Common Drug-Drug Interactions: Case Scenarios

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Case # 1
• 24 yr old Malaysian male
• New AIDS diagnosis—CD4 124 cells/cmm and VL >500,000 c/mL
• Also tested positive for Hep B—VL >1,000,000 IU/mL and active tuberculosis TB (asymptomatic)

Treatment
• Now we need to decide when to start treatment for AIDS/Hepatitis B/TB
• All three infections need to be treated so what should we do first or do we do all three at once?

Treatment guidelines
• According to the DHHS guidelines (1/11) treatment for TB/HIV co-infection should be as follows:
  • HAART should be initiated within 2-4 weeks of starting TB treatment for patients with CD4 < 200 cells/cmm

Treatment guidelines
• HAART should be initiated within 2-4 weeks or at least by 8 weeks after starting TB therapy for patients with CD4 of 200-500 cells/cmm
• For patients with CD4 > 500 cells/cmm, most DHHS panel members also recommend starting HAART within 8 weeks of starting TB therapy

Question
According to these guidelines and Drug/Drug interactions discussed earlier, what infection would we tackle first and with what medication?
Discussion
Order of treatment would be TB, AIDS then Hepatitis B

Treatment started
- For TB, the patient was started on:
  - Isoniazid
  - Rifabutin
  - Pyrazinamide
  - Ethambutol—discontinued after 8 weeks

Treatment continued
- For the HIV infection/AIDS, after 2 weeks the patient was started on:
  - Tenofovir
  - Emtricitabine
  - Efavirenz

Discussion
- Reasons patient started on this regimen were due to hepatitis B co-infection and tenofovir and emtricitabine's ability to control the hepatitis B virus, as well as rifabutin and efavirenz having fewer interactions than the rifampin

Use of Rifampin in TB/HIV
- Rifampin is a potent inducer of CYP450 leading to significant reductions in other meds including HIV PIs, NNRTIs, maraviroc, and elvitegravir
- In absence of HIV treatment, certainly reasonable
- Acceptable HIV regimens with rifampin include:
  - FDC of emtricitabine/tenofovir/efavirenz (some may increase efavirenz to 800mg daily)
  - Raltegravir/emtricitabine/tenofovir (raltegravir dosage increase to 800mg BID)

What about Rifabutin?
- Less potent effect on CYP450
- Rifabutin levels also increased by PIs
- When used with HIV meds, are there guidelines?
  - With ritonavir-boosted PIs or unboosted fosamprenavir or atazanavir:
    - 150mg DAILY or 300mg three times weekly
  - With NNRTIs
    - EFV – Rifabutin 450mg-600mg daily
    - NVP – No change needed
    - ETR – If NOT coadministered with a boosted PI, use rifabutin 300mg once daily
    - RPV – contraindicated
What about Rifabutin?
• With integrase inhibitors
  • Raltegravir – no dosage change needed
  • Elvitegravir – not recommended in current label
• With maraviroc
  • Maraviroc 150 mg BID if on a strong CYP3A4 inhibitor, 300 mg BID if on a CYP3A4 inducer or no inhibitor
  • Rifabutin standard dose

Conclusion
• The patient completed the 9 month course of treatment for TB
• He continued on the tenofovir, emtricitabine and efavirenz
  • VL <48 c/mL
  • CD4 250 cells/cmm
  • Hepatitis B VL <50 IU/mL
  • Chest x-rays are now clear

Case # 2
• 45 yr old Hispanic male
• HIV+ for 15 years
• Married with 2 children and is a stay-at-home dad

History
• On medications for 10 of those 15 years and presently on
  • Tenofovir
  • Emtricitabine
  • Lopinavir/ritonavir
  • VL < 48 c/mL
  • CD4 550 cells/cmm

History
• Patient is complaining of general malaise
  • Lack of motivation
  • Weight gain of >30 lbs
  • Lack of libido
  • Increase in sleeping
  • Diagnosis--Depression

Treatment
• Patient willing and motivated to feel better and was willing to start counseling, as well as take an antidepressant
  • Bupropion SR 150 mg/day was initiated and patient reported little relief of the symptoms, so his dose was increased to 150 mg BID
Question

• What are some common and infrequent side effects for this medication?

Side Effects

• Patient started reporting side effect of:
  • Insomnia—Started trazodone 100 mg every HS

Side Effects

After trazodone started patient also started complaining of:

• Loss of memory and inability to concentrate
• Dry mouth
• Agitation/restlessness
• What happened?

Interactions

• Ritonavir and bupropion and trazodone have interactions
• Higher dose of bupropion is needed to overcome the lopinavir/ritonavir interaction, that decreases the levels of the bupropion

Interactions

• When the trazodone was added the lopinavir/ritonavir caused an increase in the levels of the medication, therefore increasing the CNS adverse events from the trazodone.

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
    • However, sertraline levels decreased by efavirenz and darunavir/ritonavir (about 50%)

DHHS Guidelines, March 2012
Antidepressants

- Tricyclic antidepressants
  - All boosted PIs expected to increase levels of TCAs
  - Cobicistat also expected to increase TCA levels

- Dual-action agents:
  - Venlafaxine (Effexor®) & duloxetine (Cymbalta®)
  - Well tolerated without adjusting dose
  - Vilazodone (Viibryd®) likely to be increased by PIs

Conclusion

- Once the patient discontinued the trazodone, side effects of restlessness, inability to concentrate and memory loss improved

Discussion

- What could have been done to avoid the side effects the patient experienced?

