Common Pitfall and Important Drug Interactions between Antiretrovirals and Other Drugs

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Drug-drug Interactions

- Must be concerned!
- Should be considered before prescribing ARV and other drugs
- One reason of suboptimal HIV treatment response

Complexity

- Protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs)
- Cause and be affected by alterations in activity of cytochrome P450 enzymes in liver
- These enzymes are responsible for metabolizing many medications
PI, NNRTI, and NRTI Drug Interactions

- Most drug interactions with antiretrovirals are mediated through inhibition or induction of hepatic drug metabolism
- All PIs are substrates of CYP3A4
  - Their metabolic rates may be altered in the presence of CYP inducers or inhibitors
- NNRTIs are substrates of CYP3A4
  - Can act as inducer (nevirapine), inhibitor, or mixed inducer and inhibitor (efavirenz, etravirine)
- NRTIs do not undergo hepatic transformation through the CYP metabolic pathway
Influence of P450 Enzymes is Challenging

- Different drugs affect different P450 enzymes
- Dosage-related responses that influence their effects on P450 enzymes
- Formal pharmacokinetic studies on drug combinations are limited
- Clinical significance of any changes in pharmacokinetic parameters may not be clear
Influence of P450 Enzymes is Challenging

- Pharmacokinetic studies evaluating clinical significance of drug interactions involving >2 medications are less likely to be available
- P450 system is not the only influence on medication activity
  - Absorption, food-drug interactions, protein binding
  - Altered activation of medications intracellularly
  - Altered efflux-pump activity
Patients Evaluations

- **S: Subjective**
  - Medication history

- **O: Objective**
  - Review the patient’s pharmacy records for current medications

- **A: Assessment**
  - Identify interactions and class
  - Definite, probable, possible interactions
  - Classify common substrates, inducers, and inhibitors of CYP450 system

- **P: Plan**
Case 1

- Male 35 years old, make-up artist, MSM
- Presented with cervical lymphadenopathy
- AFB: positive
- CD4 37 cells/mm³
- Rx: anti-TB (with rifampin), co-trimoxazole, fluconazole
- Pus C/S: *Salmonella* spp.
  - Ofloxacin was added for 4 weeks
- At 6th weeks, HAART was initiated
Which HAART-Based Regimen?

- A. NVP
- B. EFV
- C. NRTI (eg. AZT, 3TC, TDF)
- D. LPV/r
- E. IDV/r
- F. Other PI

Current Medication: anti-TB (with rifampin), co-trimoxazole, fluconazole
# Drugs-Drugs Interaction

<table>
<thead>
<tr>
<th>Protease inhibitor</th>
<th>Effect of rifampin on PI</th>
<th>Effect of PI on rifampin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td>80% ↓</td>
<td>NR</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>35% ↓</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Indinavir</td>
<td>92% ↓</td>
<td>NR</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>82% ↓</td>
<td>NR</td>
</tr>
<tr>
<td>Amprenavir</td>
<td>81% ↓</td>
<td>NR</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>75% ↓</td>
<td>NR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Effect of rifampin on NNRTI</th>
<th>Effect of NNRTI on rifampin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>37% ↓</td>
<td>NR (unchanged)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>13% ↓</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

NR=no report

Recommended ARV Regimens with Rifampin

- **EFV containing regimens**
  - EFV is contra-indicated in pregnant women or women of child bearing potential without effective contraception
  - Dosage of EFV is 600 mg/day for weight <60 kg and 800 mg/day for weight >60 kg*

- **NVP is an alternative to EFV for patient who has taken rifampicin**
  - Lead-in NVP for the first 14 days is not necessary

Distributions of $C_{12}$ EFV and $C_{12}$ NVP in 142 HIV/TB Patients Receiving Rifampicin

* Compared percentages of the patients who had $C_{12}$ NNRTIs less than particular recommended levels

