Lecture Objectives

1. Be able to discuss the life cycle of HIV, and recognize that HIV is a retrovirus (RNA) that requires reverse transcriptase to form DNA which can then integrate into host DNA.
2. Recognize that the treatment of HIV requires multiple antiretroviral drugs.
3. Be familiar with Nucleoside Reverse Transcriptase Inhibitor (NRTIs) class of retroviral drugs and their common mechanism of action (but difference in which nucleotide they are an analogue for), adverse side effects
4. Recognize that NRTIs have both drug-specific and common adverse side effects.
5. Be familiar with the NNRTIs, and how their mechanism of action is different than NRTIs.
6. Recall which NNRTI is teratogenic, and which NNRTI is safe in pregnancy.
7. Recall the drugs that comprise the Protease Inhibitor class of antiretrovirals, and their common mechanism of action.
8. Recognize the common adverse effects and common pharmacokinetics of PIs and the potential for drug interactions that will influence the metabolism of protease inhibitors.
9. Describe the use of ritonavir (Norvir) in HIV therapy, and why it should (or shouldn't) be prescribed with other PIs.
10. Discuss why you wouldn't use two PIs in individuals with sulfonamide hypersensitivities.
11. Recall the specific adverse side effects associated with each PI.
12. Explain the unique mechanism of action for Fusion Inhibitors, recall the two drugs in this class, and when these drugs should be used.
13. Discuss the mechanism of action for Dolutegravir, an integrase inhibitor, and its importance in treating treatment-resistant patients.

HIV Drugs

Nucleoside Reverse Transcriptase Inhibitors

Lamivudine (Epivir)
Tenofovir (Viread)
Emtricitabine (Emtriv)
Abacavir (Ziagen)

Non-Nucleotide Reverse Transcriptase Inhibitors

Rilpivirine (Edurant)
Doravirine (Pifeltro)

Integrase Inhibitor

Dolutegravir (Tivicay)
Cabotegravir (Vocabria)
Bictegravir

Protease Inhibitors

Darunavir (Prezista)
Atazanavir (Reyataz)
Cobicistat (Tyboost)
Ritonavir (Norvir)

Fusion Inhibitors

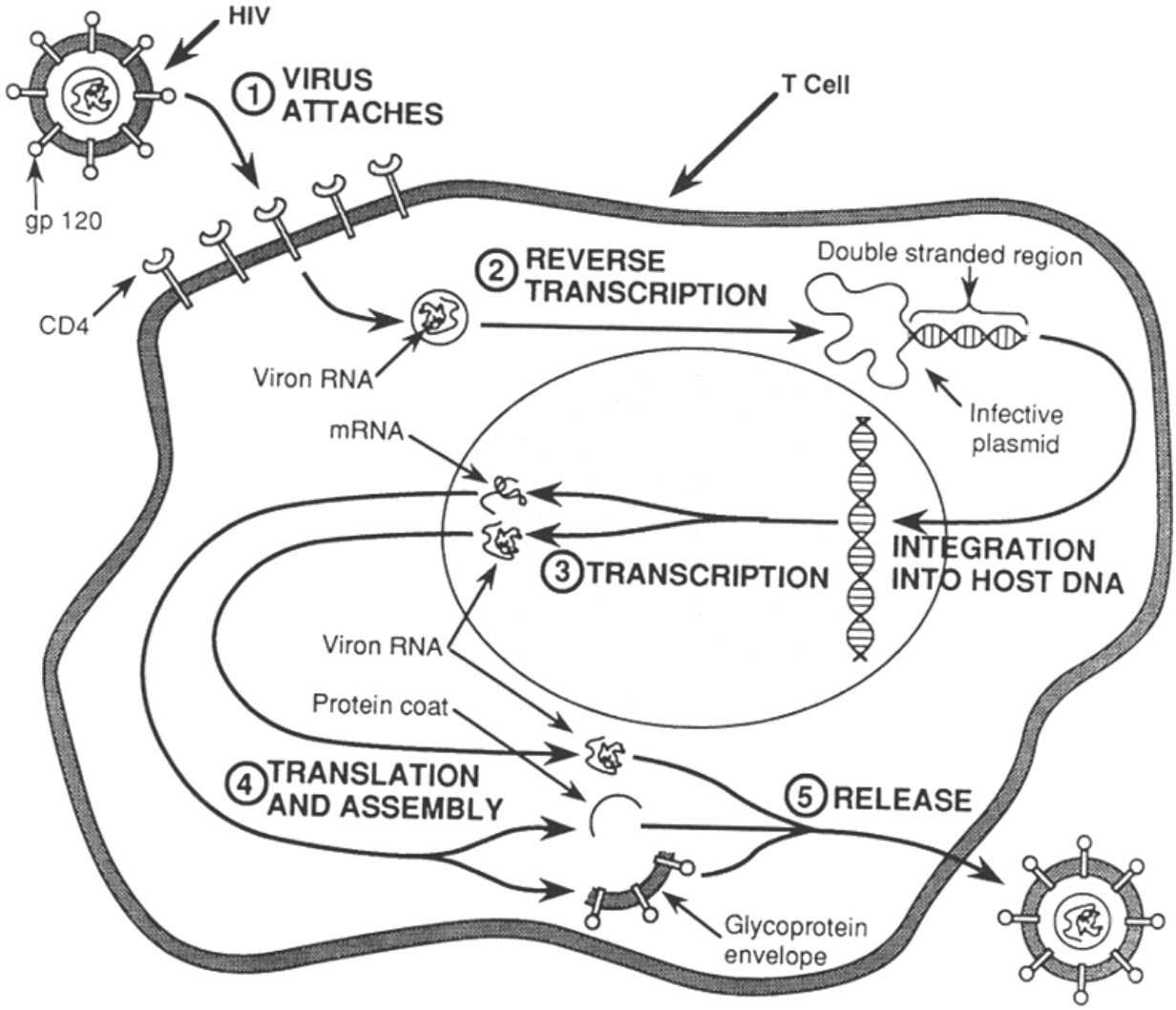
Enfuvirtide (Fuzeon)
Maraviroc (Selzentry)
Fostemsavir (Rukobia)
Ibalizumab (Trogarzo)

