Consults from the Frontline:
Applying Pharmacology to Clinical Practice

Ian R. McNicholl, Pharm.D., FCCP, BCPS (AQ-Infectious Diseases), AAHIVP
Clinical Pharmacy Specialist,
University of California-San Francisco, Positive Health Program/Department of Medicine
Associate Clinical Professor,
University of California-San Francisco, School of Pharmacy
Editor,
University of California-San Francisco, Center for HIV Information, Drug Interaction Database
Learning Objectives

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

• Identify, assess and manage clinically significant drug interactions involving antiretrovirals and concomitant medications
Faculty and Planning Committee
Disclosures
Please consult your program book.

Off-Label Disclosure
There will be no off-label/investigational uses discussed in this presentation.
Common Medications Interacting with Antiretrovirals

- Statins (simvastatin)
- Warfarin
- H$_2$-antagonists
  - (when combined with atazanavir, rilpivirine)
- Proton pump inhibitors
  - (when combined with atazanavir, rilpivirine)
- PDE5 inhibitors
- Fluticasone
- Rifamycins
- HCV NS3/4A inhibitors
- Maraviroc
- Etravirine
- Rilpivirine
- Elvitegravir/cobicistat
Pulmonary Case

WB, 52 yo African-American female, wt 81 kg, ht 178 cm

Past Medical History

– HIV
– Alcohol abuse
– Bipolar
– Asthma

Meds

– FTC/TDF 1 tab QD
– DRV/r 800/100 mg QD
– HCTZ 25 QAM
– metoprolol 50 mg BID
– albuterol HFA 1-2 puffs TID-QID PRN
– oxycodone IR 30 mg Q8H PRN

Labs

– CD4 782
– viral load < 40

At this visit, pt c/o daily SOB with 4-5 nighttime episodes/week.
How would you manage this patient’s asthma?

a. Add salmeterol 50 mcg BID
b. Add fluticasone/salmeterol 250/50 mcg 1 inh BID
c. Add budesonide/formoterol 80/4.5 mcg 2 inh BID
d. Add cromolyn 2 puffs BID
e. Increase albuterol to 4 puffs QID
How would you manage this patient’s asthma?

a. Add salmeterol 50 mcg BID
b. Add fluticasone/salmeterol 250/50 mcg 1 inh BID
c. Add budesonide/formoterol 80/4.5 mcg 2 inh BID
d. Add cromolyn 2 puffs BID
e. Increase albuterol to 4 puffs QID
<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity ≥12 years of age</th>
<th>Persistent (Moderate)</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>Intermittent: ≤2 days/week</td>
<td>&gt;2 days/week but not daily</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td>Nighttime awakenings: ≤2x/month</td>
<td>3–4x/month</td>
<td>Typically throughout the day</td>
</tr>
<tr>
<td></td>
<td>Nighttime awakenings: ≤2x/month</td>
<td>3–4x/month</td>
<td>Typically throughout the day</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td>Exacerbations requiring oral systemic corticosteroids:</td>
<td>0–1/year (see note)</td>
<td>≥2/year (see note)</td>
</tr>
<tr>
<td><strong>Impairment</strong></td>
<td>Normal FEV₁/FVC: 8–19 yr 85%</td>
<td>80%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>Interference with normal activity: None</td>
<td>Minor limitation</td>
<td>Some limitation</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td>Normal FEV₁ between exacerbations</td>
<td>FEV₁ &gt;80% predicted</td>
<td>FEV₁ &gt;60% but &lt;80% predicted</td>
</tr>
<tr>
<td></td>
<td>FEV₁/FVC normal</td>
<td>FEV₁/FVC normal</td>
<td>FEV₁/FVC reduced 5%</td>
</tr>
<tr>
<td><strong>Recommended Step for Initiating Treatment</strong></td>
<td>Step 1: In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.</td>
<td>Step 2: and consider short course of oral systemic corticosteroids</td>
<td>Step 3: and consider short course of oral systemic corticosteroids</td>
</tr>
</tbody>
</table>


ACTHIV 2013: A State-of-the-Science Conference for Frontline Health Professionals
Class Effect or Isolated Issue?

