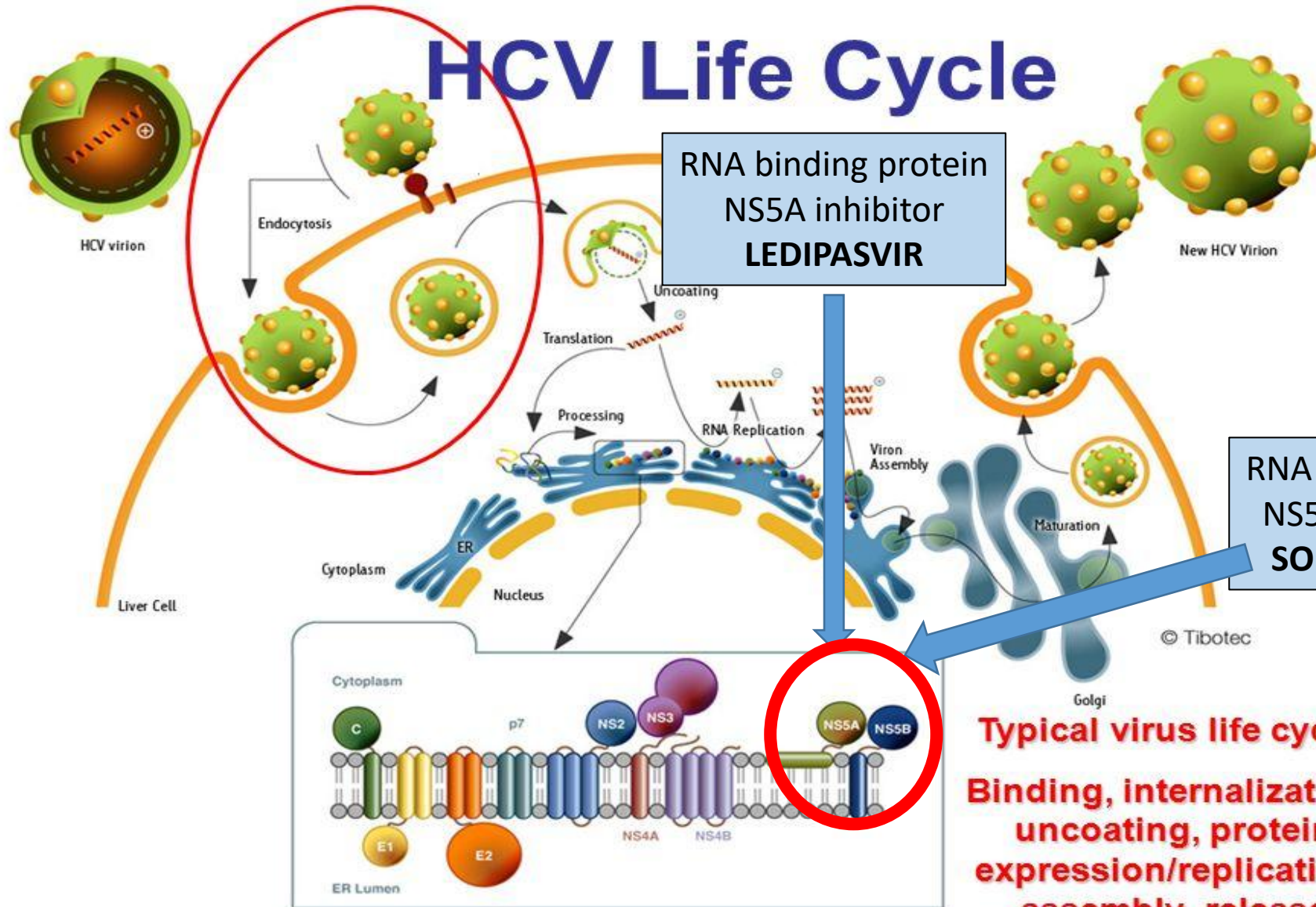
+ Sofosbuvir (NS5B inhibitor)

Once daily oral treatment, 3-month course


(99% cure, cost?)

Adverse effects (reactivate hep B, bradycardia)

Replacing interferon-based therapies



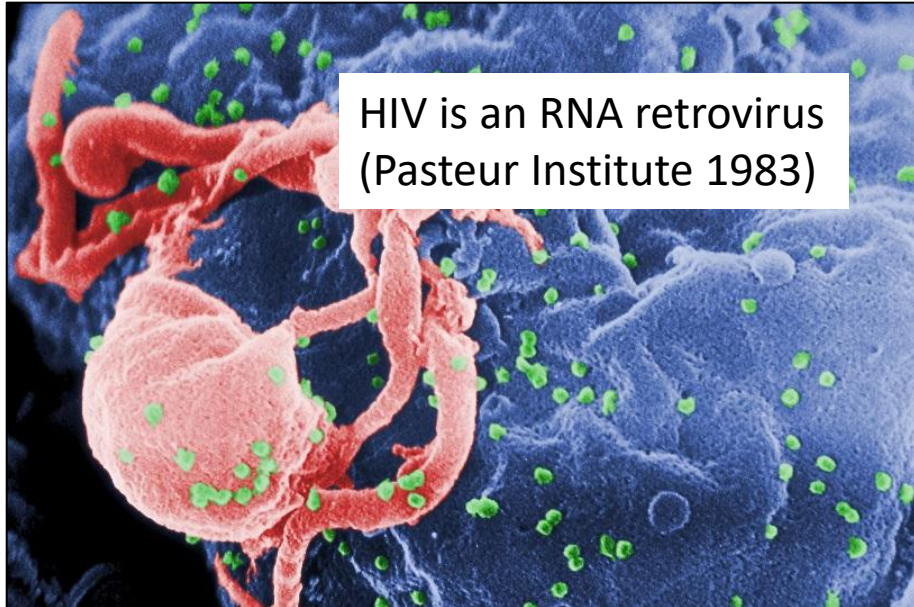
Typical virus life cycle:
Binding, internalization,
uncoating, protein
expression/replication,
assembly, release

A detailed 3D rendering of HIV virus particles. The viruses are spherical with a textured, reddish-brown surface and prominent, spiky, purple-blue projections. They are set against a blurred background of other cellular structures in shades of pink and blue.