An antiretroviral (ARV) regimen for a treatment-naive patient generally consists of:

- two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with:
- a third active ARV drug from one of three drug classes:
  - an integrase strand transfer inhibitor (INSTI),
  - a non-nucleoside reverse transcriptase inhibitor (NNRTI), or
  - a protease inhibitor (PI)

Life Cycle OF HIV (AIDS)

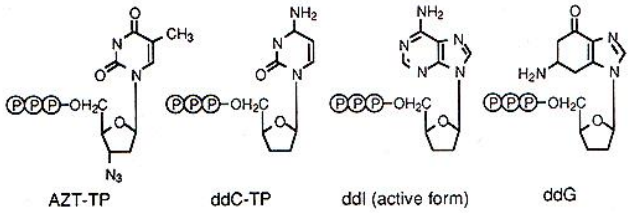
- Human immunodeficiency virus (HIV) is a **retrovirus** with a glycoprotein coat that recognizes the CD4 receptor on helper T cells
- The virus binds to the CD4 receptor, fuses with the cell membrane, loses its coat and releases RNA and an enzyme called **reverse transcriptase** into the cell.
- Reverse transcriptase copies viral RNA, making one strand the complementary strand, to form DNA.
- The viral DNA is **incorporated into the host DNA**, where it may stay inactive or form viral mRNA, which codes for proteins needed to replicate the virus.
- One long protein is formed, which is split into specific proteins by a **protease**.
- The virus then is coated with these proteins and can go on to infect other cells.
- With time, the virus leads to **destruction of the CD4$^+$ T-lymphocytes**.
- Current therapy is aimed at controlling the degree of HIV infection, and is targeted at the **reverse transcriptase** and **protease enzymes. Fusion inhibitors prevent the entry of HIV into the host cell, and are used in patients who are unresponsive to older drugs.**



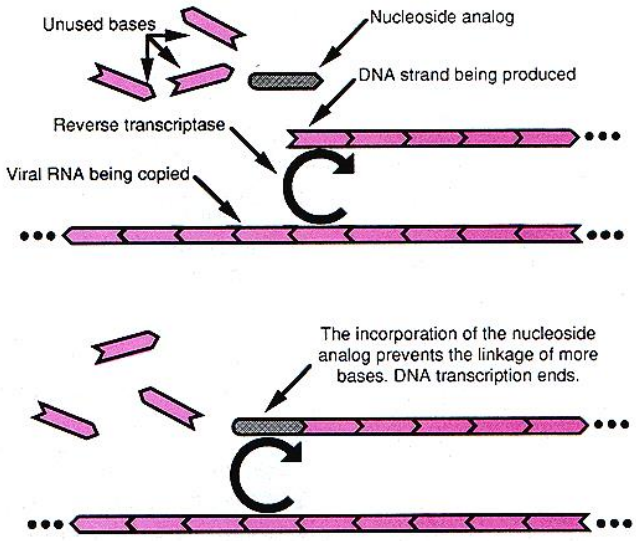
REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

