Connecting the Dots: Recognizing the Impact of Antiretroviral Therapy on Concomitant Therapies

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Rodrigo Burgos, Pharm.D., AAHIVP
Disclosures

• **Rodrigo M. Burgos**: Merck & Co.: Grant/Research Support, Other Research Support; OptumRx: Consultant

• All other planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.
Session Objectives

1) Given a patient case, evaluate the medication profile for potentially significant drug interactions.

2) Recommend appropriate therapeutic alterations to minimize harm to patients on antiretroviral therapy.

3) Predict drug interaction potential in situations where data is unavailable or unclear.
Mechanistic Understanding of Antiretroviral Drug Interactions

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Senior Clinical Content Specialist
Clinical Effectiveness
Wolters Kluwer
Learning Objectives

1) Evaluate medication profiles for potential drug-drug interactions involving antiretroviral agents

2) Apply knowledge of an antiretroviral agent’s transporter and isoenzyme effects to determine potential drug-drug interaction mechanisms

3) Perform appropriate evaluation of pharmacokinetic studies to determine potential drug-drug interaction risks
Drug Interaction Mechanism Types

• Pharmacokinetic
  – Absorption
  – Distribution
  – Metabolism
  – Elimination

• Pharmacodynamic
  – Synergistic
  – Antagonistic
JK is a 45 year old male with HIV virologically- and immunologically-controlled on an antiretroviral regimen of dolutegravir/abacavir/lamivudine 50/600/300 mg once daily is admitted to your internal medicine floor with diverticulitis and you are profiling the following medications as part of his admission order set:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage/Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin/tazobactam</td>
<td>3.375 gm intravenously q6 hours</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>650 m orally q6 hours prn pain</td>
</tr>
<tr>
<td>Magnesium hydroxide</td>
<td>30 mL daily as needed for constipation</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>4 mg intravenously every 8 hours as needed for nausea/vomiting</td>
</tr>
<tr>
<td>Temazepam</td>
<td>15 mg qHS prn sleep</td>
</tr>
<tr>
<td>Dolutegravir/abacavir/lamivudine</td>
<td>50/600/300 mg orally once daily</td>
</tr>
<tr>
<td>Dextrose</td>
<td>5% with 0.45% NaCl 75 ml/hr</td>
</tr>
<tr>
<td>Famotidine</td>
<td>20 mg intravenously twice daily</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>5 mg intramuscularly every 4 hours as needed for nausea/vomiting</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>25 mg orally three times daily as needed for itching</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>500 mg chewable tablet 2 tablets orally every 2 hours as needed for heartburn</td>
</tr>
</tbody>
</table>
Absorption

- Binding interactions (e.g. cholestyramine)
- Chelation (e.g. dolutegravir and calcium)
- Stomach acid alterations (e.g. atazanavir and proton pump inhibitors)
JK Case Question #1

• Which of the following admission orders do you expect to cause a potential drug-drug interaction with JK’s antiretroviral regimen?
  
  A. Famotidine
  B. Prochlorperazine
  C. Ondansetron
  D. Calcium carbonate
• JK’s nurse tells you he has been complaining of heartburn despite his famotidine and she would like to give him some calcium carbonate. He received his dolutegravir/abacavir/lamivudine 4 hours ago. Which of the following do you recommend?

A. It is okay to give calcium carbonate now
B. He cannot have calcium carbonate at all since he is receiving dolutegravir/abacavir/lamivudine. You should call his medical team and asked for this to be changed to Aluminum hydroxide/magnesium carbonate 31.7/119.3 mg/5 Ml
C. It's okay to give calcium carbonate now
D. Calcium carbonate can only be administered 2 hours prior to administering dolutegravir/abacavir/lamivudine
Distribution/Metabolism/Excretion
Drug-Drug Pharmacokinetic Interaction Studies

- *In vitro* studies intended to guide clinical DDI studies
- FDA has established definitions for clinical substrates, inhibitors and inducers as it relates to CYP-based interactions
  - Sometime pharmacogenetic alterations considered in lieu of clinical substrate alterations
- Results from CYP substrate-inhibitor studies can be extrapolated to other CYP inhibitors of similar magnitude (e.g. strong CYP3A4 inhibitor – substrate study can be applied to other strong CYP3A4 inhibitors)
  - Cannot extrapolate for transporters
- Drug-drug interactions can be difficult to predict with fixed dose combination (FDC) products, also when multiple mechanisms potentially at play

https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#PgpTransport; Accessed 9/26/18
Transporters

• ATP-binding cassette (ABC) family transporters
  – P-glycoprotein (P-gp)/Multi-Drug Resistance 1 (MDR1)
  – Breast cancer resistance protein (BCRP)
  – MRP