- Fluticasone PK study
  - 200 mcg intranasally QD and RTV 100 mg BID x 7 d
  - fluticasone AUC$_{0-24h}$: ↑ 36,697%; Cmax: ↑ 2572%
  - plasma cortisol AUC ↓ 86%

- Fluticasone usage
  - Most studied, most prescribed, more formulations

- Pharmacology
  - Longest glucocorticoid receptor binding t$\frac{1}{2}$
  - Very lipophilic >> beclomethasone, budesonide
  - Most HPA suppressive

## Corticosteroid Comparison

<table>
<thead>
<tr>
<th>Drug</th>
<th>Receptor Binding Affinity</th>
<th>Lung Delivery (%)</th>
<th>Protein Binding (%)</th>
<th>Oral Bioavailability (%)</th>
<th>Systemic Clearance (L/h)</th>
<th>Distribution Volume (L)</th>
<th>Half-Life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate/17-monopropionate b</td>
<td>0.4/13.5</td>
<td>50–60</td>
<td>87</td>
<td>20/40</td>
<td>150/120</td>
<td>20/424</td>
<td>0.5/2.7 UK/2.7</td>
</tr>
<tr>
<td>Budesonide</td>
<td>9.4</td>
<td>15–30 c</td>
<td>88</td>
<td>11</td>
<td>84</td>
<td>280</td>
<td>2.8</td>
</tr>
<tr>
<td>Ciclesonide/desiclesonide b</td>
<td>0.12/12.0</td>
<td>50</td>
<td>99/99</td>
<td>&lt;1/&lt;1</td>
<td>152/228</td>
<td>207/897</td>
<td>0.36/3.4 0.5/4.8</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>1.8</td>
<td>68</td>
<td>80</td>
<td>20</td>
<td>58</td>
<td>96</td>
<td>1.6</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>18</td>
<td>20 c</td>
<td>90</td>
<td>&lt;1</td>
<td>66</td>
<td>318–859</td>
<td>7.8</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>23 d</td>
<td>11 d</td>
<td>99</td>
<td>&lt;1</td>
<td>53</td>
<td>152</td>
<td>5.0</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>3.6</td>
<td>22</td>
<td>71</td>
<td>23</td>
<td>45–69</td>
<td>103</td>
<td>2.0</td>
</tr>
</tbody>
</table>

*Notes:*
- b: Data from reference 1
- c: Data from reference 2
- d: Data from reference 3

---

# Available Inhaled/Intranasal Corticosteroids

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>QVAR, Qnasal</td>
<td>CYP450 3A4</td>
</tr>
<tr>
<td></td>
<td>Beconase AQ</td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td>Pulmicort Flexhaler</td>
<td>CYP450 3A4</td>
</tr>
<tr>
<td></td>
<td>Rhinocort AQ</td>
<td></td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>Alvesco, Zetonna</td>
<td>CYP450 3A4, 2D6</td>
</tr>
<tr>
<td></td>
<td>Omnaris</td>
<td></td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Flovent, Flonase</td>
<td>CYP450 3A4</td>
</tr>
<tr>
<td></td>
<td>Advair, Veramyst</td>
<td></td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Aerobid-M, Nasarel</td>
<td>CYP450 3A4</td>
</tr>
<tr>
<td></td>
<td>Nasalide</td>
<td></td>
</tr>
<tr>
<td>Mometasone</td>
<td>Asmanex Twisthaler</td>
<td>CYP450 3A4</td>
</tr>
<tr>
<td></td>
<td>Nasonex, Dulera</td>
<td></td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Azmacort</td>
<td>CYP450 3A4</td>
</tr>
<tr>
<td></td>
<td>Nasacort AQ</td>
<td></td>
</tr>
</tbody>
</table>

**ACTHIV 2013: A State-of-the-Science Conference for Frontline Health Professionals**
Beclomethasone Pharmacokinetics

Figure 1. 17-BMP Concentration vs. Time Curves after (Phase 1) and 4 Weeks (Phase 2) of Orally Inhaled Beclomethasone alone

Figure 3. 17-BMP Concentration vs. Time Curves before (Phase 1) and after (Phase 2) DRV/r

Take-Away Messages

• Increased risk for Cushing’s/HPA suppression
  – Elderly
  – Fluticasone > 500 mcg/day
  – Ritonavir > 200 mg/day

