Overview of Drug Interactions in HIV Medicine

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Basics of Drug Elimination
Pharmacodynamic Interactions

• Pharmacodynamic defined simply as what the drug does to the body
• Select examples in HIV
  – Antagonistic interaction with zidovudine and stavudine – binding site competition
  – Zidovudine and ganciclovir – increased bone marrow toxicity
  – Stavudine and zalcitabine – increased peripheral neuropathy

Basics of Drug Elimination
Pharmacokinetic Interactions

• Most common type of interactions in HIV
  – Absorption – reduced atazanavir absorption when combined with proton pump inhibitors
  – Distribution – protein binding displacement when warfarin and SMZ/TMP are combined
  – Metabolism – elevated simvastatin levels when ritonavir inhibits CYP450 enzyme
  – Elimination – competition for renal elimination with probenicid and penicillin
• Also other transporters such as PGP, OAT, etc

CYP450 Metabolism for FDA Approved Medications

Adapted from Goodman and Gilman’s The Pharmacological Basis of Therapeutics, 9th ed.

CYP450 Induction

Key Points
• Adding a CYP3A4 INDUCER leads to DECREASED levels of the other medication that is also metabolized by CYP3A4
• Peak effect of inducer occurs SLOWLY based upon half-life of drug & time to synthesize new CYP3A4 enzyme
• Classic example - Adding efavirenz to protease inhibitors

Top CYP3A4 Inducers Important to HIV Care

- Carbamazepine
- Dexamethasone
- Efavirenz
- Etravirine
- Fosphenytion
- Nevirapine
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampin
- St John’s Wort

HIV PIs and NNRTIs likely to be DECREASED when these medications above are added
CYP450 Inhibition

Key Points
- Adding a CYP3A4 INHIBITOR leads to INCREASED levels of the other medication that is also metabolized by CYP3A4
- Peak effect occurs RAPIDLY, as soon as adequate concentrations of the CYP3A4 inhibitor being added are reached
- Classic example - Adding Lopinavir/rtv to simvastatin

Top CYP3A4 Inhibitors Important to HIV Care
- Amiodarone
- Clarithromycin
- Cyclosporin
- Delavirdine
- Diltiazem
- Erythromycin
- Fluconazole
- Grapefruit Juice
- HCV Protease Inhibitors
- HIV Protease Inhibitors
- Itraconazole
- Phenytoin
- Verapamil
- Voriconazole

The above medications are likely to be INCREASED when HIV Protease Inhibitors are added.

Why should we care about CYP450? Select Toxicities

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfuzosin</td>
<td>Severe hypotension</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Fever, diarrhea, paresthesias</td>
</tr>
<tr>
<td>Ergotamine derivatives</td>
<td>Ischemia, cyanosis, hypertension</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Cushing’s Syndrome</td>
</tr>
<tr>
<td>Midazolam (oral), triazolam</td>
<td>CNS Depression</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Sildenafil (and related drugs)</td>
<td>Syncope, hypotension</td>
</tr>
<tr>
<td>Statins (simvastatin, lovastatin)</td>
<td>Rhabdomyolysis</td>
</tr>
</tbody>
</table>

Why does it matter in HIV?

- Non-nucleoside reverse transcriptase inhibitors
  - Efavirenz, nevirapine, & etravirine are 3A4 inducers
  - Efavirenz also inhibits CYP 3A4, 2C9 & 2C19
  - Etravirine also 2C9 & 2C19 inhibitor
  - Rilpivirine also 3A4, not as potent as an inducer
- Protease inhibitors
  - CYP3A4 substrates & inhibitors
- Ritonavir one of most potent 3A4 inhibitors
  - Inhibits: 2D6, 2C9, 2C19, 1A2, 2E1, P-glycoprotein
  - Induces: 3A4, glucuronyl transferase
- Cobicistat, booster in Elvitegravir/cobicistat/tenofovir/emtricitabine
  - CYP3A4 inhibitor
  - Inhibits: P-glycoprotein

Classes of Interest

- Statins, other lipid lowering medications
- Select cardiovascular medications
- Inhaled corticosteroids
- Select psychotropics, narcotics, anti-gout meds
- BPH meds, ED medications
- Proton pump inhibitors and H2 blockers
- Rifampin/rifabutin
**Statins and Protease Inhibitors**

- Simvastatin and lovastatin considered contraindicated with ALL protease inhibitors
- Safest statins are pravastatin, pitavastatin
- Atorvastatin – Initiate at low doses, titrate, caution if >20mg
  - Do not co-administer with tipranavir/rtv
- Rosuvastatin – Initiate at low doses, titrate
- All statins – monitor CPK, myalgias, LFTs

