Drug-Drug Interactions with Antiretroviral Therapy

Case-Based Discussions

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Learning Objectives

Upon completion of this presentation, the learner should be better able to:

- List the most common pathways of drug-drug interactions involving different antiretroviral agents

- Identify key target drugs or drug classes that may cause clinically significant interactions in your patients when used with antiretroviral agents

- Develop therapeutic plans or strategies to manage potential drug interactions in your patients living with HIV
What is your primary responsibility in patient care?

1. I am not a healthcare provider
2. HIV Primary Care Physician
3. NP or PA
4. Pharmacist
5. Nurse (not NP)
6. Social worker
7. Psychiatrist
8. Case manager
9. Other
How would you rate your knowledge and understanding of drug-drug interactions?

1. Excellent
2. Good
3. Fair
4. Poor
5. I don’t know anything about drug-drug interactions, that’s why I’m here
What is the most common resource you use to assess drug-drug interactions?

1. Wikipedia
2. Web-based drug interaction programs
3. My excellent clinical pharmacist
4. ARV treatment guidelines
5. My own instinct
6. Package insert
7. I never have to look up any information
45 yo AA Male, HIV infection diagnosed in 2006

- Currently on ATV/r + TDF/FTC
- Last CD4 = 560 cells/mm$^3$, HIV RNA < 50 cpm
- Other medical history:
  - IDU – last use 2005
  - HBsAg +
  - BMI = 29 kg/m$^2$
- He presented to clinic in the past couple of months with BP around 150/90, HR 70-80
Which of the following antihypertensive agents has the greatest potential for interaction with his ART regimen (ATV/r + TDF/FTC)?

a. Lisinopril

b. Hydrochlorothiazide

c. Atenolol

d. Amlodipine

e. Diltiazem
Which of the following antihypertensive agents has the most potential for interaction with his ART regimen (ATV/r + TDF/FTC)?

a. Lisinopril
b. Hydrochlorothiazide
c. Atenolol
d. Amlodipine
e. Diltiazem
Atazanavir (+/- ritonavir) + Diltiazem

(Atazanavir, Product Information, 2011)

- Atazanavir +/- ritonavir – potent CYP3A4 inhibitor
- Diltiazem – CYP3A4 substrate
- When combined – > 2-fold inc. in diltiazem AUC
- Report of 2\textsuperscript{nd} and 3\textsuperscript{rd} degree AV block when ATV added to a stable diltiazem regimen
- Use lowest diltiazem dose with close monitoring
Drug-Drug Interactions

- Harmful Effects
- Unknown Effects
- Synergistic/Beneficial Effects
Common Mechanisms of Drug-Drug Interactions

Pharmacokinetic Interactions:

*** Alteration in drug Absorption
- Alteration in drug Distribution
*** Alteration of hepatic Metabolism
- Alteration of renal Excretion

Pharmacodynamic Interactions:
- Synergistic or antagonistic pharmacologic effects
- Overlapping or additive toxicities
Pharmacokinetics/Pharmacodynamic (PK/PD) Considerations in ART

- **Cmax**: Maximum concentration
- **Cmin**: Minimum concentration
- **Tmax**: Time to reach maximum concentration
- **AUC**: Area Under the Curve
- **IC50**: The concentration that inhibits 50% of the maximum effect
Drug Interactions May Significantly Influence Desired Outcome if it Involves Drugs with:

- **Narrow margin of safety** & conc.-related toxicities (e.g. carbamazepine, benzodiazepine)

- **Marginal efficacy** (e.g. unboosted fosamprenavir in treatment-naïve patients)
45 yo AA Male, HIV infection diagnosed in 2006, presented with hypertension

- Currently on ATV/r + TDF/FTC
- Started on lisinopril 20mg per day with good BP response
- 3 months later, he presented for follow-up, reported that a couple of months ago, he has been suffering from acid reflux
- He bought some over-the-counter omeprazole with good symptom relief
- CD4 remains stable at 600, but HIV RNA has increased to 7,000 copies/mL
Effect of Decrease in Drug Absorption on Antiretroviral Pharmacokinetics

- Atazanavir with normal gastric pH
- Atazanavir + omeprazole

- ↑ Oral bioavailability (F)
- ↑ Cmax, ↑ Cmin
- ↔ T1/2
Factors Affecting Drug Absorption

- Gastric pH
- Chelation of compounds
- Gastric emptying
- Intestinal motility
- Intestinal blood flow
- Intestinal CYP 3A4 activities
- Intestinal P-glycoprotein activities
Always Consider Drug-Drug Interactions when:

