ANTIVIRAL AGENTS

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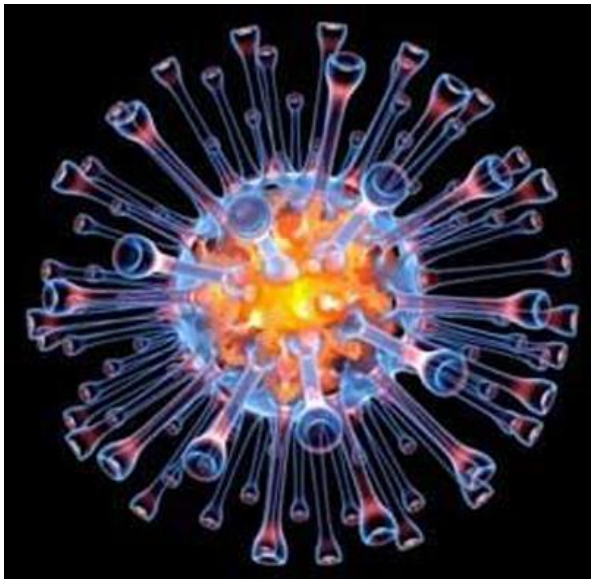
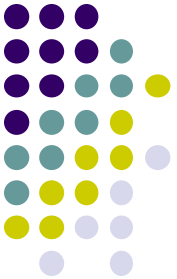


ANTIVIRAL AGENTS

Drugs for herpes



- ***acyclovir -*** guanine analogue
- ***ganciclovir -*** guanine analogue
- ***foscarnet –*** pyrophosphate analogue

Acyclovir

Mechanisms of action

acyclovir

viral thymidine kinase

⇩

acyclovir monophosphate

host cell kinases

⇩

acyclovir triphosphate

competition with deoxyguanosine triphosphate for

viral DNA polymerase

⇩

inhibition of viral DNA replication

Acyclovir
Pharmacokinetics

- oral, i.v., topical
- incomplete absorption p.o. (15 – 30%), unabsorbed after topical application
- half-life 2.5 – 3 h in adults
- **preferential uptake by virus infected cells**
- high concentrations in kidney, liver, lungs, heart
- poor metabolism, renal excretion of majority of unchanged drug

Acyclovir
Indications

- Spectrum:

- ***Herpes simplex virus*** *(HSV)* ***1 & 2***
  (labialis, ocularis, genitalis, neonatal)

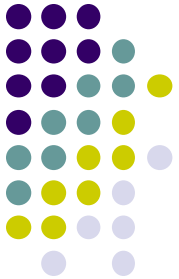
- ***Varicella zoster virus*** *(VZV)*

- **herpetic encephalitis, hepatitis**

- 10 x more potent against HSV than VZV

- no effective in treating postherpetic neuralgia
  (only against acute neuritis)

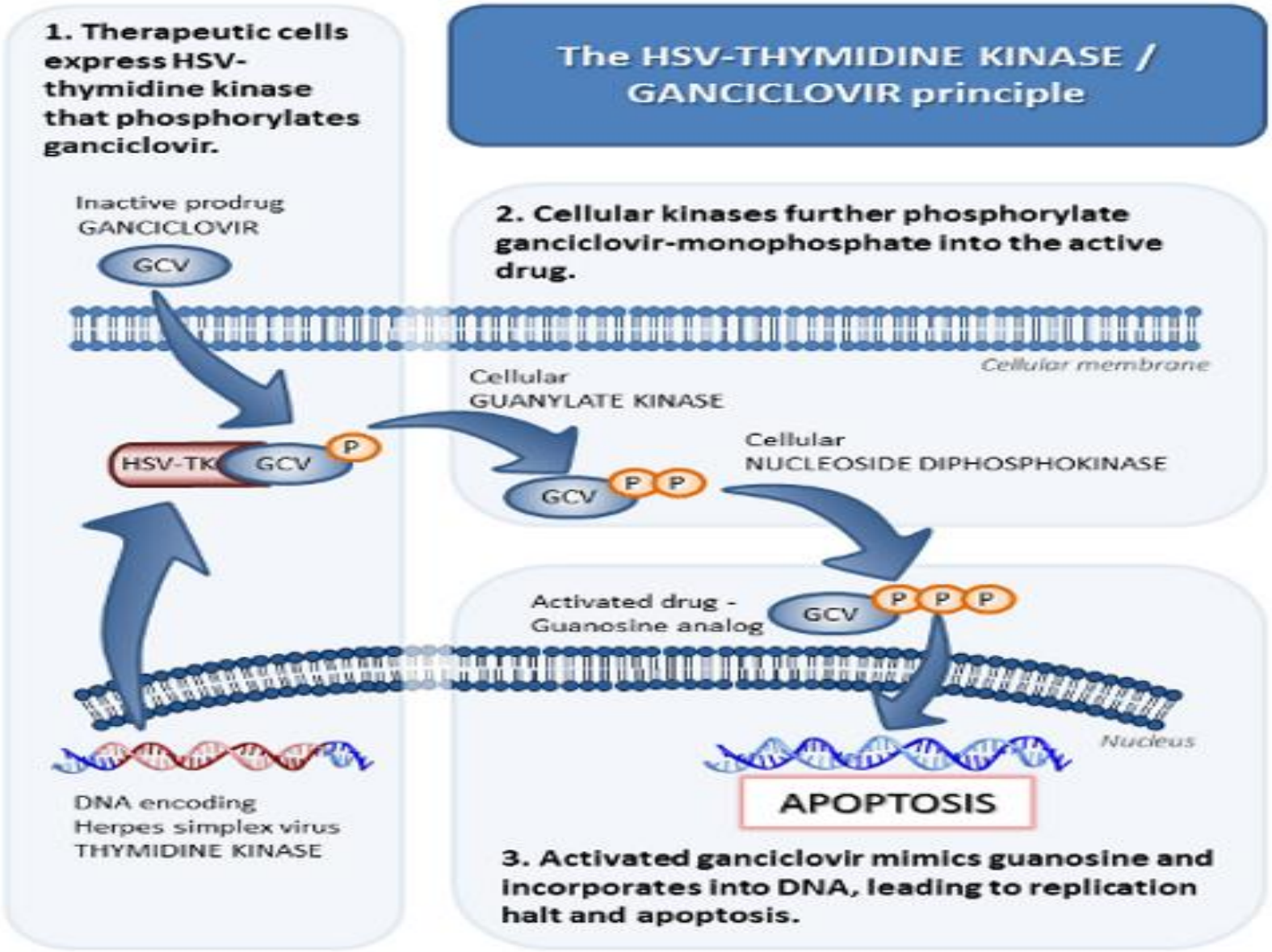
Acyclovir
Side effects



- **rare** local irritation (eye)
- **flebitis -** i.v.
- **neurological symptoms -** i.v. (very rare)
- **slow infusion & adequate hydration –** in i.v. to prevent crystalluria or interstitial nephritis