**Cardiovascular Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>PK Interaction</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarhythmics</td>
<td>• Lack of PK data</td>
<td>• Potential toxicity of antiarrhythmics</td>
</tr>
<tr>
<td></td>
<td>• CYP-450 involvement</td>
<td>• Use with caution</td>
</tr>
<tr>
<td></td>
<td>• Potential for ↑ exposure</td>
<td>• Monitor concentrations of antiarrhythmics closely</td>
</tr>
<tr>
<td>Warfarin</td>
<td>• Lack of PK data</td>
<td>• Potential warfarin toxicity or reduced efficacy</td>
</tr>
<tr>
<td></td>
<td>• CYP-450 involvement</td>
<td>• Monitor INR closely</td>
</tr>
<tr>
<td></td>
<td>• Potential for ↑ exposure of warfarin</td>
<td></td>
</tr>
<tr>
<td>CCBs</td>
<td>• ↑ exposure of diltiazem with ATV</td>
<td>• Potential CCB-associated toxicity</td>
</tr>
<tr>
<td></td>
<td>• Potential for ↑ exposure of CCBs with other PIs and cobicistat</td>
<td>• diltiazem dose by ½ with ATV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• monitor ECG and for CCB-associated toxicity with all PIs and cobicistat</td>
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</tbody>
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**Steroids and Protease Inhibitors**

- Ritonavir inhibits the CYP-450 metabolism of fluticasone
- Cushing’s syndrome reported with ritonavir-containing PI regimens and inhaled fluticasone:
  - Mean duration of fluticasone use was 75.5 weeks (range 20 days – 18 months)
  - Case reports with oral and inhaled budesonide
  - Recent reports with OCUlar topical steroids!

**Inhaled Steroids and RTV Boosted Protease Inhibitors**

- Nasal fluticasone
  - Switch to beclomethasone, possibly mometasone
- Inhaled fluticasone or budesonide
  - Switch to beclomethasone
- Salmeterol, contained in Advair®
  - Concurrent use of salmeterol and ritonavir to be avoided due to CV risk – tachycardia, QT prolongation, palpitations
  - Not clear if same risk exists for formoterol
  - Consider safer steroid listed above alone, plus montelukast, plus rescue albuterol as needed

**Antidepressants**

- **CONTRAINDICATED**
  - Fluvoxamine (Luvox®)
  - Nefazodone (Serzone®)
- **Selective Serotonin Reuptake Inhibitors**
  - Fluoxetine (Prozac®) & paroxetine (Paxil®), Pexeva®:
    - Interactions not clinically significant
  - Paroxetine (Paxil®) levels decreased by darunavir/rtv and fosamprenavir/rtv (about 50%)
  - Citalopram (Celexa®), escitalopram (Lexapro®), & sertraline (Zoloft®) have fewest interactions
  - Sertraline levels decreased by efavirenz and darunavir/ritonavir (about 50%)
- Tricyclic antidepressants
  - All boosted PIs and cobicistat expected to increase levels of TCAs
Antidepressants

- Dual-action agents:
  - Venlafaxine (Effexor®) & duloxetine (Cymbalta®)
  - Well tolerated without adjusting dose
  - Vilazodone (Viibryd®) likely to be increased by PIs
- Bupropion (Wellbutrin®, Allis®)
  - AUC decreased 57% with lopinavir/rtv
  - AUC decreased 46% with tipranavir/rtv
- Mirtazapine (Remeron®)
  - Well tolerated, although some 3A4 metabolism
- Trazodone (Deseryl®)
  - With ritonavir-boosted PIs and cobicistat, start low, titrate

Benzodiazepines

- CONTRAINDICATED
  - Triazolam (Halcion®) and oral midazolam with PIs or cobicistat
  - Midazolam (Versed®) – Single dose for sedation acceptable if in a controlled environment
- Safest to use glucuronidated benzodiazepines (LOT)
  - Lorazepam (Ativan®)
  - Oxazepam (Serax®)
  - Temazepam (Restoril®)
- Use at lower doses & titrate
  - Alprazolam, clonazepam, diazepam

Antipsychotics

- CONTRAINDICATED
  - Pimozide (Orap®)
  - Avoid chlorpromazine (Thorazine®), thioridazine (Mellaril®)
- When used with ritonavir, start with lowest dose
  - Haloperidol (Haldol®) – risk of EPS & TD
  - Olanzapine (Seroquel®), clozapine (Clozaril®), risperidone (Risperdal®)
- Metabolized by CYP3A4
  - Aripiprazole (Abilify®), ziprasidone (Geodon®), quetiapine (Seroquel®) clozapine (Clozaril®) iloperidone, lurasidone
  - Likely to be increased by protease inhibitors

Narcotics

- Methadone, buprenorphine – See AETC Pocket Guide, DHHS Guideline Tables
- Fentanyl – HIGH dose ritonavir increased fentanyl
  - Low dose patches to start, titrate slow, monitor closely
- Hydrocodone, tramadol – All have the potential to be increased with ritonavir via CYP2D6 inhibition
- Oxycodone and Lopinavir/rtv 400/100 twice daily
  - 2.6 fold increase in oxycodone levels (range 1.9-3.3 fold)
  - Use lowest doses, titrate slow, especially if on boosted PIs
  - Additional caution with longer acting narcotics