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

HIV infection

Human Immunodeficiency Virus (HIV)



2024

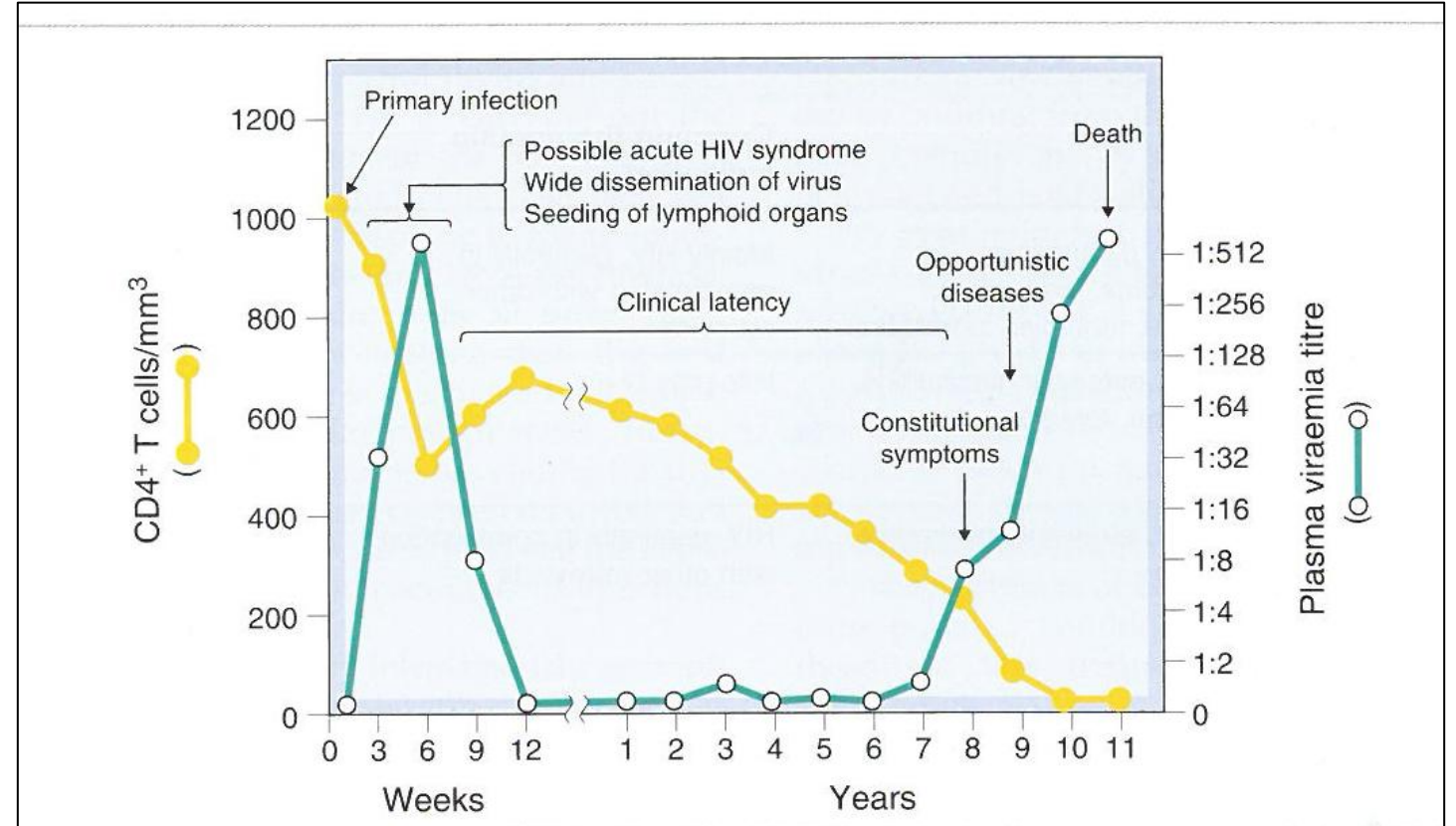
40 million have AIDS

2/3 in sub-Saharan Africa

1.3 million newly infected each year

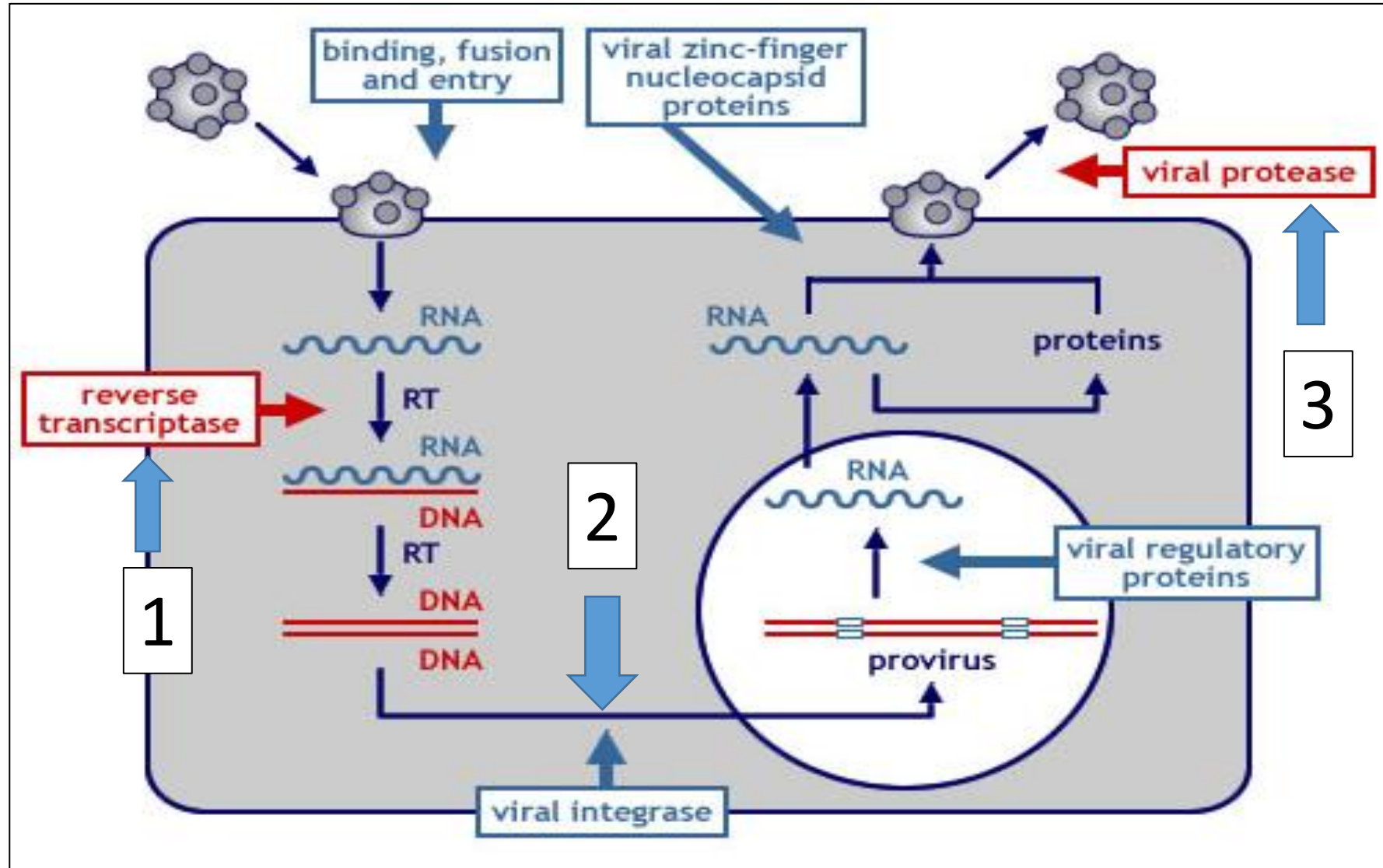
30 million access to retroviral drugs

(90 million infected/42 million died)

