Drug Interactions with HIV and Psychiatric Medications

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Guidelines
# DHHS: Changing Criteria for Initiating ART

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>&gt; 500</td>
<td>Offer if VL &gt; 20,000</td>
<td>Offer if VL &gt; 55,000</td>
<td>Consider if VL ≥ 100,000</td>
<td>Consider if VL ≥ 100,000</td>
<td>Consider in certain groups</td>
<td>Treat</td>
</tr>
<tr>
<td>350-500</td>
<td>Offer if VL &gt; 20,000</td>
<td>Offer if VL &gt; 55,000</td>
<td>Consider if VL ≥ 100,000</td>
<td>Consider in certain groups</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>200-350</td>
<td>Offer if VL &gt; 20,000</td>
<td>Offer, but controversy exists</td>
<td>Offer after discussion with patient</td>
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<tr>
<td>&lt; 200 or symptomatic disease</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
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<td>Treat</td>
<td>Treat</td>
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</tbody>
</table>

## Initial Regimens: Preferred

<table>
<thead>
<tr>
<th>NNRTI based</th>
<th>• Atripla (Efavirenz + tenofovir + emtricitabine)</th>
</tr>
</thead>
</table>
| PI based    | • Reyataz + Norvir + Truvada (Atazanavir + ritonavir + tenofovir/emtricitabine)  
• Prezista + Norvir + Truvada (Darunavir + ritonavir + tenofovir/emtricitabine) |
**Initial Regimens: Preferred**

<table>
<thead>
<tr>
<th>II based</th>
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<tbody>
<tr>
<td>- Isentress + Truvada (Raltegravir + tenofovir/emtricitabine)</td>
<td></td>
</tr>
<tr>
<td>- Tivicay + Truvada or Epzicom (Dolutegravir + tenofovir/emtricitabine OR abacavir/lamivudine)</td>
<td></td>
</tr>
<tr>
<td>- Stribild (Elvitegravir/cobicistat/tenofovir/emtricitabine)</td>
<td></td>
</tr>
</tbody>
</table>
Isentress (BID)/Truvada → 3/day
Tivicay/Truvada OR Epzicom OR → 2/day
Stribild → 1/day

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

Key points
- Majority of drugs metabolized by CYP3A4 & CYP2D6
- CYP3A4 involved with HIV PI/NNRTI/cobicistat, also HCV PI metabolism
- Enzymes can be induced or inhibited

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
- Example - Adding efavirenz to a methadone or to a PI

Steady State Levels

Drug Levels

Inducing drug added

Time
Select CYP3A4 Inducers

- Carbamazepine
- Efavirenz
- Fosphenyton
- Nevirapine
- St. John’s Wort
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampin

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 or Stribild to simvastatin
Common CYP3A4 Inhibitors

- Clarithromycin
- Cobicistat
- Delavirdine
- Erythromycin
- Fluconazole
- Grapefruit Juice
- HCV Protease Inhibitors
- HIV Protease Inhibitors
- Itraconzaole
- Ritonavir

Results of CYP450 inhibition
Select Toxicities

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfluzosin</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>
## Contraindicated Medications with Protease Inhibitors, Cobicistat

<table>
<thead>
<tr>
<th>Class</th>
<th>Specific Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Medications</td>
<td>Flecainide, propafenone, amiodarone, quinidine</td>
</tr>
<tr>
<td>Lipid Lowering Medications</td>
<td>Lovastatin, simvastatin</td>
</tr>
<tr>
<td>Antimycobacterial Medications</td>
<td>Rifampin, rifapentine</td>
</tr>
<tr>
<td>Gastrointestinal Medications</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>Pimozide</td>
</tr>
<tr>
<td>Psychotropics</td>
<td>Oral midazolam, triazolam</td>
</tr>
<tr>
<td>Ergotamine derivatives</td>
<td>DHE, ergotamine, ergonovine, etc</td>
</tr>
<tr>
<td>Herbal Therapy</td>
<td>St John’s Wort</td>
</tr>
<tr>
<td>Other</td>
<td>Alfluzosin, salmeterol, sildenafil in PAH</td>
</tr>
</tbody>
</table>

## Boosters – RTV, COBI

- **Ritonavir**
  - We know it, most major interactions worked out
  - Anything in a new drug label that mentions strong CYP3A4 inhibitors, think or ritonavir
  - Examples include ketoconazole, erythromycin, etc
  - Also inhibits PGP, CYP2D6, OAT transporters
Boosters – RTV, COBI

- New booster in QUAD pill, Stribild®, co-formulated with elvitegravir, cobicistat, tenfovir and emtricitabine
- Contraindicated medications almost identical to RTV boosted PI regimens
- Anything you would use with caution in the PI class should be used with caution with cobicistat
- Mostly a CYP3A4 inhibitor, minor 2D6, minimal if any PGP interactions
- Note that many of the HIV – cobi interactions not entirely clear yet

