Advances in the Treatment of HIV: Focus on New Therapies and Managing Comorbidities

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Learning Objectives

- Define the current national guideline recommendations for antiretroviral therapy combinations in antiretroviral naive patients.

- Identify common inpatient and outpatient medication therapy management issues in patients on antiretroviral therapy.

- Analyze potential drug-interactions between antiretroviral therapy and medications commonly used for the treatment or prevention of co-morbid conditions in an aging HIV-infected population.

I have no financial or other interests to disclose related to this presentation.
How often do you encounter HIV-infected patients in your practice?

1. Frequently
2. Occasionally
3. Rarely
HIV in the United States

Quick Facts

– More than 1.2 million people are living with HIV
– 1 in 8 of those infected are unaware
– Approximately 50,000 new HIV infections annually

<table>
<thead>
<tr>
<th>Category</th>
<th>Estimated # of Persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 13 years old, living with HIV</td>
<td>1,218,400</td>
</tr>
<tr>
<td>Unaware of their HIV infection</td>
<td>156,300 (12.8%)</td>
</tr>
<tr>
<td>Newly diagnosed with HIV infection</td>
<td>47,352</td>
</tr>
<tr>
<td>Deaths among persons with an AIDS diagnosis</td>
<td>13,712</td>
</tr>
</tbody>
</table>
Geographic distribution of HIV cases

* Data are not shown to protect privacy. ** State health department requested not to release data.

Data Source: Centers for Disease Control and Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Division of HIV/AIDS Prevention.
Age-adjusted death rates for HIV

- HAART = Highly Active Antiretroviral Therapy
- Now often called ART or cART

NOTE: HAART is highly active antiretroviral therapy.
SOURCE: CDC/NCHS, Health, United States, 2013, Figure 24. Data from the National Vital Statistics System.
Benefits and Goals of Antiretroviral Therapy (ART)

• ART should decrease the HIV viral load (HIV-RNA) to below the limit of assay detection = “undetectable”
  – Improved immune function (measured by the CD4+ cell count)
  – Improved quality of life
  – Decreased risk for both AIDS-defining and non-AIDS-defining complications
  – Decreased risk of HIV transmission

**Overall goal:** prevent HIV-associated morbidity and mortality → prolonged life
When to Start Therapy: *Balance Now Favors Earlier ART*

- US treatment guidelines now recommend early and uninterrupted ART for ALL HIV-infected individuals

- **Drug toxicity**
- **Preserve limited Rx options**
- **Risk of resistance (and transmission of resistant virus)**

- **↑** potency, durability, simplicity, safety of current regimens
- **↓** emergence of resistance
- **↓** toxicity with earlier therapy
- **↑** subsequent treatment options
- **↓** risk of uncontrolled viremia at all CD4+ cell count levels
- **↓** morbidity/mortality from both AIDS and non-AIDS defining illnesses
- **↓** transmission

DHHS ART guidelines. Available at: aidsinfo.nih.gov
Antiretroviral Therapy
HAART, cART, or ART
HIV Replication Cycle

Key abbreviations:
NRTI = nucleoside reverse transcriptase inhibitors
NNRTI = non-NRTI
INSTI = integrase strand transfer inhibitors (integrase inhibitors)
PI = protease inhibitor

NIAID. Available at: www.niaid.nih.gov.
# Current ARV Medications

## NRTI
- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zidovudine (AZT, ZDV)

## NNRTI
- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Nevirapine (NVP)
- Rilpivirine (RPV)

## PI
- Atazanavir (ATV)
- Darunavir (DRV)
- Fosamprenavir (FPV)
- Indinavir (IDV)
- Lopinavir (LPV)
- Nelfinavir (NFV)
- Saquinavir (SQV)
- Tipranavir (TPV)

## Fusion Inhibitor
- Enfuvirtide (T-20)

## CCR5 Antagonist
- Maraviroc (MVC)

## Integrase Inhibitor (INSTI)
- Dolutegravir (DTG)
- Elvitegravir (EVG)
- Raltegravir (RAL)

## Pharmacokinetic (PK) booster
- Ritonavir (RTV)*
- Cobicistat (COBI)

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*Ritonavir is not FDA approved as a pharmacokinetic enhancer or booster, this presentation describes it’s common clinical use in this way.
Antiretroviral Therapy 101

• Principle components of an ART regimen
  • Contains at least 3 antiretroviral agents
  • From two different classes of antiretrovirals
  • Choose drugs with no detected viral resistance

• Several one pill, once daily options now available
  • Efavirenz/tenofovir/emtricitabine
  • Rilpivirine/tenofovir/emtricitabine
  • Elvitegravir/cobicistat/tenofovir/emtricitabine
  • Dolutegravir/abacavir/lamivudine

• If (i.e. when) patients fail a regimen due to virologic resistance, more complex regimens are required
A case to consider – A.H.