• Solute carrier family transporters
  – Organic anion transporting polypeptides (OATP)
  – Organic anion transporters (OAT)
  – Organic cation transporters (OCT)
P-glycoprotein

YM Case

- YM is a 67 year old female with past medical history significant for atrial fibrillation for which she has been maintained on digoxin 0.25 mg daily for the last 4 years and recent diagnosis of HIV for which she was initiated on an antiretroviral regimen of tenofovir alafenamide/emtricitabine and darunavir 800 mg daily and ritonavir 100 mg daily approximately 1 month ago. She is admitted to the hospital following presentation with anorexia, nausea, vomiting, and weight loss and found to have a digoxin level was found to be >6.8 mmol/L.
### P-glycoprotein

- **Inhibitors (≥ 2-fold increase in digoxin AUC)**
  - **Antiretrovirals**
    - Lopinavir/ritonavir
    - Ritonavir
    - Saquinavir/ritonavir
    - Tipranavir/ritonavir
  - **Other**
    - Amiodarone
    - Carvedilol
    - Clarithromycin
    - Itraconazole

- **Substrates (≥ 2-fold increase in AUC with verapamil or quinidine)**
  - **Antiretrovirals**
    - Ritonavir
    - Saquinavir/ritonavir
    - Tipranavir/ritonavir
  - **Other**
    - Tenofovir AF/DF
    - Maraviroc
    - Fexofenadine

[Link to FDA website](https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#PgpTransport); Accessed 9/26/18
# Other Transporters

<table>
<thead>
<tr>
<th>Transporters</th>
<th>Substrates</th>
<th>Inhibitor Criteria</th>
<th>Inhibitors</th>
<th>Example Interaction(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OATP (OATP1B1, OATP1B3)</td>
<td>Atorvastatin Cerivastatin Glyburide Paclitaxel Paclitaxel Pravastatin Repaglanide</td>
<td>≥ 2-fold AUC increase with clinical substrate</td>
<td>Atazanavir/ritonavir Lopinavir/ritonavir Saquinavir</td>
<td>Repaglanide x atazanavir/ritonavir*</td>
</tr>
<tr>
<td>OAT (OAT1/OAT3)</td>
<td>Zidovudine</td>
<td>≥ 1.5-fold AUC increase with clinical substrate</td>
<td>Probenecid Teriflunomide</td>
<td>Zidovudine x probenecid</td>
</tr>
<tr>
<td>OCT (OCT2/MATE)</td>
<td>Dofetilide Metformin</td>
<td>≥ 1.5-fold AUC increase in metformin</td>
<td>Dolutegravir</td>
<td>Dolutegravir x metformin Dolutegravir x dofetilide</td>
</tr>
</tbody>
</table>

*CYP-based mechanisms also involved

[https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#PgpTransport](https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#PgpTransport), Accessed 9/26/18
YM Case Follow-Up

• Her medical team asks for your assistance in determining if any component of her antiretroviral regimen could be responsible for her increased digoxin levels. Which of the following do you think is the likely culprit?

A. Tenofovir AF
B. Darunavir
C. Emtricitabine
D. Ritonavir
• Design: double-blind, randomized, crossover prospective study
• Subjects: 12 healthy males
• Methods: received ritonavir (300 mg twice daily) or placebo for 11 days, digoxin 0.5 mg given intravenously on day 3
• Results:
  – Effects on digoxin pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-∞} (h x ng/mL)</td>
<td>22 ± 9</td>
<td>41 ± 17</td>
</tr>
<tr>
<td>CL_r (mL/min)</td>
<td>194 ± 23</td>
<td>126 ± 21</td>
</tr>
</tbody>
</table>
Metabolism

• Cytochrome P450 (CYP)-mediated
  – Mixed-function oxidation (MFO): NDAPH + H⁺ + O₂ + RH (oxidizable drug substrate) → NADP⁺ + H₂O + ROH (hydroxylated metabolite)
  – Nomenclature: number-letter-number (family-subfamily-gene)
  – 90% of drug oxidation occurs by 6 enzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5

• Non-CYP mediated
  – UDP-glucuronosyl transferases and esterases
  – Minor pathways: monoamine oxidases, aldehyde or alcohol dehydrogenases, N-acetyltransferases

FB Case

- FB is a 42 year old male with HIV recently initiated on an initial antiretroviral regimen of darunavir 800 mg once daily, ritonavir 100 mg daily, and tenofovir AF/emtricitabine 25/200 mg daily with a good decrease in viral load from 257,000 copies/mL to 1,225 copies/ml and increase in CD4 from 57 cells/mcL to 149 cells/mcL after 4 weeks. After being admitted to the hospital with severe shortness of breath, cough and fever, the patient is found to have upper lobe cavitation on chest xray and positive AFB smear.
## CYP450-Based Antiretroviral Interactions

