Beware: Clinically Significant Drug Interactions in the Treatment of HIV

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Disclosures
Betty J. Dong, PharmD declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

Learning Objectives
• Examine common pharmacologic mechanisms of drug-drug interactions with non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs).
• Evaluate the consequences of drug interactions associated with antiretroviral drugs and determine the incidence of clinical adverse effects from interactions.
• Formulate a list of drugs that have a high potential to interact with antiretroviral drugs.
• Establish monitoring parameters and strategies that can be used to minimize the incidence of adverse drug interactions.

Glossary
• ARV = antiretroviral agent
• ART = antiretroviral therapy
• PI = Protease inhibitor
• NNRTI = non nucleoside reverse transcriptase inhibitor
• INSTI = integrase inhibitor
• DRVI/r = darunavir/ritonavir
• ATV/r = atazanavir/ritonavir
• RPV = rilpirivirine
• /cobi = cobicistat
• /r = ritonavir
• TDF = tenofovir
• TAF = tenofovir alafenamide
• FTC = emtricitabine
• 3TC = lamivudine
• ABC = abacavir
• DTG = dolutegravir
• RAL = raltegravir
• EVG = elvitegravir

Target Audience: Pharmacists
ACPE#: 0202-0000-16-010-L02-P
Activity Type: Application-based
**Self-Assessment Question**

Which of the following would pose the lowest risk of drug interactions?

1. Raltegravir
2. Dolutegravir
3. Rilpivirine
4. Elvitegravir/cobicistat
5. Darunavir/ritonavir

Meds: Esomeprazole 20 mg daily, Al-Mg antacids prn GI distress,
Amlodipine 10 mg daily, HCTZ 25 mg daily, Ca+ (TUMS) BID
Metformin 1000 mg BID, lorazepam 2 mg prn anxiety

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**Self-Assessment Question**

Proton pump inhibitors are contraindicated with which antiretroviral agent?

1. Raltegravir
2. Rilpivirine
3. Dolutegravir
4. Atazanavir/cobicistat
5. Darunavir/ritonavir

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**Self-Assessment Question**

Which is the most appropriate action if dolutegravir, abacavir, and lamivudine (Triumeq) is selected as initial ART?

1. Reduce metformin dose
2. Increase amlodipine dose
3. Give Ca+ w/DTG on empty stomach
4. Stop esomeprazole
5. Give Al-Mg antacids at same time

Meds: Esomeprazole 20 mg daily, Al-Mg antacids prn GI distress,
Amlodipine 10 mg daily, HCTZ 25 mg daily, Ca+ (TUMS) BID
Metformin 1000 mg BID, lorazepam 2 mg prn anxiety

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**Self-Assessment Question**

Which of the following should be considered if elvitegravir, emtricitabine, tenofovir (Striibl) or Tenofovir alafenamide (Genvoya) is started?

1. Reduce metformin dose
2. Reduce amlodipine dose
3. Change lorazepam to triazolam
4. Separate esomeprazole by 6 hr
5. Give Al-Mg antacids at same time

Meds: Esomeprazole 20 mg daily, Al-Mg antacids prn GI distress,
Amlodipine 10 mg daily, HCTZ 25 mg daily, Ca+ (TUMS) BID
Metformin 1000 mg BID

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**Self-Assessment Question**

Which of the following hepatitis agents would result in the lowest risk of ARV drug interactions?

1. Sofosbuvir/ledispasvir (Harvoni)
2. Paritaprevir/ritonavir/ombitasvir/dasabuvir (ViekiraPak or PROD)
3. Sofosbuvir/simeprevir
4. Sofosbuvir/daclastasvir
5. Grazoprevir/elbasvir

Tenofovir/emtricitabine, atazanavir/ritonavir, atorvastatin,
warfarin, indomethacin, OTC ranitidine

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**Self-Assessment Question**

What can occur if ledipasvir/sofosbuvir (Harvoni) is given with tenofovir, emtricitabine, and darunavir/r regimen?

1. HCV treatment failure
2. HIV treatment failure
3. Darunavir hepatic toxicity
4. Tenofovir renal toxicity
5. Emtricitabine lipid toxicity

Tenofovir/emtricitabine, atazanavir/ritonavir, atorvastatin,
warfarin, indomethacin, OTC ranitidine
Prevalence of Clinically Significant Drug Interactions

- 27-41% of HIV+ persons
- Risk factors:
  - Age >50yr (aOR 2.5)
  - Polypharmacy: >5 non-HIV agents (OR 2.7 to 15.1)
  - Co-morbidities: dyslipidemia (aOR 1.96), anxiety (aOR 1.78)
  - Protease (OR 5.3) or NNRTI regimen
- Low recognition of CSDI—36%
  - Lower ARV concentrations
  - Suboptimal therapy
  - Toxicity
  - Death

Some Pharmacokinetic Basics...

- Substrates
- CYP450 inhibition
- CYP450 induction
- AUC: area under the curve = drug exposure
- Cmin/trough: lowest drug concentration = ARV efficacy

CYP 450 and Drug Metabolism

- Majority of medications are 3A4 substrates metabolized by 3A4 hepatic enzymes

Hepatic Metabolism

- Substrates refers to agents metabolized via the hepatic enzyme (CYP 450, UGT1A1) system agents
  - Nonnucleosides (NNRTIs), protease inhibitors (PIs), integrase inhibitor elvitegravir, statins, warfarin are metabolized via CYP 450 3A4 and associated isoenzymes
  - Integrase inhibitors (INSTI) raltegravir and dolutegravir are primarily metabolized by glucuronidation via the UGT1A1 enzyme (UDP-glucuronosyltransferases)
  - Most NRTIs (nucleoside reverse transcriptase inhibitors) are renally eliminated and do not undergo liver metabolism. Exceptions: zidovudine, abacavir

CYP450 Inhibition

- Quick onset and offset of effect when stopped (few days)
- Reduces metabolism of CYP 450 enzyme substrates
- ↑ levels of substrates (↑ toxicity/efficacy)
- Examples of inhibitors: protease inhibitors, cobicistat

CYP450 CYP 450 Induction

- Slower onset and offset of action when stopped ~ 7 to 14 days
- ↓ levels/efficacy of CYP 450 substrate
- Examples of inducers: efavirenz, rifampin
Mechanism of ARV Drug Interactions

• Most clinically relevant antiretroviral (ARV) drug interactions occur because of alterations in CYP450 metabolism (e.g. inhibition or induction) of CYP 450 substrates

• May also result from the action of drug transporters involved in moving ARVs across cellular membranes