24 year old woman presents to establish HIV care after being diagnosed through routine screening

Current medications:
- Oral contraceptive containing drospirenone/ethinyl estradiol/levomefolic acid 3 mg/0.02 mg/0.451 mg daily
- Fluticasone/salmeterol 250/50mg 1 inhalation twice daily
- Albuteral inhaler prn

No other medical conditions
- CD4+ count: 275 cells/mm³; HIV-1 RNA: 97,234 copies/mL; all other labs within normal limits

She prefers a once daily medication regimen due to her work and school schedule.
For A.H., what is your preferred choice for antiretroviral therapy?

1. Dolutegravir/abacavir/lamivudine 50/300/300 mg
   1 tablet daily

2. Tenofovir/emtricitabine 300/200 mg 1 tablet daily +
   darunavir 800 mg 1 tablet daily + ritonavir 100 mg
   1 tablet daily

3. Dolutegravir 50 mg 1 tablet daily +
   tenofovir/emtricitabine 300/200 mg 1 tablet daily
Recommended Antiretroviral Therapy for Treatment Naïve Patients

Protease Inhibitor Options
- Darunavir + ritonavir

OR

Integrate Inhibitor Options
- Raltegravir
- Elvitegravir/cobicistat
- Dolutegravir

Nucleoside Reverse Transcriptase Inhibitors
- Tenofovir + Emtricitabine (TDF/FTC)

OR

Integrate Inhibitor Options
- Abacavir + Lamivudine* (ABC/3TC)
  * Only recommended when given with dolutegravir

Alternative Antiretroviral Therapy for Treatment Naïve Patients

Protease Inhibitor Options
- Atazanavir + ritonavir OR cobicistat
- Darunavir + cobicistat

OR

Non-Nucleoside Reverse Transcriptase inhibitor Options
- Efavirenz
- Rilpivirine

Nucleoside Reverse Transcriptase Inhibitors
- Tenofovir + Emtricitabine (TDF/FTC)

OR

Abacavir + Lamivudine* (ABC/3TC)

* Only alternative when given with darunavir/ritonavir

DHHS HIV treatment guidelines available at: http://aidsinfo.nih.org
**Initial Regimens: Recommended**

| Integrase Inhibitor based | Dolutegravir/ abacavir/ lamivudine (1 pill daily)  
*only if HLA-B*5701 negative  
Dolutegravir + tenofovir/ lamivudine (2 pills daily)  
Elvitegravir/ cobicistat/ tenofovir/ lamivudine (1 pill daily)  
*only if pre-ART CrCl >70 mL/min  
Raltegravir + tenofovir/ lamivudine (2 pills AM, 1 pill PM) |
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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Protease Inhibitor based</td>
<td>Darunavir + ritonavir + tenofovir/ lamivudine (3 pills daily)</td>
</tr>
</tbody>
</table>

Requirements for *recommended* ART regimens
- Randomized controlled trials show optimal and durable virologic efficacy
- Favorable tolerability and toxicity profiles
- Easy to use

DHHS HIV treatment guidelines available at:  
# Initial Regimens: Alternative

<table>
<thead>
<tr>
<th>NNRTI based</th>
<th>PI based</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Efavirenz/ tenofovir/ emtricitabine (1 pill daily)</td>
<td>▪ Atazanavir + ritonavir OR cobicistat** + tenofovir/ emtricitabine (2-3 pills daily)</td>
</tr>
<tr>
<td>▪ Rilpivirine/ tenofovir/ emtricitabine* (1 pill daily)</td>
<td>▪ Darunavir/ cobicistat** + tenofovir/ lamivudine (2 pills daily)</td>
</tr>
<tr>
<td>*only if pre-ART HIV RNA &lt;100,000 copies/mL and CD4 &gt;200 cells/µL</td>
<td>▪ Darunavir + ritonavir OR cobicistat + abacavir/ lamivudine (2-3 pills daily)</td>
</tr>
<tr>
<td></td>
<td>* only if HLA-B*5701 negative</td>
</tr>
</tbody>
</table>