• FDA Warning
  – Salmeterol

• Difficult to control or adherence challenged patients
  – Co-formulated products
  – Budesonide/formoterol

• Continued vigilance

• Beclomethasone has minimal interaction
Seizure Case

DK 58 yo AAF, 71 kg, BP 111/75

Problem List:
- generalized epilepsy
- psychosis
- HTN
- dyslipidemia
- tobacco use
- asthma

Meds:
- LPV/r 3 tabs BID
- 3TC 150 mg BID
- AZT 300 mg BID
- phenytoin 500 mg QHS
- risperidone 2 mg QHS
- atorvastatin 10 mg QD
- HCTZ 25 mg QAM

Labs: CD4 238, vl 10345 (4/21/11)
### Immune Status Labs -- All Dates

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CD4 cells (cells/UL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV Viral Load (copies/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV Viral Load (log X)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Lymph. count (cells/CU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% CD4 T Lymph.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CD8 cells (cells/UL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4/CD8 Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLAB5701</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Meds</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Active Meds:**
- Zidovudine
- Lopinavir/rit
6/16/2011

Genotype/Phenotype/Tropism:
- Tropism: CXCR4
- NRTI: A62V
- NNRTI: V90I, K103N, P225H
- PI: L10F, V32I, L33F, M46I, 147V, F53L, I54M, A71I, V82A

Phenotype: Sensitive etravirine, partially sensitive DRV/SQV/TPV (resistant to all other PIs)
Suspect could have other TAMs
# Anticonvulsant Pharmacology

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Metabolism</th>
<th>Clin. Sig ARV Inxns?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Tegretol</td>
<td>CYP450 → induction</td>
<td>Y</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Luminal</td>
<td>CYP450 → induction</td>
<td>Y</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Dilantin</td>
<td>CYP450 → induction</td>
<td>Y</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Neurontin</td>
<td>renal elim.</td>
<td>N</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Lamictal</td>
<td>glucuronidation</td>
<td>N</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Keppra</td>
<td>hydrolysis, renal elim.</td>
<td>N</td>
</tr>
<tr>
<td>Oxcarbazine</td>
<td>Trileptal</td>
<td>CYP450</td>
<td>Y</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Lyrica</td>
<td>renal elim.</td>
<td>N</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Gabitril</td>
<td>oxidation, renal elim.</td>
<td>N</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Topamax</td>
<td>renal elim.</td>
<td>N</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Depakote</td>
<td>CYP450 → variable</td>
<td>Variable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Dose of Drug</th>
<th>Dose of Lopinavir/ritonavir</th>
<th>Effect on Drug Levels</th>
<th>Effect on Lopinavir/ritonavir Levels</th>
<th>Potential Clinical Effects</th>
<th>Mechanism of Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin&lt;sup&gt;78&lt;/sup&gt; (Dilantin) (Dilantin)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Not studied; may decrease lopinavir levels</td>
<td>Decreased lopinavir/ritonavir effects</td>
<td>Induction of CYP450 3A4 by phenytoin</td>
</tr>
<tr>
<td>Phenytoin&lt;sup&gt;224&lt;/sup&gt; (Dilantin) (Dilantin)</td>
<td>300 mg QHS for 10 days</td>
<td>400/100 mg BID on days 1-22</td>
<td>Phenytoin AUC: decreased 31%; Cmax: decreased 28%; Cmin: decreased 34%; half-life: decreased 38%</td>
<td>Lopinavir AUC: decreased 33%; Cmax: decreased 24%; Cmin: decreased 46%; half-life: decreased 51%. Ritonavir AUC: decreased 28%; Cmax: decreased 20%; Cmin: decreased 47%; half-life: decreased 38%</td>
<td>Decreased lopinavir/ritonavir and phenytoin effects</td>
<td>Induction of CYP450 3A4 by phenytoin; possible induction of CYP450 2C9 by lopinavir</td>
</tr>
</tbody>
</table>