• Renal elimination is not a common cause of ARV drug interactions

P-Glycoprotein (P-gp) Interactions

• Can significantly affect disposition of medications
  – absorption, elimination, entry into CNS, testes

• P-gp substrates: digoxin

• P-gp inducers: PB, phenytoin, rifampin, St John’s wort

• P-gp inhibitors– erythromycin, clarithromycin, diltiazem, felodipine, intraconazole, ketoconazole, nicardipine, grapefruit

Drug Transporters

• Several medications in each ARV class are affected by drug transporters present in multiple cell lines

• P-glycoprotein (P-gp):
  – efflux pump present in the intestinal epithelium, hepatocytes, renal, and other cells
  – Increasing recognition as an important factor in influencing drug pharmacokinetics and efficacy

  – Many ARVs are P-gp substrates that can be transported across cellular membranes by this protein, with potential for clinically relevant drug interactions

Recognizing Potential for ARV Drug Interactions

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

• High potential

• CYP450 substrates

• Mixed induction and inhibition effects

• Efavirenz and etravirine: induction >>> inhibition
  – Efavirenz: 3A4, 2B6 induction; 2C9, 2C19 inhibition
  – Etravirine: 3A4 induction, 2C9, 2C19 inhibition

• Rilpivirine is a CYP 3A4 substrate

• Nevirapine is an inducer of CYP 3A4 and 2B6
Protease Inhibitors (PIs) and Cobicistat

- High potential
- CYP 3A4 and p-gp substrates
- CYP 3A4 inhibitors
  - Ritonavir (r): 3A4, 2D6
  - Cobicistat (/cobi) = ritonavir: 3A4, 2D6; pharmacoenhancer to PI
  - LPV/r, TPV/r >> ATV/r, DRV/r >> SQV/r
- Variable P-gp inhibition

Protease Inhibitors (PIs)

- High potential
- CYP3A4 inducers
  - Ritonavir: 1A2, 2C8, 2C9
  - Fosamprenavir 3A4
  - Tipranavir 3A4, 1A2, 2C9
- Glucuronidation (→ estinyl estradiol)
- Mixed effects; not always possible to determine overall effects

Integrase Inhibitors (INSTI)

- Low to medium potential
- EVG> DTG> RAL are metabolized by UGT1A1
- CYP 450 enzyme effects vary.
- Dolutegravir is a 3A4 substrate.
- Raltegravir and dolutegravir are not inducers nor inhibitors
- Elvitegravir
  - CYP 3A4, 2D6, 2C9, 2C19, 2B6, and 1A2 substrate.
  - modest CYP2C9 inducer
  - Co-formulated with cobicistat, a CYP 450 inhibitor.

Potential for ARV Drug Interactions

<table>
<thead>
<tr>
<th>High</th>
<th>LOW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease Inhibitors</td>
<td>Nonnucleosides Reverse Transcriptase Inhibitors</td>
</tr>
<tr>
<td>CCR5 Inhibitors</td>
<td>Integrase Inhibitors</td>
</tr>
<tr>
<td>Nucleoside Reverse Transcriptase Inhibitor</td>
<td></td>
</tr>
</tbody>
</table>

ARVs and Interacting Drugs/Classes

| Anticoagulants/Anti-platelet | Ectasy/illicit drugs |
| Acid Reducing Agents | Ergots |
| Antifungals; azoles | Erectile dysfunction |
| Antiarrhythmics | Gout agents |
| Antimycobacterial/macrolides | HCV Direct Acting Agents |
| Anti-epileptics | Herbs |
| Anti-depressants/psychotics | Immunosuppressives |
| Anti-hypertensives | Methadone/Opiates |
| Asthma agents | Oral contraceptives |
| Benzodiazepines | Pimozide |
| Cardiac medications | Pulmonary hypertension |
| Chemothterapeutic agents | Statins |
| Cisapride | |

Protease Inhibitor/Cobicistat Contraindications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Potential Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-1 blocker; alfuzosin</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Anticonvulsants: carbamazepine, oxcarbazepine, phenytoin, Pb</td>
<td>Loss of virologic efficacy d/t lower PI/cobi levels. Consider gabapentin or levetiracetam</td>
</tr>
<tr>
<td>Rifampin, rifapentin</td>
<td>Loss of virologic efficacy d/t lower PI/cobi levels</td>
</tr>
<tr>
<td>Consider rifabutin with PI. Avoid with cobi.</td>
<td></td>
</tr>
<tr>
<td>Ergots: ergotamine, dihydroergotamine, methylergonovine</td>
<td>( \text{Risk of Cushing's causing adrenal insufficiency with both systemic and nasal fluticasone/budesonide. Consider montelukast or less potent steroid (e.g. beclomethasone).} )</td>
</tr>
<tr>
<td>St. John's wort</td>
<td>Loss of virologic efficacy d/t lower PI/cobi levels</td>
</tr>
<tr>
<td>Corticosteroids: nasal fluticasone, budesonide, injectable triamcinolone</td>
<td>Avoid chronic co-administration. Loss of virologic efficacy d/t lower PI/cobi levels</td>
</tr>
</tbody>
</table>
Protease Inhibitor/Cobi Contraindications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Potential Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines: triazolam, oral midazolam</td>
<td>Potential for life threatening/serious risk of increased sedation and respiratory depression. Consider lorazepam, temazepam or oxazepam.</td>
</tr>
<tr>
<td>Neuroleptic: pimozide, lurasidine</td>
<td>GI motility: cisapride</td>
</tr>
<tr>
<td>Statins: simvastatin, lovastatin, red rice yeast</td>
<td>Presence of statin’s risk of myopathy and rhabdomyolysis. Use lowest dose of other statins (e.g. atorvastatin, pitavastatin, pravastatin, rosuvastatin)</td>
</tr>
<tr>
<td>Inhaled β-agonists: salmeterol</td>
<td>Avoid co-administration or risk of CV ADR (QT, palpitations, sinus tachycardia). Consider formoterol</td>
</tr>
<tr>
<td>PDE-5 inhibitor sildenafil (Revatio)</td>
<td>Risk of pulmonary artery hypertension (sildenafil ADRs (visual, hypotension, prolonged erection or priapism, syncope)</td>
</tr>
</tbody>
</table>

Case 1 Presentation:

- PJ is a 38-yr-old HIV positive woman who has never taken antiretroviral therapy (ART) before (“treatment naive”)
- PMH: GERD, type 2 diabetes, hypertension, anxiety
- Social history: smokes 1 PPD, denies alcohol, illicit agents
- Allergy: on lisinopril
- Medications:
  - Esomeprazole 20 mg daily
  - Aluminum magnesium antacids prn gastric distress
  - Calcium carbonate (TUMS) bid
  - Amlodipine 10 mg daily
  - Lorazepam 2 mg prn anxiety
  - Metformin 1000 mg bid

Questions to Consider:

- Can we honor PJ’s request for a single tablet ARV?
- If so, which single dose antiretroviral co-formulation would be most appropriate?
- Identify if any drug interactions are expected with the addition of each single dose co-formulated first line recommended regimen?
- If so, what modifications to her DM, HTN, or GERD therapy would be necessary to incorporate antiretroviral therapy?