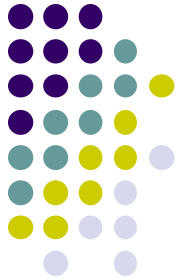
Ganciclovir

Mechanism of action



Ganciclovir

Spectrum & side effects



- Spectrum:
  - ***HSV***
  - ***VZV***
  - ***human herpes virus (HHV) 6 & 8***
  - ***CMV - cytomegalovirus*** (even in immunocompromised patients - such as those with HIV)

- dose-limiting adverse effects:
  - **myelosuppression**
  - **thrombocytopenia**
  - **anaemia**
  - **leukopenia**

- other:
  - crystaluria
  - mucositis, rash, fever
  - nausea, hepatotoxicity, diarrhea
  - seizures
  - hematotoxicity

Ganciclovir

Indications

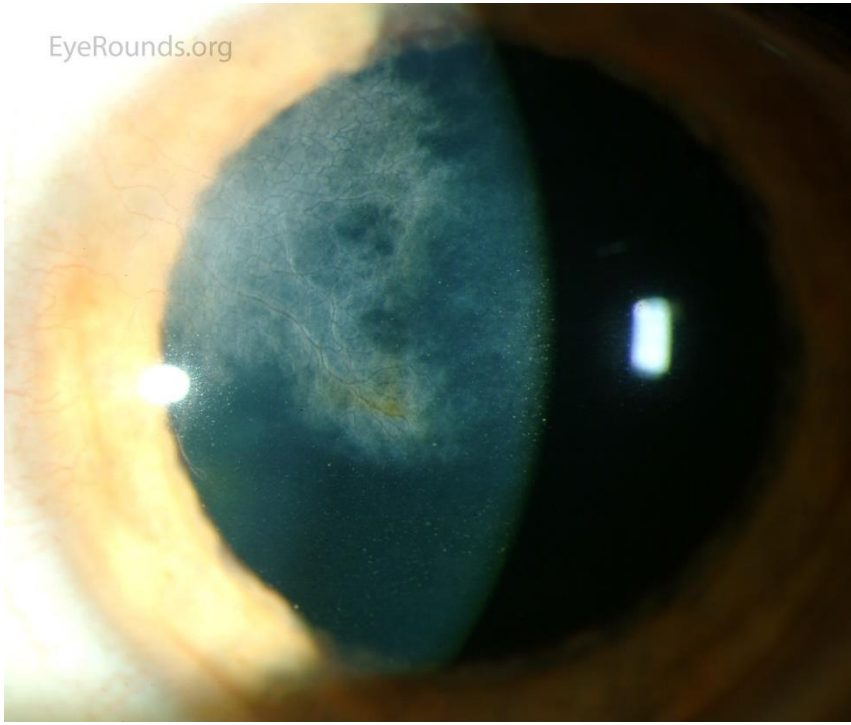
100 x more potent against CMV than ***acyclovir:***

- CMV colitis or esophagitis in HIV-infected patients
- CMV prevention in transplant recipients & HIV-infected patients
- Herpes epithelial keratitis (0.15% gel)
- CMV retinitis – i.v.

  Initial: 5 mg/kg BD for 14-21 days;

  Maintenance: 5 mg/kg or 6 mg/kg OD for 5 days/week

➢ + intraocularly



Foscarnet

Mechanisms of action

foscarnet does not require activation by

viral thymidine kinase

⇩

***foscarnet* acts as an inhibitor of**

viral RNA & DNA polymerase

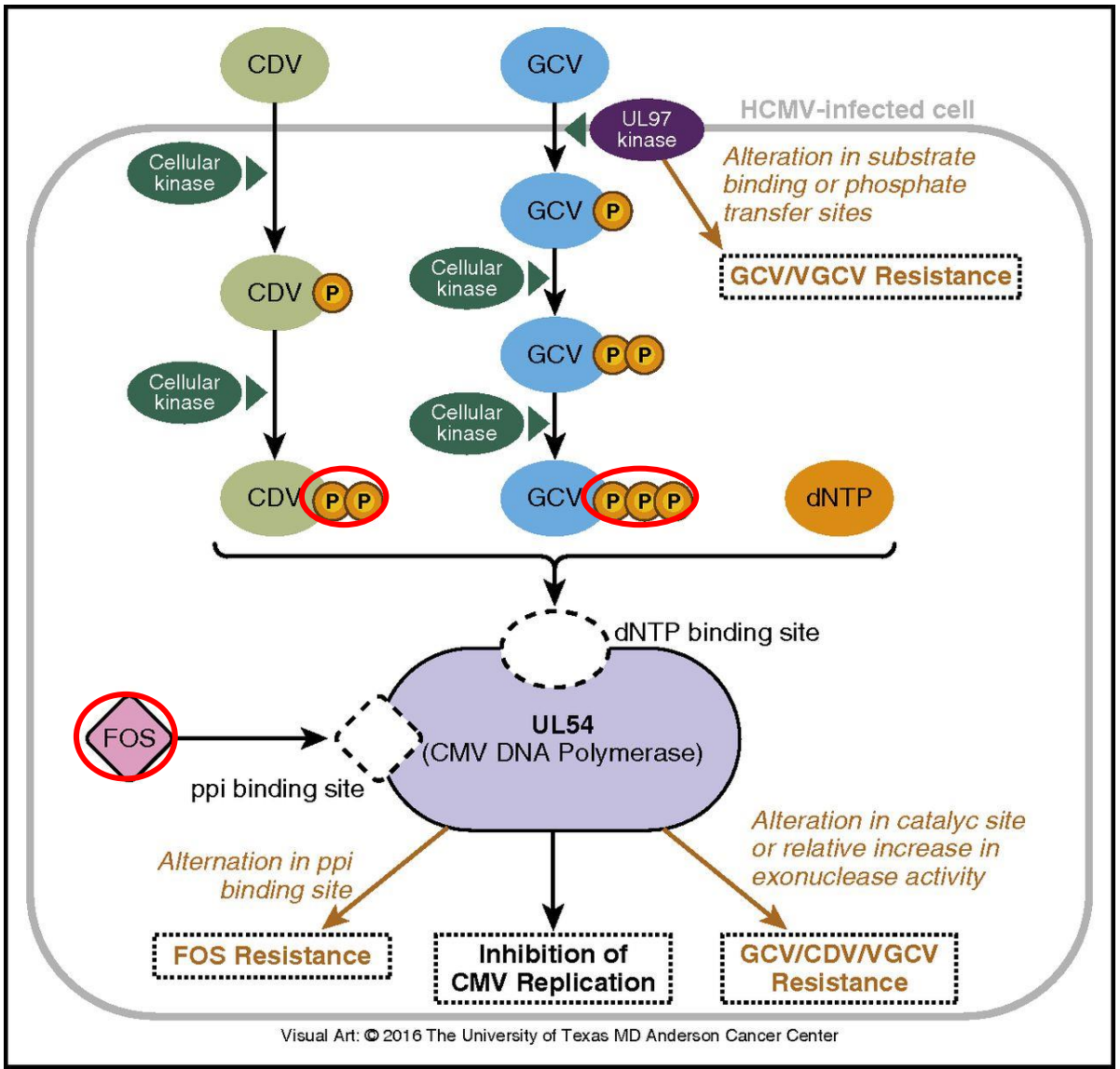
⇩

***foscarnet* acts as an inhibitor of**

HIV reverse transcriptase

Some antivirals

Mechanism of action & resistance



- CDV - *cidofovir*
- GCV - *ganciclovir*
- FOS - *foscarnet*
- VGCV - *valganciclovir*