Interventions

• 5/12/11  Pt referral for increasing VL
• 5/27/11  Created and implemented titration schedule
  – Lamotrigine 25 mg BID; phenytoin 400 mg QHS x 2 weeks
  – Lamotrigine 50 mg BID; phenytoin 300 mg QHS x 2 weeks
  – Lamotrigine 75 mg BID; phenytoin 200 mg QHS x 2 weeks
  – Lamotrigine 100 mg BID; phenytoin 100 mg QHS then off
  – Levetiracetam 500 mg BID
• Every 2 week appts for ADR and adherence monitoring
Seizure Case F/U

DK

Problem List:
- generalized epilepsy
- psychosis
- HTN
- dyslipidemia
- tobacco use
- asthma

Meds:
- DRV/r 600/100 mg BID
- ETR 200 mg BID
- RAL BID
- FTC/TDF
- levetiracetam 1500 mg BID
- lamotrigine 150 mg BID
- risperidone 2 mg QHS
- atorvastatin 10 mg QD
- HCTZ 25 mg QAM

Labs: CD4 285, vl < 40 (1/17/13)
Take-Away Messages

• Detrimental effects of drug induction on CYP450
  – Loss of virologic suppression
  – Potential resistance

• Induction
  – 2 weeks to allow for return to baseline

• Avoid phenytoin and ARVs

• Levetiracetam acceptable
“Putting it all Together”

AT, 44 yo BM, wt 65 kg, ht 173 cm, BP 120/75, P71

Emigrated from Eritrea 8 mo ago, presents to Urgent Care with cough

Past Medical History
- HIV (dx’d 6/24)
- AIDS
- TB (dx’d 6/28)

Labs
- CD4 84 (6/28)
- Viral load 281,000 (6/28)

Meds
- rifampin 600 mg QD
- ethambutol 1000 mg QD
- isoniazid 300 mg QD
- pyrazinamide 1250 mg QD

June 24 – admitted for R/O TB vs. KS vs. PCP
June 27 – RIPE started
July 3 – Recommendation to start ARVs

An atazanavir/ritonavir 300/100 mg QD based regimen is initiated.
How would you modify his TB and/or HIV tx?

a. No change needed
b. Reduce rifampin to 300 mg QD
c. Change ATV/r 300 mg QD to LPV/r 800/200 mg BID
d. Change rifampin to rifabutin 150 mg QD
Relapse and Acquired Rifampin Resistance

Retrospective cohort study, HIV/TB patients, NYC 1997-2000,
• 807 HIV+ patients and 2054 HIV- patients
• Results
  – HIV infected patients more likely to have
    • treatment failure
    • relapse
      – intermittent RIF dosing (HR 9.9, 95% CI 1.4-70.3)

Retrospective chart review, HIV/TB pts, SF TB Program, 1990-2001
• 700 patients, 264 (38%) HIV+
• Results
  – Relapse associated with
    • shorter course of TB treatment (6 mo vs. longer treatment)
    • intermittent therapy vs daily (HR 4.12, p=0.04)

Considering Daily Reduced Dose Rifabutin

- RFB PK and LPV/r 400/100 mg BID PK study
  - Addition of 150 mg RFB,
    - 9/10 patients had low Cmax and 8/10 pts received ↑ rifabutin to 300 mg QD
- Association between acquired rifamycin resistance and RFB PK
  - 102 pts in TBTC 23 PK substudy
  - Rifamycin resistance associated with (OR 10.5, 95% CI 1.1-100)
    - RFB AUC
    - Low RFB AUC OR 23, p=0.003
- Clinical considerations
  - Data suggestive of 150 mg TIW may be underdosing
  - RFB AUC not available in clinical settings, possibly obtain Cmin
  - Serious RFB AEs not yet noted on daily reduced doses

Modifying his TB or HIV treatment

a. No change needed
b. Reduce rifampin to 300 mg QD
c. Change ATV/r 300 mg QD to LPV/r 800/200 mg BID
d. Change rifampin to rifabutin 150 mg QD
Take-Away Messages

• Consider patient as whole
  – Psychosocial factors
  – Support
  – Insurance
  – Coping skills
  – Discharge planning

• Rifamycin interactions require proactivity
Primary Care/Dyslipidemia

YY, 37 yo African-American female, wt 68 kg, ht 162 cm

Past Medical History
- HIV x 6 yrs
- + tobacco 2 ppd
- dyslipidemia
- HTN

Meds
- emtricitabine/tenofovir 1 tab QD
- darunavir 800 mg QD
- ritonavir 100 mg QD
- benazepril 10 mg QD