DHHS Guidelines: 2015 Recommended First-line Antiretroviral (ART) Regimens

<table>
<thead>
<tr>
<th>Class</th>
<th>Recommended ART Regardless of BL VL or CD4+ Count</th>
<th>Alternative Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTI</td>
<td>RAL + TDF/FTC</td>
<td>ATV/3TC (Triumeq)†</td>
</tr>
<tr>
<td></td>
<td>EVG/CIB/TDF/FTC (Strivix)†</td>
<td>DTG/ABC/3TC (Triumeq)†</td>
</tr>
<tr>
<td></td>
<td>EVG/CIB/TAF/FTC (Stribild)*</td>
<td>DTG + TDF/FTC</td>
</tr>
<tr>
<td></td>
<td>DTG + TDF/FTC</td>
<td></td>
</tr>
<tr>
<td>Boosted PI</td>
<td>DRV/3TC + TDF/FTC</td>
<td>ATV/3TC (Triumeq)†</td>
</tr>
<tr>
<td></td>
<td>DRV/3TC + TDF/FTC</td>
<td>DRV/3TC (Prezista)†</td>
</tr>
<tr>
<td></td>
<td>DRV/3TC + ABC/3TC(Prezista)†</td>
<td>DRV/3TC (Prezista)†</td>
</tr>
<tr>
<td>NNRTI</td>
<td>EFV/TDF/FTC (Atripla)</td>
<td>RPV/TDF/FTC (Complera)‡</td>
</tr>
</tbody>
</table>

Considerations for Selecting The Initial Antiretroviral Regimen

<table>
<thead>
<tr>
<th>Resistance Testing</th>
<th>Co-morbid Conditions (e.g. Hepatitis CV Disease, Mental Illness)</th>
<th>Lifestyle Adherence Dosing Pill Burden Preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency</td>
<td>Initial ART Treatment</td>
<td>Drug Interactions</td>
</tr>
<tr>
<td>Toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Term</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long Term</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Only if CrCl ≥ 70 mL/min. †Only if CrCl ≥ 30 mL/min
- ‡Avoid if initial VL >100,000 c/mL and CD4+ < 200 c/mm³.
Single Dose Combinations (SDC) One Pill Once Daily ART Regimens

<table>
<thead>
<tr>
<th>Product</th>
<th>Components</th>
<th>Food Requirements</th>
<th>Drug interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atripla</td>
<td>Efavirenz 600 mg</td>
<td>YES, Empty stomach</td>
<td>3A4 inducer&gt; inhibition</td>
</tr>
<tr>
<td></td>
<td>Tenofovir 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emtricitabine 200 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complera</td>
<td>Rilpivirine 25 mg</td>
<td>YES &gt; 400 Kcal meal</td>
<td>3A4 substrate</td>
</tr>
<tr>
<td></td>
<td>Tenofovir 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emtricitabine 200 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stribild</td>
<td>Elvitegravir (EVG) 150 mg</td>
<td>cobi 3A4 interactions = protease inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tenofovir 300 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emtricitabine 200 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genvoya</td>
<td>EVG50mg/cobi 150 mg</td>
<td>cobi 3A4 interactions = protease inhibitors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tenofovir alafenamide 10mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emtricitabine 200 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triumeq</td>
<td>Dolutegravir 50 mg</td>
<td>NO</td>
<td>OK, 1:2 interactions</td>
</tr>
<tr>
<td></td>
<td>Abacavir 600 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lamivudine 300 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Advantages and Disadvantages of SDC

**Advantages**
- Simplicity
- Convenience
- Fewer copays
- Reduces selective non-adherence to regimen components

**Disadvantages**
- Inability to adjust dosage component if needed
- Drug–drug interactions
- Tolerability
- Renal or hepatic insufficiency
- Not available for all ART regimens

Self-Assessment Question
Which is the most appropriate recommendation if dolutegravir, abacavir, and lamivudine (Triumeq) is selected as her initial ART?

1. Reduce metformin dose
2. Increase amlodipine dose
3. Give CA+ w/DTG on empty stomach
4. Stop esomeprazole
5. Give Al-Mg antacids at same time

Dolutegravir Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyvalent cations (e.g., Mg, Al, Fe, or Ca)</td>
<td>Antacids, laxatives, sulcrate, or buffered meds</td>
<td>Concurrent Al++ Mg++, or Ca++-containing antacids, laxatives, iron, or sulcrate six hours before or two hours after DTG</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>DTG</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>Dofeptide</td>
<td>dofeptide</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>DTG AUC 49% and Cmin 73%</td>
<td>DTG 50 mg bid in naive pts. Consider oxcarbamazepine</td>
</tr>
<tr>
<td>Rifampin</td>
<td>DTG</td>
<td>DTG 50 mg bid in treatment-naive or treatment experienced if INSTI-naive. Consider rifabutin.</td>
</tr>
<tr>
<td>Metformin</td>
<td>Metformin AUC 79%, Cmax 80%, Cmin 5% BID DTG</td>
<td>Adjust metformin to maximum of 1000 mg daily. Adjust metformin dose when stopping/starting DTG</td>
</tr>
<tr>
<td>PPI and H2 blockers</td>
<td>No interaction</td>
<td>Standard DTG dosage</td>
</tr>
</tbody>
</table>

Self-Assessment Question
Which of the following should be considered if elvitegravir, emtricitabine, tenofovir (Stribild) or Tenofovir alafenamide (Genvoya) is selected as her initial ART?