Discussion

- Bupropion SR was at the correct dose of 150 mg BID

- Trazodone should have been initiated at 50 mg every HS, or even 25 mg to start and monitor for effectiveness. Start low and titrate up.

- Patient also could have been started on citalopram, which has very few interactions, instead of bupropion

Case # 3

- 50 year old African American female
- HIV+ for 20 years
- Treatment experienced and recently restarted medications.
- Presently on FDC of tenofovir, emtricitabine and efavirenz
  - CD4 940 cells/cmm
  - VL<48 c/mL
History
- Patient has been pre-hypertensive for approximately 2 years and has been trying to avoid more medication
- Recent BPs have been 150/94
- Patient now ready to start medications and primary care office started patient on amlodipine 5 mg daily

Discussion
- Efavirenz will induce metabolism of the calcium channel blocker through the CYP 3A system, therefore this patient will need higher doses of the medication in order to be effective

Cardiovascular Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>PK Interaction</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-arrhythmics</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 ↑ or ↓ exposure of warfarin</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</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>
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Treatment
- BP readings over the course of 4 weeks do not really change.
- Why did this occur?
  - 5 mg is the usual dose for this medication, so why was the BP unchanged?

Patient reluctantly increased amlodipine to 10 mg daily and after 2 weeks her BP was 130/84.
- Patient still working on decreasing BP further by weight loss, stress reduction and diet, due to not wanting to add any more medication.
Case 4

- 50 year old male with history of AIDS, DVT/PE, and remote cardiomyopathy
- CD4 450 cells/cumm
- VL < 40 c/mL
- Pre-op clearance ECG for ENT surgery shows a QTc of 570 milliseconds
- **Not** cleared for surgery

Medications

- Tenofovir/emtricitabine with lopinavir/ritonavir for many years
- Methadone 50 mg 3 times daily for severe and chronic orthopedic pain
- Warfarin, gabapentin, lisinopril, omeprazole, furosemide, potassium, iron, stool softener, vitamins, and albuterol and tiotropium inhalers.

Normal QTc

- QTc should be less than 450 milliseconds
- Consider heart disease
- Consider medications
- Can be congenital

Work-up

- QTc was normal on ECG < 1 year ago
- Cardiac evaluation, including catheterization was now normal
- Look at suspect medications
- Methadone
- Lopinavir/ritonavir

Buprenorphine and HIV Medications

<table>
<thead>
<tr>
<th>HIV Medication</th>
<th>Pharmacokinetic Information and Clinical Implications</th>
</tr>
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<tbody>
<tr>
<td>Efavirenz</td>
<td>Buprenorphine AUC decreased 50%; norbuprenorphine AUC decreased 71%; no change recommended</td>
</tr>
<tr>
<td>Etavirine</td>
<td>Buprenorphine AUC decreased 25%, no change recommended</td>
</tr>
<tr>
<td>Atazanavir (boosted)</td>
<td>Buprenorphine AUC increased 93%; norbuprenorphine AUC increased 78%; decreased atazanavir possible; do not co-prescribe</td>
</tr>
<tr>
<td>Atazanavir (unboosted)</td>
<td>Buprenorphine AUC increased 68%; norbuprenorphine AUC increased 100%; monitor for sedation; buprenorphine dosage reduction may need</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Buprenorphine, no change; norbuprenorphine AUC increased 48%; Cmin increased 71%; no change recommended</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Buprenorphine, no change; norbuprenorphine AUC increased 15%; no change recommended</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Buprenorphine, no change; norbuprenorphine decreased 80%; Tipranavir Cmin reduced 19% to 40%; consider TPV therapeutic drug monitoring</td>
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Methadone and HIV Medications

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<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 26% 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</td>
<td>No data; with amprenavir, R-methadone Cmin decreased 27%; Monitor and increase methadone as needed</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Methadone AUC decreased 40%; methadone withdrawal common; monitor and increased methadone as needed</td>
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Methadone and HIV Medications

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<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 20% to 53%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated</td>
</tr>
<tr>
<td>Fosamprenavir/ritonavir</td>
<td>Methadone AUC decreased 19%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated</td>
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<tr>
<td>Lopinavir/ritonavir</td>
<td>Methadone AUC decreased 48%; methadone withdrawal unlikely but possible; increase methadone dose as clinically indicated</td>
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<td>Saquinavir/ritonavir</td>
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<td>Tipranavir/ritonavir</td>
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DHHS Guidelines March 2012

Plan

- Cardiology referral
- Patient averse to changing his methadone
- Explore change in antiretroviral regimen
- Has past resistance to zidovudine, NNRTIs, and possibly lamivudine.
- Checking DNA tropism assay to see if maraviroc is an option to replace PI
- Could also use integrase inhibitor, or etravirine, based on his NNRTI mutations

Summary

- All four cases show the importance of checking for drug/drug interactions of all the medications the patient is taking.
- Questions?