**Requirements for Alternative ART regimens**
- Effective but have potential disadvantages, limitations in certain patient populations, or less supporting data
- May be the optimal regimen for individual patients

**ritonavir may be substituted with cobicistat if pre-ART CrCl >70 mL/min, but this is an alternative regimen due to the lack of randomized, controlled trials of this combination**

# Selecting Initial ART Regimen: Selected Clinical Scenarios

| CD4 <200 | Do not use: higher rate of virologic failure  
|          | • Rilpivirine-based ART |
| HIV RNA >100,000 | Do not use: higher rate of virologic failure  
|          | • Rilpivirine-based ART  
|          | • Abacavir/ lamivudine + efavirenz or atazanavir |
| HLA-B*5701 positive | Do not use abacavir: risk of abacavir hypersensitivity  
|          | • HLA testing PRIOR to initiation of abacavir  
|          | • If HLA-B*5701 positive, patient is classified as having an abacavir allergy |
## Key Considerations during Medication Therapy Review for ART

<table>
<thead>
<tr>
<th>Food effects</th>
<th>Should be taken <strong>with food:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Protease inhibitor based regimens</td>
</tr>
<tr>
<td></td>
<td>• Elvitegravir/ cobicistat/ tenofovir/ emtricitabine</td>
</tr>
<tr>
<td></td>
<td>• Rilpivirine/ tenofovir/ emtricitabine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Should be taken <strong>on an empty stomach:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Efavirenz</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal insufficiency (eGFR &lt;60 mL/min)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• All NRTIs (except abacavir) require dosage adjustment with renal insufficiency</td>
<td></td>
</tr>
<tr>
<td>• Tenofovir disoproxil is associated with renal impairment</td>
<td></td>
</tr>
<tr>
<td>• Co-formulated products can make dose adjustment challenging</td>
<td></td>
</tr>
</tbody>
</table>
HIV-Infected Patients are at High Risk for Drug Interactions

• Recent evaluations have identified that over 30% of HIV-infected patients had a drug interaction of moderate or major significance

• Why?
  – HIV therapy requires the use of 3-4 medications
  – Most of these drugs significantly impact CYP450
  – Multiple drug transporters, food, and gastric pH are also implicated in drug interactions
  – HIV is a chronic disease, patients are developing more comorbidities (liver disease, cardiovascular disease, etc.)
  – Often have multiple healthcare providers

Not all interactions are bad ... Antiretroviral “Boosting”

• Using ritonavir or a pharmacokinetic enhancer (e.g. cobicistat) to inhibit cytochrome P450 (CYP)
  – Gut effect: Increased absorption (bioavailability)
  – Liver effect: Decreased metabolism

• Ritonavir and cobicistat also inhibit P-glycoprotein and many other transporter pathways
  – Gut effect: Increased absorption
  – Liver effect: Decreased elimination
Regimen 2 with PK enhancement

PK benefit

Area of potential replication

IC$_{90}$
Common regimen specific drug-interaction concerns

This is a very broad overview, consult an up-to-date drug information resource for drug-specific details

- **NRTI** components are not commonly involved with DDIs
- **Protease inhibitors**, ritonavir or cobicistat-containing regimens
  - CYP and p-glycoprotein substrates
  - Pharmacokinetic enhancement via *inhibition* of several CYP enzymes
    - Most notably CYP3A, 2D6 and p-glycoprotein
  - Ritonavir and possibly cobicistat may induce CYP2C9, 2C19 and UGT
Common regimen specific drug-interaction concerns

- **Non-nucleoside reverse transcriptase inhibitors** – Potential for interaction is highly variable by drug
  - Rilpivirine – CYP 3A substrate
    - Requires acidic environment for absorption, contraindicated with proton pump inhibitors
    - NOT a clinically significant inhibitor or inducer on CYP or p-glycoprotein
  - Efavirenz – CYP 2B6, 2A6 and 3A4 Substrate
    - Potent CYP3A and 2B6 enzyme induction
    - Can be a CYP2C9 and 2C19 inhibitor
# Antiretroviral agents + oral anticoagulants

