HIV Drug Interactions
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Approach to Drug Interactions
- Interactions 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, completely based upon clinical practice
- Either way, try to give options, not answers

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 probenecid 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/NRTI/cobicistat, also HCV PI metabolism
- Enzymes can be induced or inhibited

Select CYP3A4 Inducers
- Carbamazepine
- Efavirenz
- Fosphenyton
- Nevirapine
- St. John’s Wort
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Rifabutin
- Rifampin
CYP450 Inhibition

Drug Levels
Inhibiting drug added

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
- Itraconazole
- 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>Syncpe, 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>Csapride</td>
</tr>
<tr>
<td>Neuroleptics</td>
<td>Pimozide</td>
</tr>
<tr>
<td>Psychotropic</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

Case from AMC
- Patient stable on Kaletra+Raltegravir
- Started on Atorvastatin 80mg HS after vascular procedure, discharged to short term rehab facility
- Back in 2 weeks, acute renal failure, rhabdomyolysis
- What happened here?


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

Statins and Protease Inhibitors
- Pitavastatin
  - 12 week randomized, blinded trial
  - Pitavastatin 4 mg vs Pravastatin 40 mg
  - LDL-C 130-220 mg/dL, TG ≤400 after 4 wk washout/dietary stabilization period
  - N = 126/arm
  - Baseline LDL-C 155, TC 238, TG 174, HDL 49

Cardiovascular Medications

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

*Similar adverse events

* p < 0.001
Cardiovascular Medications

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<thead>
<tr>
<th>Medication</th>
<th>PK Interaction</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta blockers</td>
<td>• Potential for ↑ exposure of metoprolol and timolol with PIs (no PK data)</td>
<td>• potential for toxicity of beta-blockers which are metabolized by CYP-450</td>
</tr>
<tr>
<td></td>
<td>• negligible effect on atenolol when administered with ATV</td>
<td>• monitor for beta-blocker-associated toxicity</td>
</tr>
<tr>
<td></td>
<td>• may use atenolol safely with other PIs, no data</td>
<td>• may use atenolol safely with ATV (likely with other PIs, no data)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>• ↑ exposure of digoxin when administered with ATV, SQV/r, DRV/r</td>
<td>• potential for digoxin toxicity</td>
</tr>
<tr>
<td></td>
<td>• p-glycoprotein inhibition by ATV</td>
<td>• monitor digoxin concentrations closely</td>
</tr>
<tr>
<td></td>
<td>• likely with other boosted PIs as well, not with clofibrate</td>
<td>• monitor for digoxin-associated toxicity</td>
</tr>
</tbody>
</table>

Case

- Patient admitted to outside hospital for Acute Coronary Syndrome,
- Long history of HIV, though controlled on Etravirine + Raltegravir + Tenofovir + Emtricitabine
- Undergoes PCI, has 3 stents placed
- Discharge meds include new Rxs for Prilosec and Plavix
- Any problems here?

Anti-platelet Meds

- Clopidogrel (Plavix) – used commonly post-stent after PCI
- Requires activation to an active metabolite via CYP2C19
- Prasugrel (Effient) – used commonly post-stent after PCI
- Also requires activation to an active metabolite, but via CYP3A4 and 2B6 primarily
- Etravirine is a mild inducer of CYP3A4, but also inhibits CYP2C19
- By inhibiting the action of 2C19, likely to get less production of the active metabolite for Plavix
- Prasugrel may be a better choice in this situation, theoretically
- More recent studies have also found no significant effect of dextansoprazole, lanosoprazole, or pantoprazole and the effect on platelet inhibition from Plavix.

Other Anticoagulants?

- Warfarin (Coumadin)
- Dabigatran (Pradaxa)
- Stroke reduction in non-valvular Afib
- Rivaroxaban (Xarelto)
- VTE prophylaxis following hip/knee arthroplasty
- Stroke reduction in non-valvular Afib
- Treatment of VTE
- Apixiban (Eliquis)
- Stroke reduction in non-valvular Afib

Dabigatran Drug Interactions

- P-glycoprotein inhibitors
  - E.g. Verapamil, amiodarone, quinidine, clarithromycin
  - No dose adjustments are necessary
  - Avoid if CrCl < 30 ml/min
  - Ketocazole and dornadare
  - CCl3 = 50 ml/min
  - Dabigatran 75mg PO twice a day
  - What does that mean for rilaonavir, other PIs, cobicistat?
- P-glycoprotein inhibitors
  - E.g. Rifampin, carbamazepine
  - Inducers should be avoided
  - Not listed to avoid in current DHHS guidelines...