- Reviewing medication profile
- Conducting a medication history (always ask about OTC, herbal products)
- Starting a new medication
- Stopping an existing medication (to assess if it will affect current meds)
- If patients use multiple providers
### Hepatic Metabolism of Drugs

- Conversion of lipophilic compounds into ionized metabolites for renal excretion

**Phase I (non-synthetic) | Phase II (synthetic)**

<table>
<thead>
<tr>
<th>(I°ly via CYP450)</th>
<th>Glucuronidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidation (UGT)</td>
<td>Sulfation</td>
</tr>
<tr>
<td>Reduction</td>
<td>Acetylation</td>
</tr>
<tr>
<td>Hydrolysis</td>
<td></td>
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<tr>
<td>Dealkylation</td>
<td></td>
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<tr>
<td>Demethylation</td>
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</table>
Hepatic Cytochrome P450 Isoenzymes

(In: Piscitelli & Rodvold, Drug Interactions in Infectious Diseases, 2nd Ed, 2005)

- **CYP450** - accounts for majority of the metabolic pathway of exogenous & endogenous biochemicals

- Drugs metabolized via CYP 450 can be substrates, inhibitors, and/or inducers

- Metabolic pathway of many older drugs - have not been evaluated, thus interactions unknown

![Hepatic Cytochrome P450 Isoenzymes Pie Chart]

- 3A4/5: 36%
- 2D6: 19%
- 2C19: 8%
- 2C8/9: 16%
- 2B6: 3%
- 2A6: 3%
- 1A1/2: 11%
- 2EI: 4%
Mechanism and Results of CYP Interactions

- **Substrate** – A chemical that is primarily metabolized by one or more CYP isoenzymes, whereby its metabolic rate can be influenced by the presence of an CYP enzyme inhibitor or inducer

- **Inducer + Substrate** – speeds up metabolism, resulting in: (1) lower concentrations; (2) shorter half-life; (3) reduce drug efficacy

- **Inhibitor + Substrate** – slows down metabolism, resulting in: (1) higher concentrations; (2) longer half-life; (3) potential for increasing potency (e.g. ritonavir + lopinavir); or (4) potential for increased toxicities
CYP-P450 Mediated Metabolism of PI, NNRTIs, & Maraviroc

**PIs**
- All PIs are metabolized via CYP 450 (primarily via 3A4 isoenzyme)
- Ritonavir & most PIs – 3A4 substrate & inhibitor
- Tipranavir – 3A4 inducer, but TPV/r - inhibitor

**NNRTIs**
- *Delavirdine* – 3A4 Inhibitor
- *Efavirenz* – mixed inducer and inhibitor
- *Etravirine* – 3A4 substrate & inhibitor; 2C9 & 2C19 substrate & Inhibitor
- *Nevirapine* – 3A4 inducer

**CCR5 Antagonist**
- *Maraviroc* – 3A4 substrate
# Clinical Significant CYP 3A4 Inhibitors and Inducers

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>Inducers</th>
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</thead>
<tbody>
<tr>
<td>Ritonavir &amp; other PIs</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Macrolides (Clari,Ery.)</td>
<td>Rifabutin</td>
</tr>
<tr>
<td>Azoles</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>Diltiazem, verapamil</td>
<td>Nevirapine</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>St. John’s Wort</td>
</tr>
<tr>
<td>Grapefruit juice (intestinal only)</td>
<td>Carbamazepine</td>
</tr>
</tbody>
</table>
Clinically Significant Substrates of CYP 3A4

<table>
<thead>
<tr>
<th>Anti-Arrhythmics</th>
<th>Ergot Alkaloids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisapride</td>
<td>Terfenadine</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>“Statins”</td>
<td>Estrogens</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>Ca^{++} Channel Blockers</td>
<td>Chemotherapeutic agents</td>
</tr>
<tr>
<td>agents</td>
<td></td>
</tr>
<tr>
<td>Sildenafil/Vardenafil</td>
<td>Buspirone</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Triazoles</td>
</tr>
</tbody>
</table>
42 yo male, recently started on EFV/TDF/FTC

- Pre-ART CD4 = 100 cells/mm³, HIV RNA = 150,225 copies/mL
- Tolerated ART x 4 weeks
- Presented with fever up to 39 degree, eventual diagnosis was disseminated histoplasmosis
- Received liposomal amphotericin B x 2 weeks, then switched to oral itraconazole
- Other medications: dapsone, lisinopril, metformin
What potential significant interaction would you expect?