<table>
<thead>
<tr>
<th>Anticoagulants</th>
<th>DDI mechanism</th>
<th>Clinical management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Substrate of P-gp</td>
<td>No dosage adjustment if CrCl &gt; 50 mL/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AVOID USE with any P-gp inhibitor (ritonavir or cobicistat) in patients with CrCl &lt; 50 ml/min or in any patient aged &gt; 80 years</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Substrate of P-gp and CYP3A4</td>
<td>AVOID USE with P-gp and CYP3A4 strong inhibitors = ritonavir or cobicistat</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Substrate of P-gp and CYP3A4</td>
<td>AVOID USE with P-gp and CYP3A4 strong inducers = efavirenz</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Substrate of CYP2C9, 1A2, 3A4</td>
<td>Ritonavir may INCREASE warfarin dose requirements via CYP 2C9 induction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown with cobicistat, but may be similar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recommendation: Monitor INR</td>
</tr>
</tbody>
</table>
Common regimen specific drug-interaction concerns

• **Integrase Inhibitors**
  • Metabolism and interaction potential vary by agent
  • Absorption interactions are shared among the class:
    • Chelation by divalent and trivalent cations can reduce absorption
      – For DTG, overcome with dose timing separation or co-administration with food
      – General recommendation: *Administer INSTI 2 hours before or 6 hours after polyvalent cation supplement.*
Common regimen specific drug-interaction concerns (4)

- Specific Integrase Inhibitor considerations
  - Elvitegravir – CYP3A substrate, **must** be co-prescribed with a PK enhancer to achieve adequate concentrations
    - See Protease Inhibitor section for potential DDIs
  - Raltegravir
    - Primarily substrate of UGT
    - Dose adjustment required with potent inducers of this pathways (ex. rifampin)
  - Dolutegravir
    - Primarily metabolized by UGT, minor CYP3A
      - Dose adjustment required with potent inducers of these pathways (ex. carbamazepine and rifampin)
    - Potent inhibitor of renal transporters (ex. OCT2 and MTE)
A case to consider – A.H.

24 year old woman presents to establish HIV care after being diagnosed through routine screening

Current medications:
- Oral contraceptive containing drospirenone/ethinyl estradiol/levomefolic acid 3 mg/0.02 mg/0.451 mg daily
- Fluticasone/salmeterol 250/50mg 1 inhalation twice daily
- Albuteral inhaler prn

No other medical conditions
- CD4+ count: 275 cells/mm³; HIV-1 RNA: 97,234 copies/mL; all other labs within normal limits

She prefers a once daily medication regimen due to her work and school schedule.
For A.H., what is your preferred choice for antiretroviral therapy?

1. Dolutegravir/abacavir/lamivudine 50/300/300 mg 1 tablet daily

2. Tenofovir/emtricitabine 300/200 mg 1 tablet daily + darunavir 800 mg 1 tablet daily + ritonavir 100 mg 1 tablet daily

3. Dolutegravir 50 mg 1 tablet daily + tenofovir/emtricitabine 300/200 mg 1 tablet daily
Corticosteroids + Antiretrovirals

• PK interaction → inhibition of steroid metabolism by potent ritonavir-mediated CYP3A4 inhibition
  ▪ RTV 100 mg bd + fluticasone 50 mcg nasal inhalation 4 times daily x 7 days in healthy subjects
    ▪ Significant (350-fold) increase in plasma fluticasone AUC
    ▪ Subsequent 86% decrease in intrinsic cortisol levels

• Over 50 cases reported of Cushings syndrome resulting from this interaction and/or onset of adrenal insufficiency (upon steroid withdrawal)

• Same interaction expected with cobicistat as a PK enhancer

• Alternative steroid option: beclomethasone due to alternative metabolism via estrase in tissues

Dollfus C. et al. 10t EACS, Dublin 2005, #PE 15
Learning Assessment: Answer

1. Dolutegravir/abacavir/lamivudine 50/300/300 mg 1 tablet daily
   NO – AH is HLA-B*5701 positive. This is a contraindication to abacavir therapy.

2. Tenofovir/emtricitabine 300/200 mg 1 tablet daily +
   darunavir 800 mg 1 tablet daily + ritonavir 100 mg 1 tablet daily
   No – drug-drug interaction between fluticasone and darunavir/ritonavir

3. Dolutegravir 50 mg 1 tablet daily +
   tenofovir/emtricitabine 300/200 mg 1 tablet daily
   Yes – this is the best option for this patient
Resources to assess drug-drug interactions with ART
Case 2 – M.B.