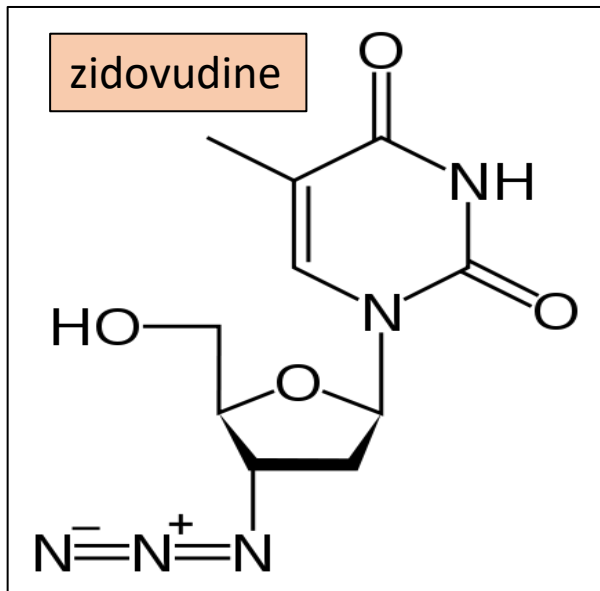
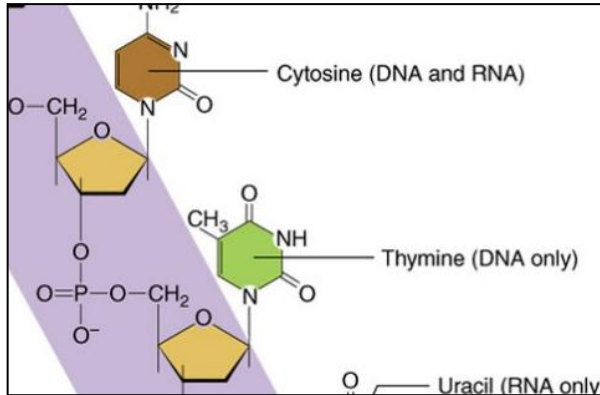


Rang & Dale Pharmacology fig 52.4 p647

Antiviral Drugs for HIV (RNA Retrovirus)



Reverse Transcriptase Inhibitors (NRTI): **NUCLEOSIDES**



Zidovudine (azidothymidine AZT 1986)

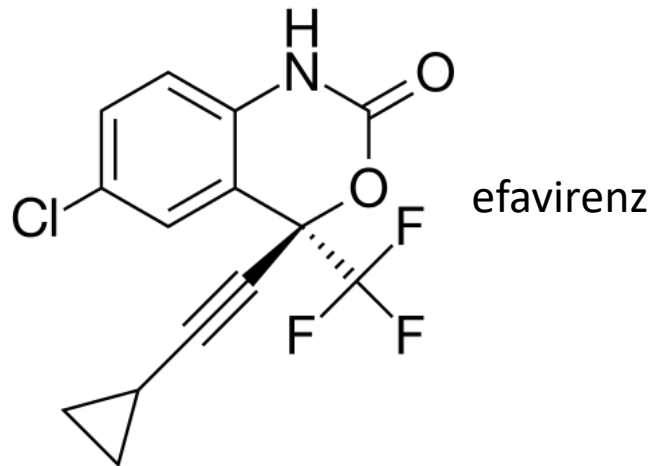
1st treatment approved for HIV

– 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)