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>Inducers</th>
<th>Substrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3A4</td>
<td>Efavirenz $^5$</td>
<td>Efavirenz, Etravirine, Nevirapine, Rilpivirine, Doravirine Darunavir, Atazanavir, Ritonavir Elvitegravir, Cobicistat Maraviroc</td>
</tr>
<tr>
<td>Ritonavir*</td>
<td>Etravirine*</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Cobicistat*</td>
<td>Etravirine*</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Itraconazole*, Ketoconazole*, Fluconazole $^5$</td>
<td>Rifampin</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin*</td>
<td>Atazanavir, Darunavir, Ritonavir Elvitegravir, Cobicistat Maraviroc</td>
<td></td>
</tr>
<tr>
<td>2C9</td>
<td>Carbamazepine $^5$</td>
<td>Etravirine</td>
</tr>
<tr>
<td>Fluconazole $^5$</td>
<td>Rifampin $^5$ Ritonavir $^5$</td>
<td></td>
</tr>
<tr>
<td>2C19</td>
<td>Rifampin*</td>
<td>Etravirine</td>
</tr>
<tr>
<td>Fluoxetine*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2B6</td>
<td>Efavirenz $^5$, Ritonavir $^5$</td>
<td>Efavirenz Bupropion</td>
</tr>
<tr>
<td></td>
<td>Rifampin $^5$ Carbamazepine*</td>
<td></td>
</tr>
</tbody>
</table>

*Strong, $^5$Moderate

[Link to FDA Website](https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#PgpTransport); Accessed 9/26/18
Ketoconazole effects on Rilpivirine and Doravirine

• Pharmacokinetic study: ketoconazole x doravirine
  – ketoconazole (400 mg daily) and doravirine (100 mg single dose)
  – doravirine AUC, Cmax and Cmin increased by 3.1-fold, 1.3-fold, and 2.8-fold, respectively

• Pharmacokinetic study: ketoconazole x rilpivirine
  – Ketoconazole (400 mg daily) and rilpivirine (150 mg daily)
  – Rilpivirine AUC, Cmax and Cmin increased by 1.49-fold, 1.3-fold and 1.76-fold, respectively

• Results from both studies determined not to be clinically significant

FB Case – Question #1

• The medical team would like to empirically initiate an anti-tuberculous regimen of ethambutol, isoniazid, rifampin and pyrazinamide. Which of the following of these medications is most likely to cause drug-drug interactions with the patients antiretroviral regimen?

A. Ethambutol  
B. Isoniazid  
C. Rifampin  
D. Pyrazinamide
FB Case – Question #2

• Which of the following antiretroviral agents poses an interaction concern with rifampin?

A. Tenofovir AF
B. Emtricitabine
C. Darunavir
D. Ritonavir
FB Case – Question #3

• Which of the following would be a potential drug-drug interaction strategy to recommend for FB?
  
  A. Increase darunavir dose to 600 mg twice daily and ritonavir dose to 100 mg twice daily
  B. Change rifampin to rifabutin
  C. Change darunavir and ritonavir to efavirenz
  D. Change darunavir and ritonavir to dolutegravir
(renal) Elimination

- Glomerular Filtration
- Proximal tubular secretion
- Distal tubular reabsorption

KEY TAKEAWAYS

1) DRUG-DRUG INTERACTIONS CAN OCCUR AT VARIOUS POINTS IN THE PHARMACOKINETIC PROCESS (ADME)

2) STATISTICALLY SIGNIFICANT PHARMACOKINETIC CHANGES NOTED IN CLINICAL STUDIES DO NOT ALWAYS TRANSLATE TO CLINICALLY SIGNIFICANT OUTCOMES

3) TRANSPORTER EFFECTS HAVE TO BE CONSIDERED, ALONG WITH CYP-BASED MECHANISMS, WITH MIXED EFFECTS BEING UNPREDICTABLE
Impact of HIV Pharmacotherapy On Key Therapeutic Areas

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Clinical Assistant Professor
Section of Infectious Diseases Pharmacotherapy
College of Pharmacy, University of Illinois at Chicago
Objectives

1. Based on a patient case, evaluate a medication list for potential drug-drug interactions involving antiretrovirals

2. Based on a patient case, design a therapeutic plan to manage drug-drug interactions

3. List resources to help identify drug-drug interactions with antiretrovirals
Some Abbreviations Throughout

ART: Antiretroviral
NRTI: Nucleoside reverse transcriptase inhibitor
NNRTI: Non-NRTI
PI: Protease inhibitor
INSTI: Integrase strand inhibitor
DRV/r: Darunavir/ritonavir
EVG/c: Elvitegravir/cobicistat
PK: Pharmacokinetic
PD: Pharmacodynamic
SABA: Short-acting beta₂-agonist
LABA: Long-acting beta₂-agonist
ICS: Inhaled corticosteroid
RTG: Raltegravir
DTG: Dolutegravir
Potential Drug-Drug Interactions in a Swiss HIV Cohort