• M.B. is a 45 year-old man who remains stable on his first antiretroviral regimen:
  – Atazanavir + ritonavir + tenofovir/emtricitabine - all taken once daily

• Relevant Labs:
  – CD4+ = 450 cells/mm³, viral load = <20 copies/mL, SCr = 0.9 mg/dL, ALT 18 units/L

• Other medications: NKDA
  – Multivitamin – 1 tablet daily
  – Calcium carbonate – 2 or 3-750mg tablets as needed for heartburn

• At his PCP visit today, the physician would like the prescribe a proton pump inhibitor for a newly diagnosed peptic ulcer.
Resources to assess drug-drug interactions with antiretrovirals

• Useful references:
  • DHHS guidelines can be accessed at aidsinfo.nih.gov
  • Adult and Adolescent guidelines Tables 17-20 deal with drug-drug interactions

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>PI</th>
<th>Effect on PI and/or Concomitant Drug Concentrations</th>
<th>Dosing Recommendations and Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid Reducers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATV/c, ATV/r</td>
<td>↓ ATV</td>
<td>PPIs should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naive patients. PPIs should be administered at least 12 hours before ATV/c or ATV/r.</td>
</tr>
<tr>
<td>PPIs</td>
<td>DRV/r</td>
<td>omeprazole AUC ↓ 42%</td>
<td>No dosage adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>DRV/c</td>
<td>No significant effect expected</td>
<td>No dosage adjustment necessary.</td>
</tr>
</tbody>
</table>

• HIV-druginteractions.org (note there is also a HEP-druginteractions.org for Hepatitis drug-drug interactions)
Now Includes Dolutegravir

Access our comprehensive, user friendly, free, drug interactions charts

Providing clinically useful, reliable, up-to-date evidence-based information

To view low bandwidth version click here

We have produced a series of printable tables showing interactions between key antiretrovirals and drugs used to treat a range of common comorbidities. The tables can be accessed from the Printable Chart & Treatment: Selector sub menu on the Interaction Charts menu.

HIV iChart - an interaction app for mobile devices

iOS7 - We have recently become aware that the update function on the app may not work properly with iOS7 on some devices. We are currently working to determine the nature and extent of the problem and to rectify this.

Free for Apple and Android devices.
Step 1: Select antiretroviral regimen
Step 2: Concomitant medication class
Step 3: Add individual drugs

<table>
<thead>
<tr>
<th>Antiretrovirals (Integrase Inhibitors)</th>
<th>Antiretrovirals (NNRTIs)</th>
<th>Antiretrovirals (Nucleoside/tide Analogues)</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Dolutegravir</td>
<td>□ Delavirdine</td>
<td>□ Abacavir</td>
</tr>
<tr>
<td>□ Elvitegravir/cobicistat</td>
<td>□ Efavirenz</td>
<td>□ Didanosine (ddl)</td>
</tr>
<tr>
<td>▢Raltegravir</td>
<td>□ Etravirine</td>
<td>□ Emtricitabine (FTC)</td>
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<td>□ Nevirapine</td>
<td>□ Lamivudine (3TC)</td>
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<td>□ Stavudine (d4T)</td>
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<td>□ Tenofovir</td>
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<td>□ Zidovudine (AZT/ZDV)</td>
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<table>
<thead>
<tr>
<th>Antiretrovirals (Protease Inhibitors)</th>
<th>Gastrointestinal Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>▢ Atazanavir</td>
<td>□ Aluminium hydroxide</td>
</tr>
<tr>
<td>□ Darunavir</td>
<td>□ Antacids</td>
</tr>
<tr>
<td>□ Fosamprenavir</td>
<td>□ Cimetidine</td>
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<tr>
<td>□ Indinavir</td>
<td>□ Cisapride</td>
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<tr>
<td>□ Lopinavir</td>
<td>□ Esomeprazole</td>
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<tr>
<td>□ Nelfinavir</td>
<td>□ Famotidine</td>
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<tr>
<td>▢ Ritonavir</td>
<td>□ Lansoprazole</td>
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<td>□ Saquinavir</td>
<td>□ Loperamide</td>
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<td>□ Tipranavir</td>
<td>□ Mesalazine</td>
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<td>□ Omeprazole</td>
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<td></td>
<td>□ Pantoprazole</td>
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<td>□ Ranitidine</td>
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www.hiv-druginteractions.org
Step 4: Final report