Product Information, Stribild 2013

Primary Care Meds Likely to Interact with HIV Meds

- 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
Antidepressants

• Selective Serotonin Reuptake Inhibitors
  • Fluoxetine (Prozac®) & paroxetine (Paxil®, Pexeva®):
    • 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%)
  • Vilazodone (Viibryd®) – reduce dose to 20mg when used with HIV PIs or cobicistat

DHHS Guidelines, February 2013

Antidepressants

• Tricyclic antidepressants
  • All boosted PIs and cobicistat expected to increase levels of TCAs
  • IE: desipramine levels increased 59% with ritonavir
  • Cobicistat (in Stribild) shown to increase desipramine levels 65%
  • Similar increases likely for amitriptylin, imipramine, nortripyline
  • Monitor for anticholinergic side effects, EKG, TCA levels

DHHS Guidelines, February 2013
Other Antidepressants

- **SNRIs:**
  - Mirtazapine (Remeron®) & duloxetine (Cymbalta®)
    - Generally well tolerated
  - Venlafaxine (Effexor®) and desvenlafaxine (Pristiq®)
    - PIs and Cobicistat may increase levels use caution
- **Bupropion** (Wellbutrin®, Zyban®)
  - AUC decreased 57% with lopinavir/rtv
  - AUC decreased 46% with tipranavir/rtv
- **Trazodone** (Deseryl®)
  - With ritonavir-boosted PIs and cobicistat, start low, titrate
  - Avoid nefazodone, fluvoxamine

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Other Antidepressants

- **MAOIs**
  - Avoid other antidepressants, mepridine, tramadol, sumatriptan, dextromethorhpen, linezolid
  - Other drugs may also be a problem
  - Beware of 14 day washout period prior to starting
Benzodiazepines

- **CONTRAINDICATED with COBI and RTV**
  - 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 with all PIs and cobicistat
  - Alprazolam, clonazepam, diazepam

DHHS Guidelines, February 2013

Non-Benzodiazepine Sedative Hypnotics

- Zolpidem and zaleplon
  - Use lowest doses with PIs and cobicistat
  - Label changes for women, dose NTE 5mg zolpidem
- Eszopiclone
  - Use lowest dose, if at all, with PIs and cobicistat ketoconazole shown to more than double levels
- Buspirone levels likely to be increased by PIs and cobicistat

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Antipsychotics

- **CONTRAINDICATED**
  - Pimozide (Orap®)
  - Avoid chlorpromazine (Thorazine®), thioridazine (Mellaril®)
  - When used with ritonavir, start with lowest dose
    - Haloperidol (Haldol®) – risk of EPS & TD
    - Olanzapine (Zyprexa®), clozapine (Clozaril®), risperidone (Risperdal®)
  - Metabolized by CYP3A4
    - Aripiprazole (Abilify®), ziprasidone (Geodon®), quetiapine (Seroquel®) clozapine (Clozaril®) iloperidone, lurasidone
  - Isolated case reports demonstrating toxicity with boosted PIs
  - Most are likely to be increased by protease inhibitors

Atypical Antipsychotic Metabolism

<table>
<thead>
<tr>
<th>Atypical antipsychotic</th>
<th>CYP450 metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>3A4, 2D6</td>
</tr>
<tr>
<td>Asenapine</td>
<td>1A2</td>
</tr>
<tr>
<td>Clozapine</td>
<td>3A4, 2D6, 1A2, 2C19</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>3A4, 2D6</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>3A4</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2D6, 1A2</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>No effect</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>3A4</td>
</tr>
<tr>
<td>Risperidone</td>
<td>2D6, 3A4</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>3A4</td>
</tr>
</tbody>
</table>
HIV and Second Generation Antipsychotic Use

- Data from UCSD, retrospective, over 2200 patients
- Concomitant SGAs were frequent (12%) in this large, diverse cohort of ARV treated HIV+ individuals
- Psychiatric comorbidities were common among those taking SGAs
- Among ARV-treated HIV+s, those on concomitant SGAs had higher rates of diabetes mellitus and hypertriglyceridemia, and had elevated BMI and mean arterial blood pressure
- Just be cautious of additional contribution of newer antipsychotics to metabolic changes


Anticonvulsants and Stimulants

- In general with carbamazepine, phenobarbital, phenytoin, oxcarbazepine
  - Avoid with NNRTIs, PIs, cobicistat, elvitegravir
  - with maraviroc, need to increase dose to 600mg BID if used withOUT a CYP3A4 inhibitor
- Ritonavir boosted PIs may increase modafanil, methylphenidate, amphetamine, and dextroamphetamine levles

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Narcotics

- Fentanyl – HIGH dose ritonavir increased fentanyl
  - Low dose patches to start, titrate slow, monitor closely
  - Caution regarding recreational use and bucal absorption
- Hydrocodone, tramadol – Potential to be increased with ritonavir via CYP2D6 inhibition
- Oxycodone and Lopinavir/ritv 400/100 twice daily
  - 2.6 fold increase in oxycodone levels (range 1.9-3.3 fold)
  - Likely similar with other PIs, cobicistat? Mild CYP2D6 inhibitor