• Observational cohort
• Prospective analysis of medications use between Apr-2008 and Jan-2009
• Assessed the prevalence of potential drug-drug interactions with antiretrovirals assessed with customized version of drug interaction database of University of Liverpool. Classified as:

<table>
<thead>
<tr>
<th>Red flag interactions</th>
<th>Contraindicated, co-administration may lead to serious adverse events or decrease ART efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange flag interactions</td>
<td>Potential drug-drug interaction that may require dose adjustment or close monitoring</td>
</tr>
</tbody>
</table>

Potential Drug-Drug Interactions in a Swiss HIV Cohort

$N = 1,497$ patients treated with ART
68% (1,013/1,497) with concomitant medications
40% (599/1,497) with ≥1 potential drug-drug interaction

<table>
<thead>
<tr>
<th>Red flag interactions</th>
<th>2% (21/1,013)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange flag interactions</td>
<td>59% (597/1,013)</td>
</tr>
</tbody>
</table>

Independent factors associated with potential drug-drug interactions:
- Combinations with PIs and NNRTIs, OR=3.06 (95% CI, 1.44–6.48)
- ≥2 concomitant medications, OR=1.89 (95% CI, 1.32–2.70)
- Current illicit drug use, OR=2.00 (95% CI, 1.29–3.10)
- HCV co-infection, OR=1.74 (95% CI, 1.19–2.56)

Drug Contraindications in a Large US Database

**N = 25,919 ART-Naïve Patients Between April 2014 and March 2015**

- DRV/r + TDF/FTC: 3.20%
- EVG/c/TDF/FTC: 2.80%
- RTG + TDF/FTC: 0.27%
- DTG + NRTIs: 0.00%

** DRV/r: darunavir/ritonavir; EVG/c: elvitegravir/cobicistat; RTG: raltegravir; TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; NRTIs: nucleoside reverse transcriptase inhibitors**

Drug Contraindications in a Large US Database

*N* = 25,919 ART-Naïve Patients Between April 2014 and March 2015

<table>
<thead>
<tr>
<th>ART Regimen</th>
<th>DRV/r + TDF/FTC (n=3,386)</th>
<th>EVG/c/TDF/FTC (n=8,783)</th>
<th>RTG + TDF/FTC (n=10,508)</th>
<th>DTG + NRTIs (n=3,246)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contraindicated drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol (44)</td>
<td>Salmeterol (80)</td>
<td>Al(^{2+}) or Mg(^{2+}) antacids (28)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Simvastatin (24)</td>
<td>Simvastatin (53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin (12)</td>
<td>Phenytoin (19)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban (8)</td>
<td>Rivaroxaban (17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin (3)</td>
<td>Rifabutin (15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban (2)</td>
<td>Rifampin (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED agents (4)</td>
<td>Carbamazepine (13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Triazolam (10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ED agents (11)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drug-Drug Interactions: Why It Matters

- Retrospective case-control study
- US Military HIV Natural History Study, 1986 to 2011
- ≥18 years of age
- On NNRTI- or PI-based + 2 NRTIs, for ≥ 6 months
- All episodes of antiepileptic drugs for ≥28 days

<table>
<thead>
<tr>
<th>CYP 450 Inducers</th>
<th>phenytoin, carbamazepine, phenobarbital</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 450 Non-Inducers</td>
<td>levetiracetam, lamotrigine, zonisamide, pregabalin, ethosuxamide, topiramate, gabapentin, tiagabine</td>
</tr>
</tbody>
</table>

### Drug-Drug Interactions: Why It Matters

**US Military HIV Natural History Study, 1986 to 2011**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CYP 450 Inducer</th>
<th>CYP 450 Non-Inducer</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA ≥400 c/mL</td>
<td>63.3% (19/30)</td>
<td>27.9% (34/122)</td>
<td>4.29 (1.51 - 12.21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.006</td>
</tr>
<tr>
<td>HIV-1 RNA &lt;400 c/mL at 6 months</td>
<td>28.6% (8/28)</td>
<td>69.4% (84/121)</td>
<td>0.17 (0.06 - 0.53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.002</td>
</tr>
<tr>
<td>HIV-1 RNA &lt;400 c/mL at 12 months</td>
<td>39.1% (9/23)</td>
<td>74.0% (71/96)</td>
<td>0.21 (0.07 - 0.61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.004</td>
</tr>
</tbody>
</table>

Virologic failure more common in patients with periods of taking enzyme inducers

My Approach to Identifying and Solving Drug-Drug Interactions in Patients Taking ARTs

**ARTs**
- Possible interaction pathways? PK or PD?
- Their reputation? NNRTIs (inducers), PIs (inhibitors)

**Concomitant Drugs**
- Possible interaction with ARTs?
- Any data demonstrate interaction?
- Use a drug-interaction checker!