Recommended ARV Regimen

- If the patient cannot tolerate EFV or NVP
  - Consider using non-rifampin containing anti-TB treatment and PI-based ART
  - Consider using rifampin containing anti-TB treatment and combination of saquinavir (400 mg twice daily) and ritonavir (400 mg twice daily) or doubling of lopinavir/r; however, increase risk of hepatotoxicity*
- Rifampicin-containing anti-TB treatment can be used for a patient who develops TB and is already being treated with NVP-based ART

Lopinavir/ritonavir Levels with Rifampin


- LPV/r 400/100 BID
- LPV/r 800/200
- LPV/r 400/400 BID + rifam

Study Day

Concentration (mg/L)

Case 1

- At 8th week: pus C/S for mycobacteria: MAC
- Adjusted to clarithromycin and ethambutal
- Current HAART: TDF/FTC + EFV
- Any problems?

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</thead>
<tbody>
<tr>
<td>Clarithromycin 90 (Biaxin)</td>
<td>500 mg Q12H x 7 days</td>
<td>400 mg x 7 days</td>
<td>Clarithromycin AUC: decreased 39%; Cmax: decreased 26%; 14-hydroxyl clarithromycin AUC: increased 34%; Cmax: increased 49%</td>
<td>No significant change</td>
<td>-</td>
<td>Inhibition of CYP450 3A4 by efavirenz</td>
<td>Dose adjustment not established</td>
</tr>
</tbody>
</table>

"-" indicates that there are no data available

Case 1

- At 6th month: CD4 138 cells/mm³
- HIV RNA 23,800 copies/mL
- ART was changed to AZT + TDF + LPV/r
- Any problems?

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</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin⁷⁸ (Biaxin)</td>
<td>-</td>
<td>-</td>
<td>May increase clarithromycin levels</td>
<td>-</td>
<td>Increased clarithromycin effects</td>
<td>Inhibition of CYP450 3A4 by lopinavir/ritonavir</td>
<td>No dose adjustment necessary</td>
</tr>
</tbody>
</table>

Case 2

- Male 30 years old
- Pulmonary TB, veno-occlusive disease
- Stable clinical conditions for 2 years
- Current medications
  - Stavudine/lamivudine/nevirapine
  - Isoniazid, rifampicin
  - Warfarin
  - Ranitidine (off and on)
- Last CD4 250 (12%) cells/mm$^3$, HIV RNA <40 copies/mL
Case 2

- Developed headache with positive cerebellar signs
- CT brain: intracerebellar hemorrhage
- INR: 6.5
- What is the problem?

**Potential drug-drug interactions**

- Nevirapine vs. rifampin
- Nevirapine vs. warfarin
- Isoniazid vs. warfarin
- Rifampin vs. warfarin
Monitor/Modify Tx

Coumadin and Isoniazid
- Monitor INR: combo may incr. INR, risk of bleeding (hepatic metab. inhibited)

Coumadin and Rifampin
- Monitor INR: combo may decr. INR, warfarin efficacy; isoniazid combinations may incr. INR (hepatic metab. induced, inhibited by isonizid)

Coumadin and Nevirapine
- Monitor INR: combo may incr. INR, warfarin efficacy (hepatic metab. induced)

Caution Advised

Isoniazid and Nevirapine
- Combo may incr. nevirapine levels, risk of adverse effects (hepatic metab. inhibited)

Rifampin and Nevirapine
- Combo may alter nevirapine levels, decr. efficacy or incr. adverse effects (hepatic metab. induced by rifampin, inhibited by isonizid)
Cautious Use with Antiretroviral Drugs

- **Anti-TB**
  - Rifampin

- **Antibiotics**
  - Clarithromycin

- **Antifungals**
  - Azoles

- **Oral contraceptives**

- **Anticonvulsants**
  - Carbamazepine
  - Phenobarbital
  - Phenytoin

- **Cardiac agents**
  - Amiodarone
  - Digoxin
  - Diltiazem
  - Flecainide
  - Propafenone
  - Quinidine

