Human Immunodeficiency Virus
Retrovirus - integrated into host genome
One single-strand RNA 7,000 bases
HIV1 > HIV2 > HIV0
Pathology
Destruction of CD4+ T lymphocytes
Loss of immune function
Opportunistic infections, death

HIV Life Cycle

HIV - Life cycle
Binding to CD-4 receptors on T-lymphocytes
Fusion of viral and cell membranes
Uncoating
Reverse transcriptase makes DNA complement of vRNA, then second strand DNA
Integrase splices vDNA into host chromosome
Synthesis of viral mRNA
Synthesis of gag and gag-pol polyproteins
Cleavage by HIV protease into HIV proteins
Budding from cell surface

Anti-HIV therapy – Nucleosides
Nucleoside Reverse Transcriptase Inhibitors - NTRIs
Very similar in action to anti-Herpes acyclovir
1. All are both competitive inhibitors of HIV-RT and chain terminators - lack 3′OH
2. All selectively inhibit and are incorporated by HIV-RT, not cellular DNA polymerases
3. Can’t be removed by HIV-RT once incorporated, because RT has no editing function

HIV therapy - Principles
HIV reverse transcriptase (RT) is one of the most error-prone polymerases known, with one mistake per ~1700 bases and no “editing” ->
Rapid onset of drug resistance ->
Need to stop replication effectively and rapidly ->
Usually use 3 or even 4 drugs immediately ->
Large pill burden, esp. with antibiotics, analgesics
Numerous Interactions
Problems with compliance

Human Immunodeficiency Virus Structure
Anti-HIV Therapy - nucleosides

Thymidine (T) analogues:
- Zidovudine, Stavudine

Adenosine analogue: Didanosine

Cytidine analogues:
- Zalcitabine, Lamivudine

Guanosine analog: Abacavir

Zidovudine selectivity

Selective competitive inhibitor of HIV reverse transcriptase but not human DNA polymerase

HIV RT \( K_i = 0.04 \) uM

Human DNA pol alpha, \( K_i = 230 \) uM

Zidovudine - clinical use

The first effective anti-HIV drug

AIDS treatment:
- 200 mg oral 3x/day, usually with 2 other drugs
- For prevention of mother-to-child transmission
  - 100 mg 5x/day during pregnancy
  - 1 mg/kg IV during delivery
  - 2 mg/kg 4x/day to newborn (syrup) for 6 weeks
  - 23% reduction in transmission
Zidovudine

Resistance: mutant HIV-RT
1-2 mutations -> low-level resistance
3-5 mutations -> high-level resistance
Withdrawal of drug sometimes results in reversion to zidovudine sensitivity
Tox: immune suppression
Inhibition of cellular DNA polymerase
Other Tox: GI, headaches, lactic acidosis

Zidovudine
Pharmacokinetics
Half-life: 1 hr in serum, 3 hr in cell (phosphate)
Glucuronidated (liver) -> renal excretion
Interactions
Myelosuppression exacerbated by (e.g.): Ganciclovir, cytotoxic cancer drugs
Bioavailability increased by (e.g.): Lamivudine, methadone
RT resistance to Lamivudine, Didanosine sometimes restores Zidovudine sensitivity

Stavudine (d4T) {Zerit}
A thymidine analogue, chain terminator

Stavudine
Excellent oral bioavailability (86%)
Dosage: 20-40 mg bid
Resistance: HIV-RT mutants:
I50T
V75T - cross-resistance to dideoxys (didanosine, zalcitabine)
Tox: Peripheral neuropathy - due to inhibition of mitochondrial DNA polymerase \( \gamma \) (gamma)

Dideoxys
Didanosine (dideoxyinosine, ddI)
Zalcitabine (dideoxycytidine, ddC)

Didanosine {Videx}
Clinical use - similar to Zidovudine
Pharmacokinetics
Degraded by acid - buffered formulation
Long 12-24 hr half life in cells (phosphate)
Tox: pancreatitis, peripheral neuropathy, CNS
Interactions:
Potentiated by hydroxurea, which depletes dATP
RT ddI resistance can restore zidovudine sensitivity to resistant strains harboring mutant RT
Zalcitabine (ddC)
Pharmacokinetics - similar to Didanosine
Tox: peripheral neuropathy, usually reversible
Correct dosage critical - renal insufficiency
Interactions
Renal impairment due to e.g. aminoglycosides, foscarnet, may cause overdose
Avoid coadministration of other neuropathic drugs (Didanosine, Stavudine)

Abacavir (Ziagen)
A guanosine analogue

Abacavir
Clinical use, pharmacokinetics similar to Zidovudine
The most effective of the current NRTIs
Tox: hypersensitivity reactions common
GI distress, rash, fever, occasionally fatal
Few drug interactions
Resistance: 2-3 mutations in HIV-RT required for high-level resistance