- CMV - cytomegalovirus
- dNTP - deoxynucleoside triphosphate
- ppi – pyrophosphate binding site

- UL97 - viral protein kinase
- UL54 - viral DNA polymerase

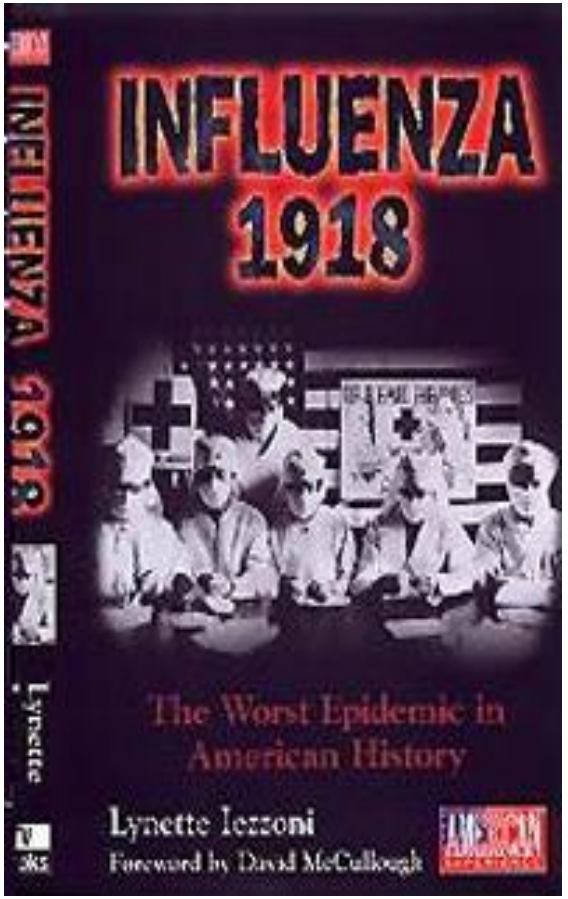
(gene mutations in both enzymes confer resistance)

ANTIVIRALS

Drugs for influenza

RNA virus:

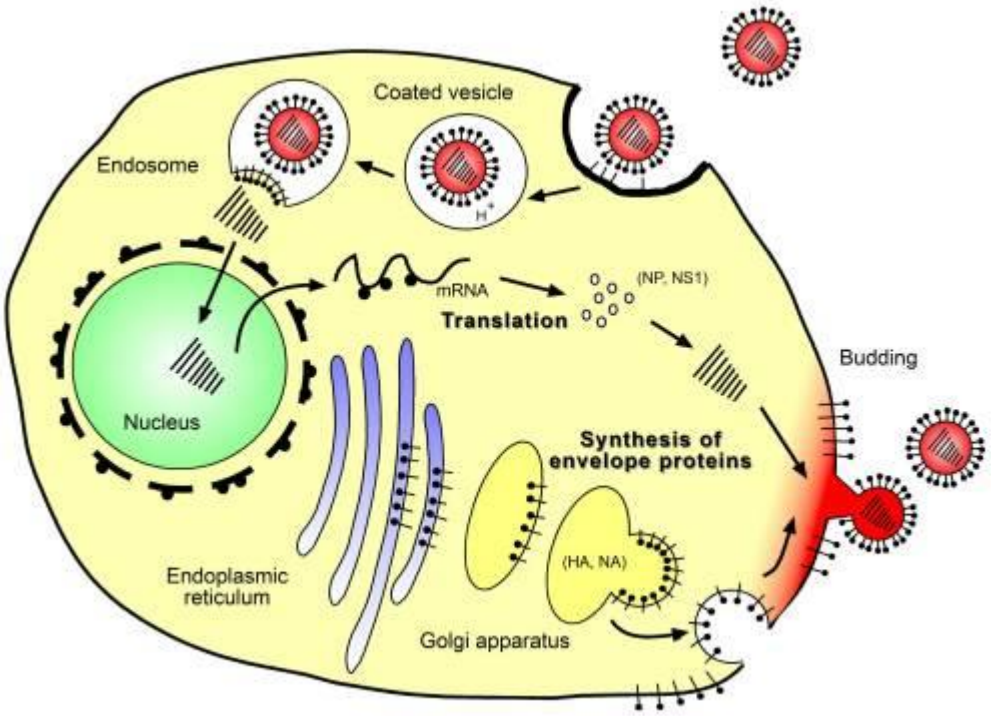
- **virus A** (water fowl, poultry, humans) - serotypes (hemagglutinin & neuraminidase):
- **H1N1** – Spanish flu 1918 & pork flu 2009
- **H2N2** – Asian flu 1957
- **H3N2** – Hong-kong flu 1968
- **H5N1** – avian flu 2004
- **virus B** (humans)
- **virus C** (humans, dog, pig)