Labs
- CD4 586
- viral load 1800
- Fasting lipids
  - Tchol 290
  - HDL 40
  - LDL 190
  - TG 300
How do we manage YY’s dyslipidemia?

a. simvastatin 10 mg QD
b. pravastatin 40 mg QD
c. atorvastatin 10 mg QD (NON-formulary)
d. omega-3-fatty acids 4 g QD
e. exetimibe 10 mg QD (NON-formulary)
How do we manage YY’s dyslipidemia?

a. simvastatin 10 mg QD
b. pravastatin 40 mg QD
c. atorvastatin 10 mg QD (NON-formulary)
d. omega-3-fatty acids 4 g QD
e. exetimibe 10 mg QD (NON-formulary)
## LDL Goals for Drug Therapy

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL (mg/dL) Primary target</th>
<th>Non-HDL (mg/dL) Secondary target</th>
<th>LDL to Consider Drug Therapy (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High</td>
<td>&lt; 70</td>
<td>&lt; 100</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>High CHD or CHD Risk Equivalents (10-year risk &gt; 20%)</td>
<td>&lt; 100</td>
<td>&lt; 130</td>
<td>≥ 100</td>
</tr>
<tr>
<td>Moderately High</td>
<td>&lt; 130</td>
<td>&lt; 160</td>
<td>≥ 130</td>
</tr>
<tr>
<td>≥ 2 Risk Factors (10-year risk 10-20%)</td>
<td>&lt; 100 (optional)</td>
<td>&lt; 130 (optional)</td>
<td>(100–129: drug optional)</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt; 130</td>
<td>&lt; 160</td>
<td>≥ 160</td>
</tr>
<tr>
<td>≥ 2 Risk Factors (10-year risk &lt; 10%)</td>
<td>&lt; 130</td>
<td>&lt; 160</td>
<td>≥ 160</td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 160</td>
<td>&lt; 190</td>
<td>≥ 190</td>
</tr>
<tr>
<td>0–1 Risk Factor</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Estimating 10 Year Risk of MI and Coronary Death

Interactions between LPV/r and Rosuvastatin

- Rosuvastatin (ROS) not metabolized by CYP450
- HIV-infected patients on LPV/r (400/100 BID, n=22) with TC = 239 mg/dL treated with ROS for 12 wks
- Rosuvastatin increase 1.5–1.9-fold, may be used with caution

<table>
<thead>
<tr>
<th>Dose</th>
<th>Median (IQR) ROS trough levels (ng/mL)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>This study</td>
<td>Historic controls</td>
</tr>
<tr>
<td>10 mg (n=13)</td>
<td>0.97 (0.70–1.5)</td>
<td>0.63 (0.27–1.2)</td>
</tr>
<tr>
<td>20 mg (n=14)</td>
<td>2.5 (1.3–3.3)</td>
<td>1.6 (0.54–4.1)</td>
</tr>
<tr>
<td>40 mg (n=10)</td>
<td>5.5 (3.3–8.8)</td>
<td>2.9 (1.7–3.6)</td>
</tr>
</tbody>
</table>

van der Lee M, et al. 13th CROI, Denver 2006, #588
## Dyslipidemia Treatment Comparison

<table>
<thead>
<tr>
<th>Medication</th>
<th>LDL</th>
<th>HDL</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG CoA</td>
<td>↓ 18-55%</td>
<td>↑ 5-15%</td>
<td>↓ 7-30%</td>
</tr>
<tr>
<td>Fibric acids</td>
<td>↓ 5-20%</td>
<td>↑ 10-35%</td>
<td>↓ 20-50%</td>
</tr>
<tr>
<td>Niacin</td>
<td>↓ 5-25%</td>
<td>↑ 15-35%</td>
<td>↓ 20-50%</td>
</tr>
<tr>
<td>Ω-3 Fatty Acids</td>
<td>↑ 1-44%</td>
<td>↑ 3-9%</td>
<td>↓ 30-45%</td>
</tr>
<tr>
<td>Exetimibe</td>
<td>↑ 18-21%</td>
<td>↔</td>
<td>↓ 0-10%</td>
</tr>
</tbody>
</table>