Lamivudine (Epivir)
Mechanism similar to Zidovudine
Synergistic with Zidovudine, Stavudine
Long half-life in cells: 10-16 hr (phosphorylated)
Resistance:
Single M184V mutation gives high-level resistance
Cross resistance to:
Zidovudine, Abacavir, Didanosine
Tox: mild; headache, insomnia, GI

Mutations Associated with Resistance to Nucleoside and Nucleotide HIV Reverse Transcriptase Inhibitors
HIV therapy: non-nucleotide reverse transcriptase inhibitors (NNRTIs)

Bind to RT at a hydrophobic site near NRTI binding site
Resistance: K103N (& Y181C/I) confers resistance to all NNRTIs, so cross-resistance is common, but NOT cross-resistant with NTRIs
Resistance tends to develop quickly, therefore never treat HIV with an NNRTI alone
Pharmacokinetics: Good oral availability; metabolized by various cytochromes P450

NNRTIs: Nevirapine {Viramune}
Clinical use:
Combination chemotherapy for AIDS
Prevention of mother-to-child transmission
200 mg during labor, 2 mg/kg to newborn
Tox: Rashes can be life-threatening
Escalate dose gradually
Metabolized by CYP3A
Induces CYP3A

NNRTIs: Efavirenz {Sustiva}
Clinical use: AIDS combination chemotherapy
Tox: CNS effects & skin rash usually resolve with continued use
Fetal abnormalities in pregnancy
Metabolized by CYP3A4, CYP2D6
Induces CYP3A4→ decreased bioavailability of many other drugs

HIV therapy: Protease Inhibitors

Human cellular genes:
One DNA sequence -> one mRNA -> one protein

HIV:
One DNA sequence -> one mRNA ->
2 large polyproteins (via frameshift)
Each polyprotein -> individual proteins (cleavage by protease)
HIV protease function

HIV protease cleaves Phe-Pro or Tyr-Pro protein bonds, which are not cleaved by any cellular protease; therefore structures resembling such bonds may selectively block HIV protein synthesis by competitive inhibition.

Saquinavir: drug design
Hydroxyethylamine replaces peptide linkage - binds to protease but can't be cleaved
XVII = Saquinavir

Protease Inhibitors - general features
Structure - peptide like, hydrophobic ends
Metabolism - P-450 cytochromes esp. CYP3A(4) major effects on bioavailability
Resistance - mutant HIV protease
 Often but not always cross-resistant to other PIs
Tox: varied, but mostly GI
Administration: oral, usually with food

Mutations Associated with Resistance to HIV Protease Inhibitors

Major mutation, frequently observed or associated with high level resistance, avoid drug if possible.
Common mutation, alone or with other mutations can be associated with resistance, use with caution.
Less frequent mutations or common polymorphisms, not generally associated with high level resistance.
Drug does not select for mutation but mutation may cause some degree of cross resistance.

PI Structure
All have:
Peptide-like backbone
Phenyl side chain
Hydrophobic ends
Saquinavir {Invirase}
Metabolized by CYP3A4 -- availability decreased by CYP3A4 inducers

Ritonavir {Norvir}
Potent CYP3A inhibitor -- increases availability of many other drugs
Escalate dose slowly

HIV - Treatment Strategy
Start treatment aggressively - generally 3 drugs
e.g.: [Zidovudine or Stavudine] + [Didanosine or Lamivudine] + Any protease inhibitor
Monitor HIV levels (RT-PCR)
Failures: Genotype HIV-RT & protease, then choose 2 new drugs with no predicted cross-resistance

Indinavir {Crinixan}
Take without food
Tox: renal (crystallization) - hydration req.
Numerous drug interactions:
Induces CYP3A4
Metabolized by CYP3A4

Amprenavir {Agenerase}
Inhibits CYP3A4

HIV Life Cycle

Fusion Inhibitors
Target the HIV gp41 protein
Prevent the conformational change that promotes fusion of cell and viral membranes
Can sometimes reduce viral load to undetectable levels in patients where NRTI/NNRTI/PI therapy has failed
Summary - HIV Therapy
Nucleosides (NRTIs)- all chain terminators
Resistance (for all) - mutant HIV-RT
Tox: (for many) peripheral neuropathy
Zidovudine (AZT)
  Tox: immune suppression
Abacavir - most effective
Didanosine - acid-sensitive - buffered
Lamivudine, Zalcitabine, Stavudine

Summary
NNRTIs: Nevirapine, Efavirenz
  Generally no NRTI cross-resistance
  Tox: skin rashes
CYP3A interactions
PIs: Saquinavir, Indinavir, Ritonavir
  Tox: GI, mild
  CYP3A interactions
Fusion Inhibitor: Enfuvirtide
  Tox: mild irritation at injection site

Fusion Inhibitors: Enfuvirtide (T-20) {Fuzeon}
Administration: 90 mg twice/day by injection
Toxicity:
  irritation at site of injection
Long-term effects unknown
Cost: $20,000/yr