- nucleoside analogues

Emtricitabine (Emtriva)
Tenofovir (Viread®)
Lamivudine (Epivir®; 3TC)
Abacavir (Ziagne®)



MOA - inhibits the replication of retroviruses after first being activated via three phosphorylation steps producing the NRTI- 5'-triphosphate. The phosphorylated drug **inhibits the activity of the HIV reverse transcriptase** by incorporation into viral DNA. **The lack of a 3'-OH** group in the incorporated nucleoside analog prevents the formation of 5' to 3' phosphodiester linkage essential for DNA chain elongation, and, therefore**, viral DNA growth is terminated** and production of new virions is inhibited.



Combination Therapy: These drugs are generally used in combination to decrease resistance an improve responsiveness. The most commonly used combinations are **tenofovir and emtricidabine**, *or* **abacavir and lamivudine.**

Adverse effects: **Lactic acidosis** and **hepatotoxicity** are rare, but serious side effects that may occur with any of the NRTIs.

TENOFOVIR (Viread™)

- Adenosine analogue, inhibitor of **reverse transcriptase**
- active against HIV-1 which has become resistant to other drugs
- Oral, should be administered with food to increase bioavailability
- **Nausea, vomiting, abdominal pain and flatulence** most common side effects

EMTRICITABINE (Emtriva™)

- Cytosine analogue, very similar to lamivudine, but more potent against HIV
- Cross-resistance likely with lamivudine
- Also inhibits HBV- alternate treatment for hepatitis B
- Very well tolerated; **diarrhea, nausea and rash** most common side effects

combination

LAMIVUDINE (Epivir®)

- cytosine analogue, inhibitor of **reverse transcriptase**
- drug-induced mutation in reverse transcriptase causes resistance to lamivudine, combined with zidovudine or abacavir
- good oral absorption; no hepatic metabolism, excreted by kidney
- very well tolerated; **mild side effects** include headache, fatigue, insomnia, GI upset

ABACAVIR (Ziagen™)

- Guanosine analogue
- Often used in combination with lamivudine or zidovudine
- **SERIOUS hypersensitivity** reactions occur in about 5% of patients; fever, malaise, skin rash, chills, difficulty breathing. Discontinue drug and **DO NOT RESTART** – fatal. The reaction is due to binding of HLA-B-5701
- Common side effects – nausea, vomiting, diarrhea

combination

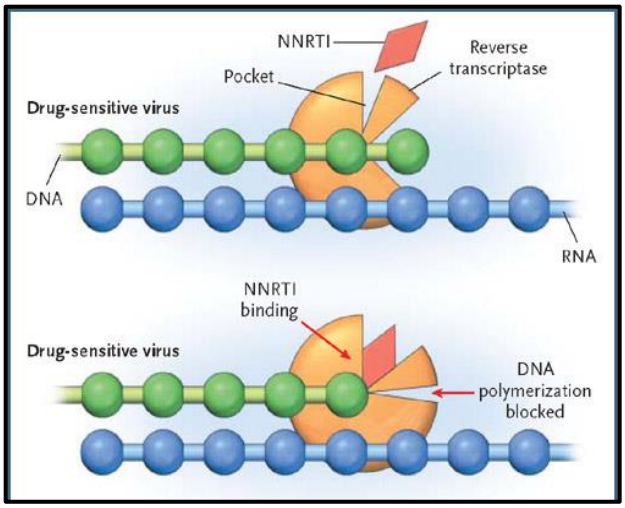
> **Lactic acidosis** and **hepatotoxicity** are very rare, but serious side effects that may occur with any of **the nucleoside reverse transcriptase inhibitors.** It is more likely if the patient is obese, has previous liver disease, or takes the drugs for a long time.

NON-NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)

Rilpivirine (Edurant)
Doravirine (Pifeltro)

Mechanism

- **bind directly to reverse transcriptase** and prevent conversion of RNA to double strand
- **do not require phosphorylation** for activity
- **combined with zidovudine** or other NRTIs; resistance develops rapidly if used alone!