- **Immunosuppressant**
  - Cyclosporin
  - Dexamethasone
  - Tacrolimus

Cautious Use with Antiretroviral Drugs

- **Lipid-lowering agents**
  - Lovastatin
  - Simvastatin

- **Oral anticogaulant**
  - Warfarin

- **Gastrointestinal drugs**
  - Acid reducers
  - Cisapride

- **Phosphodiesterase Type 5 Inhibitors**
  - Sildenafil

- **Neuroleptics**
  - Pimozide

- **Psychotropics**
  - Midazolam
  - Triazolam

- **Ergot alkaloids**
  - Dihydroergotamine
  - Ergotamine
  - Ergonovine
  - Methylergonovine

- **Herbs**
  - St. John’s wort

Case 3

- 36 yo female
- History of PCP
- 1/05 CD4 129 (15%) cells/mm$^3$, HIV RNA 460,000 copies/mL
- GPO-VIR → rash → lost to follow up
- 7/05 started d4T, 3TC, EFV
- 1/06 CD4 194 (9%) cells/mm$^3$, HIV RNA 4,470 copies/mL
Choose the Second Regimen: Backbone

A. AZT + ddI  
B. AZT + 3TC  
C. TDF + ddI  
D. TDF/FTC  
E. TDF + ABC  
F. TDF + AZT


Nucleoside and Nucleotide RT Inhibitors Resistance Interpretation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Resistance Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>zidovudine (AZT)</td>
<td>No Evidence of Resistance</td>
</tr>
<tr>
<td>didanosine (ddI)</td>
<td>No Evidence of Resistance</td>
</tr>
<tr>
<td>lamivudine (3TC)/emtricitabine (FTC)</td>
<td>Resistance</td>
</tr>
<tr>
<td>stavudine (d4T)</td>
<td>Resistance</td>
</tr>
<tr>
<td>abacavir (ABC)</td>
<td>No Evidence of Resistance</td>
</tr>
<tr>
<td>tenofovir (TDF)</td>
<td>No Evidence of Resistance</td>
</tr>
</tbody>
</table>

Non-nucleoside RT Inhibitors Resistance Interpretation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Resistance Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>nevirapine (NVP)</td>
<td>Resistance</td>
</tr>
<tr>
<td>efavirenz (EFV)</td>
<td>Resistance</td>
</tr>
</tbody>
</table>
TDF + DDI: A Combination to AVOID

- Drug-drug interaction, possibly increasing ddI toxicity\(^1\)
- Impaired CD4 response despite virologic suppression\(^2\)
- High rates of virologic failure and resistance when used as initial therapy with EFV or NVP\(^3,4\)

## Drug-drug Interactions among ARV

<table>
<thead>
<tr>
<th>Protase Inhibitors</th>
<th>NNRTIs</th>
<th>NRTIs</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV, DRV, FPV, IDV, LPV, NVP, RTV, SQV</td>
<td>DRV, DDI, ABC, 3TC, d4T, FTC, TDF, ZDV</td>
<td>ABC, ddI, ABC, FTC, 3TC, d4T, TDF, ZDV, MVC, RAL</td>
<td></td>
</tr>
</tbody>
</table>
Thai Guideline for ART in HIV 2010

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred</td>
<td>AZT + 3TC</td>
<td>EFV or NVP</td>
<td>LPV/r</td>
</tr>
<tr>
<td></td>
<td>TDF + 3TC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF/FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alternative</td>
<td>ABC + 3TC</td>
<td></td>
<td>ATV/r</td>
</tr>
<tr>
<td></td>
<td>d4T + 3TC</td>
<td></td>
<td>DRV/r</td>
</tr>
<tr>
<td></td>
<td>ddl + 3TC</td>
<td></td>
<td>SQV/r</td>
</tr>
</tbody>
</table>