**Indication**
- Is concomitant medication needed?
- Is it consistent with disease state guidelines?
- Medication reconciliation process

**Guidance**
- Any guidance about drug-drug interaction?
- Any alternatives to concomitant medication?
- Any alternatives to interacting ARTs?

Or use your own system 😊
Patient Case: CYP 3A4 Inhibition

JD is a 48 yo male with medical history significant for HIV since 1998, asthma since childhood, DM Type 2, HTN, vitamin D deficiency, and allergic rhinitis.

**Home Medication List**

- Tenofovir/emtricitabine/elvitegravir/cobicistat 300/200/150/150 mg po daily
- Darunavir 800 mg po daily
- Metformin 500 mg po daily
- Hydrochlorothiazide 25 mg po daily
- Ergocalciferol 50,000 International Units po weekly
- Fluticasone/salmeterol 100/50 mcg 2 puffs bid
- Albuterol MDI 2 puff q6h prn wheezing
- Fluticasone nasal spray to each nostril daily
Patient Case: CYP 3A4 Inhibition

During interview you discover that JD complains of frequent heart palpitations. A possible drug-drug interaction that could likely explain his cardiac symptoms is:

A. Fluticasone and metformin
B. Hydrochlorothiazide and boosted darunavir
C. Albuterol and boosted darunavir
D. Albuterol and boosted elvitegravir
E. Salmeterol with boosted darunavir and elvitegravir
Guidelines from the National Asthma Education and Prevention Program  
Expert Panel Report 3 (2012 Revision)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Intermittent</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Preferred Treatment</td>
<td>SABA</td>
<td>Low-ICS</td>
<td>Low-ICS + LABA or Med-ICS</td>
<td>Med-ICS + LABA + oral steroid (consider omalizumab if allergies)</td>
</tr>
<tr>
<td>Alternative Treatment</td>
<td>SABA</td>
<td>Cromolyn, LTRA, or theophylline</td>
<td>Low-ICS + LTRA, theophylline or zileuton</td>
<td>Med-ICS + LTRA, theophylline or zileuton</td>
</tr>
</tbody>
</table>

Patient Case: CYP 3A4 Inhibition

Salmeterol use has been associated with increased risk of cardiovascular events, including heart palpitations, acute coronary syndrome, blood pressure alteration, hypertension, cardiac dysrhythmia, heart failure, prolonged QT interval, tachycardia.

Patient Case: CYP 3A4 Inhibition

Inhibition of CYP 3A4 by darunavir, elvitegravir, cobicistat (theoretically) increase concentrations of salmeterol (substrate of CYP 3A4).

<table>
<thead>
<tr>
<th>CYP 3A4 Substrate</th>
<th>CYP 3A4 Inhibitor</th>
<th>Effect</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol</td>
<td>Darunavir</td>
<td>Increased salmeterol exposure</td>
<td>Do not co-administer due to potential salmeterol toxicity</td>
</tr>
<tr>
<td></td>
<td>Elvitegravir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cobicistat</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All protease inhibitors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Formoterol metabolized primarily by glucuronidation. No interaction expected.


Patient Case: CYP 3A4 Inhibition

During interview you discover that JD complaints of frequent heart palpitations. A possible drug-drug interaction that could likely explain his cardiac symptoms is:

A. Fluticasone and metformin  
B. Hydrochlorothiazide and boosted darunavir  
C. Albuterol and boosted darunavir  
D. Albuterol and boosted elvitegravir  
E. Salmeterol with boosted darunavir and elvitegravir
Patient Case: CYP 3A4 Inhibition

What would be an appropriate inhaler substitution for the long-term management of JD’s asthma?

A. Budesonide/formoterol MDI
B. Mometasone/formoterol MDI
C. Beclomethasone MDI + formoterol DPI
D. Beclomethasone MDI + tiotropium MDI
E. Albuterol MDI
Patient Case: CYP 3A4 Inhibition

Inhibition of CYP 3A4 by darunavir, elvitegravir, cobicistat increases concentrations of corticosteroids (substrate of CYP 3A4), including topical, inhaled, intranasal, eyedrops, and systemic corticosteroid preparations.

