ANTIRETROVIRAL THERAPY is an ART

HIV Life Cycle

- Infection of CD4+ T-lymphocyte
  - Entry requires cell surface receptors: CD4 receptors + co-receptors (CCR5*, CXCR4)
  - CD4 receptors interact with protein complexes embedded on surface of viral envelope
    - Protein complexes: two glycoproteins (extracellular GP120 + transmembrane GP41*)
- Attachment: GP120 binds to CD4 receptor
- Co-receptor causes conformational change in GP120 → allows GP41 to unfold & insert its hydrophobic end into the cell membrane
- GP41 folds back on itself → facilitates fusion of viral and cell membranes
- Viral nuclear capsid enters host cell → breaks in
- Capsid releases two viral RNA strands + 3 essential replication enzymes
  - Replication enzymes: reverse transcriptase, integrase, & protease
- Reverse transcriptase*: RNA → RNA/DNA double helix → DNA double helix
- Integrase*: cleaves dinucleotide from each 3' end of DNA creating two sticky ends
  - Transfers DNA into cell nucleus
  - Facilitates its integration into host cell genome
  - Transcription of pro-viral DNA into mRNA
  - Viral mRNA migrates into cell cytoplasm
  - Building blocks for new virus are synthesized
  - Immature virions still need to be processed by viral protease
- Protease*: cleaves long proteins into core proteins (crucial to create infectious virus)
- Two viral RNA strands + replication enzymes come together → core proteins assemble around them → forms capsid of immature virus
- Leaves cell, acquiring new membrane and proteins
- Virus matures → becomes ready to infect new cells
- HIV replication 3D medical animation: http://www.youtube.com/watch?v=RO8MP3wMvqg

**Indicates a drug target*

CCR5 ANTAGONISTS

Blocks the CCR5 co-receptor so that HIV cannot bind to host cell

- ***Maraviroc*** *(Selzentry)*
- Only works for newer patients
  - Problem: with increased time, sickness, and antiretroviral therapy use, the virus switches to using the CXCR4 co-receptor for which we currently have no drugs to block it
- Requires tropism test prior to Maraviroc treatment
  - Two types of HIV virus: R5 or X4 which use the co-receptors CCR5 and CXCR4, respectively
  - Maraviroc only binds to CCR5, patients can do a tropism test to determine if it is an R5 virus infection
- Drug interactions: Maraviroc is a strong CYP3A4 substrate (though neither an inhibitor or inducer)
- SE: abdominal pain, cough, dizziness, rash (prior to hepatotoxicity), URTI, CV events
  - Due to effect on immune system cells → ↑risk of developing infections and cancers
- Resistance: mutations in V3 loop; tropism test = resistance test

FUSION INHIBITOR

Blocks fusion to and entry into CD4 cell

- ***Enfuvirtide*** *(T-20/Fuzeon)*
- Binds to viral glycoprotein GP41, thereby preventing conformational change needed for fusion
- FDA indication: patients with ART resistance (later to be approved for treatment naïve patients)
- Injectable: 90mg subcutaneous injection bid
  - Requires mixing prior to administration
  - Fuzeon Kit ($1700): dry powder for reconstitution, syringe, sterile water, alcohol, sharps container
  - Counseling points: do not shake vial, takes 45-60 minutes to dissolve, administer within 24 hours of mixing, refrigerate after mixing if not using right away, requires separate syringes specific for this agent
- Drug interactions: none
- SE: injection site reaction experienced by almost everyone → should see bruising (√ adherence monitoring)