- ATV 300 mg + RTV 100 mg QD
- TDF: standard
- Atazanavir Cmin: decreased 20%
## Significant Drug-drug Interactions among ARV

<table>
<thead>
<tr>
<th>Protease inhibitors</th>
<th>Efavirenz (EFV)</th>
<th>Nevirapine (NVP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atazanavir (ATV)</strong></td>
<td>Naïve patients: ATV 400 mg + RTV 100mg) QD</td>
<td>Do <strong>not</strong> coadminister with ATV +/- RTV</td>
</tr>
<tr>
<td></td>
<td>Do <strong>not</strong> coadminister in treatment-experienced patients</td>
<td></td>
</tr>
<tr>
<td><strong>Darunavir (DRV)</strong></td>
<td>Clinical significance unknown. Use standard doses and monitor closely</td>
<td>Standard</td>
</tr>
<tr>
<td><strong>Indinavir (IDV)</strong></td>
<td>IDV 800 mg + RTV 100–200 mg BID</td>
<td>IDV 800mg + RTV 100–200 mg BID</td>
</tr>
<tr>
<td></td>
<td>EFV standard</td>
<td>NVP standard</td>
</tr>
<tr>
<td><strong>Lopinavir/ritonavir (LPV/r)</strong></td>
<td>LPV/r 500/125 mg BID</td>
<td>LPV/r 500/125 mg BID</td>
</tr>
<tr>
<td></td>
<td>EFV standard</td>
<td>NVP standard</td>
</tr>
</tbody>
</table>

Case 4

- Male 40 years old
- History of IDU, quit for 10 years
- HCV co-infection
- Plan to receive treatment for HCV infection
- LFT: AST 89, AST 100 U/L, TB 2.0 mg/dL
- Which ARV regimen should be selected for him?
Patients with Hepatitis C Virus Co-infection

- **Didanosine and ribavirin**
  - Life-threatening didanosine-associated mitochondrial toxicity including hepatomegaly/steatosis, pancreatitis, and lactic acidosis

- **Zidovudine and ribavirin**
  - Higher rates of anemia

- **Abacavir and peginterferon plus ribavirin**
  - Associated with decreased response in some studies
  - Insufficient to recommend avoiding this combination

- **Growth factors (e.g., erythropoietin)**
  - AZT may increase the need for adjuvant growth factors due to increased bone marrow suppression
Patient Education

- HIV medications, PIs and NNRTIs, have a high potential for significant drug interactions
- Take all medicines, including any herbal supplements and over-the-counter remedies, with them to all medical appointments
- Primary care provider or pharmacist should review any newly prescribed medications along with their current list of medicines
- Not "borrow" medications from friends or family
Patient Education

- If considering buying a new nutritional or herbal supplement or an over-the-counter product
  - Should consult pharmacist or primary care provider about interactions with drugs on current medication list
- Not all drug interactions are cause for alarm
- Warn patients not to stop taking any medicines without advice of primary care provider
Prevention of Drug Interactions

- No specific guidelines
- Most important is to conduct a thorough medication history at each visit
  - Questions about prescription, over-the-counter, herbal, and recreational drugs and prescriptions received from other healthcare providers
- Clinicians’ self-education about drugs that are associated with clinically significant drug interactions with HAART
  - To avoid drug interactions or
  - To monitor patients for virologic failure or toxicity

Resources for Consultations
Drug Interaction Charts – Quality of Evidence

The online interaction charts have a new feature – Quality of Evidence. The charts have always indicated a strength of recommendation for coadministration of HIV drugs and co-medications (i.e., red, amber, green), but there was no indication of the quality of evidence behind those recommendations. We have introduced a system that categorises the quality of evidence from high to very low based on the GRADE classification. This additional information is shown when you click on a solid symbol for the details of an interaction with an NNRTI, NRTI, integrase or maraviroc (Pls in progress).