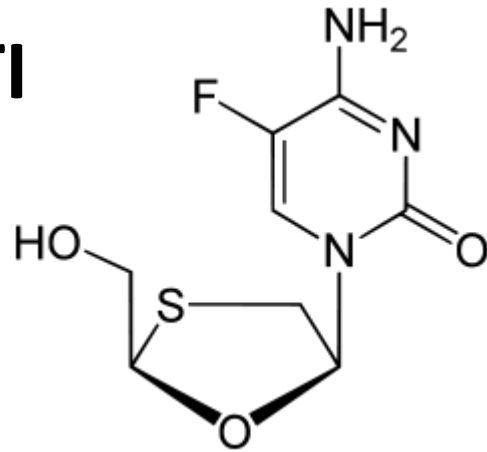
(high risk groups)

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

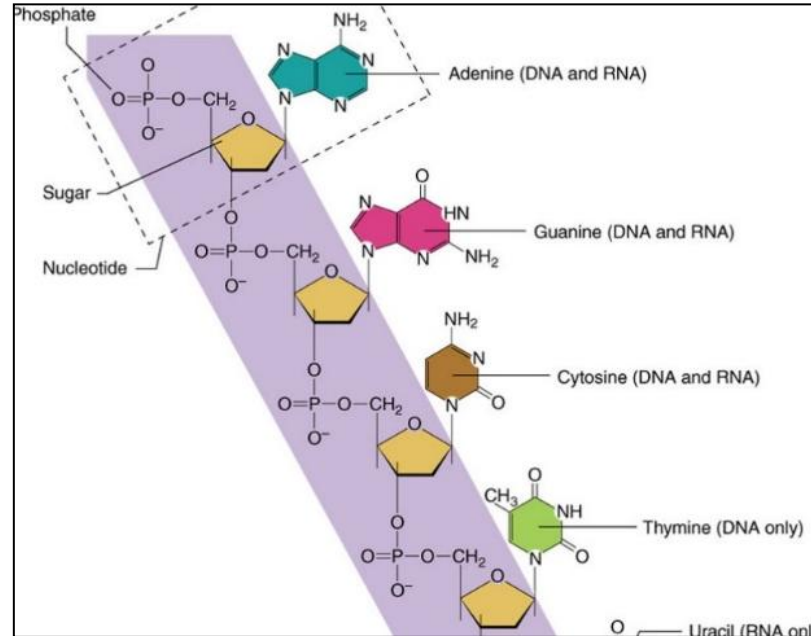
Potential treatment issues over adherence

PrEP Therapy

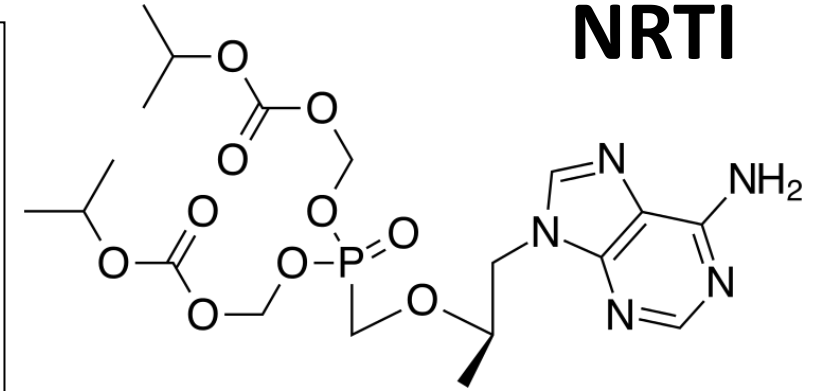
NRTI



Emtricitabine
cytidine analogue



NRTI



Tenofovir disproxil
(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 disproxil [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)

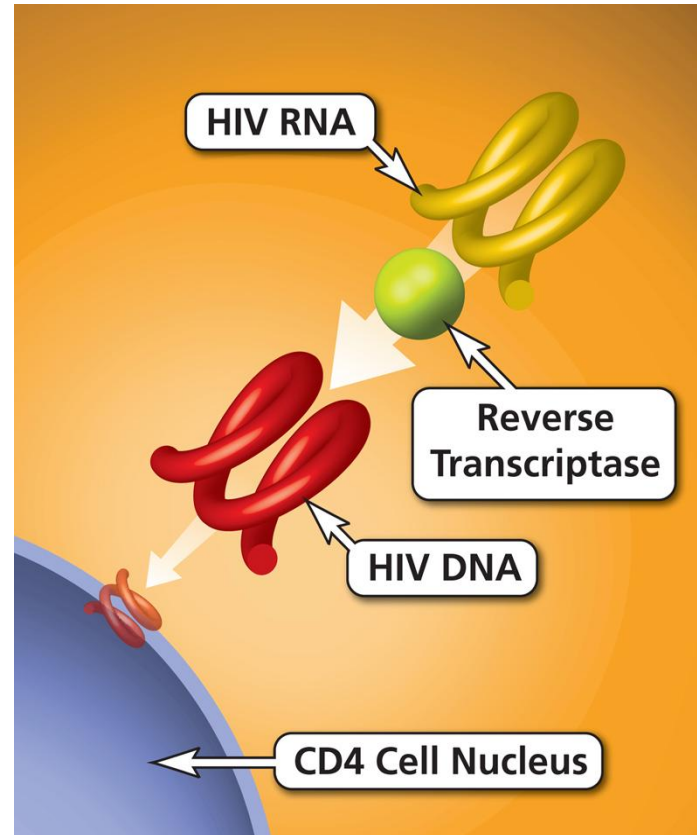
Preferred initial regimen

(WHO 2013)

tenofovir

+ **lamivudine** (or emtricitabine)