1. Itraconazole may increase lisinopril conc.
2. Itraconazole may significantly decrease efavirenz concentration.
3. Efavirenz may significantly reduce itraconazole concentration
4. Itraconazole may increase dapsone concentration
5. None of the above
42 yo with histoplasmosis

- The patient was discharged on itraconazole 200mg twice daily
- Returned to clinic one week later with complaints of fever, fatigue, and shortness of breath
- Urine histoplasma Ag rose from 2.5 IU at discharge to 10.5 IU
- Itraconazole conc. = 0.2 mcg/mL
35 yr old male, w/ KS, HBV, & Depression

- Chronic low back pain L4-L5 herniation
- On LPV/r + TDF/FTC with HIV RNA < 50 copies/mL for > 2 years, CD4 = 475 cells/uL
- Other medications: trazodone, rabeprazole, gabapentin, fexofenadine, oxycodone/acetaminophen, cyclobenzaprine
- The patient presented to HIV clinic with complaints of facial swelling
35 yo M, w/ KS, HBV, & depression (2)

- P.E. remarkable for:
  - BP 157/100 (1st recorded high BP), wt gain of 2 kg in the past month
  - Moon faces & presence of dorsocervical fat pad
  - Non-healing left index finger (injury > 4 days prior)
- Lab findings:
  - AM plasma cortisol < 1 mcg/dL (10-20 mcg/mL)
  - 60 min. co-syntropin stim test, cortisol = 1.2 mcg/dL
  - Fasting blood glucose = 140 mg/dL
Pt reported visiting a neurosurgeon since the last visit – received 2 epidural injections of triamcinolone acetonide (60mg and 80mg) one week apart

Iatrogenic Cushing’s Syndrome, adrenal insufficiency – increasing reports with ritonavir-based regimen & locally administered steroids (local injection, inhaled, topical)
Triamcinolone Acetonide and Cortisol Levels Following Epidural Steroid Injection

Ramanathan R, et al. CID 2008
35 yo Kenyan male with TB and DVT

<table>
<thead>
<tr>
<th>Date</th>
<th>Warfarin Dose</th>
<th>INR</th>
<th>Interacting Meds</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-09-09</td>
<td>10 mg</td>
<td>3.11</td>
<td>EFV, REP</td>
</tr>
<tr>
<td>30-09-09</td>
<td>10 mg</td>
<td>2.53</td>
<td>EFV, REP</td>
</tr>
<tr>
<td>07-10-09</td>
<td>10 mg</td>
<td>2.47</td>
<td>EFV, REP</td>
</tr>
<tr>
<td>14-10-09</td>
<td>10 mg</td>
<td>2.29</td>
<td>EFV, REP</td>
</tr>
<tr>
<td>11-11-09</td>
<td>10 mg</td>
<td>2.22</td>
<td>EFV, REP</td>
</tr>
<tr>
<td>09-12-09</td>
<td>10 mg</td>
<td>2.87</td>
<td>EFV, REP</td>
</tr>
<tr>
<td>06-01-10</td>
<td>10 mg</td>
<td>2.03</td>
<td>EFV, REP</td>
</tr>
<tr>
<td>25-01-10</td>
<td>10 mg</td>
<td>2.03</td>
<td>EFV</td>
</tr>
<tr>
<td>22-02-10</td>
<td>7.5 mg</td>
<td>3.06</td>
<td>EFV</td>
</tr>
<tr>
<td>08-03-10</td>
<td>7.5 mg</td>
<td>2.76</td>
<td>EFV</td>
</tr>
<tr>
<td>06-04-10</td>
<td>7.5 mg</td>
<td>2.76</td>
<td>EFV</td>
</tr>
<tr>
<td>05-05-2010</td>
<td>7.5 mg</td>
<td>1.95</td>
<td>EFV</td>
</tr>
</tbody>
</table>
34 yo male from Ethiopia with HIV/TB

- **Sep ‘09** - diagnosed with pulmonary TB & HIV, CD4 = 12 cells/mm³, HIV RNA = 122,000 copies/mL
- **Nov ‘09** – 1st visit to HIV clinic, on TB maintenance therapy (INH + rifampin) via DOT
- Other meds: TMP-SMX, azithromycin, valacyclovir (for recurrent HSV)
- **Dec ‘09** – started on EFV/TDF/FTC
34 yo male from Ethiopia with HIV/TB (2)