<table>
<thead>
<tr>
<th>CYP 3A4 Substrate</th>
<th>CYP 3A4 Inhibitor</th>
<th>Effect</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>All corticosteroids, except beclomethasone, flunisolide</td>
<td>Darunavir</td>
<td>Increased corticosteroid exposure</td>
<td>Do not co-administer unless benefits outweighs risk.</td>
</tr>
<tr>
<td></td>
<td>Elvitegravir</td>
<td></td>
<td>Monitor for adrenal insufficiency</td>
</tr>
<tr>
<td></td>
<td>Cobicistat</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All protease inhibitors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patient Case: CYP 3A4 Inhibition

Numerous case reports in patients on ritonavir-boosted protease inhibitors

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
</table>
### Patient Case: CYP 3A4 Inhibition

<table>
<thead>
<tr>
<th>Corticosteroid</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No significant increase in active</td>
<td></td>
</tr>
<tr>
<td></td>
<td>metabolite, 17-BMP</td>
<td></td>
</tr>
</tbody>
</table>

**Beclomethasone** and **flunisolide**: least potential for accumulation and adrenal suppression and corticosteroid toxicity in general.
Patient Case: CYP 3A4 Inhibition

What would be an appropriate inhaler substitution for the long-term management of JD’s asthma?

A. Budesonide/formoterol MDI
B. Mometasone/formoterol MDI
C. Beclomethasone MDI + formoterol DPI
D. Beclomethasone MDI + tiotropium MDI
E. Albuterol MDI
LS is a 40 yo female with h/o HIV since 2010, HTN, and with a recent diagnosis of dyslipidemia and unstable angina (NSTEMI), status post placement of drug-eluding stent. You are consulted for initiation of a statin on this patient.

**Home Medication List**
- Abacavir/lamivudine 600/300 mg po daily
- Darunavir 800 mg po daily
- Ritonavir 100 mg po daily
- ASA 325 mg po daily
- Prasugrel 10 mg po daily
- Lisinopril 10 mg po daily
Patient Case: CYP 3A4 Inhibition

What would be an appropriate initial statin dose for LS?

A. Simvastatin 10 mg po daily
B. Lovastatin 20 mg po daily
C. Rosuvastatin 10 mg po daily
D. Pravastatin 40 mg po daily
E. Atorvastatin 40 mg po daily
## Statin Recommendations for Primary Prevention

<table>
<thead>
<tr>
<th>ACC/AHA</th>
<th>CCS</th>
<th>ESC/EAS</th>
<th>USPSTF</th>
<th>VA-DoD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Threshold</strong></td>
<td>Age 40–75: if risk ≥7.5%</td>
<td>Age 40–75: if risk ≥20%</td>
<td>Age 40–65: if risk 5-10% and LDL-C ≥ 100</td>
<td>Age 40-75: risk ≥ 10% and one other atherosclerotic CVD risk factor</td>
</tr>
<tr>
<td></td>
<td>Age ≥ 21: if LDL-C ≥190</td>
<td>Any age and LDL-C ≥193</td>
<td>Risk ≥ 10% and LDL-C ≥ 70</td>
<td></td>
</tr>
<tr>
<td><strong>Recommend</strong></td>
<td>Risk ≥7.5%: M or H</td>
<td>Target ≥ 50% reduction or LDL-C &lt; 77</td>
<td>Max tolerated dose to achieve goal</td>
<td>Risk &gt; 10%: L to M</td>
</tr>
<tr>
<td></td>
<td>Risk &gt;5% but &lt;7%: M</td>
<td></td>
<td></td>
<td>Risk 6-12%: M in some</td>
</tr>
</tbody>
</table>

**ACC. Major Dyslipidemia Guidelines and Their Discrepancies, 2018.**
# Statin Recommendations for Secondary Prevention

<table>
<thead>
<tr>
<th></th>
<th>ACC/AHA</th>
<th>CCS</th>
<th>ESC/EAS</th>
<th>USPSTF</th>
<th>VA-DoD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommend:</td>
<td>Age ≤ 75: H</td>
<td>Target LDL-C &lt; 77 or ≥ 50% reduction</td>
<td>Max tolerated dose to achieve goal</td>
<td>Not addressed</td>
<td>Generally M, but H if ACS, multiple uncontrolled risk factors or recurrent CV events</td>
</tr>
<tr>
<td></td>
<td>Age &gt; 75, contraindications or safety concerns: M</td>
<td>If LDL-C ≥ 193, reduce by ≥ 50%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Patient Case: CYP 3A4 Inhibition

Drug interactions between boosted darunavir and statins

<table>
<thead>
<tr>
<th>Statin</th>
<th>Effect/Recommendation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10 mg + DRV/r similar to 40 mg alone, max dose 20 mg/day</td>
<td>Hoetelmans et al. <em>ICAAC</em>, 2004;Poster H-865.</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Significant increase in lovastatin, contraindicated</td>
<td>Theoretical</td>
</tr>
</tbody>
</table>

Many interactions between other protease inhibitors and statins: Consult DHHS or other references for guidance

Patient Case: CYP 3A4 Inhibition

Drug interactions between boosted darunavir and statins

<table>
<thead>
<tr>
<th>Statin</th>
<th>Effect/Recommendation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>Increase in pravastatin AUC, 81% single-dose, 23% steady state. Titrate dose, lowest dose</td>
<td>Sekar et al. 8th <em>Interntl Workshop Clin Pharmacol</em>, 2007;Abstract 54.</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Significant increase in simvastatin, contraindicated</td>
<td>Theoretical</td>
</tr>
</tbody>
</table>

Many interactions between other protease inhibitors and statins:
Consult DHHS or other references for guidance.