Colchicine (Colcrys®)

- Fatalities reported with concurrent use of colchicine and clarithromycin, a strong CYP3A4 inhibitor
- Increases in colchicine also expected with ritonavir-boosted protease inhibitors, ketoconazole, itraconazole
- Dosing if on a protease inhibitor + ritonavir
  - Acute attack – Max of 0.6mg, followed by 0.3mg (1/2 tab) one hour later. Do not repeat for 3 DAYS!
  - Prevention – cut dose in half – IE: if on 0.6mg daily, max per day is 0.3mg
- See insert for additional info – chart available in label, and in DHHS Drug Interaction Tables

BPH & HIV Meds

- Avodart (dutasteride)
  - Metabolized by CYP3A4, CONTRAINDICATED in Norvir Label
- Ursoxal (alfuzosin)
  - Metabolized by CYP3A4, CONTRAINDICATED with potent CYP3A4 inhibitors
- Cardura (doxazosin)
  - Metabolized by 3A4, drug levels can be increased PIs (esp. ritonavir)
- Flomax (tamsulosin)
  - Metabolized by CYP3A4 and CYP2D6, drug levels can be increased by PIs (esp ritonavir and in poor metabolizers)
- Detrol LA (tolterodine)
  - Not metabolized by 3A4
**Erectile Dysfunction Meds**

- All are CYP3A4 substrates
- Potential for hypotension, cardiac complications and abnormal vision if protease inhibitors used concomitantly
- Start with lowest possible doses
  - Viagra® (sildenafil): 25 mg q 48 hours
  - Cialis® (tadalafil): 10 mg q 72 hours
  - Levitra® (vardenafil): 2.5 mg q 72 hours
- See DHHS Guidelines for PAH dosing

**Proton Pump Inhibitors**

- Proton pump inhibitors such as omeprazole, lansoprazole, esomperazole, etc.
- Atazanavir
  - Do not use if atazanavir unboosted
  - If ARV experienced, proton pump inhibitors not recommended
  - If ARV naïve and using atazanavir with ritonavir, can use up to the equivalent of omeprazole 20mg daily
- Rilpivirine, nelfinavir, delavirdine
  - Proton pump inhibitors not recommended at all
  - Contraindicated with rilpivirine, also Complera®

**H2 Blockers**

- Boosted Atazanavir
  - H2 blockers simultaneously with and/or 10 hours after the H2 receptor antagonist (H2RA)
  - Maximum H2RA dose equivalent to famotidine 20mg BID for treatment-experienced, and 40mg BID for naïves
- Unboosted atazanavir
  - Atazanavir given at least 2 hours before and at least 10 hours after the H2RA
  - Only acceptable in treatment naïve patients
- Fosamprenavir
  - Fosamprenavir given at least 2 hours before H2RA

**Rifampin and Rifabutin**

- Rifampin – potent CYP450 inducer, contraindicated with PIs
  - Efavirenz – can use together, consider 800mg EFV (>60kg)
  - Raltegravir – increase RAL to 800mg BID
  - Etravirine, rilpivirine – not recommended
- Rifabutin – less potent inducer, but still problematic
  - All boosted PIs – 150mg every day or TIW
  - Most studies in healthy volunteers, TOM recommended
  - Efavirenz – Rifabutin 450-600mg daily or 600mg three times weekly if NOT on a boosted PI
  - Etravirine – if with a boosted PI, not recommended, otherwise, rifabutin 300mg once daily
  - Rilpivirine – not recommended

**Cobicistat**

- New booster in QUAD pill, Stribild®, co-formulated with elvitegravir, cobicistat, tenofovir and emtricitabine
- Contraindicated medications almost identical to boosted PI regimens – ie Alfluzosin, lovastatin, simvastatin, pimozide, ergotamine derivatives, rifampin, St Johns Wort, etc
- Review product label prior to using other medications with cobicistat
- anything you would use with caution in the PI class should be used with caution with cobicistat

**HCV Protease Inhibitors**

- See Drug Interactions with Major CA Virus 184/RA Protease Inhibitors and HIV Medications: A Quick Guide for Clinicians
- Note: Procedures in table not in this guide but can be found online:  [Cobicistat Interactions](https://www.clinicaltrials.gov/ct2/results?term=cobicistat&search=)
Web Resources of Interest

- DHHS Guideline Tables – BEST RESOURCE
  • Go to Tables 11, 14, 15a-e, 16a,b
- University of Liverpool
  • [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
- NY/NJ AIDS Education and Training Center
  • [http://www.nynjaetc.org/](http://www.nynjaetc.org/)

www.hiv-druginteractions.org

- Upper Left Corner: New data, reports
- Top middle: Charts and Recommendations

NY/NJ AETC – www.nynjaetc.org