+ **efavirenz**



Atripla

Efavirenz 600mg

Emtricitabine 300mg

Tenofovir disoproxil 300mg

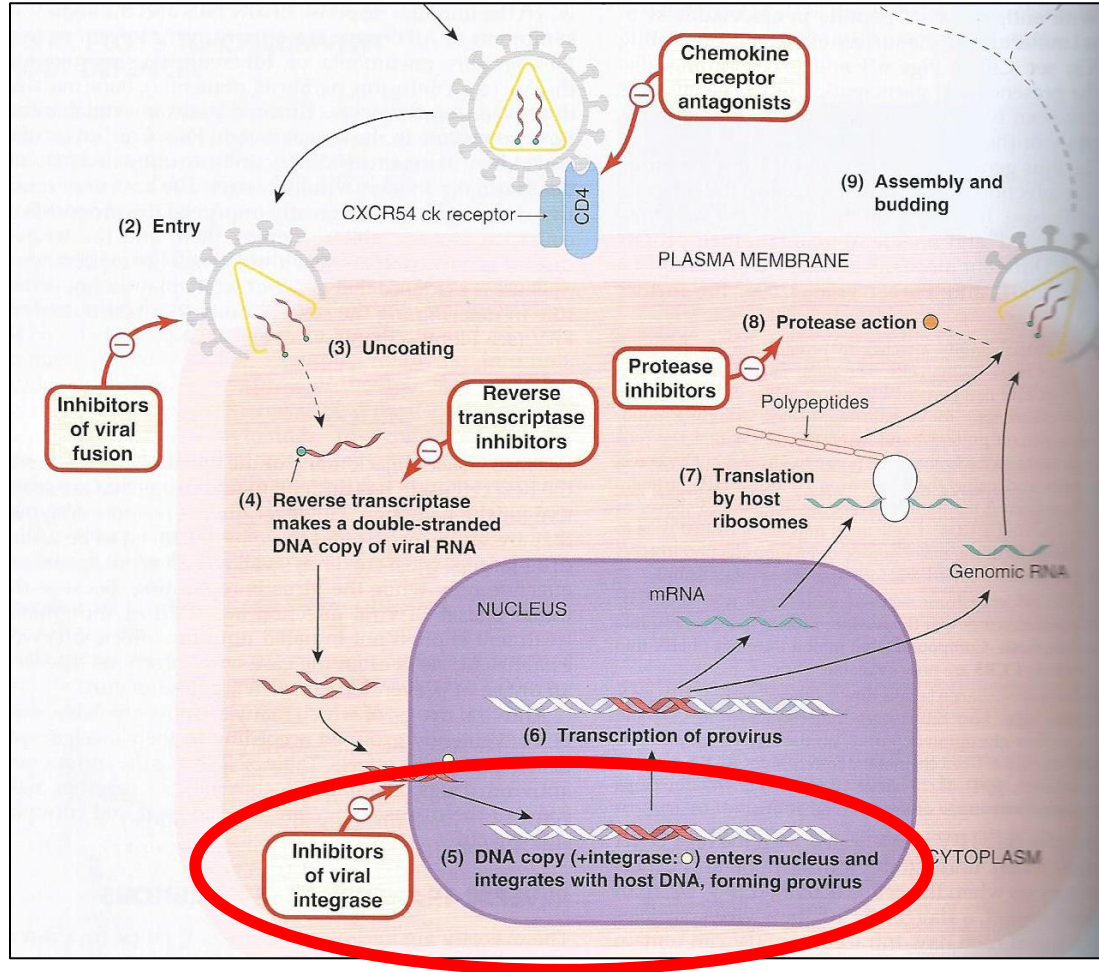


Combined once a day fixed dose combinations improves

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

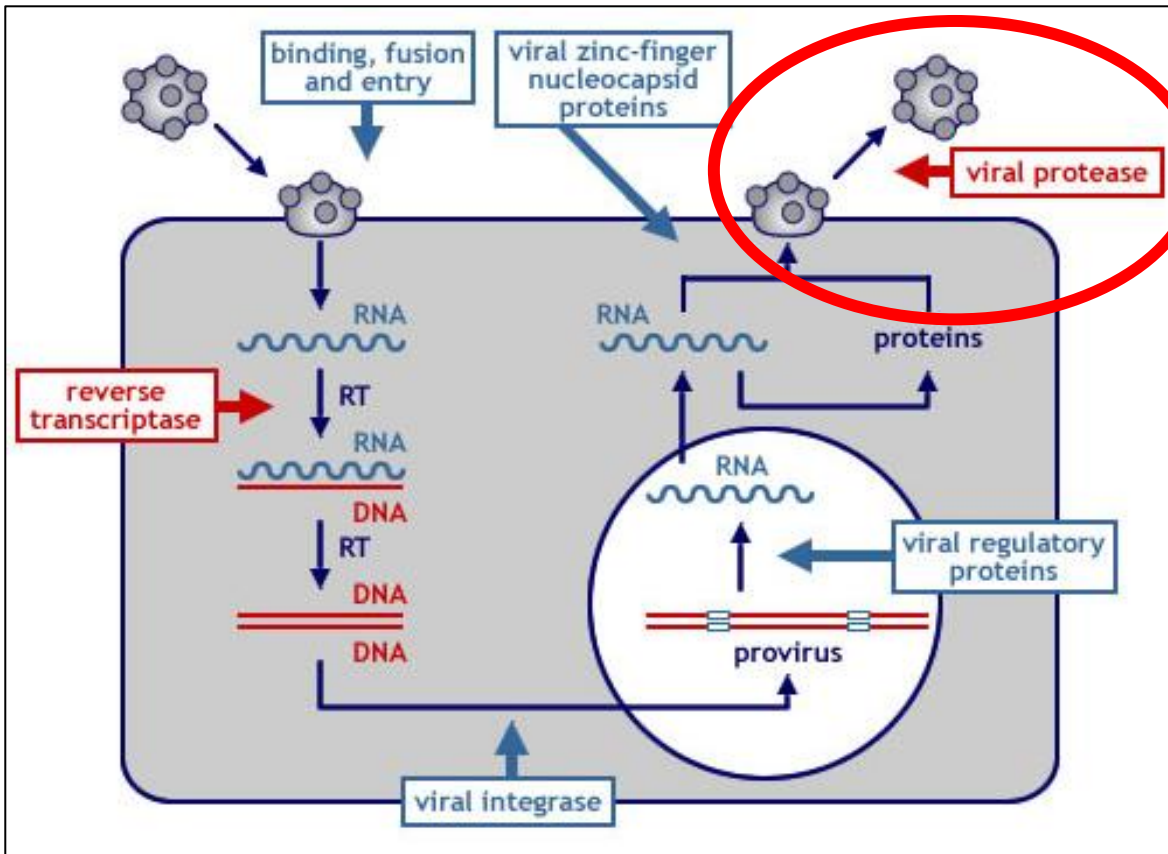
rashes are common, can be severe
(muscle pain/mouth ulceration/angioedema)