Patient Case: CYP 3A4 Inhibition

What would be an appropriate initial statin dose for LS?

A. Simvastatin 10 mg po daily
B. Lovastatin 20 mg po daily
C. Rosuvastatin 10 mg po daily
D. Pravastatin 80 mg po daily
E. Atorvastatin 40 mg po daily
Patient Case: CYP 3A4 Inhibition

Which of the following statements are true regarding antiplatelet agents in combination with darunavir/ritonavir in this patient?

A. Prasugrel may not be effective
B. It may increase plasma concentration of ticagrelor
C. No interaction is expected with clopidogrel
D. Clopidogrel would be a preferred P2Y_{12} inhibitor for this patient
E. All of the above are true statements
## ACC/AHA Guidelines for Adjunctive Antithrombotic Therapy for Primary PCI for NSTEMI, 2014

<table>
<thead>
<tr>
<th>Recs</th>
<th>Before PCI</th>
<th>After PCI with stent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td>Aspirin 81–325 mg</td>
<td>One P2Y&lt;sub&gt;12&lt;/sub&gt; inhibitor loading dose: Clopidogrel Prasugrel Ticagrelor (All level B)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Class IIa</strong></td>
<td>Prasugrel &gt; clopidogrel if not at high risk of bleeding (Level B)</td>
<td>Aspirin 81 mg daily (Level B)</td>
</tr>
</tbody>
</table>

## Patient Case: CYP 3A4 Inhibition

Drug interactions between boosted darunavir and antiplatelet agents

<table>
<thead>
<tr>
<th>Statin</th>
<th>Effect/Recommendation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor</td>
<td>Increase in ticagrelor plasma concentrations. Coadministration not recommended.</td>
<td>Theoretical</td>
</tr>
<tr>
<td>Clopidrogel</td>
<td>No significant interactions expected</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Many interactions between other protease inhibitors and antiplatelet agents: Consult references for guidance

Patient Case: CYP 3A4 Inhibition

Which of the following statements are true regarding antiplatelet agents in combination with darunavir/ritonavir in this patient?

A. Prasugrel may not be effective
B. It may increase plasma concentration of ticagrelor
C. No interaction is expected with clopidogrel
D. Clopidogrel would be a preferred P2Y$_{12}$ inhibitor for this patient
E. All of the above are true statements
TW is a 30 yo male with h/o HIV/AIDS since 2010, HTN, major depression and a smoking history of 12 pack-years. He was started on depression treatment with bupropion 6 months ago, and reports ongoing depression symptoms as well as ongoing tobacco use.

**Home Medication List**
- Tenofovir/emtricitabine/efavirenz 300/200/600 mg po daily
- Lisinopril 40 mg po daily
- Bupropion 300 mg XL po daily
Patient Case: CYP 3A4 Induction

What are possible explanations for TW’s ongoing depression symptoms?

A. Decreased adherence to bupropion
B. Efavirenz induction of bupropion metabolism
C. Depression is a known side effect of efavirenz
D. All of the above are possible explanations
### 2010 APA Practice Guideline for the Treatment of Patients with Major Depressive Disorder

<table>
<thead>
<tr>
<th>First Line Attempts</th>
<th>Antidepressant Switch</th>
<th>Augmentation Strategies</th>
<th>Atypical Antipsychotic Augmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>First weeks</td>
<td>2 months</td>
<td>4 months</td>
<td>6 months</td>
</tr>
</tbody>
</table>

- SSRI
- DNRI (bupropion)
- SNRI
- Non MAOI Class
- MAOIs/TCAs

Patient Case: CYP 3A4 Induction

Drug interactions between NNRTIs and bupropion

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Effect/Recommendation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>Titrate bupropion based on clinical response.</td>
<td></td>
</tr>
</tbody>
</table>

Many interactions between NNRTIs and antidepressants: Consult DHHS or other references for guidance

Patient Case: CYP 3A4 Induction

What are possible explanations for TW’s ongoing depression symptoms?

A. Decreased adherence to bupropion
B. Efavirenz induction of bupropion metabolism
C. Depression is a known side effect of efavirenz
D. All of the above are possible explanations
Patient Case: Other Mechanisms

MJ is a 59 yo male with h/o HIV/AIDS since 1997, HTN, uncontrolled diabetes mellitus type 2, diabetic neuropathy. He has poor adherence with his insulin.