Take-Away Messages

• Many interactions with statins
  – Some are significant
• Statins most effective for reducing LDL
  – Negligible effect on TG
• Pravastatin and atorvastatin most used
• Need to consider non P450 mediated interactions
  – e.g. rosuvastatin
Treating Co-Infected Patients

SM, 51 yo CF wt 60 kg, ht 164 cm

### Past Medical History
- HIV
- Hepatitis C geno 1
- Diabetes type 2

### Labs
- CD4 465
- Viral load < 40
- Hepatitis C viral load 5 million copies
- F3

### Meds
- Emtricitabine/tenofovir 1 QD
- Darunavir 800 mg QD
- Ritonavir 100 mg QD
- Metformin 1000 mg BID
- Pegylated interferon 180 mcg QW
- Ribavirin 1200 mg QD
- Boceprevir 800 mg TID

What changes do you want to make to this regimen?
HCV Protease Inhibitor Drug Interactions

- Boceprevir and telaprevir metabolized by CYP3A4
- CYP 3A4 inducers ↓ NS3/4A concentrations
- CYP 3A4 inhibitors ↑ NS3/4A concentrations
  - Increased toxicity?
- Complete med list reconciliation required
  - May need to change or discontinue concomitant meds prior to HCV PI therapy
# HCV Protease Inhibitor Drug Interactions

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Contraindicated With BOC</th>
<th>Contraindicated With TVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha 1-antagonist</td>
<td>Alfuzosin</td>
<td>Alfuzosin</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Carbamazepine, phenobarbital, phenytoin</td>
<td>N/A</td>
</tr>
<tr>
<td>Antimycobacterials</td>
<td>Rifampin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Ergot derivatives</td>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
<td>Dihydroergotamine, ergonovine, ergotamine, methylergonovine</td>
</tr>
<tr>
<td>GI motility agents</td>
<td>Cisapride</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Herbal products</td>
<td>Hypericum perforatum</td>
<td>Hypericum perforatum</td>
</tr>
<tr>
<td>HMG CoAs</td>
<td>Lovastatin, simvastatin</td>
<td>Atorvastatin, lovastatin, simvastatin</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Drosipreneone</td>
<td>N/A</td>
</tr>
<tr>
<td>Neuroleptic</td>
<td>Pimozide</td>
<td>Pimozide</td>
</tr>
<tr>
<td>PDE5 inhibitor</td>
<td>Sildenafil or tadalafil</td>
<td>Sildenafil or tadalafil</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>PO midazolam; triazolam</td>
<td>PO midazolam, triazolam</td>
</tr>
</tbody>
</table>

## Telaprevir-ARV Interactions

<table>
<thead>
<tr>
<th>ARV</th>
<th>TVR AUC</th>
<th>TVR (C_{\text{min}})</th>
<th>ARV AUC</th>
<th>ARV (C_{\text{min}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>↓ 20%</td>
<td>↓ 15%</td>
<td>↑ 17%</td>
<td>↑ 85%</td>
</tr>
<tr>
<td>DRV/r</td>
<td>↓ 35%</td>
<td>↓ 32%</td>
<td>↓ 40%</td>
<td>↓ 42%</td>
</tr>
<tr>
<td>FPV/r</td>
<td>↓ 32%</td>
<td>↓ 30%</td>
<td>↓ 47%</td>
<td>↓ 56%</td>
</tr>
<tr>
<td>LPV/r</td>
<td>↓ 54%</td>
<td>↓ 52%</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>EFV</td>
<td>↓ 18%</td>
<td>↓ 25%</td>
<td>↓ 18%</td>
<td>↔</td>
</tr>
<tr>
<td></td>
<td>TVR 1125 mg Q8H</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETR</td>
<td>↓ 16%</td>
<td>↓ 25%</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>RPV</td>
<td>↔</td>
<td>↔</td>
<td>↑ 78%</td>
<td>↑ 93%</td>
</tr>
<tr>
<td>RAL</td>
<td>↔</td>
<td>↔</td>
<td>↑ 31%</td>
<td>↑ 78%</td>
</tr>
</tbody>
</table>