Methadone and HIV Medications

<table>
<thead>
<tr>
<th>HIV Medication</th>
<th>Pharmacokinetic Information and Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Methadone clearance increased 22%; no change recommended</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Stavudine AUC decreased 23%, Cmax decreased 44%; no change recommended</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Zidovudine AUC increased 29% to 43%; monitor for zidovudine related adverse effects</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Methadone AUC decreased 52%; methadone withdrawal common; increased methadone dose likely required</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Methadone AUC decreased 41%; methadone withdrawal common; increased methadone dose likely required</td>
</tr>
<tr>
<td>Fosamprenavir (unboosted)</td>
<td>No data; with amprenavir, R-methadone Cmin decreased 21%; Monitor and increase methadone as needed</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Methadone AUC decreased 40%; methadone withdrawal rare; monitor and increased methadone as needed</td>
</tr>
</tbody>
</table>
### Methadone and HIV Medications

<table>
<thead>
<tr>
<th>HIV Medication</th>
<th>Pharmacokinetic Information and Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir/ritonavir</td>
<td>Methadone AUC decreased 16% to 18%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated</td>
</tr>
<tr>
<td>Darunavir/ritonavir</td>
<td>Methadone AUC decreased 25% to 53%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated</td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir</td>
<td>Methadone AUC decreased 48%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Methadone AUC decreased 16% to 18%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated</td>
</tr>
<tr>
<td>Saquinavir/ritonavir</td>
<td>Methadone AUC decreased 19%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated</td>
</tr>
<tr>
<td>Tipranavir/ritonavir</td>
<td>Methadone AUC decreased 48%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated</td>
</tr>
</tbody>
</table>

### Buprenorphine and HIV Medications

<table>
<thead>
<tr>
<th>HIV Medication</th>
<th>Pharmacokinetic Information and Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>Buprenorphine AUC decreased 50%; norbuprenorphine AUC decreased 71%; no change recommended</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Buprenorphine AUC decreased 25%, no change recommended</td>
</tr>
<tr>
<td>Atazanavir (unboosted)</td>
<td>Buprenorphine AUC increased 93%; norbuprenorphine AUC increased 76%; decreased atazanavir possible; do not co-administer</td>
</tr>
<tr>
<td>Atazanavir/rtv</td>
<td>Buprenorphine AUC increased 66%; norbuprenorphine AUC increased 105%; monitor for sedation, buprenorphine dosage reduction may need</td>
</tr>
<tr>
<td>Darunavir/rtv</td>
<td>Buprenorphine, no change; norbuprenorphine AUC increased 46%, Cmin increased 71%; no change recommended</td>
</tr>
<tr>
<td>Fosamprenavir/rtv</td>
<td>Buprenorphine, no change; norbuprenorphine AUC decreased 15%; no change recommended</td>
</tr>
<tr>
<td>Tipranavir/rtv</td>
<td>Buprenorphine, no change; norbuprenorphine decreased 80%; Tipranavir Cmin reduced 19% to 40%. Consider TPV TDM</td>
</tr>
</tbody>
</table>
What’s UP? ED Meds

- All are CYP3A4 substrates
- Potential for hypotension, cardiac complications and abnormal vision if protease inhibitors used concomitantly
- Start with lowest possible doses with PIs, COBI
  - Viagra® (sildenafil): 25 mg q 48 hours
    - AUC ↑ 11-fold by ritonavir
  - Cialis® (tadalafil): 10 mg q 72 hours
    - AUC ↑ 125% by ritonavir
  - Levitra® (vardenafil): 2.5 mg q 72 hours
    - AUC ↑ 49-fold & 16-fold by Indinavir/rtv
- Avanafil – 13 fold in crease with RTV 600mg BID not recommended with any boosted PI
- See DHHS Guidelines for PAH dosing

DHHS Guidelines March 2013.

Herbal Therapy

- St Johns Wort – contraindicated with all PIs
- Garlic – data with saquinavir showing a reduction in ARV levels, even after stopping
- Milk Thistle – interaction data with Darunavir/r showed no change needed
- Ecinacea – data with etravirine – no interaction
- Ginseng – recent report of hepatotoxicity in a patient on Isentress, Kaletra
- General statements
  - Often no data with HIV meds
  - Often capsules or tabs contain an herbal “mix”
  - If patients insist on using an herbal with no data, simply separating from ARVs is important – may minimize the interaction
Resources for You

Drug Interaction Questions

- Interaction has a clear answer, cut and dry PK data
- Interaction has an answer for similar drugs with similar properties where we can at least make comparisons
- Interaction has no answer, rely on trial and error to see
- Either way, try to give options, not answers
Databases “Issues”

- Some over call interactions
  - Entire class versus individual medications
- Some miss case reports, so incomplete
- Always do a medline search
  - ie: warfarin and lactulose on lexicomp
- Stick to reputable HIV driven references for first step to screen for interactions

www.hiv-druginteractions.org
www.hiv-druginteractions.org

Upper Left Corner
New data, reports

Top middle – Charts and Recommendations

http://aidsinfo.nih.gov/guidelines/
Questions