ANTIVIRAL AGENTS

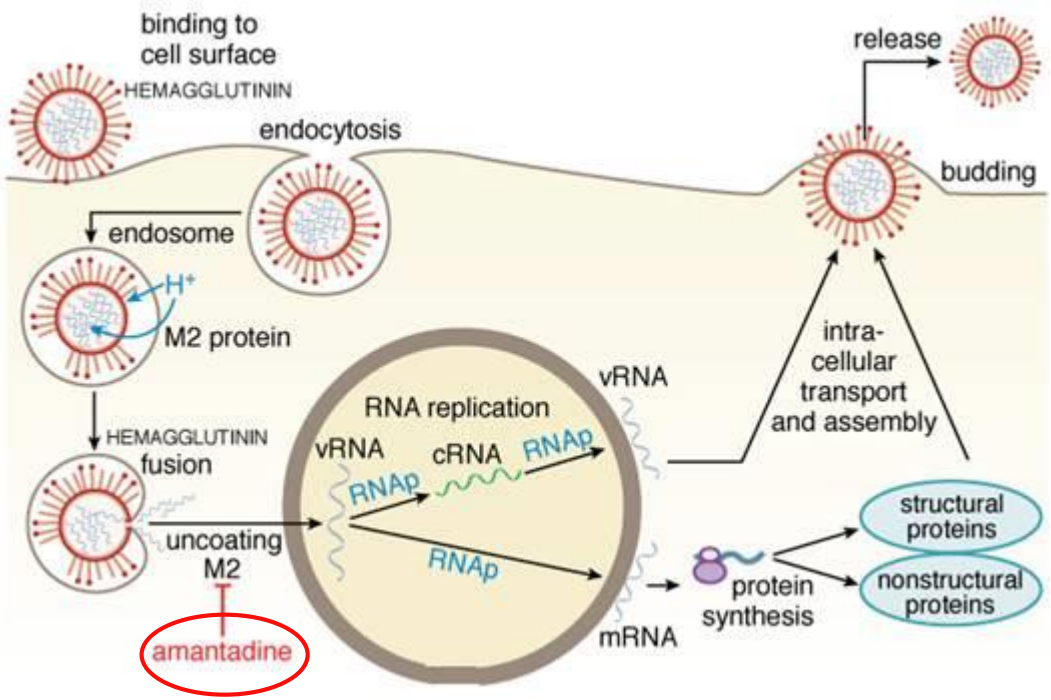
Drugs for influenza

- ***amantadine***
- ***rimantadine***
- ***oseltamivir***
- ***zanamivir***

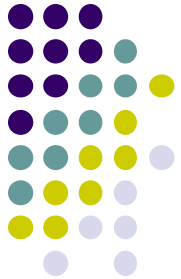


Amantadine (rimantadine)
Mechanism of action

- inhibit an early step in virus replication by blocking the viral M_2 ion channel protein, which **prevents viral uncoating**
- effective against the influenza A virus **only**



Amantadine
Indications



- Spectrum:

- ***influenza virus A***
- **prophylaxis against influenza**
- can reduce the duration of symptoms

  (if given within 48 h after contact)

- Other non-infectious disease processes:

- Parkinson´s disease
- drug-induced extrapyramidal symptoms
- it may have anticholinergic effects

Amantadine
Side effects

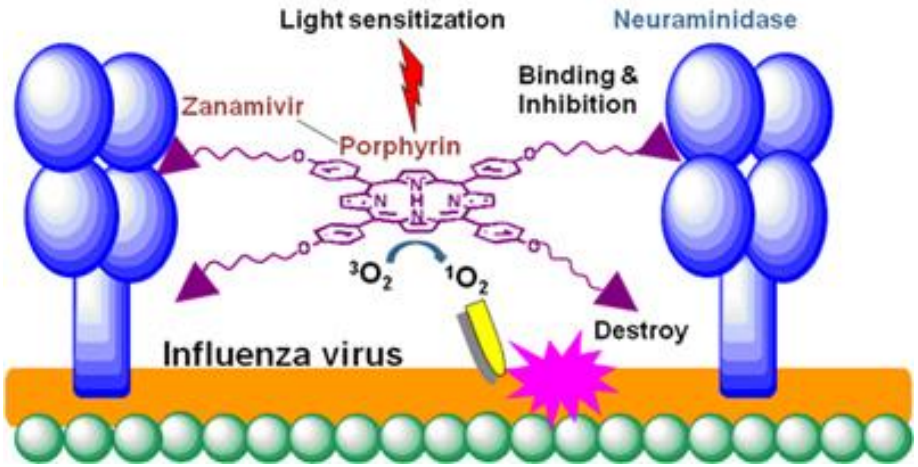
- ***amantadine:***
  - nervousness, insomnia, seizures
  - orthostatic hypotension
  - peripheral edema, dry nose, xerostomia
  - nausea, anorexia

- ***rimantadine:***
  - longer half-life
  - requires no dosage adjustment in renal failure

Oseltamivir & zanamivir

Mechanism of action

- inhibitors of **neuraminidases**
- ⇓ the **viral penetration** into host cell
- **act against influenza A & B** & are currently active against both H3N2 & H1N1 strains

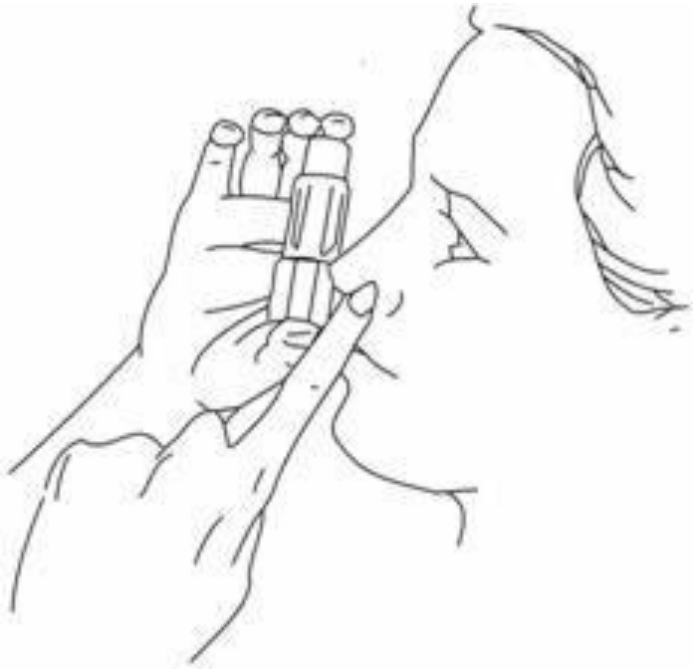


- **H3N2** (avian & human)
- **H1N1** (porcine, avian & human virus combination)

Oseltamivir & zanamivir
Pharmacokinetics

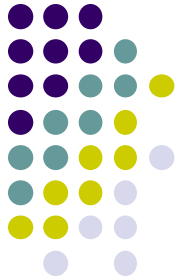
- ***olsentamivir -*** oral, prodrug activated in the gut & liver

- **zanamivir** – intranasal or oral inhalation route



www.drugs.com

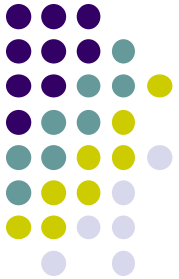
HIV
Treatment strategy



- initiation of treatment – **3 or more** antiretroviral drugs (highly active antiretroviral therapy – HAART)
- if possible, **before** symptoms appear
- it can slow or reverse the increases in viral RNA load that normaly accompany progression of disease
- HAART slows or reverses the decline in **CD4** cells & ⇓ the incidence of **opportunistic infections**