RILPIVIRINE (EDURANT)

- Safe in pregnancy! Not teratogenic
- Adverse effects: depression, increased cholesterol and headache
- Not recommended for patients with hepatitis co-infection, may increase liver enzymes

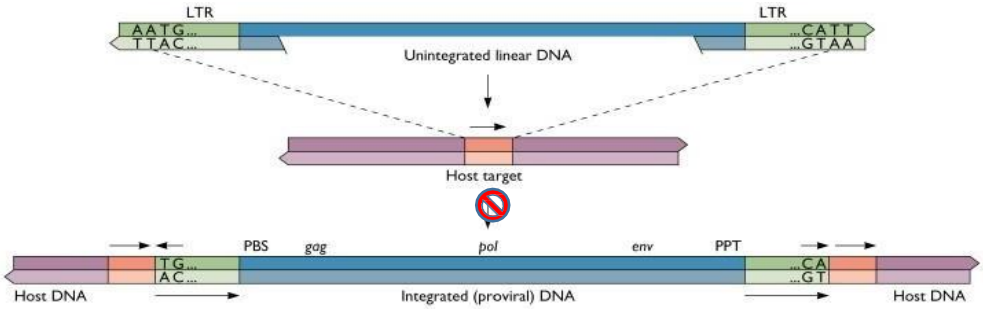
DORAVIRINE (Pifeltro)

- Oral
- Adverse effects: CNS (headache, fatigue), cardiovascular, GI, rash
- Approved 2018 as a single oral treatment, or in combination with tenofovir and lamivudine.
- Pregnancy safety undetermined.

INTEGRASE INHIBITORS

Dolutegravir (Tivicay)
Cabotegravir (Vocabria)
Bictegravir

Mechanism of action - Integrase is an enzyme needed for replication and insertion of viral DNA into host DNA. Therefore, **this class inhibits the integration of viral DNA to host cell DNA**



DOLUTEGRAVIR (Tivicay)

- oral
- most common adverse effects are headache and insomnia, GI, hyperglycemia

CABOTEGRAVIR (Vocabria)

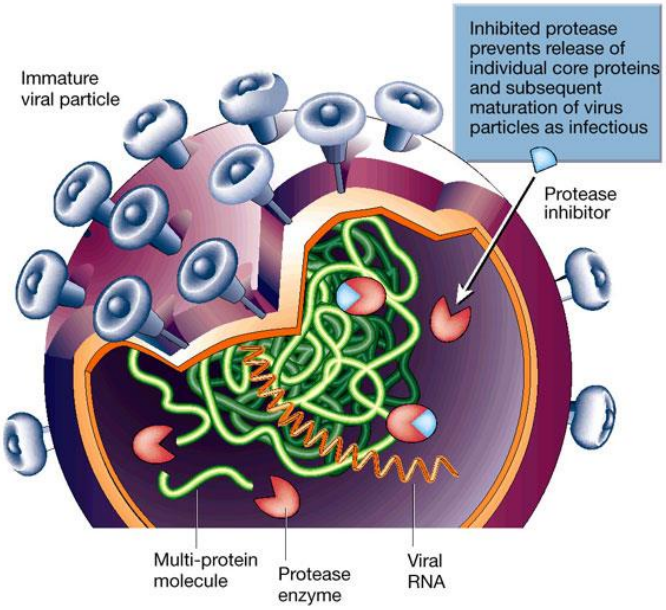
- Oral, IM
- Adverse effects: rash, depression, headache, insomnia

BICTEGRAVIR

- Approved 2018
- Complete treatment regimen – bictegravir, emtricitabine (NRTI), tenofovir (NRTI)
- Oral, taken once daily
- Adverse effects: nephrotoxicity, lactic acidosis, hepatotoxicity

PROTEASE INHIBITORS (PIs)

Ritonavir (Norvir)
Cobicistat (Tybost)
Darunavir (Prezista)
Atazanavir (Reyataz)



- A significant advance in the treatment of HIV came with the advent of the protease inhibitors.
- After transcription in the nucleus, viral mRNA enters the cytoplasm and uses the host's cellular machinery to manufacture virus proteins.
- Core proteins are produced as part of long polypeptides, which must be **cut into smaller fragments by the enzyme protease in order to form mature, functional proteins**.

Mechanism of Action: Protease inhibitors bind to the site where protein cutting occurs, and so **prevent the enzyme from releasing the individual core proteins**. In this way the new viral particles are unable to mature or become infectious.