<table>
<thead>
<tr>
<th>Date (ARV Wk #)</th>
<th>CD4 (cells/mm³)</th>
<th>HIV RNA (copies/mL)</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/2/09 (wk 0) EFV/TDF/FTC</td>
<td>12</td>
<td>85,831</td>
<td>WT</td>
</tr>
<tr>
<td>12/15/09 (wk 2)</td>
<td>36</td>
<td>229</td>
<td></td>
</tr>
<tr>
<td>12/29/09 (wk 4)</td>
<td>52</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>1/25/10 (wk 8)</td>
<td>66</td>
<td>&lt;50</td>
<td></td>
</tr>
<tr>
<td>3/4/10 (wk 13)</td>
<td>73</td>
<td>27,695</td>
<td></td>
</tr>
<tr>
<td>3/23/10 (wk 16)</td>
<td>-</td>
<td>15,772</td>
<td>K65R, G190E</td>
</tr>
</tbody>
</table>
Key considerations when designing a new regimen

- Rifampin’s effect on EFV
- Rifampin’s effect on other ARVs
- What new regimen to use?
- How long does rifampin’s induction effect last?
- Interaction of rifabutin and ARVs
- Adherence, dosing frequency, and other considerations
- Is there a role of Therapeutic Drug Monitoring?
<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on ARVs</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>AUC ↓ 22%</td>
<td>600 mg/d (800mg/d in some pts)</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Not known, potential for significant ↓ AUC</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>levels ↓ 20- 58%</td>
<td>Do not co-administer or use with caution – if use, monitor virologic responses</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>AUC ↓ 64%</td>
<td>600mg bid or use rifabutin</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>AUC ↓ 60%</td>
<td>Use with caution or use rifabutin</td>
</tr>
</tbody>
</table>

DHHS Antiretroviral Guidelines for Adults and Adolescents, Jan 2011; [http://aidsinfo.nih.gov](http://aidsinfo.nih.gov)
Effect of CYP 3A4 Enzyme Induction on Antiretroviral Pharmacokinetics

LPV/r alone

LPV/r + rifampicin

LPV/r + Rifampicin:
- ↓ Cmax, ↓ Cmin
- ↓ T₁/₂
- IC₅₀ > Cmin

Time (Hours)

Concentration

IC₅₀
<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on PIs</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>AUC ↓ 57-72%, C&lt;sub&gt;min&lt;/sub&gt; ↓ 98%</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>DRV/r</td>
<td>Potential for AUC ↓</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>FPV (APV)</td>
<td>AUC ↓ 82%, C&lt;sub&gt;min&lt;/sub&gt; ↓ 92%</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>IDV or IDV/r</td>
<td>AUC ↓ 89%/conc. ↓ 84%</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>LPV/r</td>
<td>AUC ↓ 75%, C&lt;sub&gt;min&lt;/sub&gt; ↓ 99%</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>NFV</td>
<td>AUC ↓ 82%</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>SQV; SQV/r</td>
<td>AUC ↓ 84%; hepatotoxicity</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>TPV/r</td>
<td>Potential for AUC ↓</td>
<td>Do not co-administer</td>
</tr>
</tbody>
</table>
Alternative Dosing of PIs + Rifampin

- Double dose LPV/r
- Increase ritonavir doses (studied with atazanavir, LPV/r, saquinavir)
- May overcome induction effect of rifampin
- Healthy volunteer studies – stopped prematurely due to inc. in Grade 3/4 hepatotoxicities
- Other disadvantages: pill burden, GI toxicities
Rifabutin as Alternative  [DHHS Antiretroviral Guidelines Jan 2011]

- Alternative anti-TB, less potent CYP3A4 inducer
- CYP3A4 substrate
- When use with PI – current recommendation: 150mg QOD
- Low concentration & acquired rifamycin resistance reported in HIV/TB co-infected pts
- When use with EFV – increase dose to 450-600mg/d
Summary

- Assessment of drug-drug interactions should be a critical part of patient management, esp. when:
  - Starting a regimen – select one with the least interactions & yet maintain efficacy
  - Stopping any drug – esp. if one or more interacting drugs are to be stopped (e.g. completion of TB Tx)
  - When patients are experiencing toxicities at normal doses
  - When suboptimal clinical response is seen despite medication adherence
Antiretroviral Interaction Resources

- [www.hivinsite.ucsf.edu](http://www.hivinsite.ucsf.edu) - on-line search engine
- [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
- [http://HIV.medscape.com](http://HIV.medscape.com) - drug interaction calculator, CME, drug interaction charts