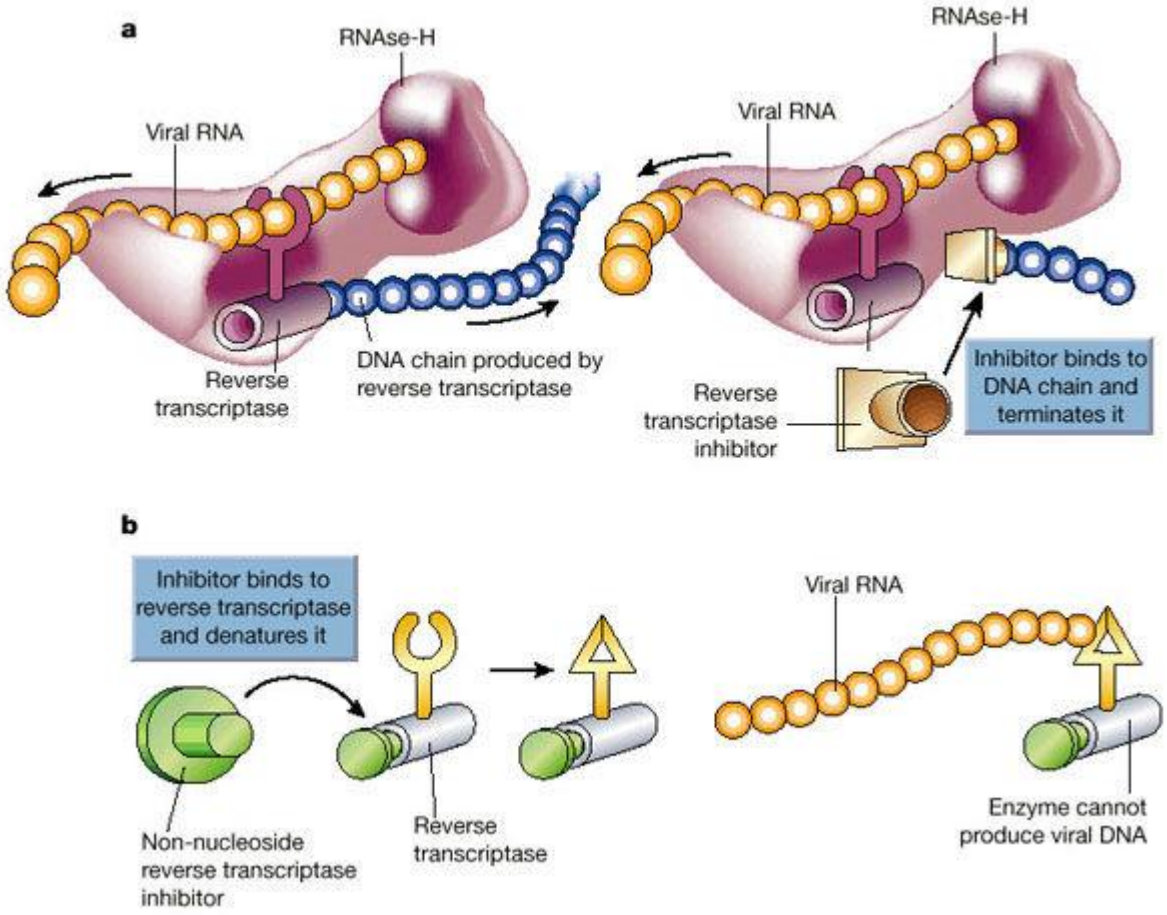
ANTIVIRAL AGENTS

Drugs for HIV



- **reverse transcriptase inhibitors** (RTI)
  - nucleoside RTI (NRTI)
  - non-nucleoside RTI
- **protease inhibitors**
- **entry inhibitors**
- **integrase strand transfer inhibitors**

Nucleoside & Non-nucleoside RTI



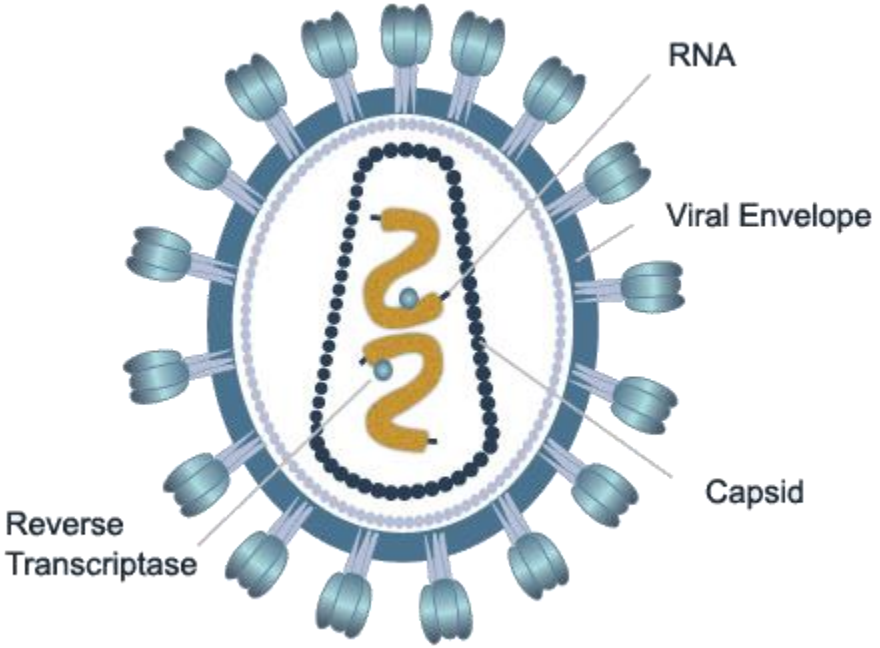
a. Nucleoside RTI

b. Non-nucleoside RTI

Nucleoside RTI
Drugs for HIV

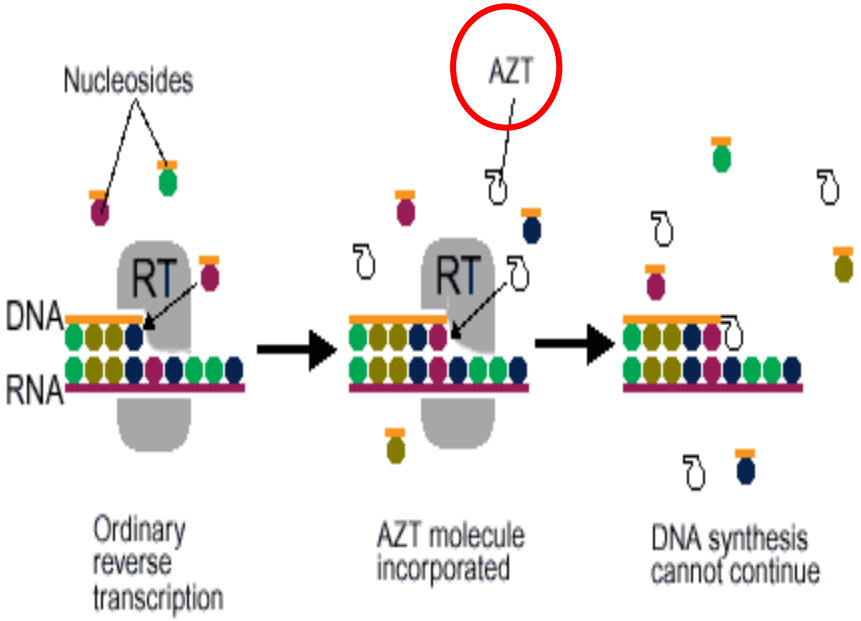
- ***zidovudine*** (protopyte)
- ***stavudine***
- ***lamivudine***
- ***didanosine***
- ***abacavir***
- ***emtricitabine***

- ***tenofovir*** **-** the only available **nucleotide** RTI



Zidovudine (AZT)
Mechanism of action

- prodrugs converted by host cell kinases to triphosphates
- they competitively ⇓ binding of natural nucleotides to the binding site of RT
  &
- also act as chain terminators (attachement of next nucleotide is impossible)