<table>
<thead>
<tr>
<th>Gastrointestinal Agents</th>
<th>Atazanavir</th>
<th>Ritonavir</th>
<th>Efavirenz</th>
<th>Raltegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
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<tr>
<td>Omeprazole</td>
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</tbody>
</table>

Symbol key:

- **I**: These drugs should not be coadministered
- **I**: Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration
- **I**: No clinically significant interaction expected
- **I**: There are no clear data, actual or theoretical, to indicate whether an interaction will occur
- **I**: Data not available
  
www.hiv-druginteractions.org
A tool for clinical decision making

Summary
Omeprazole decreased atazanavir AUC by 75%. Co-administration is contraindicated for treatment-experienced patients in the US Prescribing Information and not recommended for all patients in the European SPC. If co-administration is judged unavoidable, close clinical monitoring is recommended and doses of omeprazole should not exceed 20 mg and must be taken approximately 12 hours prior to the atazanavir/ritonavir. The European SPC recommends increasing the dose of atazanavir to 400 mg with 100 mg of ritonavir.

Description
Co-administration of atazanavir/ritonavir with proton pump inhibitors is not recommended. Co-administration of omeprazole (40 mg once daily) and atazanavir/ritonavir (400/100 mg once daily; 2 hours after omeprazole) decreased atazanavir AUC, Cmax and Cmin by 61%, 56% and 85%, respectively. When compared to atazanavir/ritonavir 300/100 mg once daily, co-administration of 20 mg once daily) and atazanavir/ritonavir (400/100 mg once daily, 1 hour after omeprazole) decreased atazanavir AUC, Cmax and Cmin by 30%, 31% and 31%. The decrease in AUC, Cmax, and Cmin was not mitigated when an increased dose of atazanavir/ritonavir (400/100 mg once daily) was temporarily separated from omeprazole by 12 hours. This decrease in atazanavir exposure might negatively impact the efficacy of atazanavir. The mechanism of interaction is decreased solubility of atazanavir as intra-gastric pH increases with proton pump inhibitors. If the combination of atazanavir/ritonavir with a proton pump inhibitor is judged unavoidable, www.hiv-druginteractions.org

• Overall summary statement, highlighting areas of controversy which may impact clinical judgment
• Detailed description of drug-interaction studies to date
• Allows clinicians to determine the appropriate course of action, given the patient’s characteristics and available pharmacokinetic data.
## Atazanavir: Effect of Stomach pH on Drug Absorption

<table>
<thead>
<tr>
<th>Acid suppressing agent</th>
<th>Effect on Atazanavir/ritonavir</th>
<th>Clinical management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
<td>Unboosted: &gt; 80% ↓ in AUC</td>
<td>Give antacid 1 hour before, or 2 hours after atazanavir</td>
</tr>
</tbody>
</table>
| Famotidine 40 mg BID    | ~ 20-30% ↓ in AUC, Cmin         | Give ATV/r simultaneously or 10 hours after famotidine.  
  *If treatment experienced patient, and receiving TDF, increase ATV/r dose. |
| Famotidine 20 mg BID    | Unboosted: ~ 10-20% ↓ in AUC, Cmin | Give ATV/r simultaneously or 10 hours after famotidine |
| Omeprazole 20 mg daily  | ~ 30-40% ↓ in AUC, Cmin         | Treatment naïve patients: give omeprazole 12 hours prior to ATV/r  
  *Avoid in treatment experienced patients |
| Omeprazole 40 mg daily  | ~ 50-75% ↓ in AUC, Cmin         | Avoid use |

Summarized from: Therrien R. Atazanavir (Reyataz) and gastric acid-reducing agents. URL in reference list.
What is the likely diagnosis and cause of these symptoms?