## Boceprevir-ARV Interactions

<table>
<thead>
<tr>
<th>ARV</th>
<th>BOC AUC</th>
<th>BOC $C_{\text{min}}$</th>
<th>ARV AUC</th>
<th>ARV $C_{\text{min}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>↔</td>
<td>↓ 18%</td>
<td>↓ 35%</td>
<td>↓ 49%</td>
</tr>
<tr>
<td>DRV/r</td>
<td>↓ 45%</td>
<td>↓ 57%</td>
<td>↓ 34%</td>
<td>↓ 43%</td>
</tr>
<tr>
<td>LPV/r</td>
<td>↓ 32%</td>
<td>↓ 35%</td>
<td>↓ 44%</td>
<td>↓ 59%</td>
</tr>
<tr>
<td>ETV</td>
<td>↓ 19%</td>
<td>↓ 44%</td>
<td>↑ 20%</td>
<td>↔</td>
</tr>
<tr>
<td>RAL</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>RPV</td>
<td>↔</td>
<td>↔</td>
<td>↑ 39%</td>
<td>↑ 51%</td>
</tr>
</tbody>
</table>

Treating Co-Infected Patients

SM, 51 yo CF wt 60 kg, ht 164 cm

Past Medical History
- HIV
- Hepatitis C geno 1
- Diabetes type 2

Labs
- CD4 465
- Viral load < 40
- Hepatitis C viral load 5 million copies
- F3

Meds
- Emtricitabine/tenofovir 1 QD
- Darunavir 800 mg QD
- Ritonavir 100 mg QD
- Metformin 1000 mg BID
- Pegylated interferon 180 mcg QW
- Ribavirin 1200 mg QD
- Boceprevir 800 mg TID

What changes do you want to make to this regimen?
How would you manage a 60 year old patient receiving pegIFN, ribavirin and telaprevir with concomitant medications atenolol, terazosin, atorvastatin and metformin?

a. Change atorvastatin to simvastatin
b. Hold atorvastatin until telaprevir course is complete
c. Discontinue telaprevir
d. No intervention is needed
How would you manage a 60 year old patient receiving pegIFN, ribavirin and telaprevir with concomitant medications atenolol, terazosin, atorvastatin and metformin?

a. Change atorvastatin to simvastatin
b. Hold atorvastatin until telaprevir course is complete
c. Discontinue telaprevir
d. No intervention is needed
Take-Away Messages

- Neither anemia nor RBV dose reduction affects SVR
  - PI monotherapy results in resistance
  - Cross-resistance
- NS3/4A Q8H dosing
- Increased influx of HCV patients eligible for tx
- Transition from GI/Hep to Primary Care
  - Tx Segmentation
    - Tx-naïve – Primary Care
    - Tx-experienced – Gastroenterology, Hepatology
- Multidisciplinary team approach
Clinical Pearls

- Rilpivirine
- Recreational substances
- EVG/COBI boosted PIs
How Many Calories are REALLY Required for Rilpivirine Absorption?

- PK, randomized, crossover study, n=23 healthy subjects

### Table 2. RPV Pharmacokinetic Parameters

<table>
<thead>
<tr>
<th>RPV PK Parameter (Mean [%CV])</th>
<th>Standard Meal (n=24)</th>
<th>Fasting (n=24)</th>
<th>Light Meal (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{inf} (ng*h/mL)</td>
<td>3030 (34)</td>
<td>2770 (40)</td>
<td>2880 (41)</td>
</tr>
<tr>
<td>AUC_{last} (ng*h/mL)</td>
<td>2770 (35)</td>
<td>2460 (39)</td>
<td>2670 (41)</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>99.5 (38)</td>
<td>83.2 (42)</td>
<td>104 (35)</td>
</tr>
<tr>
<td>T_{max} (h)*</td>
<td>4.75 (3.50, 5.00)</td>
<td>3.75 (3.25, 5.00)</td>
<td>3.50 (3.00, 5.00)</td>
</tr>
</tbody>
</table>