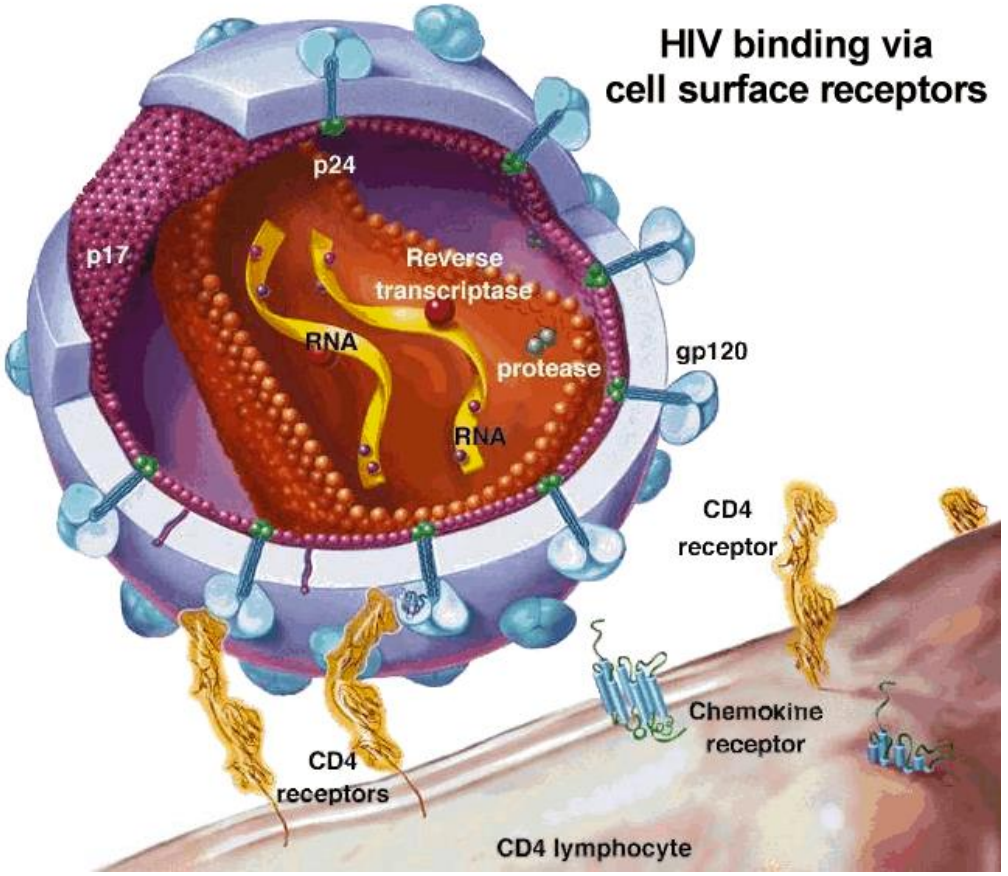
Zidovudine (AZT)
Pharmacokinetics & side effects

- oral; distributed to most tissues (including CNS)
- hepatic metabolism to glucuronides & renal excretion
- **Side effects:**
- **bone marrow suppression** – anaemia & neutropenia, thrombocytopenia (may require transfusion)
- myalgia, headache
- GI distress, cholestatic hepatitis
- agitation, insomnia

Non-nucleoside RTI

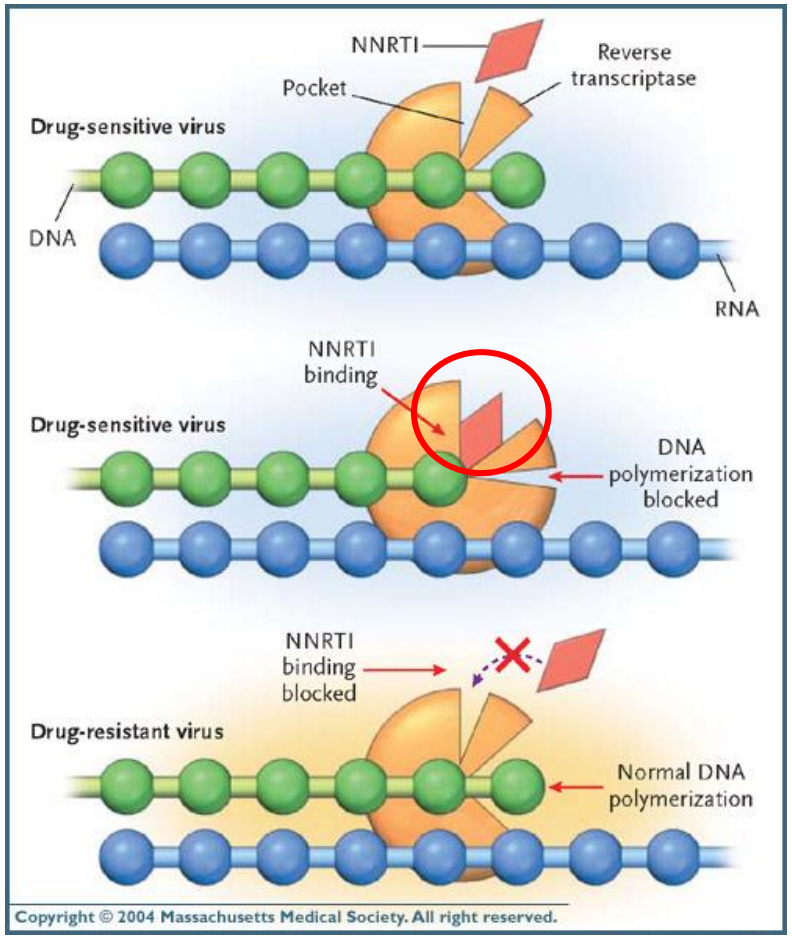
Drugs for HIV

- ***delaviridine***
- ***efavirenz***
- ***etravirine***
- ***nevirapine***



Non-nucleoside RTI
Mechanism of action

- bind to RT site **different** from the binding site of NRTI
- they do not require phosphorylation to be active
- they do not compete with nucleoside triphosphates
- there is **no cross-resistance** with NRTI

