The antiretroviral class most commonly involved in drug interactions is:

1. Nucleoside reverse transcriptase inhibitors
2. Non-Nucleoside reverse transcriptase inhibitors
3. Protease inhibitors
4. Fusion inhibitors

The class of antiretrovirals associated with lactic acidosis is:

1. Nucleoside reverse transcriptase inhibitors
2. Non-Nucleoside reverse transcriptase inhibitors
3. Protease inhibitors
4. Fusion inhibitors

Which of the following acts by inhibiting retrovirus fusion?

1. Saquinavir
2. Enfuvirtide
3. Nevirapine
4. Abacavir
Three Main Classes

1. Nucleoside reverse transcriptase inhibitors
2. Non-Nucleoside reverse transcriptase inhibitors
3. Protease inhibitors
   - Key issues in the selection of antiretrovirals
     - Pharmacokinetics
     - Drug interactions
     - Resistance profiles
     - Adherence

HIV Viral Replication

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- Inhibit reverse transcriptase & decrease or prevent HIV replication
- Most taken in 2 or 3 daily doses without regard to meals
- Generally free of drug interactions
- May cause potentially fatal syndrome of lactic acidosis with hepatic steatosis due to mitochondrial toxicity
Antiretroviral Agents
John A. Bosso, Pharm.D.

**NRTIs**

- **Zidovudine (AZT, ZDV; Retrovir)**
  - Available alone & in combos
  - With lamivudine & abacavir
  - Available as tablets, capsules, oral solution and solution for injection
  - Often used alone or in combo for prophylaxis after exposure

- **Zidovudine (con’d)**
  - Eliminated by metabolism (~85%) and through kidneys (~15%)
  - ADRs: anemia, neutropenia, nausea, vomiting, HA, fatigue, confusion, malaise, myopathy, hepatitis

- **Stavudine (d4T; Zerit)**
  - Available as capsules and oral solution
  - Cross resistance with zidovudine is frequent
  - 40-50% eliminated unchanged by kidneys
  - Fatal lactic acidosis may be more common
  - Do not combine with didanosine
  - ADRs: dose-related peripheral neuropathy, increased serum aminotransferase

- **Didanosine (ddI; Videx)**
  - Available as buffered tablets, buffered and non-buffered powder, non-buffered enteric-coated capsules
  - Buffered tabs can inhibit absorption of drugs requiring gastric acidity
  - Eliminated by kidneys 50% as unchanged drug
NRTIs

- Didanosine (con’d)
  - ADRs: dose-related peripheral neuropathy*, pancreatitis*, GI disturbances
  - Do not combine with zalcitabine (parallel toxicities)
  - (*increased when combined with stavudine)

- Lamivudine (3TC; Epivir)
  - Available as tablets and oral solution
  - In combination with zidovudine
  - Best tolerated but perhaps highest rates of resistance
  - Also active vs HBV
  - 70% eliminated unchanged by kidneys
  - ADRs: uncommon but include mitochondrial toxicity, pancreatitis in children

- Abacavir (ABC; Ziagen)
  - Available alone & in combo products (tablets and oral solution)
  - Cross resistance with other NRTIs
  - Chiefly eliminated through metabolism
  - ADRs: hypersensitivity reactions in 3% (fever, respiratory compromise, GI sx, malaise, rash)
    - May occur early in therapy, do not rechallenge patient
  - Drug interaction with alcohol

- Zalcitabine (ddC; Hivid)
  - Available as oral tablets
  - Least effective of the NRTIs
  - >70% eliminated unchanged by kidneys
  - ADRs: dose-related peripheral neuropathy, rash, stomatitis, esophageal ulceration, pancreatitis, fever
### NRTIs

- **Emtricitabine (FTC: Emtriva)**
  - Available as oral capsules
  - Administered once daily
  - Eliminated unchanged by kidneys
  - Common ADRs: headache, diarrhea, nausea, rash (less commonly: hyperpigmentation of palms and soles, lactic acidosis, severe hepatomegaly with fatty liver)
  - Also active vs. HBV

### NRTI Combination Products

- **Twice daily use:**
  - Combivir
    - Zidovudine & lamivudine
  - Trizivir
    - Zidovudine, lamivudine, abacavir

- **Once daily use:**
  - Epzicom
    - Abacavir & lamivudine
  - Truvada
    - Emtricitabine/tenofovir