1. Reduce metformin dose
2. Reduce amlodipine dose
3. Change lorazepam to triazolam
4. Separate esomeprazole by 6 hr
5. Give Al-Mg antacids at same time

Selected Dolutegravir Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>DTG</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>Dofeptide</td>
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<td>DTG AUC</td>
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<td>Metformin AUC</td>
<td>Adjust metformin to maximum of 1000 mg daily. Adjust metformin dose when stopping/starting DTG</td>
</tr>
<tr>
<td>PPI and H2 blockers</td>
<td>No interaction</td>
<td>Standard DTG dosage</td>
</tr>
</tbody>
</table>
**Cobicistat 150 mg (/cobi)**
- Stribild: CrCL >70 cc/min with tenofovir
- Genvoya: CrCL >30cc/min with tenofovir alafenamide (TAF)
- Pharmacokinetic booster = ritonavir but no HIV activity
- Take with food to increase absorption
- Mean Scr 0.14 mg/dl, max 0.4 mg/dL
  - Interference with creatinine tubular secretion
  - eGFR before starting, urine prot/gluc, P04 with tenofovir
- ADR: HA, GI distress, nausea, lipid changes
- FDC: atazanavir 300 mg/cobi 150 mg (Evotaz)
darunavir 800 mg/cobi 150 mg (Prezcobix)

**Elvitegravir/Cobi (Genvoya, Stribild) Drug Interactions (DI)**

### Agent Interaction Recommendations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Interaction</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>COBI increases levels of 3A4 substrate drugs</td>
<td>Give EVG/c 2 hr before or 6 hr after AL+ and/or Mg+-antacids, Fe+, Ca+, Zn+ supplements</td>
<td></td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Administer Al++, Mg++, Ca++antacids/laxatives, iron or sulcrate six hours before or two hours after DTG or take DTG and Ca++ supplements or iron together with food,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>metformin 2 fold; maximum 1000 mg daily; monitor clinically when starting/stopping DTG</td>
</tr>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>metformin 2 fold; maximum 1000 mg daily; monitor clinically when starting/stopping DTG</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Avoid co-administration with avanafil.</td>
<td></td>
</tr>
<tr>
<td>PDE5 inhibitors for erectile dysfunction</td>
<td>Avoid PDE5 levels</td>
<td></td>
</tr>
<tr>
<td>Hormonal contraceptives</td>
<td>Monitor for opioid toxicity. Normal opioid doses, adjust as needed</td>
<td></td>
</tr>
<tr>
<td>Narcotics: (buprenorphine, naltrexone, methadone)</td>
<td>Watch for sedative and cognitive opioid effects.</td>
<td></td>
</tr>
<tr>
<td>Nonnucleoside reverse transcriptase inhibitors, (NNRTI)</td>
<td>Monitor for toxicity. doses as warranted</td>
<td></td>
</tr>
</tbody>
</table>

**Elvitegravir/Cobi (Genvoya, Stribild) DI**

### Agent Interaction Recommendations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Interaction</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics and digoxin levels (41% Cmax; 8% AUC).</td>
<td>Monitor antiarrhythmic levels and adjust as necessary.</td>
<td></td>
</tr>
<tr>
<td>Antifungals (itraconazole, ketoconazole, voriconazole)</td>
<td>Antifungal levels Ketocconazole and itraconazole: NTE 200 mg/day. Voriconazole: evaluate risks vs benefits</td>
<td></td>
</tr>
<tr>
<td>Antihypertensives (β blockers (2D6): metoprolol, carvedilol timolol);</td>
<td>Monitor BP/HR and β-blockers toxicity; dose prn.</td>
<td></td>
</tr>
<tr>
<td>Antidepressants, Anxiety Neuroleptics</td>
<td>SSRI (except sertraline), TCA, buspiron, lexotane, meperidine, promazine, thioridazine</td>
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**Summary: Selected INSTI Drug Interactions**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Potential Drug-Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elvitegravir/cobi</td>
<td>COBI increases levels of 3A4 substrate drugs Give EVG/c 2 hr before or 6 hr after AL+ and/or Mg+-antacids, Fe+, Ca+, Zn+ supplements</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Administer Al**, Mg**, Ca**antacids/laxatives, iron or sulcrate six hours before or two hours after DTG or take DTG and Ca++ supplements or iron together with food, metformin 2 fold; maximum 1000 mg daily; monitor clinically when starting/stopping DTG</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agent</th>
<th>Potential Drug-Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir</td>
<td>Avoid AL+ and/or Mg-containing antacids, no interaction with CA+ Give RAL at least 2 hr before or 6 hr after polyvalent cations Rifampin decreases RAL levels, RAL 800 mg BID</td>
</tr>
</tbody>
</table>

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Case 1 Presentation
PJ is a 38-yr-old HIV positive woman who has never taken antiretroviral therapy (ART) before (“treatment naive”)
• PMH: GERD, type 2 diabetes, hypertension, anxiety
• Social history: smokes 1 PPD, denies alcohol, illicit agents
• Allergy: cough on lisinopril
• Medications:
  – Esomeprazole 20 mg daily
  – Aluminum magnesium antacids prn gastric distress
  – Calcium carbonate (TUMS) bid
  – Amlodipine 10 mg daily
  – Lorazepam 2 mg prn anxiety
  – Metformin 1000 mg BID

Questions to Discuss
• Which SDC would be most appropriate for PJ?
  – Stribild, Genvoya, Triumeq
  – Avoid Complera since baseline VL > 100,000 c/ml
• What drug interactions are expected with each SDC first line regimen?
• What modifications to her DM, HTN, or GERD therapy would be necessary?
  – Continue PPI and lorazepam and CA
  – Separate Al/Mg antacids by at least 6 hr after or stop
  – Reduce metformin to 500 mg bid with Triumeq, if A1c @goal
  – Monitor BP/HR with amlodipine and Genvoya and Stribild

Case 2 Presentation
RJ is a 55 year old HIV-infected male lawyer with multiple co-morbidities who is reluctant to start ART due to concerns about side effects affecting his ability to function and think clearly.
• Allergy: NKA
• PMH/Medications:
  – Hemophiliac: weekly Factor 7 transfusions
  – Allergic rhinitis—nasal fluticasone BID
  – Hypertension—lisinopril 40 mg + diltiazem 300 mg daily
  – Dyslipidemias—simvastatin 20 mg daily
  – Severe GERD—pantoprazole 20 mg BID
  – Depression—sertraline 100 mg daily
• PE: BP 140/90, HR 62 beats/min, R 12. 02 sat 95%
• Labs:
  – BUN 18/Scr 1. 3, CrCL 60 cc/min
  – AST 14 ALT 16
  – Tchol 294 mg/dl, LDL 130 mg/dl, HDL 45 mg/dl
  – Baseline HIV Genotype: Wild type, no mutations
  – HLA-B5701 positive
  – HBV and HCV AB negative
  – CD4 500 cells/mm3
  – HIV RNA: 147,500 copies/ml

Self-Assessment Question
Which is most appropriate action to consider if efavirenz, tenofovir, emtricitabine (Atripla) is selected as RJ’s initial ART?
1. Reduce diltiazem by 50%
2. Increase simvastatin dose
3. Reduce sertraline dose
4. Stop nasal fluticasone
5. Change pantoprazole to ranitidine