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

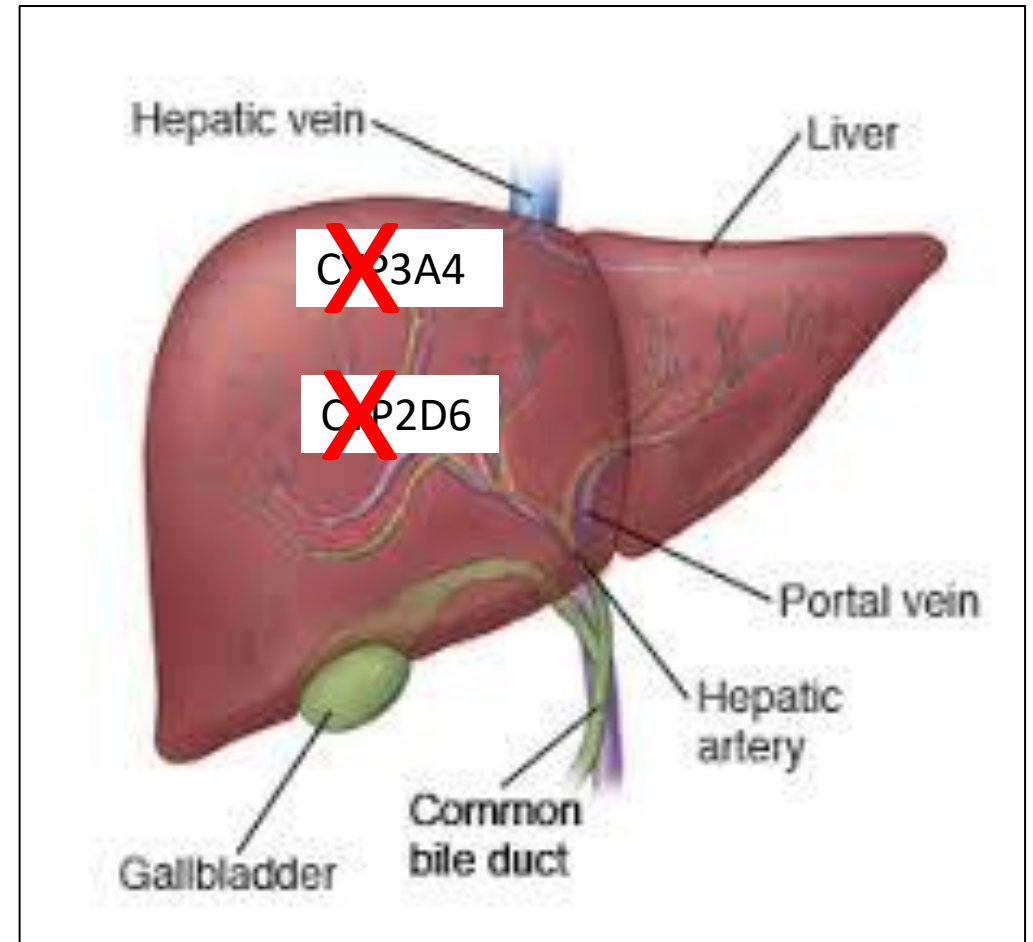
Ritonavir

Inhibits major drug metabolising enzymes -
CYP3A4 & CYP2D6

Induces CYP1A2

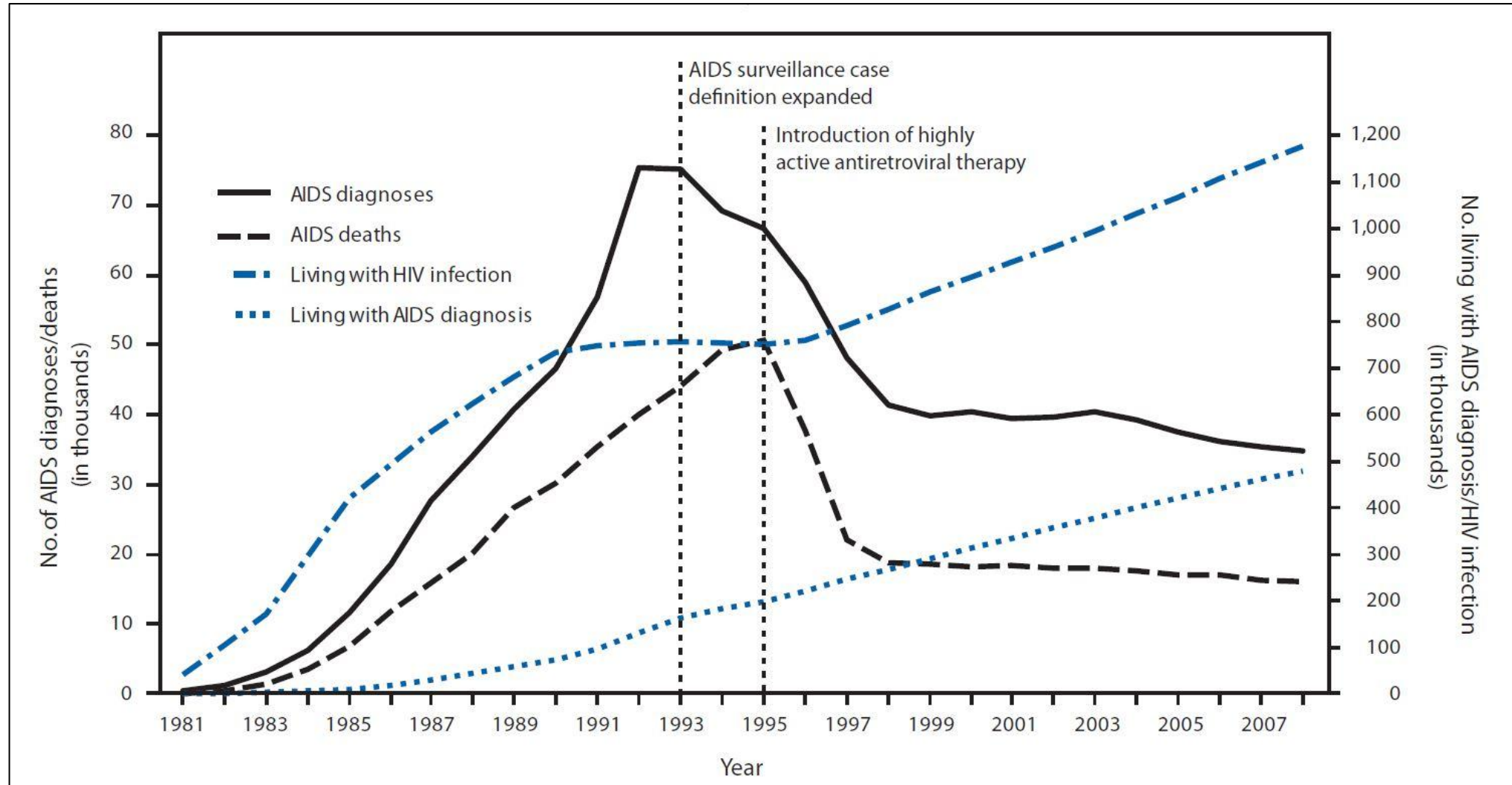
New use in low dose (100mg)
elevate plasma levels of other protease
inhibitors such as saquinavir.