Rivaroxaban – Drug Interactions

<table>
<thead>
<tr>
<th>P-glycoprotein /Strong 3A4 inhibitors</th>
<th>Less potent P-glycoprotein /3A4 inhibitors</th>
<th>P-glycoprotein /Strong 3A4 inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents:</td>
<td>Agents:</td>
<td>Agents:</td>
</tr>
<tr>
<td>Conivaptan, itraconazole, ketocazole,</td>
<td>Azithromycin, clarithromycin, diltiazen,</td>
<td>Carbamazepine, phenytoin, rifampin, St. John’s Wort</td>
</tr>
<tr>
<td>lopinavir/ritonavir, ritonavir</td>
<td>dornadare, erythromycin, verapamil</td>
<td></td>
</tr>
<tr>
<td>Management:</td>
<td>Management:</td>
<td>Management:</td>
</tr>
<tr>
<td>- Avoid combination</td>
<td>- Do not use combination in mild renal impairment (CrCl 30 – 60 ml/min)</td>
<td>- Avoid combination if possible</td>
</tr>
</tbody>
</table>

DHHS Guideline: February 2013

Heartmath Package Insert. Last updated 11/2012
Prinexalid (2012) NIH/OD 5K 07
Apixaban – Drug Interactions

<table>
<thead>
<tr>
<th>P-glycoprotein /Strong 3A4 inhibitors</th>
<th>P-glycoprotein /Strong 3A4 inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agents: Itraconazole, ketoconazole, ritonavir, clarithromycin</td>
<td>Agents: Carbamazepine, phenytoin, rifampin, St. John’s Wort</td>
</tr>
<tr>
<td>Management: - Decrease dose to 2.5mg PO twice a day - If patient is already on 2.5mg, avoid combination</td>
<td>Management: - Avoid combination</td>
</tr>
</tbody>
</table>

Case
- Which injectable steroids can be used in my patient who is on a boosted PI?
- Case reports or Iatrogenic Cushings Syndrome, mostly with injectable triamcinolone
  - I recommended methylprednisolone, with the caveat that NO case reports does not equal does not happen
  - Also cases of ocular steroids with same toxicity – dexamethasone eye drops used

Inhaled Steroids and Protease Inhibitors
- Which steroids can we use with PIs?
  - Ritonavir inhibits the 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 – 16 months)
  - Case reports with oral and inhaled budesonide
  - Recent reports with OCULAR dexamethasone
  - Now cases reported with injectable steroids for joint inflammation – usually triamcinolone

Beclomethasone and DRV/rtv
- Beclomethasone inhaled alone, with RTV 100mg BID, and with DRV/RTV 600/100 mg twice daily
- Cosyntropin stim test at baseline and prior to adding regimens
- Baseline adrenal function (day 1) was compared to adrenal function during BDP treatment in the presence and absence of RTV or DRV/r
- No reductions in basal or peak cortisol levels at day 14, 28 or 42 in any group and no significant differences between groups at any time-point (p > 0.05).
- Combined use of BDP and RTV or DRV/r for 28 days does not cause significant adrenal suppression in healthy volunteers.
- Inhaled BDP is preferable to inhaled fluticasone for treatment of HIV+ patients receiving PI.

Antidepressants
- CONTRAINDICATED:
  - Paroxetine (Paxil®)
  - Nefazodone (Serzone®)
- Selective Serotonin Reuptake Inhibitors
  - Fluoxetine (Prozac®) & paroxetine (Paxil®, Paxeva®):
    - 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®, Zyban®)
  - 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

DHHS Guidelines, February 2013, Prescribing Information, Viibryd, Prescribing Information, Stribild

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

DHHS Guidelines, February 2013

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

  - Likely to be increased by protease inhibitors

DHHS Guidelines, February 2013

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+, 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

Porcasi ML et al. 2012. Abstract MOPE097

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/rtv 400/100 twice daily
    - 2.6 fold increase in oxycodone levels (range 1.9-3.3 fold)
    - Likely similar with other PIs
  - Cocciabell? Mild CYP2D6 inhibitor