Efavirenz, TDF/FTC (Atripla)
• No longer recommended as first line therapy
• Side effects concerns:
  – CNS: depression, cognitive impairment, insomnia, “weird dreams”, suicidal tendencies
  – Rash
  – Dyslipidemia: ↑ TC, LDL, HDL
  – Vitamin D deficiency
• Potential drug interactions 3A4 induction
  – simvastatin, diltiazem, sertraline levels/efficacy
  – no interactions: lisinopril, pantoprazole, nasal fluticasone
Association Between EFV as Initial Therapy and Suicidality

- Analysis of 4 ACTG studies in ART-naive pts randomly assigned to initial therapy with EFV vs EFV-free regimens
- HR for suicidality increased with EFV vs EFV-free regimens: 2.28 (95% CI: 1.27-4.10; p = .006)

Selected Efavirenz (EFV) Induction Drug Interactions

<table>
<thead>
<tr>
<th>Agent</th>
<th>Interaction</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>→ sertraline AUC 39% and bupropion AUC 55%</td>
<td>Monitor clinical response and increase dose if warranted</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>→ EFV, phenytoin, carbamazepine, phenobarbital</td>
<td>Monitor anticonvulsant level. Avoid efavirenz or use other anticonvulsants</td>
</tr>
<tr>
<td>Calcium channel blockers (CCBs)</td>
<td>→ diltiazem AUC 69% → other CCBs ??</td>
<td>Titrate CCB dose based on clinical responses</td>
</tr>
<tr>
<td>Statins</td>
<td>→ simvastatin AUC 58% atorvastatin 43%, pravastatin 44%, lovastatin</td>
<td>Require higher statin doses. Prefer simvastatin, atorvastatin, rosuvastatin, or pitavastatin</td>
</tr>
</tbody>
</table>

Self-Assessment Question
Which is most appropriate action in RJ if rilpivirine, tenofovir, emtricitabine (Complera) is being considered as his initial ART?

1. Reduce diltiazem by 50%
2. Increase simvastatin dose
3. Reduce sertraline dose
4. Stop nasal fluticasone
5. Stop pantoprazole

Selected Ripivirine Drug Interactions

<table>
<thead>
<tr>
<th>Agent</th>
<th>Interaction</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
<td>↑ RPV</td>
<td>Administer antacids 2 hrs before or 4 hrs after RPV</td>
</tr>
<tr>
<td>H2-Receptor Antagonists (HRA)</td>
<td>↑ RPV AUC 76% if RPV given 2 hr after HRA</td>
<td>Administer RPV 4 hr before or 12 hrs after famotidine</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>↑ RPV Cmax 31%, AUC 62%, Cmin 48%, 50 mg Cmax ↑43%, AUC ↑16%, Cmin 7%</td>
<td>Give additional 25 mg dose of rilpivirine = 50 mg daily</td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>↑ RPV, ↑ azoles</td>
<td>Monitor for fungal infection breakthrough</td>
</tr>
<tr>
<td>Macrolides</td>
<td>↑ macrodides</td>
<td>Consider azithromycin</td>
</tr>
</tbody>
</table>

Rilpivirine (RPV) Drug Interactions and Absolute Contraindications

- CYP3A substrate, no inhibition, slight induction
- Absolute contraindications: ↑ RPV levels
  - Proton Pump Inhibitors: ↑ gastric pH
  - Potent 3A4 inducers:
    - St John’s wort, ginko biloba
    - Anticonvulsants: carbamazepine, oxcarbazepine, phenobarbital, phenytoin
    - Antimycobacterials: rifampin, rifapentine
    - Exception: rifabutin
  - More than one dose of dexamethasone

Rilpivirine (RPV) vs Efavirenz (EFV) in Treatment-Naïve Pts

<table>
<thead>
<tr>
<th>% &lt; 50 copies/mL at Week 96</th>
<th>Rilpivirine 77%</th>
<th>Efavirenz 77%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>1</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

0 20 40 60 80 100
% Patients (%)

Common AEs of Interest, %

<table>
<thead>
<tr>
<th>PV 96 Outcome, %</th>
<th>Rilpivirine (n = 550)</th>
<th>Efavirenz (n = 546)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine failure</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Most Common AEs of Interest, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal lab data</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Anemia</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td><strong>•</strong> RPV failure if</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV VL &gt; 100K c/mL and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 &lt; 200 c/mm3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Self-Assessment Question
Which is most appropriate action in RJ if ritonavir (or cobi) boosted darunavir, tenofovir, and emtrictabine is selected as initial ART?
1. Increase diltiazem dose
2. Change simvastatin to pitavastatin
3. Reduce sertraline dose
4. Change to nasal budesonide
5. Separate pantoprazole co-administration from ritonavir (or cobi) boosted darunavir

Ritonavir (or Cobicistat) Boosted Darunavir
• Sensitive regimen since no PI or other mutations
• Not best option unless medication changes occur
• No sulfa allergy—okay to consider DRV/r
• Drug interactions:
  – Contraindications: simvastatin, nasal fluticasone, and nasal budesonide
  – DRV/r ↓ sertraline levels
  – Diltiazem and CCB levels may increase
  – No interaction with lisinopril or pantoprazole

Darunavir/r Statin Drug Interactions

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EFFECT</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>• Simvastatin/lovastatin AUC 500-3000% (myositis, rhabdomyolysis) concomitant with simvastatin and lovastatin (red rice yeast)</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>DRV/r</td>
<td>• Atorvastatin AUC 70-836%</td>
<td>DRV/r + atorvastatin 10 mg = 40 mg/day, DNE 20 mg/day.</td>
</tr>
<tr>
<td></td>
<td>• Pravastatin AUC 81% (single dose)</td>
<td>Use lowest effective dose.</td>
</tr>
<tr>
<td></td>
<td>• Rosuvastatin AUC 48%, Cmax 139%</td>
<td>Use lowest effective dose.</td>
</tr>
<tr>
<td></td>
<td>• No significant effects on pitavastatin</td>
<td>Use normal doses.</td>
</tr>
</tbody>
</table>