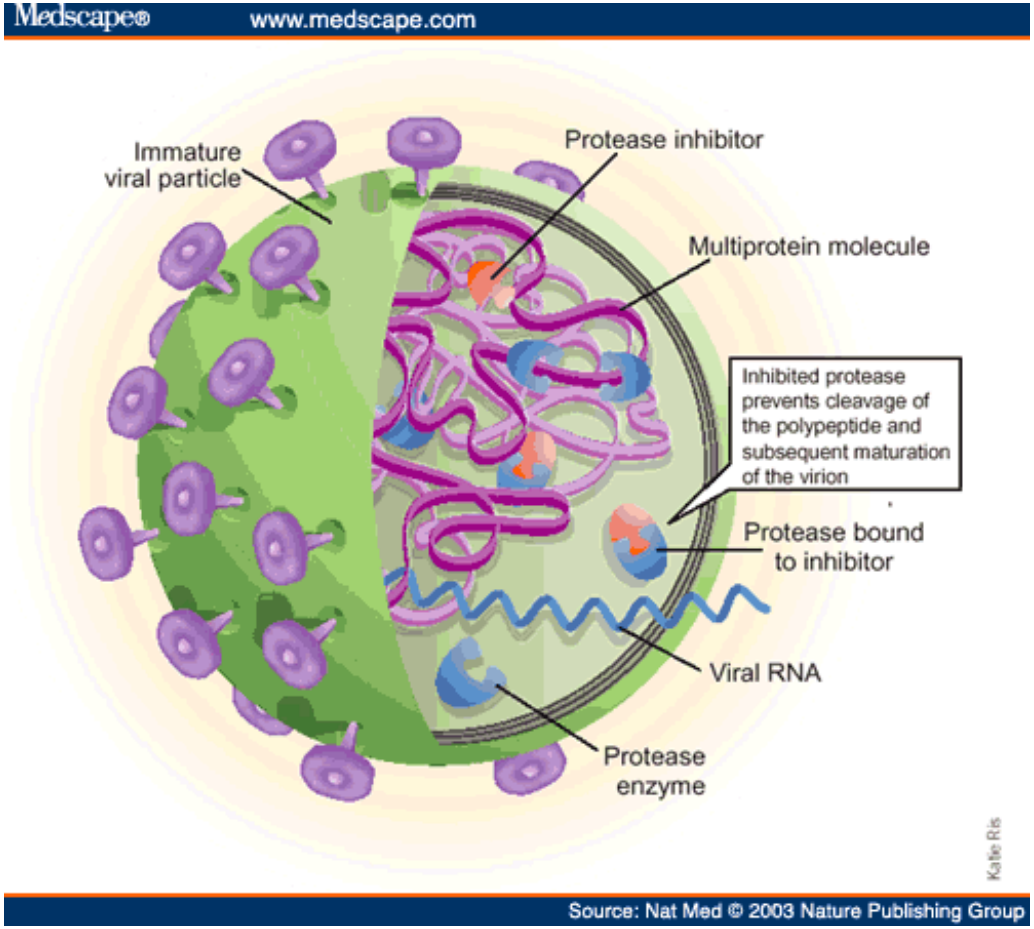


Protease inhibitors

Drugs for HIV

- ***atazanavir***
- ***darunavir***
- ***fosamprenavir***
- ***indinavir***
- ***ritonavir***

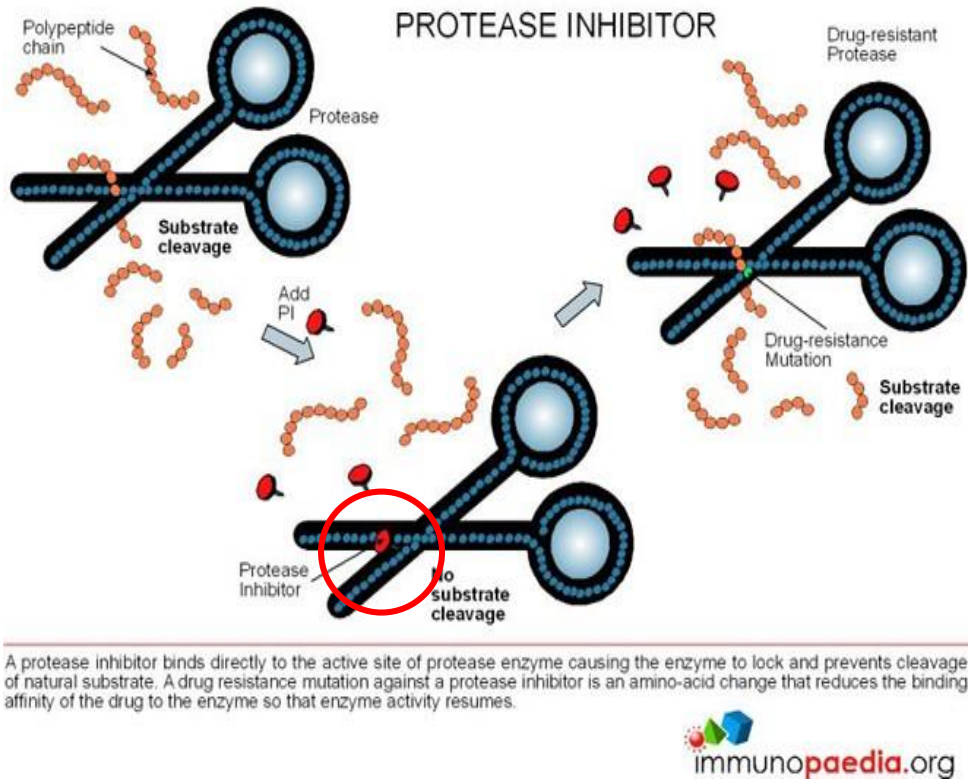
& many more



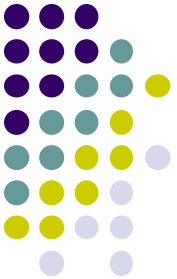
Protease inhibitors

Mechanism of action

- aspartate protease (HIV-1 protease)
- cleaves precursor polyproteins to form the final structural proteins of the mature virion core
- PIs have important clinical use in HIV



Entry inhibitors
Drugs for HIV

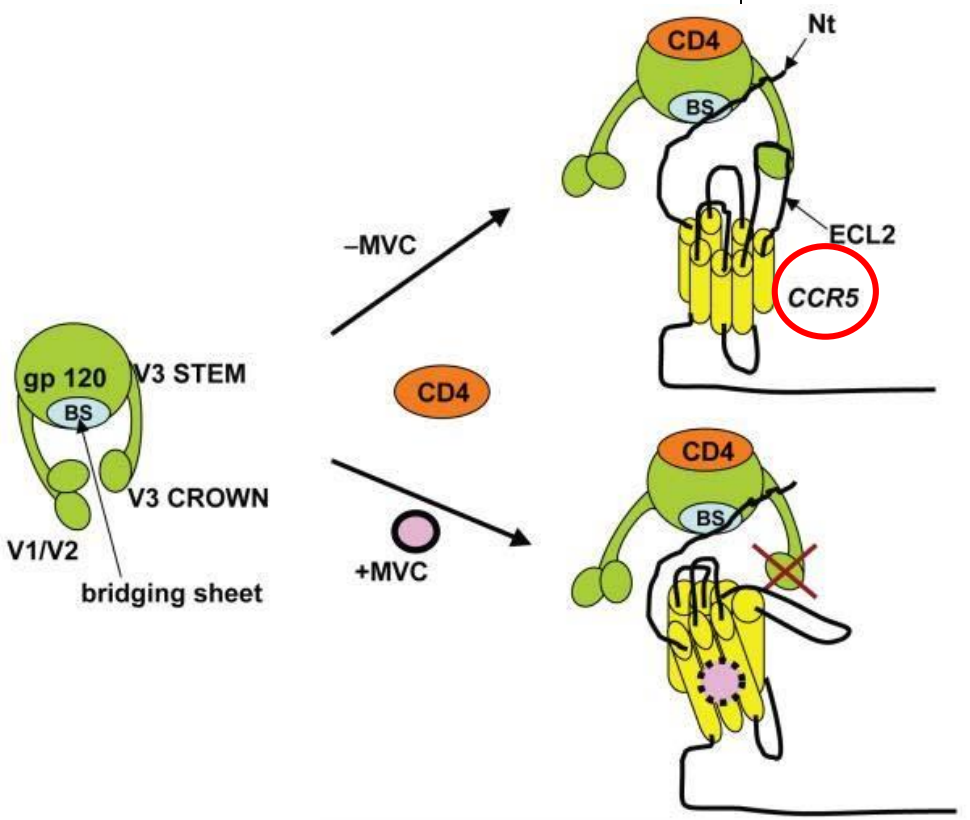


- ***maraviroc* – oral;** good tissue penetration
- ***enfuvirtide* – s.c.;** in previously drug-treated patients with **persistent HIV-1 replication** **despite ongoing therapy**
- there is **minimal cross-resistance** with other antiretroviral drugs