Fentanyl – HIGH dose ritonavir increased fentanyl

Methadone and HIV Medications

- Methadone:
  - Abacavir: Methadone clearance increased 22%; no change recommended
  - Stavudine: Stavudine AUC decreased 23%, Cmax decreased 44%; no change recommended
  - Zidovudine: Zidovudine AUC increased 29% to 43%; monitor for zidovudine related adverse effects
  - Efavirenz: Methadone AUC decreased 52%; methadone withdrawal common; increased methadone dose likely required
  - Nevirapine: Methadone AUC decreased 41%; methadone withdrawal common; increased methadone dose likely required
  - Indinavir: Methadone AUC decreased 21%; methadone withdrawal common
  - Atazanavir: No data; with amprenavir, R= methadone Cmin decreased 21%; monitor and increase methadone as needed
  - Nevirapine: Methadone AUC decreased 40%; methadone withdrawal rare; monitor and increased methadone as needed
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

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 15%; 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>Etravirine</td>
<td>Methadone AUC decreased 40%; 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>Atazanavir (unboosted)</td>
<td>Buprenorphine AUC increased 15%; 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%; atazanavir possible; do not co-administer</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 10% to 40%; Consider TPV 100m</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 ↑ 19-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/ritavir
  - Avanafil – 13 fold in crease with RTV 600mg BID not recommended with any boosted PI
- See DHHS Guidelines for PAH dosing

Proton Pump Inhibitors

- Proton pump inhibitors such as omeprazole, lansoprazole, esomprazole, etc.
- Atazanavir
  - Do not use if atazanavir unboosted
  - If ARV experienced, proton pump inhibitors not recommended
  - If ARV naive 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
  - Maximum H2RA dose equivalent to famotidine 20mg BID
- Only acceptable in treatment naïve patients
- Fosamprenavir
  - Fosamprenavir given at least 2 hours before H2RA

Herbal Therapy

- St John’s Wort – contraindicated with all PIs
- Garlic – data with saquinavir showing a reduction in ARV levels, even after stopping
- Milk Thistle – interaction data with triterpenoids and flavonoids (CYP3A4 pathway)
- Ginseng – recent report of hepatotoxicity in a patient on etravirine
- Echinacea – data with etravirine – no interaction
- Simeprevir
  - 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
  - Only acceptable in treatment naïve patients
- Fosamprenavir
  - Fosamprenavir given at least 2 hours before H2RA

Drug Interactions Considerations

- Sofosbuvir
  - Substrate for P-glycoprotein
  - Intracellular metabolism mediated by hydrolase and nucleotide phosphorylation pathways
  - Minimal drug interactions expected
- Simeprevir
  - Mild inhibitor of CYP1A2 activity and intestinal CYP3A4
  - Does not affect hepatic CYP3A4 activity
  - Inhibits OATP1B1/3 and P-glycoprotein
  - Multiple drug interactions expected

Rifampin and Rifabutin

- Rifampin – potent CYP450 inducer, contraindicated with PIs
  - Efavirenz – can use together, consider 800mg EFV (4X1200kg)
  - Raltegravir – increase RAL to 800mg BID
  - Etravirine, ritelivirine – 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
  - Rifampin – potent CYP450 inducer, contraindicated with all PIs

HIV/HCV Co-Infection, GT1

- Preferred
  - Sovaldi (SOF) + Peg/rib (WB) or RBV
  - IFN ineligible: Sof + Peg/rib for 48 weeks, SMV x 12 weeks + Peg/rib/WB x 24 weeks
  - IFN eligible: none
- Alternative
  - Treatment experienced, prior Peg/rib
  - Nonresponders, regardless of IFN eligibility:
    - Sof + Peg/rib for 12 weeks
  - Sof + Peg/rib/WB x 24 weeks

Other Drug Interactions with Simeprevir (1 of 2)

<table>
<thead>
<tr>
<th>Medication and/or Class</th>
<th>Interactions Avoiding with Simeprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticancer agents</td>
<td>Co-administration with these medications is likely to reduce concentrations of simeprevir and lead to reduced simeprevir efficacy. Co-administration not recommended.</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Co-administration with these medications is likely to increase concentrations of simeprevir. Co-administration not recommended.</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Co-administration with these medications is likely to decrease concentrations of simeprevir and lead to reduced simeprevir efficacy. Co-administration not recommended.</td>
</tr>
<tr>
<td>Antifungals</td>
<td>Co-administration with these medications is likely to increase concentrations of simeprevir due to CYP3A4 inhibition from the antifungals. Co-administration not recommended.</td>
</tr>
<tr>
<td>Antibacterials</td>
<td>Co-administration with these medications is likely to reduce concentrations of simeprevir and lead to reduced simeprevir efficacy. Co-administration not recommended.</td>
</tr>
<tr>
<td>Antivirals</td>
<td>Co-administration with these medications is likely to reduce concentrations of simeprevir and lead to reduced simeprevir efficacy. Co-administration not recommended.</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Co-administration with these medications is likely to reduce concentrations of simeprevir and lead to reduced simeprevir efficacy. Co-administration not recommended.</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>Co-administration with these medications is likely to reduce concentrations of simeprevir and lead to reduced simeprevir efficacy. Co-administration not recommended.</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Co-administration with these medications is likely to increase concentrations of simeprevir due to CYP3A4 inhibition from the anticonvulsants. Co-administration not recommended.</td>
</tr>
</tbody>
</table>