Selected Darunavir/r Drug Interactions

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EFFECT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCBs:</td>
<td>• Amlodipine</td>
<td>Beclomethasone preferred, use cautiously. C/FLUTICASONE, Budesonide</td>
</tr>
<tr>
<td></td>
<td>• Diltiazem</td>
<td>RISK OF CCB AND DILTIAZEM LEVELS—NO STUDIES EXCEPT WITH INDINAVIR: AMLODIPINE AUC ↑ 90% AND DILTIAZEM AUC ↑ 27%</td>
</tr>
<tr>
<td>Inhaled</td>
<td>• Beclomethasone; case reports of Cushingoid with DRV/r and TAC injections</td>
<td>Monitor BP/HR and titrate to response (diltiazem dose 50% w/ ATV/r)</td>
</tr>
<tr>
<td>steroids</td>
<td>• Pravastatin AUC 81%</td>
<td>Use lowest effective dose.</td>
</tr>
<tr>
<td>SSRI</td>
<td>• Paroxetine AUC 39%</td>
<td>Higher SSRI/bupropion may be required. Monitor for antidepressant efficacy</td>
</tr>
<tr>
<td></td>
<td>• Sertraline AUC 49%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bupropion AUC 50-60% by LPV/r, TPV/r</td>
<td></td>
</tr>
</tbody>
</table>

Case 2 Presentation
RJ is a 55 year old HIV-infected male lawyer with multiple co-morbidities who is reluctant to start ART due to concerns about side effects affecting his ability to function and think clearly.
- Allergy: NKA
- PMH/Medications:
  - Hemophilic: weekly Factor 7 transfusions
  - Allergic rhinitis—nasal fluticasone BID
  - Hypertension—lisinopril 40 mg + diltiazem 300 mg daily
  - Dyslipidemias—simvastatin 20 mg daily
  - Severe GERD—pantoprazole 20 mg BID
  - Depression—sertraline 100 mg daily

Self-Assessment Question
In RJ, which of the following initial ART regimen is most appropriate to achieve the lowest risk of drug interactions and side effects?
1. Darunavir 800 mg/ritonavir 100 mg), TDF/FTC
2. Dolutegravir, TDF/FTC)
3. Atripla (efavirenz, TDF/FTC)
4. Genvoya (elvitegravir/cobi, TAF/FTC)
5. Complera (rilpivirine, TAF/FTC)
6. Triumeq (dolutegravir, ABC/3TC)

TDF/FTC = tenofovir/emtricitabine; ABC abacavir, 3TC lamivudine; TAF = tenofovir alafenamide,
Case 3: Interactions Among ARVs

- You receive a new prescription for a new ARV regimen prescribed for a treatment experienced HIV+ person who has failed multiple regimens. His medication profile shows the following:
  - Depression: bupropion 15 mg TID PO
  - Insomnia: trazodone 100 mg @ bedtime PO
  - Methadone maintenance: 30 mg daily PO

New prescription:
- dolutegravir (Tivicay) 50 mg – take one tablet daily
- tenofovir/emtricitabine (Truvada) one tablet daily
- etravirine (Intelicence) 200 mg one tablet bid

Which of the following would be the most appropriate to recommend to the prescriber about the new ARV regimen?

A. Bupropion dose increase may be warranted
B. Watch for methadone withdrawal
C. Watch for increased trazodone side effects
D. HIV VL suppression may be insufficient
E. Monitor for increased risk of renal toxicity from tenofovir

Dolutegravir (DTG) and Antiretroviral Drug Interactions

<table>
<thead>
<tr>
<th>ARVs</th>
<th>Interaction</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r, DRV/r, LPV/r, RPV</td>
<td>No interaction</td>
<td>Usual DTG dosage</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>✗ DTG</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>Etravirine</td>
<td>✗ DTG</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>EFV, fosamprenavir, tipravir</td>
<td>✗ DTG</td>
<td>Need to co-administer with PI</td>
</tr>
<tr>
<td>DTG 50 mg bid if integrase naive, otherwise, avoid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Etravirine (ETR) and PI Drug Interactions

- ETR Pharmacokinetics
  - 3A4, 2C9 and 2C19 substrate
  - 3A4 inducer (weak)
  - 2C9, 2C19, and p-gp inhibitor

- **Cautious administration** ETR with:
  - Tipranavir/r → ETR AUC 76%, Cmin 82%
  - TPV AUC 18% and Cmin 24%
  - Fosamprenavir/r → APV AUC 69% and Cmin 77%
  - Atazanavir/cobicistat → ATV and cobi
  - Darunavir/cobicistat → DRV and cobi

Etravirine (ETR) Administration with Protease Inhibitors (PI)

- **Cautious co-administration of ETR and “SALoD”**
  - SAQ 1 gm/r 100 mg bid → ETR Cmin 29% NS SAQ levels
  - ATV 300 mg/r 100 mg daily → ETR AUC/Cmin 30% ATV Cmin18%
  - LPV 400 mg/r 100 mg bid → ETR AUC 35%, LPV AUC 13% (NS)
  - DRV 600 mg/r 100 mg bid → ETR AUC 37%, Cmin 49% (ok DUET trial)
Dolutegravir (DTG) and Antiretroviral Drug Interactions

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<tbody>
<tr>
<td>ATV/r, DRV/r, LPV/r, RPV</td>
<td>No interaction</td>
<td>Usual DTG dosage</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>↓ DTG</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>Etravirine</td>
<td>↓ DTG</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>Eltrombopag, fosamprenavir/r, tipranavir/r</td>
<td>↓ DTG</td>
<td>DTG 50 mg bid if integrase naïve, otherwise, avoid</td>
</tr>
</tbody>
</table>

ARVs Interaction Recommendation
- ATV/r, DRV/r, LPV/r, RPV: No interaction. Usual DTG dosage.
- Nevirapine: DTG Avoid co-administration.
- Etravirine: DTG Avoid co-administration.
- Eltrombopag, fosamprenavir/r, tipranavir/r: DTG 50 mg bid if integrase naïve, otherwise, avoid.

Case 4 Presentation
- Mr RJ is a 63 yr old male who is interested in taking new HCV agents that can cure HCV. He is reluctant to change his HIV regimen “since it works better than his past regimens of 8 tablets daily and he notices no side effects.”
- PMH:
  - Hep C genotype 1a, no cirrhosis – failed pegylated interferon, ribavirin
  - HIV infection – CD4 585 c/mm3 with undetectable HIV viral load on tenofovir/emtricitabine (Truvada) plus atazanavir 300/r 100 mg daily
  - Dyslipidemia—on atorvastatin 40 mg daily
  - Hx Afib and s/p CVA on warfarin 6 mg daily (INR stable at 2.5)
  - Gout—indomethacin 500 mg every 8hr prn acute flares
  - GERD—prn OTC ranitidine

Case Presentation
- PE: BMI 32; BP 140/80
- Labs: Scr 1.0 mg/dL; CrCL > 60 mL/min
- CBC, AST, ALT and liver ultrasound are normal
- HLA-B*5701 negative
- CD4+ cell count 585 cells/mm³ (30 %)
- HCV RNA 5,890,670 IU/mL
- Immune to hepatitis A and B

Ritonavir Boosted Atazanavir (ATV/r)
- No longer recommended as initial ART therapy
- Side effects concerns:
  - GI effects (n,v,d)
  - Jaundice (“stigma”) 43% (ACTG 5257)
- Adverse effects
  - Dyslipidemia:
    - lower FBS, TC, non-HDL cholesterol, TG. vs LPV/r
    - similar lipid changes as DRV/r but worse than RAL
  - Hyperglycemia
    - FBS 4.8 mg/dl (EFV) vs 0.4 mg/dl (ATV/r)@96 wks
  - Others: renal stones, 2x cholethiasis (onset 42 mo)

Self-Assessment Question
Considering his ART therapy, which of the following is the most appropriate to recommend to RJ’s doctor?