- Always used in **combination with reverse transcriptase inhibitors** for treatment of HIV

Common Pharmacokinetics:

- Most have poor bioavailablitity, and are **metabolized by CYP3A4**. Therefore **drugs which inhibit CYP3A4 will increase levels of PIs.** Ritonavir or cobicistat are powerful inhibitors of CYP3A4, and can often combined with other protease inhibitors to increase bioavailability. **Drugs which induce CYP3A4 will decrease PI levels** (e.g. rifampin, rifabutin, phenytoin, phenobarbital, carbamazepine).
- **St John's Wort** can increase metabolism of protease inhibitors, rendering them ineffective

PHARMACOKINETIC ENHANCERS (that are also weak protease inhibitors)

RITONAVIR (Norvir®) and COBICISTAT (Tybost®)

Mechanism

- **inhibits CYP3A4** – inhibits metabolism of many other protease inhibitors, **is often combined for this purpose**; permits lower or less frequent dosing (or both) with greater tolerability and enhanced antiviral activity when administered with other PI agents.
- inhibitor of both **HIV-1 and HIV-2 proteases**
- oral, good bioavailability that improves with food
- Inhibition of CYP3A4 may cause dramatic elevation in levels of many other drugs

Adverse effects:

Ritonavir:

- nausea, vomiting, weakness and diarrhea, and elevated liver enzymes
- Formulation contains **ethanol; do not give with disulfiram, metronidazole or cephalosprorins.**
- **DO NOT combine with saquinavir – QT risk**

COBICISTAT (Tybost®)

- Hepatic, CNS (headache, dreams), rash

Common Adverse Effects to all of the protease inhibitors include:

- **Altered body fat distribution**- buffalo hump and truncal obesity, with facial and peripheral atrophy
- **Insulin resistance** and hyperglycemia
- Increases in serum **cholesterol;** but since many of the protease inhibitors are strong inhibitors of CYP3A4, they should **not** be combined with statins
- Spontaneous **bleeding** in patients with hemophila A or B

*Individual side effects or interactions are listed with specific drugs.

DARUNAVIR (Prezista®)

- Safe and effective; **drug of first choice**
- Common side effects – rash, nausea, headache, bad dreams
- Combined with **ritonavir** to increase bioavailability
- Must be taken with food
- **Has a sulfonamide moiety**

ATAZENAVIR (Reyataz®)

- **Drug of second choice**
- Less effect of lipoproteins than other protease inhibitors
- Rash, nausea, hyperglycemia
- May cause an increase in **bilirubin** due to inhibition of UGT

FUSION INHIBITORS

Enfuvirtide (Fuzeon)
Maraviroc (Selzentry)
Fostemsavir (Rukobia)
Ibalizumab (Trogarzo)

ENFUVIRTIDE (Fuzeon®)

- **binds to the gp41subunit of the viral envelope** glycoprotein, this prevents a conformational change that is required for membrane fusion and viral entry into target cells.
- **No cross-resistance with other antiretroviral agents**
- Used primarily in patients with advanced disease, who are treatment experienced.
- Fuzeon is a peptide, therefore only route of administration is **subcutaneous**
- Increased risk of bacterial pneumonia, injection site reaction, GI

MARAVIROC (Selzentry®)

- **Inhibits fusion by binding to the CCR5 receptor** of the CD4+ T cell.
- Only inhibits viral fusion for HIV that use this receptor
- **ONLY used in patients with CCR5-tropic HIV infection**
- Rash, cough, hepatoxicity

FOSTEMSAVIR (Rukobia)

- Oral
- **Binds to gp120 subunit, preventing interaction with CD4 receptor and entry of virus**
- Used primarily in treatment experienced patients

- New approved (2020), adverse effect profile minimal
  - May increase hepatic enzymes, bilirubin, cholesterol and triglycerides
  - Nausea and diarrhea possible

IBALIZUMAB (Trogarzo)

- Binds to the CD4 receptor to block viral entry; binds specifically at extracellular domain 2 and prevents conformational changes in CD4 and gp120 that allows virus to enter host cell.
- Effective against both CXCR4- and CCR5-tropic strains
- For patients when other treatments begin to fail; combined with other treatments
- Long acting, IV every two weeks
- Adverse effects - diarrhea, dizziness, nausea, and rash (new drug, unknown adverse effects)