### Table 3. Food Effect on RPV AUC and C_{max}

<table>
<thead>
<tr>
<th>RPV PK Parameter</th>
<th>GMR (%) 90% CI Standard Meal/Fasting</th>
<th>GMR (%) 90% CI Light Meal/Fasting</th>
<th>GMR (%) 90% CI Light Meal/Standard Meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{inf}</td>
<td>116 (98.6, 137)</td>
<td>109 (92.2, 129)</td>
<td>93.8 (79.2, 111)</td>
</tr>
<tr>
<td>AUC_{last}</td>
<td>119 (101, 142)</td>
<td>113 (95.4, 135)</td>
<td>94.9 (79.9, 113)</td>
</tr>
<tr>
<td>C_{max}</td>
<td>126 (105, 153)</td>
<td>134 (111, 163)</td>
<td>106 (87.6, 129)</td>
</tr>
</tbody>
</table>

Rilpivirine Take Away Messages

• Must be dosed with 400 calorie meal
• Screen for adherence barriers
  – Predicted adherence must be >95%
• Baseline viral load < 100K
• Drug Interactions
  – NO PPIs
    • RPV AUC ↓ 40%
  – H₂-antagonists
    • 12 hours prior
    • O/W RPV AUC ↓ 76%
# Recreational Drug Metabolism

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route</th>
<th>ARV Inter?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>2D6 substrate</td>
<td>Y</td>
</tr>
<tr>
<td>Amyl nitrite</td>
<td>hydrolytic denitration</td>
<td></td>
</tr>
<tr>
<td>Barbs</td>
<td>3A4 inhibition/induction</td>
<td>Y</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>3A4 substrate</td>
<td>Y</td>
</tr>
<tr>
<td>Cocaine</td>
<td>t/p esterases, 3A4 substrate (minor)</td>
<td></td>
</tr>
<tr>
<td>GHB</td>
<td>2D6 substrate</td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>glucuronidation, 3A4</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>2B6, 3A4, 2C9 substrate</td>
<td>Y</td>
</tr>
<tr>
<td>LSD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marijuana</td>
<td>hydroxylation, 3A4, 2C9, 2C6</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>3A4, 2D6, 2C19, 2B6, ? Substrates</td>
<td>Y</td>
</tr>
<tr>
<td>MDMA</td>
<td>2D6 demethylation</td>
<td>Y</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>2D6 substrate then 3A4 substrate</td>
<td></td>
</tr>
<tr>
<td>PCP</td>
<td>3A4, 2C11 substrate, 2B1 inhibitor</td>
<td>Y</td>
</tr>
</tbody>
</table>

Drug Interaction Resources


- HIV Center for HIV Information, Drug Interaction Database. Available at [http://arv.ucsf.edu](http://arv.ucsf.edu)

- Toronto General Hospital Immunodeficiency Clinic, Drug interactions Available at [http://www.hivclinic.ca/main/drugs_interact.html](http://www.hivclinic.ca/main/drugs_interact.html)
Database of Antiretroviral Drug Interactions

Jon R. McIntosh, PharmD, BCPS, Editor

Search by Antiretroviral Drug
Select an FDA-approved antiretroviral and view interactions with other drugs specified by drug name or drug class, or view "all interactions".

Search by Interacting Drug
Select any drug in the database and view all interactions with FDA-approved antiretrovirals.

Search by Interacting Drug Class
Select any drug class in the database and view all interactions with FDA-approved antiretrovirals.

Related Resources
About the Database
APV Drug Profiles
Dosage Adjustments for APV
APV Drug Interactions (Adult Dosage)
Adverse Events of Antiretroviral Drugs
More on Interactions
Drug Information Links

About  |  Site Map  |  Feedback  |  Subscribe  |  Sponsors  |  Donate  |  Disclaimer

HIV InSite is a project of the UCSF Center for HIV Information. Copyright 2009, Regents of the University of California.
Questions?
Contact Information

Ian R. McNicholl, PharmD, FCCP, BCPS(AQ-Infectious Diseases), AAHIVP
Clinical Pharmacy Specialist,
UCSF Positive Health Program/Department of Medicine
Associate Clinical Professor,
UCSF School of Pharmacy
Editor,
UC-San Francisco Center for HIV Information, Drug Interaction Database

Phone: (415) 206-2421
Email: imcnicholl@php.ucsf.edu