www.hcvguidelines.org
**Other Drug Interactions with Simeprevir (2 of 2)**

<table>
<thead>
<tr>
<th>Medication and or Class</th>
<th>Rationale for Avoiding with Simeprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids – dexamethasone</td>
<td>Co-administration with dexamethasone is likely to decrease concentrations of simeprevir and lead to reduced simeprevir efficacy. Co-administration not recommended.</td>
</tr>
<tr>
<td>Propulsives – cisapride</td>
<td>Co-administration with cisapride may result in increased concentrations of cisapride leading to potential cardiac arrhythmias.</td>
</tr>
<tr>
<td>Herbal products – Milk Thistle, St. John’s Wort</td>
<td>Co-administration with milk thistle is likely to increase concentrations of simeprevir. Co-administration not recommended. Co-administration with St. John’s Wort is likely to increase concentrations of simeprevir leading to reduced simeprevir efficacy, due to intestinal P-glycoprotein (P-gp) induction associated with St. John’s Wort.</td>
</tr>
</tbody>
</table>

**Drugs Requiring Monitoring or Dose Limits with Simeprevir**

<table>
<thead>
<tr>
<th>Medication and or Class</th>
<th>Rationale for Avoiding with Simeprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>Increased digoxin levels expected, monitor levels</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>Potential increase in levels, monitor levels if possible</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Potential increase in levels, monitor for hypotension</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Increased atorvastatin levels, use lowest doses, do not exceed 40mg daily</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Increased rosuvastatin levels, initiate with 5mg daily, do not exceed 10mg daily</td>
</tr>
<tr>
<td>Simvastatin, pravastatin, lovastatin, infantin</td>
<td>Use lowest dose possible, titrate carefully</td>
</tr>
<tr>
<td>Oral midazolam, triazolam</td>
<td>Increased levels expected, titrate carefully, use lowest doses</td>
</tr>
</tbody>
</table>

**Other Drug Interactions with Sofosbuvir**

<table>
<thead>
<tr>
<th>Medication and or Class</th>
<th>Rationale for Avoiding with Sofosbuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants – carbamazepine, oxcarbazepine, phenobarbital, phenytoin</td>
<td>Co-administration with these medications is likely to reduce concentrations of sofosbuvir leading to reduced sofosbuvir efficacy. Co-administration not recommended.</td>
</tr>
<tr>
<td>Antibacterials – rifampin, rifabutin, rifapentin</td>
<td>Co-administration with these medications is likely to reduce concentrations of sofosbuvir leading to reduced sofosbuvir efficacy due to intestinal P-glycoprotein (P-gp) induction from rifampin.</td>
</tr>
<tr>
<td>Herbal products – St. John’s Wort</td>
<td>Co-administration with these medications is likely to reduce concentrations of sofosbuvir leading to reduced sofosbuvir efficacy due to intestinal P-glycoprotein (P-gp) induction associated with St. John’s Wort.</td>
</tr>
</tbody>
</table>

**Short list of Acceptable HIV Regimens with SIM/SOF**

- **NNRTI – Based**
  - Complera
  - If NOT on a proton pump inhibitor
- **INSTI – Based**
  - Isentress + Truvada or Epzicom
  - Tivicay + Truvada
  - Triumeq
- **EI – Based**
  - Selzentry + Truvada or Epzicom

**HIV Regimens to be AVOIDED with SIM/SOF**

- CAN NOT USE the following
  - All HIV PIs with or without RTV
  - Stridil
  - Atripla, also Sustiva
  - Viramune
  - Retrovir containing regimens

**Resources for You**

- [www.nynjaetc.org](http://www.nynjaetc.org)
- [www.hcvguidelines.org](http://www.hcvguidelines.org)
Databases “Issues”

- Some overall interactions
  - Entire class versus individual medications
- Some miss case reports, so incomplete
- Always do a Medline search
  - I.e.: warfarin and lactulose on Lexicomp
- Stick to reputable HIV driven references for first step to screen for interactions

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

www.hcvguidelines.org
Released 1/29/14!

www.nynjaetc.org
HIV Drug Interactions

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