Combination tablet
lopinavir with ritonavir

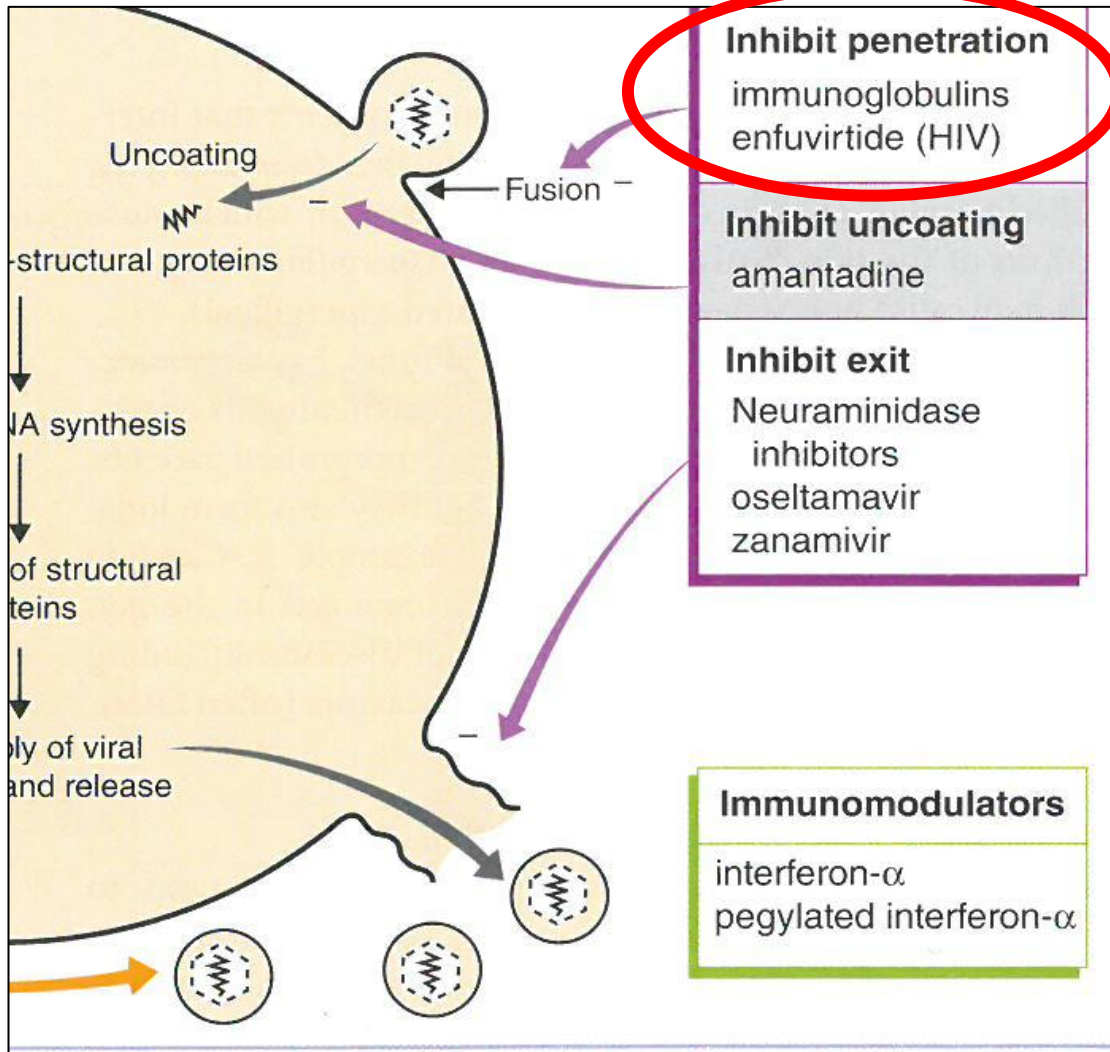


Success of HIV antiretroviral therapy

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

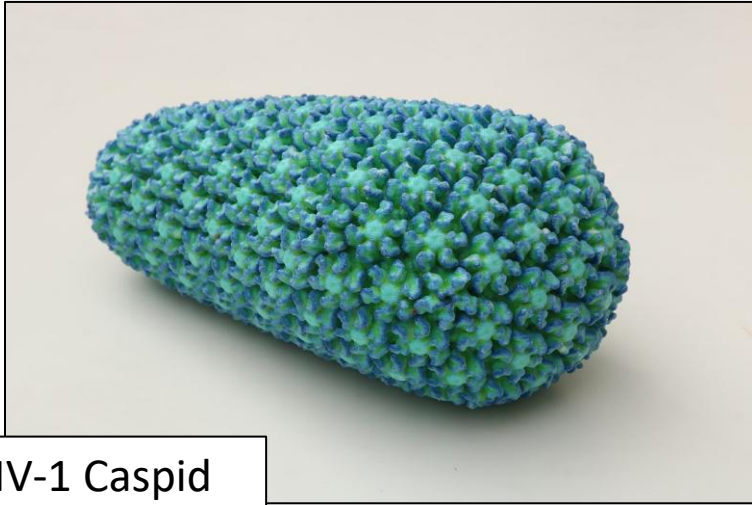
Mimics the domain (gp41) of the HIV viral membrane (gp41) involved in fusion with the host cell.

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

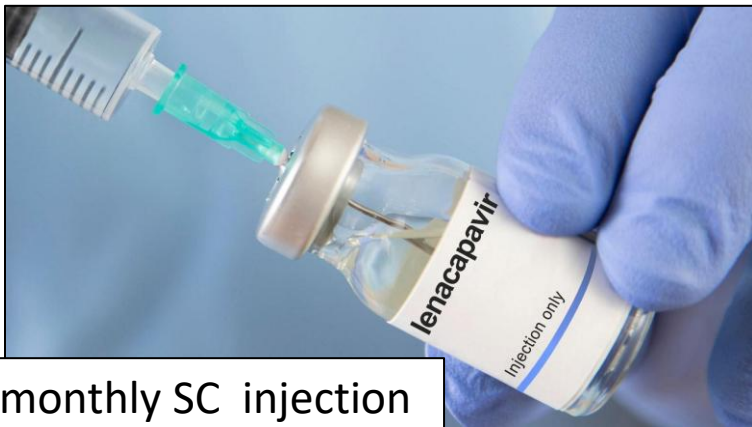
Subcutaneous injection

Salvage use in multi-drug resistant HIV

Capsid Inhibitor - Lenacapavir



HIV-1 Caspid



6 monthly SC injection