**Home Medication List**

- Tenofovir/emtricitabine 25/200 mg po daily
- Dolutegravir 50 mg po daily
- ASA 81 mg po daily
- Lisinopril 40 mg po daily
- Metformin 1000 mg po bid *(recently increased from 500 mg po bid)*
- Insulin detemir 50 Units sc qhs
- Insulin aspart 10 Units sc tid with meals
- Pregabalin 150 mg po bid
Patient Case: Other Mechanisms

MJ is a 59 yo male with h/o HIV/AIDS since 1997, HTN, uncontrolled diabetes mellitus type 2, diabetic neuropathy. He has poor adherence with his insulin.

Pertinent Laboratories

- **CD4+ T-cell count:** 451 cells/mm³ 636 cells/mm³ 461 cells/mm³
- **HIV-1 RNA:** <20 copies/mL <20 copies/mL <20 copies/mL
- **Metabolic panel:** within normal within normal within normal
- **Hgb A1c:** 10.9 9.3 11.7
<table>
<thead>
<tr>
<th>Hgb A1C &lt; 9</th>
<th>Hgb A1C ≥9</th>
<th>Hgb A1C ≥10 + metabolic complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy: Lifestyle modifications + metformin</td>
<td>Dual therapy: Lifestyle modifications + metformin ± additional agent</td>
<td>Combination injectable therapy: Initiate basal insulin + metformin ± other non-insulin agent</td>
</tr>
<tr>
<td>Consider dual therapy if A1C not at goal after 3 months</td>
<td>Consider triple therapy if A1C not at goal after 3 months: Lifestyle modifications + metformin + two agents</td>
<td></td>
</tr>
</tbody>
</table>

ADA. *Diabetes Care*, 2018;41(Suppl 1).
Patient Case: Other Mechanisms

Which of the following are true statements regarding MJ’s recent increase in metformin dose:

A. The maximum dose of metformin while on DTG is 1000 mg/day
B. MJ will almost certainly develop lactic acidosis
C. Metformin should be discontinued in this patient
D. It is reasonable to up titrate metformin with careful monitoring
E. None of the above are true
Patient Case: Other Mechanisms

Drug interaction between dolutegravir (DTG) and metformin

<table>
<thead>
<tr>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>With DTG 50 mg daily + metformin 500 mg bid, increased metformin AUC by 79%</td>
<td>Song et al. J Acquir Immune Defic Syndr, 2016;72(4):400-7.</td>
</tr>
</tbody>
</table>

Clear interaction between DTG and metformin, partly explained by DTG inhibition of organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1).

# Patient Case: Other Mechanisms

**Drug interaction between dolutegravir (DTG) and metformin: How significant?**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>With DTG 50 mg daily + metformin &gt;1000 mg/day, increased GI distress,</td>
<td>Masich et al. <em>Int J STD AIDS</em>, 2017;28(12):1229-1233.</td>
</tr>
<tr>
<td>hypoglycemia in retrospective analysis <em>(n=19)</em></td>
<td></td>
</tr>
<tr>
<td>retrospective analysis <em>(n=15)</em></td>
<td></td>
</tr>
</tbody>
</table>

---

**In patients on DTG:** Up titrate metformin based on glycemic control. **In patients on metformin:** May need to dose-adjust metformin when starting or stopping DTG.

Patient Case: Other Mechanisms

Which of the following are true statements regarding MJ’s recent increase in metformin dose:

A. The maximum dose of metformin while on DTG is 1000 mg/day
B. MJ will almost certainly develop lactic acidosis
C. Metformin should be discontinued in this patient
D. It is reasonable to up titrate metformin with careful monitoring
E. None of the above are true
Drug Interaction Resources

- **www.aidsinfo.nih.gov**
  DHHS HIV Treatment Guidelines with drug interaction tables and guidance

- **http://hivinsite.ucsf.edu/interactions**
  Interactive tool and database, University of California, San Francisco

- **www.hiv-druginteractions.org/checker**
  Drug interaction checker, interactive tool, University of Liverpool

- **www.hivmedicationguide.com**
  Medication guide and drug interaction database

- **Micromedex**: Comprehensive drug database (subscription required)
- **Lexicomp**: Comprehensive drug database (subscription required)
KEY TAKEAWAYS

1) DRUG INTERACTIONS WITH ANTIRETROVIRALS ARE COMMON
    Particularly among patients taking NNRTIs and PIs.
    Drug-drug interactions may have serious consequences.

2) IMPOSSIBLE TO MEMORIZE ALL DRUG-DRUG INTERACTIONS
    Develop your own systematic approach for checking.
    Often guidance/data on interaction available.

3) USE A DRUG INTERACTION CHECKER
    Many resources available online or by subscription