### Atripla

**NNRTI/NRTI Combination**

- Once daily, single combination tablet
  - 600 mg efavirenz (Susteva, an NNRTI)
  - 200 mg emtricitabine (Emtriva, an NRTI)
  - 300mg tenofovir DF (Viread, an NRTI)
- For use as initial therapy in treatment naïve patients
- ADRs: Similar to the individual drugs alone

### Atripla NNRTI/NRTI Combination

- Drug interactions:
  - Mainly due to efavirenz
    - A substrate, inducer and inhibitor of CYP450 isoenzymes
  - Contraindicated in patient taking voriconazole, ergot derivatives and some benzodiazepines
  - Opioid withdrawal can occur in patients taking methadone
### Lactic Acidosis and NRTIs

- **Mitochondrial toxicity**
  - Secondary to NRTI inhibition of mitochondrial DNA polymerase gamma
  - Particularly associated with zidovudine and stavudine
  - Can lead to:
- **Lactic acidosis and death secondary to dyspnea and cardiac arrhythmia**

### Nucleotide RTI

- **Tenofovir disoproxil fumarate** (TDF; *Viread*)
  - A phosphorylated nucleoside
  - Produrg of tenofovir
  - Same MOA as NRTIs
  - For use in combo regimens in patients who have failed other tx
  - Probably will see increased use in treatment-naïve patients due to proven efficacy, convenience, and safety
  - ADRs: nausea, vomiting, diarrhea

### Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- **Efavirenz** (EFV; *Sustiva*)
  - Available as oral tablets
  - Once daily dosing
  - High fat meals ↑ conc’s 50%
  - Chiefly eliminated by metabolism
  - CYP3A4 inhibitor/inducer
  - ADRs: rash (15%), dizziness, HA, insomnia, vivid dreams, nightmares, hallucinations*
  - Contraindicated in pregnancy (Class D)

*CNS side effects often subside within a few weeks of therapy
NNRTIs

• Nevirapine (NVP; Viramune)
  – Often combined with 2 NRTIs
  – Available as tablets and oral suspension
  – Eliminated chiefly by metabolism
  – CYP3A4 inducer
  – ADRs:
    • Severe hepatotoxicity, hepatic failure, death
    (including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, has been reported in patients treated with Viramune. These events are often associated with rash. Women, and patients with higher CD4 counts, are at increased risk of these hepatic events)
    • Rash - 30% (seldom Stevens-Johnson Syndrome)
    • Fever, nausea, HA

• Delavirdine (DLV; Rescriptor)
  – Available as oral tablets
  – Less effective than others
  – Increases serum concentrations of PIs
  – Do not co-administer with antacids, didanosine, H2 blockers, or PPIs
  – CYP3A4 inhibitor
  – ADRs: rash (35%), ↑LFTs, nausea, HA

Protease Inhibitors

• Prevent cleavage of protein precursors needed for HIV maturation, infection of new cells and viral replication
• Resistance to various PIs depends on number of mutations
• Involved in numerous drug interactions
• All cause GI distress, increased bleeding in hemophiliacs, hyperglycemia, insulin resistance & hyperlipidemia, fat wasting, reaccumulation and redistribution

• All, but especially ritonavir may cause hepatotoxicity
• Newer PIs (lopinavir/ritonavir, atazanavir and fosamprenavir) are dosed less frequently and have more favorable side effect profiles
• Metabolized by CYP450
  – Drug interactions are common
• If concomitant rifamycin therapy is needed, use rifabutin
## Protease Inhibitors

**Saquinavir (SQV)**
- 2 capsule products available (hard gel cap: *Invirase* & soft gel cap: *Fortovase*)
- *Fortovase* has much better bioavailability
- Mostly eliminated by metabolism
- Well tolerated (ADRs mostly GI)

**Ritonavir (RTV; *Norvir*)**
- Available as capsules* and oral solution†
  - *refrigerate*
  - †43% alcohol
- Should be administered with food but avoid antacids
- Eliminated by metabolism
- ADRs are common but dose-related
- More likely to cause hypertriglyceridemia
- Also causes perioral and peripheral paresthesias, altered taste, nausea, vomiting
- Because of potent CYP450 inhibition, often used in combination to “boost” effect of other PIs yielding better dosing flexibility and efficacy