NRTI/NtRTI

Blocks transcription from RNA to DNA by binding to active site

- ***Zidovudine*** *(AZT, Retrovir),* ***Didanosine*** *(Videx),* ***Lamivudine*** *(Epivir),* ***Abacavir*** *(Ziagen),* ***Tenofovir*** *(Viread),* ***Emtricitabine*** *(Emtriva)* (think: "ZALTED")
  - **Z**idovudine: okay for pregnant women
  - **A**bacavir: long t½ , doesn't need renal adjustment
  - **L**amivudine: used in children
  - **T**enofovir: different structure, inexplicable SE (↓atazanavir conc.), renal adjustment by ↑interval
  - **E**mtricitabine: used often in combinations
  - **D**idanosine EC: on empty stomach
- NRTI (nucleo*side* reverse transcriptase inhibitor) & NtRTI (nucleo*tide* reverse transcriptase inhibitor)
  - Imitators of natural DNA building blocks → tricks reverse transcriptase
- MOA: entry into cell → metabolized via kinases to triphosporylated form → triphosphate form is the active form that is incorporated into viral DNA → blocks attachment of next DNA building block → inhibits chain growth
- Some are also used to treat HBV: different dosing for HIV+HBV and HBV alone
  - "Let it B": Lamivudine, Emtricitabine, Tenofovir
- Class has structural similarities (exception: tenofovir) yet are not cross resistant
- SE: subjective/immediate SE differ but objective/long term SE are similar
  - Class effects: mitochondrial toxicity (lipoatrophy, lactic acidosis, myopathy, neuropathy)
  - Abacavir: check HLA B-5701 prior to use → positive = serious hypersensitivity reaction → do not take!
- Combinations: Combivir (Retrovir + Lamivudine), Epzicom (Lamivudine + Abacavir), Trizivir (Retrovir + Lamivudine + Abacavir), Truvada (Tenofovir + Emtricitabine), Atripla (Efavirenz + Tenofovir + Emtricitabine)

NNRTI

Blocks transcription from RNA to DNA by binding to an allosteric site

- ***Nevirapine*** *(Viramune),* ***Efavirenz*** *(Sustiva),* ***Etravirine*** *(Intelence)*
  - Efavirenz: take on empty stomach, teratogenic
  - Etravirine: bid dosing, with food, use if resistance to others
  - Nevirapine: titrate up, induces its own metabolism after two weeks, fear of liver failure
- MOA: bind to allosteric site causing conformational change → reverse transcriptase cannot bind viral RNA
  - No intracellular metabolic activation necessary (as in NRTI/NtRTI)
- Class characteristics:
  - Structurally diverse but similar toxicities
    - SE: rash, hepatotoxicity
  - Resistance: low barrier, cross resistance
  - Drug interactions: many due to CYP450 substrates (inducers and/or inhibitors)
    - Notable: lipid lowering agents (statins), erectile dysfunction agents
  - P'kinetics: CNS penetration, long t½

INTEGRASE INHIBITORS

Blocks integration of viral DNA into human DNA

- ***Raltegravir*** *(Isentress)*
- 400mg po bid
- Drug interactions: none mediated by CYP450 or with other antiretrovirals (possibly with rifampin, phenytoin)
- Metabolism: glucuronidation
- No boosting required
- SE: ↑creatinine kinase, myopathy, rhabdomyolysis

PROTEASE INHIBITORS

Inhibits maturation of baby virion

- ***Atazanavir*** *(Reyataz),* ***Darunavir*** *(Prezista),* ***Fosamprenavir*** *(Lexiva),* ***Lopinavir/RIT*** *(Kaletra),* ***Nelfinavir*** *(Viracept),* ***Ritonavir*** *(Norvir),* ***Saquinavir*** *(Invirase),* ***Tipranavir*** *(Aptivus)*
  - Preferred agents: atazanavir, darunavir
  - Darunavir: always with ritonavir
  - Lopinavir/RIT: ok for pregnant women
  - Ritonavir: booster
  - Tipranavir: check for drug resistance, strong CYP450 inducer (problems)
  - Nelfinavir: cannot boost with ritonavir, food = booster
- MOA: stops protease from cleaving new long viral polyprotein into smaller essential protein products → new virion stays a baby and unable to infect
- Class characteristics:
  - P'kinetics: short t ½, little CNS penetration
  - SE: short term differ, long term similar
    - Longer term: hyperlipidemia, hyperglycemia, fat misdistribution, ↑LFTs
    - Atazanavir: hyperbilirubinemia occurs in *all* patients, used to monitor for adherence
    - Darunavir, fosamprenavir: skin rash, possibility of Steven-Johnson Syndrome (SJS) due to sulfa
    - Lopinavir/R: GI intolerance
    - Nelfinavir: diarrhea occurs in 75% of patients, therefore not used often
    - Saquinavir: well tolerated
    - Tipranavir: intracranial hemorrhages, sulfa rash
  - Drug interactions: many mediated by CYP3A4
  - Resistance: high barrier (especially with boosting), less cross resistance
  - Boosting: necessary for better p'kinetics (↓dosing frequency to qd or bid→↓SE)