1. Change atorvastatin to rosuvastatin
2. Start rivaroxaban for warfarin
3. Substitute colchicine for indomethacin
4. Start omeprazole 40 mg daily
5. Atazanavir 400 mg/r 100 mg daily
6. Change ranitidine to ATC with ART

Atazanavir (ATV/r) and Acid Reducing Agents
- Acid reducing agents
  - increase gastric pH
  - can significantly reduce atazanavir absorption
- Atazanavir requires acidic pH for optimal absorption
  - Solubility is 1.1 mg/ml at pH <1 vs. <0.002 at pH5
  - Give ATV 2 hr before or 1 hr after antacid
Atazanavir/ritonavir or cobi interaction with Acid Reducing Agents

- **H2 RA**
  - ARV naïve: DNE famotidine 40 mg BID (ranitidine 300 mg bid, cimetidine 800 mg bid, nizatidine 300 mg bid)
  - ARV experienced: DNE famotidine 20 mg BID (ranitidine 150 mg bid, cimetidine 400 mg bid, nizatidine 150 mg bid)
  - Give ATV/r with and/or ≥10 hours after the H2RA
  - ATV 400 mg/r 100 mg daily if given with tenofovir + H2RA in ART experienced persons.

Atazanavir and Proton Pump Inhibitors (PPI)

- Use PPI only in ARV-naïve persons
  - DNE 20 mg/day of omeprazole
  - Administer PPI 12 hours before ATV 300/r 100 mg
- Avoid PPI in treatment-experienced persons

Atazanavir/r and PI Anticoagulant Drug Interactions

<table>
<thead>
<tr>
<th>DRUG</th>
<th>PK EFFECTs Recommendations</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>Rivaroxaban with bleeding risk</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Apixaban (ELIQUI®)</td>
<td>Apixaban with bleeding risk</td>
<td>Reduce apixaban dose by 50% or avoid use</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Dabigatran (p-gp substrate)</td>
<td>Cautious use. Avoid if CrCl &lt; 50 mL/min.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>or warfarin possible</td>
<td>Monitor INR and adjust</td>
</tr>
</tbody>
</table>

Atazanavir/r Statin Drug Interactions

<table>
<thead>
<tr>
<th>DRUG</th>
<th>PK EFFECTs Recommendations</th>
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</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Simvastatin/lovastatin AUC 500-3000% (myositis, rhabdomyolysis)</td>
<td>Contraindicated with simvastatin and lovastatin (red rice yeast).</td>
</tr>
<tr>
<td>ATV/r</td>
<td>Atorvastatin possible</td>
<td>Use lowest dose</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Dabigatran AUC 3 fold, Cmax 7 fold</td>
<td>Use lowest dose, DNE 10 mg/day</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>dabigatran AUC 31%, Cmax 60%</td>
<td>Use normal doses</td>
</tr>
<tr>
<td>Warfarin</td>
<td>No interaction with pravastatin</td>
<td>Use normal doses</td>
</tr>
</tbody>
</table>

Selected Atazanavir/r or PI DI

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EFFECT COMMENTS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCBs: Amlodipine Diltiazem</td>
<td>Risk of CCB and diltiazem levels—no studies</td>
<td>Monitor BP/HR and titrate to response (diltiazem dose 50% w/ ATV/r)</td>
</tr>
<tr>
<td>Colchicine</td>
<td>RTV 100 mg BID, colchicine AUC 28%, Cmax 184%</td>
<td>Colchicine 0.6 mg x 1 dose, then 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. Reduce prophylaxis to daily or every other day</td>
</tr>
<tr>
<td>SSRI</td>
<td>paroxetine AUC 39%</td>
<td>Higher SSRI/bupropion may be required. Monitor for antidepressant efficacy</td>
</tr>
</tbody>
</table>

Questions to Discuss

- What drug interactions are expected with appropriate DAA for his hepatitis C infection?
- What modifications to his co-morbid conditions would be necessary to accommodate the HCV therapy?
Genotype 1 HCV Agents

Protease Inhibitors

- Simeprevir
- Paritaprevir/ritonavir

Polymerase Inhibitors

- Sofosbuvir
- Dasabuvir
- Ombitasvir
- Daclatasvir (DCV)

NS5A Inhibitors

- Ledipasvir

Other

- Ribavirin

Self-Assessment Question

Which of the following HCV GT 1a recommendations would result in RJ’s lowest risk of drug interactions?

1. Sofosbuvir/ledispasvir (Harvoni)
2. Paritaprevir/ritonavir/ombitasvir/dasabuvir (ViekiraPak or PROD)
3. Sofosbuvir/simeprevir
4. Sofosbuvir/daclastasvir
5. Grazoprevir/elbasvir

Tenoforv/emtricitabine, atazanavir/ritonavir, atorvastatin, warfarin, indomethacin, OTC ranitidine

Ledipasvir/Sofosbuvir (LDV/SOF) Drug Interactions

- LDV/SOF are p-gp and BRCP substrates
- LDV but not SOF are pgp and BRCP inhibitors
- Avoid co-administration:
  - Amiodarone
  - St. John’s wort: ledipasvir/sofosbuvir
  - Anticonvulsants: Pb, phenytoin, carbamazepine
  - Anti-mycobacterials: rifampin, rifabutin, rifapentine
  - Rosuvastatin: risk myopathy
  - Use atorvastatin, pravastatin, simvastatin

Update to sofosbuvir and ledipasvir/sofosbuvir US package inserts

Update to simeprevir US package insert

Ledipasvir/Sofosbuvir (LDV/SOF) Drug Interactions with Acid Reducing Agents

- pH ledipasvir solubility
- Antacids: separate from LDV/SOF by 4 hrs
- H2 RA: separate from LDV/SOF by 4 hrs
- Target Study: no PPI: 3.02 OR of achieving SVR
- Try to avoid all, especially PPI despite current labeling