**Indinavir (IDV; *Crixivan*)**
- Available as oral capsules
- Poor bioavailability (60%)
  - Administer 1 hr before or 2 hr after meals
  - Fatty meals further decrease absorption
- Mainly eliminated by metabolism
- ADRs include ↑ indirect bilirubin, kidney stones and renal insufficiency, alopecia, drug skin and mucous membranes, paronychia, and ingrown toenails
- Drinking 1.5-2 L water/day helps minimize the renal side effect

**Nelfinavir (NFV; *Viracept*)**
- Inconsistent bioavailability (20-80%)
  - Administer with food
- Available as tablets & oral powder
- Eliminated mainly by metabolism
- Best tolerated PI and therefore the most commonly used
- Most common ADR is diarrhea
Protease Inhibitors

- **Amprenavir (APV; Agenerase)**
  - Available as capsules & oral solution
  - Mostly eliminated by metabolism
  - Contains a large amount of vitamin E (exceeds RDA)
  - Most common ADRs are nausea, diarrhea, perioral paresthesias, vomiting, rash

Protease Inhibitors

- **Fosamprenavir (908; Lexiva)**
  - Prodrug of amprenavir
  - Available as oral tablets
  - Less frequent dosing (qd or bid)
  - More favorable ADR profile than amprenavir and other older PIs
  - 19% incidence of skin rash
  - May be taken with or without food

Protease Inhibitors

- **Atazanavir (Reyataz)**
  - An azapeptide, structurally different from other PIs
  - Available as oral capsules
  - Administered once daily
  - Food increases absorption & bioavailability
  - Eliminated thru metabolism
  - Common ADRs include indirect hyperbili-rubinemia; can prolong PR interval

Protease Inhibitors

- **Tipranavir (Aptivus)**
  - Available as capsule
  - Used in phase III in combo with ritonavir for treatment experienced patients
  - May have more heptotoxicity than other PI's
  - Tipranavir/ritonavir combo is a net inhibitor of CYP3A and 2D6, and a net inducer of P-glycoprotein
Protease Inhibitors

- Darunavir (Prezista)
  - Approved for tx of treatment-experienced adult patients (including those with protease-resistant strains)
  - To be co-administered (2 x 300mg tabs twice daily) with 100mg ritonavir
    - To be taken with food
  - A potent inhibitor of CYP3A
  - Most common ADRs: nausea, diarrhea, headache and nasopharyngitis
    - Can cause severe skin rash including SJS
    - Use with caution in patients with sulfa allergy

Protease Inhibitors Combo

- Lopinavir/ritonavir (Kaletra)
  - Lopinavir is only available in the USA in this fixed combo
  - Available as capsules and oral solution
  - Elimination chiefly by metabolism
  - Common ADRs include diarrhea, nausea, HA and asthenia

Select Protease Inhibitor ADRs

- Fat redistribution
  - Body fat accumulation
    - Dorsoceval fat (buffalo hump)
    - Visceral fat (protease paunch)
    - Breast enlargement
  - Body fat loss
    - Facial fat or subcutaneous fat of extremities
  - Seen in HIV infection alone but increased incidence with ART

Select Protease Inhibitor ADRs

- Dyslipidemia
  - Elevation of serum lipids
    \[ \uparrow \text{triglycerides, total cholesterol & LDL cholesterol} \]
  - Incidence increased with HAART
  - Seen more often with ritonovir-containing regimens
Select Protease Inhibitor ADRs

- Hyperglycemia/Diabetes
  - Perhaps due to peripheral insulin resistance

- Bleeding in hemophiliacs
  - Often cited but unclear whether actually an ADR of ART

Fusion Inhibitor

- Enfuvirtide (Fuzeon)
  - A fusion inhibitor
    - Binds to the transmembrane glycoprotein subunit (gp41) of the viral envelope preventing fusion to the host cell membrane, and thus entry into the cell
    - Must be administered SQ bid
    - Often active against HIV strains resistant to other antiretrovirals but should not be used alone
    - ADRs mostly injection site reactions:
      - Pain, erythema, induration, nodules or cysts in 98%
      - Other: eosinophilia 10%, hypersensitivity 0.6%

Detailed Antiretroviral Information

http://aidsinfo.nih.gov/drugs/

Experimental
(as of January 2004)

- Vaccines
- Immunomodulators
- Antiretroviral agents
  - NRTIs (7)
  - Entry and fusion inhibitors (5)
  - PIs (2)
  - Vaginal microbicides (7)