CASPID

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

LENACAPAVIR

Caspid 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?

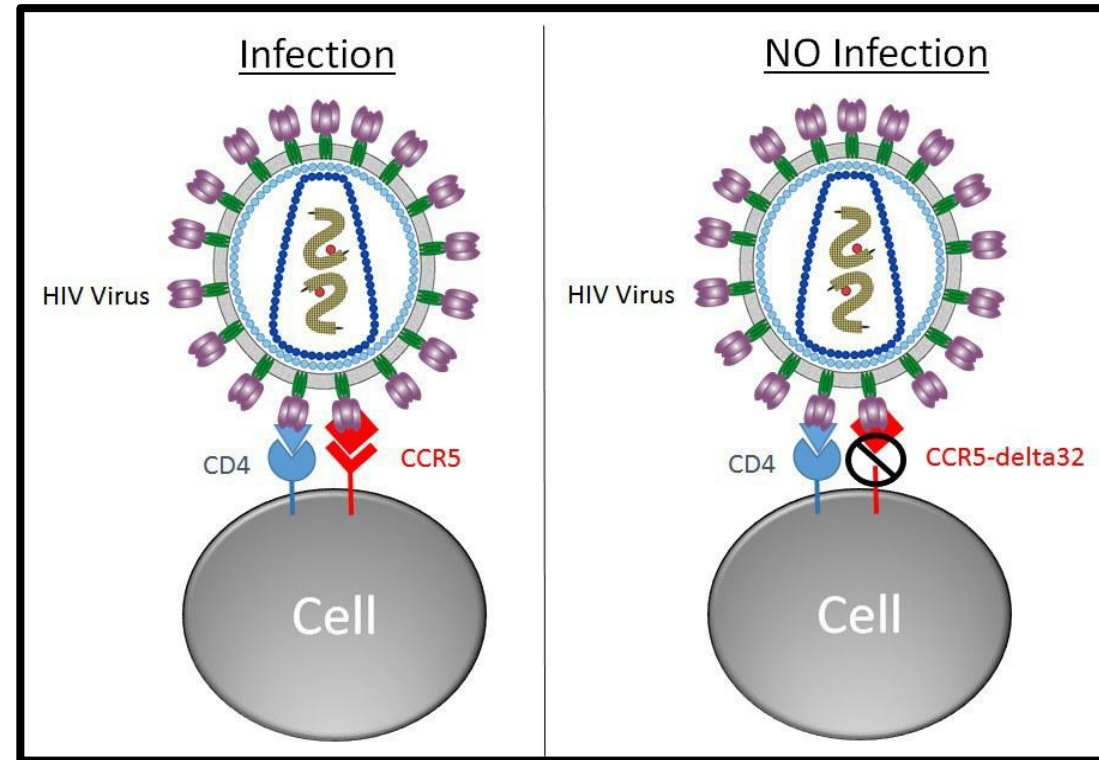
(can you live free from HIV infection in the absence of antiretroviral drugs)

Berlin Patient

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

Timothy Brown



Important Antiviral Drugs

General

- **Aciclovir**
- **Ganaciclovir**
- **Nirsevimab**
- **Oseltamivir**
- **Peginterferon 2 alpha ***

HIV

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