Tenoforv/emtricitabine, atazanavir/ritonavir, atorvastatin, warfarin, indomethacin, OTC ranitidine
No Baseline PPI Use on Ledipasvir Sofosbuvir
SVR Results (HCV-TARGET)

<table>
<thead>
<tr>
<th></th>
<th>No PPI @ baseline</th>
<th>OR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
</tbody>
</table>

SVR12 (%)

98 93 98 93


Tenofovir (TDF) Drug interaction with Ledipasvir (LDV)/Sofosbuvir (SOF)
- TDF AUC 20-30% with boosted PI
- Addition of LDV TDF AUC
- Mechanism: ?? LDV p-glycoprotein or BCRP inhibition

<table>
<thead>
<tr>
<th>ARV Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use cautiously; TDF AUC and risk of renal dysfunction. Lowest risk with INSTI vs NNRTI and PI (highest risk)</td>
</tr>
<tr>
<td>MVC</td>
</tr>
<tr>
<td>No interactions, standard dosing</td>
</tr>
<tr>
<td>Not recommended; risk TDF toxicity</td>
</tr>
<tr>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

ARV Interactions: Ledispasvir/Sofosbuvir (Harvoni)

ARV Interactions: Paritaprevir-Ritonavir + Ombitasvir, Dasabuvir (PROD, Viekira Pak)

ARV Interactions: Daclatasvir (DCV, Daklinza)

Antiretroviral Interactions with Sofosbuvir

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Antiretroviral Interactions with Simeprevir

<table>
<thead>
<tr>
<th>ARVs</th>
<th>Simeprevir</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease Inhibitors</td>
<td>Avoid</td>
<td>↑ or ↓ Simeprevir</td>
</tr>
<tr>
<td>NNRTI (EFV, NVP, ETR)</td>
<td>Avoid</td>
<td>↓ Simeprevir</td>
</tr>
<tr>
<td>INSTI</td>
<td>Rilpivirine OK</td>
<td>No interaction</td>
</tr>
<tr>
<td></td>
<td>Raltegravir</td>
<td>OK</td>
</tr>
<tr>
<td>Cobicitat</td>
<td>Avoid</td>
<td>↑ Simeprevir</td>
</tr>
<tr>
<td>NRTI</td>
<td>OK</td>
<td>No interaction</td>
</tr>
<tr>
<td>CCR5: maraviroc</td>
<td>OK</td>
<td>No interaction</td>
</tr>
</tbody>
</table>

ARV Interactions: Grazoprevir (GZR) and Elbasvir (EBR)

- GZR is 3A, p-gp, and OATP substrate, weak 3A inhibitor
- EBR is 3A and p-gp substrate

<table>
<thead>
<tr>
<th>ARV</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI: Tenofovir</td>
<td>No interactions, standard dosing</td>
</tr>
<tr>
<td>NNRTI: rilpivirine</td>
<td></td>
</tr>
<tr>
<td>INSTI: dolutegravir, raltegravir</td>
<td>No interactions with dolutegravir</td>
</tr>
<tr>
<td>Protease inhibitors (ATV, DRV, LPV)</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Cobicistat</td>
<td>Simeprevir</td>
</tr>
<tr>
<td>Elaviren</td>
<td></td>
</tr>
</tbody>
</table>

Strategies to Identifying and Reducing Risk of Drug Interactions

- Review risk factors for DI
- Review list of all medications, including herbas, OTC, supplements
- Understand metabolism for all medications
- If feasible, design INSTI regimens; avoid PI and NNRTI
- Utilize medication management services (e.g. pharmacists)
- Check drug interaction drug databases
- Hold drug or adjust dose, therapeutic interchange
- Counsel patient about interacting agents
- Inform prescriber about potential interactions

HIV Drug Interaction Website

HCV Drug Interaction Websites

Additional HIV and HCV Resources

- Clinicians’ Consultation Center: 1-800-933-3413 http://www.nccc.ucsf.edu/
- Conference on Retrovirus and Opportunistic Infections (CROI 2016) http://retroconference.org/
- Clinical Care Options HIV and HCV : http://www.clinicaloptions.com
- HIV Insite: http://hivinsite.ucsf.edu
- HIV-Associated Resources on the Web. (http://www.iasusa.org)
Key Points

• Drug Interactions are common with ART
• Drug Interactions can lead to ART failure and/or toxicity
• The CYP450 system are major reasons for ART drug interactions.
• Important to review all medications, including OTC, herbal
• Pharmacists can play a major role in preventing drug interactions and improving HIV care
• Difficult to know all drug interactions, use drug interaction websites and drug metabolism to identify potential drug interactions.

Self-Assessment Question

Which of the following would pose the lowest risk of drug interactions?

1. Raltegravir
2. Dolutegravir
3. Rilpivirine
4. Elvitegravir/cobicistat
5. Darunavir/ritonavir

Self-Assessment Question

Proton pump inhibitors are contraindicated with which antiretroviral?

1. Raltegravir
2. Rilpivirine
3. Dolutegravir
4. Atazanavir/cobicistat
5. Darunavir/ritonavir

Self-Assessment Question

Which is the most appropriate recommendation if dolutegravir, abacavir, and lamivudine (Triumeq) is selected as initial ART?

1. Reduce metformin dose
2. Increase amlodipine dose
3. Give CA w/DTG on empty stomach
4. Stop esomeprazole
5. Give Al-Mg antacids at same time

Self-Assessment Question

Which of the following should be considered if elvitegravir, emtricitabine, tenofovir (Stribild) or Tenofovir alafenamide (Genvoya) is started?

1. Reduce metformin dose
2. Reduce amlodipine dose
3. Change lorazepam to triazolam
4. Separate esomeprazole by 6 hr
5. Give Al-Mg antacids at same time

Self-Assessment Question

Which of the following hepatitis agents would result in the lowest risk of ARV drug interactions?

1. Sofosbuvir/ledispasvir (Harvoni)
2. Paritaprevir/ritonavir/ombitasvir/dasabuvir (ViekiraPak or PROD)
3. Sofosbuvir/simeprevir
4. Sofosbuvir/daclastasvir
5. Grazoprevir/elbasvir
What can occur if ledipasvir/sofosbuvir (Harvoni) is given with tenofovir, emtricitabine, and darunavir/r regimen?

1. HCV treatment failure
2. HIV treatment failure
3. Darunavir hepatic toxicity
4. Tenofovir renal toxicity
5. Emtricitabine lipid toxicity

Tenofovir/emtricitabine, atazanavir/ritonavir, atorvastatin, warfarin, indomethacin, OTC ranitidine