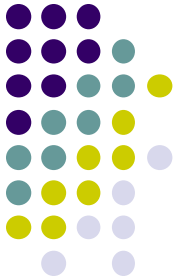
Maraviroc

Mechanism of action

- HIV-1 infection begins with attachement to CD4 molecules on Th
- attachement involves a transmembrane chemokine receptor CCR5
- CCR5 is a target of ***maraviroc***, which blocks viral attachement



Entry inhibitors
Side effects



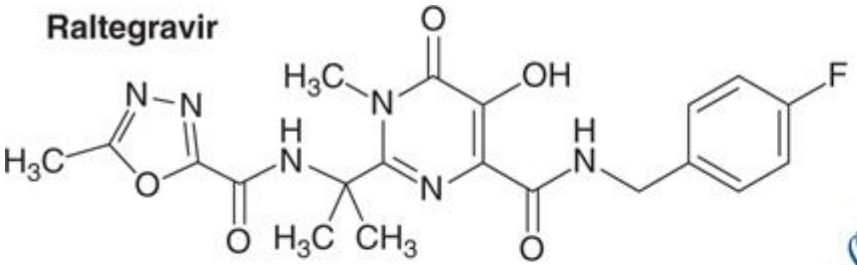
- ***maraviroc:***
- cough
- diarrhea
- muscle & joint pain
- increases in hepatic transaminases

- ***enfuvirtide:***
- injection site reactions
- hypersensitivity
- increased incidence of bacterial pneumonia

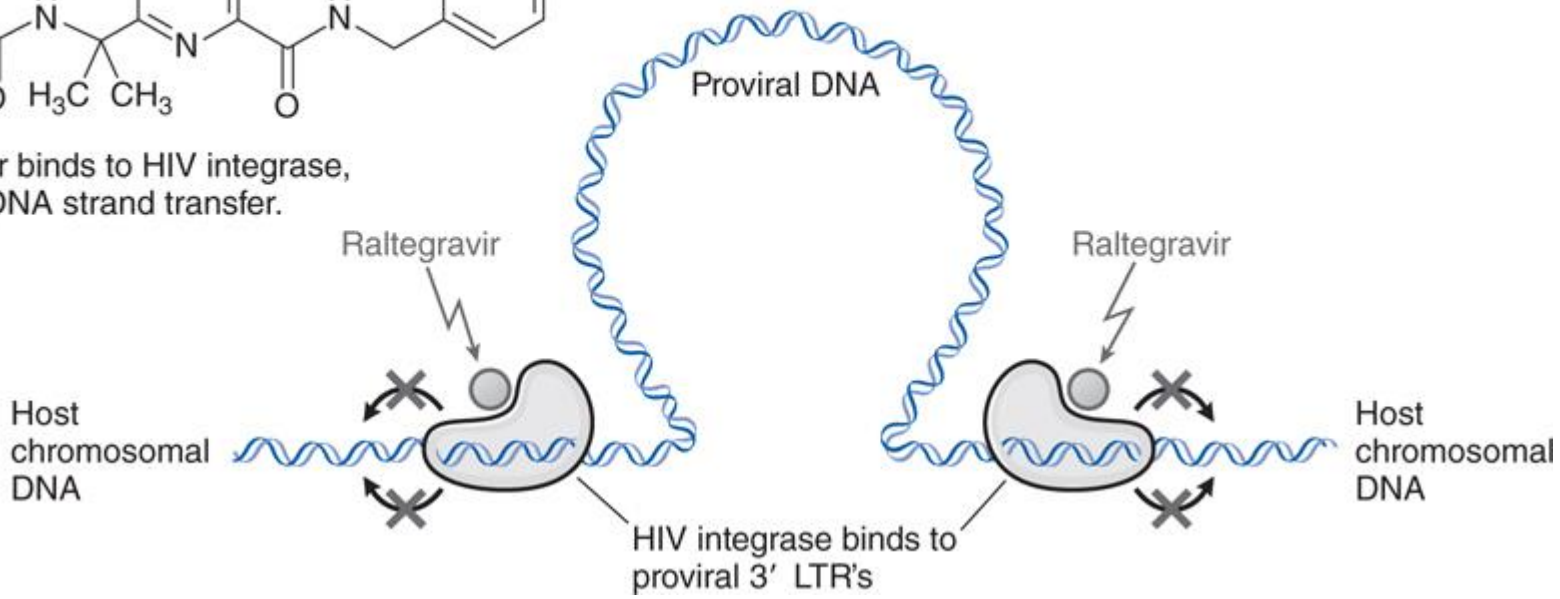
Integrase strand transfer inhibitors

Drugs for HIV

- binds to **integrase** (an enzyme essential to replication of both HIV-1 & HIV-2)
- **integration of reverse-trascribed HIV DNA** into host cell chromosomes is inhibited



Raltegravir binds to HIV integrase, prevents DNA strand transfer.

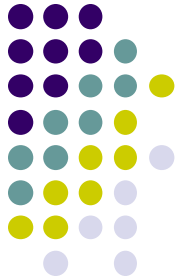


Raltegnavir
Drugs for HIV

- pyrimidine derivative
- oral application
- metabolized via glucuronidation, excreted in feces & urine
- generally well tolerated when used in combination with optimized background therapy regimens
- **treatment of HIV-1 infection** in conjunction with other antiretrovirals

ANTIVIRAL AGENTS

Drugs for HBV & HCV



- **Drugs for HBV –** supressive rather than curative
- **Drugs for HCV** – primary goal – viral eradication
- ***lamivudine*** - NRTI **- chronic HBV**
- ***adefovir*** - RTI **- HBV**
- ***entacavir*** - NRTI **- HBV** (lamivudine-resistant)
- ***telbivudine*** - RTI **- chronic HBV**
- ***tenofovir*** - NRTI **- chronic HBV** (lamivudine- & entacavir-resistant)
- ***ribavirin*** - several mechanisms (e.g. viral mRNA polymerase inhibition...) **- chronic HCV** (with INF-α)