Case 3

- 45 yo HIV+ male recently failed his first-line HIV regimen of efavirenz/tenofovir/emtricitabine and was switched to lamivudine, dolutegravir, darunavir/ritonavir
  - PMH: HIV, HTN, diabetes, and obesity.
  - Concurrent medications
    - Metformin 1000mg BID
    - Atorvastatin 80 mg daily
  - The patient presents to his PCP 10 days later with complaints of fatigue, weakness, and severe muscle pains “all over”
    - Chemistry panel: ALT 100 u/L, SCr 250 umol/L
    - CPK is also ordered and comes back at 10x ULN
HMG-CoA-Reductase Inhibitors ("statins") + Antiretrovirals

- Metabolized in part by CYP450 (exception: pravastatin)
Statin Exposure with PI/r

- Statin exposure when given with concomitant ritonavir-boosted protease inhibitor
Darunavir/ritonavir + Statins

- 15 subjects received atorvastatin 40mg qday alone, followed by darunavir/ritonavir (DRV/r) + atorvastatin 10mg qday
  - Atorvastatin 10mg concentrations with DRV/r:
    - $C_{\text{max}}$ ↑ 44% vs. atorvastatin 40mg alone
    - $AUC$ ↑ 15% vs. atorvastatin 40mg alone
    - $C_{\text{min}}$ ↑ 81% vs. atorvastatin 40mg alone
  - HIV guidelines and product labeling suggest starting with the lowest possible dose (10mg) and titrating to a maximum of 20mg daily

Prezista package insert.
PK + PD Interaction: Rosuvastatin + DRV/r

Rosuvastatin + DRV/r vs. Rosuvastatin alone:
- Total cholesterol ↑ 10%
- Triglyceride levels ↑ 56%
- HDL ↓ 13%

PK + PD Interaction:
Rosuvastatin + DRV/r

Proposed mechanism: Inhibition of transporter at site of action (liver)

It’s not just “CYP and P-gp” anymore!

- Growing area of research evaluating the role of various drug transporters on PK and drug-drug interactions!

From presentation by Dr. Steven Taylor, CROI2014

Speaking of transporters…

- What we understand about dolutegravir’s drug-drug interactions are evolving, OCT2 and MAT1 are known to be inhibited by dolutegravir
  - FDA updated the package inserts for both products that contain dolutegravir

- When TRIUMEQ is used with metformin, limit the total daily dose of metformin to 1,000 mg either when starting metformin or TRIUMEQ. When stopping TRIUMEQ, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of Tivicay is recommended.

- Back to the case: recent switch to lamivudine, dolutegravir, darunavir/ritonavir
  - PMH: HIV, HTN, diabetes, and obesity.
  - Concurrent medications
    - Metformin 1000mg BID
    - Atorvastatin 80 mg daily
# Statins + ritonavir or Cobicistat vs NNRTIs

<table>
<thead>
<tr>
<th>Statin</th>
<th>PI/r Effect on Statin</th>
<th>Clinical Mgmt ( with PI)</th>
<th>NNRTI Effect on Statin</th>
<th>Clinical Mgmt (with NNRTI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>↑ AUC &gt; 500%</td>
<td>Contraindicated</td>
<td>↓ AUC 68%</td>
<td>Monitor for efficacy</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Sig. ↑ AUC</td>
<td>Contraindicated</td>
<td>↓ AUC</td>
<td>Monitor for efficacy</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>↑ AUC 6-fold</td>
<td>Start with lowest dose</td>
<td>↓ AUC 43%</td>
<td>Monitor for efficacy</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>NS w/ most; * DRV/r</td>
<td>With DRV/r,</td>
<td>↓ AUC 40%</td>
<td>Monitor for efficacy</td>
</tr>
<tr>
<td></td>
<td>↑ AUC 5-fold in some</td>
<td>start with lowest dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>AUC ↑ 2-fold</td>
<td>Start with lowest dose,</td>
<td>None expected</td>
<td>Standard dosing</td>
</tr>
<tr>
<td></td>
<td>with LPV/r (*)</td>
<td>Monitor efficacy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

www.hiv-druginteractions.org
www.aidsinfo.nih.gov (US DHHS Guidelines)
Conclusion

• Antiretroviral therapy has significantly impacted mortality for patients living with HIV
• Several highly effective antiretroviral therapy options are available, each with pros and cons to be considered when selecting a medication regimen
• Management of drug interactions is one example of the pharmacist’s important role in HIV medication therapy management
  • Numerous mechanisms for ARV interactions (eg. cytochrome P450 enzymes, transporters, stomach pH)
  • Consult up-to-date references for available data to guide therapy