Further information on Quality of Evidence and GRADE can be found here (pdf file).
### Drug Interaction Charts

#### Step 1: Searching by Nevirapine

- **Amend Selection**

#### Step 2: Searching by Antibacterials, Antiretrovirals (NNRTIs)

- **Amend Selection**

#### Step 3: Searching by Clarithromycin, Nevirapine

- **Amend Selection**

#### Step 4: View results

---

**Key to symbols:**

- A solid symbol within a table will give further information on the interaction.
- Empty symbols indicate that the combination has not been studied and an interaction has been predicted based on the metabolic profiles of the drugs.

- **/ /** These drugs should not be coadministered

- **/ /** Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration

- **/ /** No clinically significant interaction expected

- **/ /** There are no clear data, actual or theoretical, to indicate whether an interaction will occur

- **/ /** Data not available

---

<table>
<thead>
<tr>
<th>Antibacterials</th>
<th>Nevirapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antiretrovirals (NNRTIs)</th>
<th>Nevirapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Database of Antiretroviral Drug Interactions

Search by Antiretroviral Drug

Step 1. Select an antiretroviral drug from the pull-down list

Lopinavir/ritonavir (Kaletra)

Step 2. Choose one of the following:

- All interactions
- By drug class
- By individual drug

Submit
### Database of Antiretroviral Drug Interactions

#### All Interactions with Lopinavir/ritonavir (Kaletra)

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Amodarone&lt;sup&gt;28&lt;/sup&gt; (Cordarone)</td>
<td>-</td>
<td>-</td>
<td>Not studied; may increase amiodarone levels</td>
<td>-</td>
<td>Increased amiodarone effects (eg. cardiac arrhythmias, hypotension)</td>
<td>Inhibition of CYF450 3A4 by lopinavir/ritonavir</td>
<td>Monitor and adjust amiodarone as indicated</td>
</tr>
<tr>
<td>Amprenavir&lt;sup&gt;28, 29&lt;/sup&gt; (APV)(Agenerase)</td>
<td>450 mg BID x 5 days, 750 mg BID x 5 days</td>
<td>400 mg/100 mg BID x 22 days</td>
<td>No significant change</td>
<td>Lopinavir AUC: decreased 15%; lopinavir Cmax: no significant change; Cmin: decreased 19%</td>
<td>-</td>
<td>-</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>Amprenavir&lt;sup&gt;35&lt;/sup&gt; (APV)(Agenerase)</td>
<td>600 mg BID</td>
<td>400 mg/100 mg BID</td>
<td>Amphenavir Cmin: decreased 37% (when compared to standard curve obtained from in vitro assay)</td>
<td>Not studied</td>
<td>Decreased amphenavir levels</td>
<td>Not established</td>
<td>Dose adjustment not established</td>
</tr>
</tbody>
</table>
http://aidsmeds.com/cmm/DrugsNewContent.asp

Check My Meds
Check My Meds allows you to take the preventive step of determining whether the drugs you are taking interact with each other, or interact with certain foods, and cause a bad reaction in your body.

Build your Medications List by retrieving a previously saved list and/or searching for and adding all the drugs you're on or want to check, repeating Steps 1 & 2 for each drug. Then, proceed to Step 3 to check for possible interactions.

1. Type in a drug name, then click search. All possible matches will appear in "Drug Search Results" below, so proceed to Step 2 to add this drug to "Your Drug List". If you previously saved a list of drugs, you can start by clicking the "Retrieve" button below, then add or remove drugs to it.

2. Click & highlight the exact drug you want to add to your drug list. Then click "Add>>". Return to Step 1 to search for and add more drugs to build your complete list.

3. After your list is complete, you have the option of saving it for future interactions checks (just click the "Save" button above), and/or click here for your personal drug interactions report.
http://www.epocrates.com/
Other Websites

- www.aidsinfo.nih.gov
- www.hiv-druginteractions.org
- www.hopkins-hivguide.org
- Package insert