Interactive Training Activities for Clinicians

AETC AIDS EDUCATION & TRAINING CENTERS

Providing Healthcare Professionals with Quality Education to Improve HIV Care

HIV Drug Interactions Workshop

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HIV DRUG INTERACTIONS WORKSHOP
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San Francisco Area
PACIFIC AIDS Education and Training Center

HIV Drug Interactions Workshop:
An Interactive Training Activity for Clinicians

Introduction and Overview

HIV Drug Interactions Workshop is an interactive, case-based learning activity designed to give training participants the opportunity to apply problem-solving skills to different HIV antiretroviral and related opportunistic infection medication drug interaction scenarios.

This Workshop Instructor's Guide includes:

- ☑ Complete instructions for conducting the interactive case study exercise.
- ☑ Seven case study scenarios and accompanying handouts to use in small groups for reviewing antiretroviral drug interactions.
- ☑ Instructor's Notes for each case, identifying key drug interactions and discussion points.
- ☑ Tips for timing case-based activities and leading case discussions.
- ☑ Handouts and reference materials for learners:

1. Systematic Approach to HIV Drug Interaction Evaluation
2. Select Antiretroviral Drug Interaction Resources
3. AETC Clinical Manual Chapter: Drug-Drug Interactions with HIV-Related Medications
4. Dosage Adjustments for ARV-ARV Drug Interactions
5. Select Tables from *Guidelines for the Use of Antiretroviral Agents Among HIV-Infected Adults and Adolescents*

Target Audience

This interactive training activity is best suited for community and clinic-based pharmacists with an intermediate level of knowledge of HIV disease and AIDS, antiretroviral medications, and important HIV drug interactions.

Instructor Requirements

This interactive training activity should be facilitated by an experienced HIV pharmacist, primary care provider or other clinician with advanced knowledge of HIV antiretroviral and related opportunistic infection medication drug interactions.

Learning Objectives

Pharmacists completing this interactive training workshop session will be able to:

1) Review a patient's drug profile and identify potentially interacting HIV drugs.
2) List the expected outcome of the interaction.
3) Formulate a patient counseling strategy and pharmaceutical care plan for handling the drug interaction.

How the Workshop is Structured

This interactive learning activity uses case scenarios to review antiretroviral drug interactions. Learners work through the case scenarios in small groups as pharmacists performing a dispensing shift at their local community or hospital/clinic-based outpatient pharmacy. Learners are provided with references for looking up drug interactions; and chart paper and markers to list their responses to the following tasks for their assigned case(s):

1. Identify the significant drug interactions presented in the case scenario.
2. List expected outcomes of the interactions.
3. Prescribe an appropriate pharmaceutical care plan to address the interactions.
4. Describe important patient counseling points and messages around the significant drug interactions.

Upon completion of the small-group case work, the instructor facilitates a report-back session, emphasizing key concepts of antiretroviral drug interaction management.

Timing for Case-based Activities and Discussion

The suggested time required to conduct this workshop activity is 1½ hours (90 minutes) but the actual time will vary, depending on the knowledge and clinical skills of the learner group and number of case scenarios to be covered. At a minimum each small group should be given 15 minutes to work through their assigned case, and then at least 5 minutes to report back their findings. The instructor facilitates the case discussion based on the small-group reports and feedback or questions from the whole group. The time required for sufficiently covering the key concepts of each case and answering questions from the large group will depend on the group size and knowledge level. Instructors should allow plenty of time for processing discussion, which will add to the overall time allotment required for this workshop activity.

HIV Drug Interactions Workshop

Purpose:	To review HIV antiretroviral and related opportunistic infection medication drug interactions.
Time Required:	Varies, depending on group size, knowledge/experience level of learners, and number of case scenarios. **The suggested minimum time requirement is 1½ hours (90 minutes.)**
Materials Needed:	1. Case scenario handouts – one complete set for each learner 2. Extra Case Study Worksheets for each learner 3. Easel/chart paper – one blank piece for each small group 4. Chart paper, markers, and masking tape for each small group 5. Additional resource handouts for learners: ▪ Select Antiretroviral Drug Interaction Resources ▪ Drug interaction tables from current *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*

Instructions for Trainer/Facilitator

Preparation **Prior to Training**	1. Review and choose case scenarios appropriate for learning audience. 2. Prepare copies of case scenarios, Case Study Worksheets, and resource handouts for learners.
Opening and Introductions **5 minutes**	1. Welcome learners and complete any introductory or housekeeping tasks required before the start of the training session. 2. Quickly divide learners into small-group teams. Assign each team a case scenario. Depending on the size of the group, not all case scenarios may be used. 3. Ask learners to quickly introduce themselves one at time to their small groups: name, profession or discipline, organization they are representing, and current job role. 4. Give each small group: 1) Blank piece of chart paper and markers 2) Copies of the case scenarios: one complete set for each learner 3) Sufficient extra copies of Case Study Worksheet 4) Any additional reference materials you may wish to use.

Instructions

5 minutes

1. Invite learners to read the "Directions for Small Groups" and explain the small group tasks:
   1) *Create a chart on your blank piece of paper just like the diagram shown on your case scenario handout.*
   2) *Choose a reporter/scribe to keep notes, and someone to read the case to the group and serve as the timekeeper.*
   3) *You are all pharmacists performing a dispensing shift at your local community or hospital outpatient pharmacy. Take 15 minutes to discuss the case scenario and fill in the pertinent information on your chart. For patient counseling points, write them in lay language, as you would address the patient.*
   4) *Try and respond to all of the questions on the chart/Case Study Worksheet, even if this means you must be very brief.*
   5) *You may use any resources at your disposal to look up drug interaction references.*

Small-group Case Study Exercise

20 minutes

1. Explain that the reporter/scribe will have about **five minutes** to summarize the group's work during the report-back.
2. Ask for and respond to any questions or need for clarification about the case study exercise.
3. Give the small groups 15 minutes to work on the case scenarios; provide "time checks" out loud every five minutes.

Report-back

and

Large-group Processing Discussion

50 minutes

1. Reconvene the large group.
2. Remind the teams that their reporter will have **about five minutes** to summarize their approach to the case and their responses posted on their chart.
3. Ask for a volunteer from one group to begin, and have the reporter post the group's chart at the front of the room.
4. Facilitate the small-group report-back from each team:
   a. Ask everyone to review the case scenario in their handout packet as the teams report back. Tell learners they may use the extra Case Study Worksheets to take notes on any of the case report-backs.
   b. Ask the reporter to state the key drug interaction issues identified by the team.

   c. Ask the reporter to state at least one patient counseling point the team identified as a possible way of addressing the drug interaction with the patient.

5. Facilitate the Q&A/case discussion session by asking for feedback or questions from other members of the team, then from the whole group.
6. At the conclusion of the report-backs, thank the teams for their hard work. Summarize by reminding learners of the importance of routine assessment for HIV drug-drug interactions in their patients, and encouraging them to practice a consistent method of evaluating drug interactions.
7. Provide learners with copies of any drug interaction resources you wish them to have, if they have not already received them. Remind learners that these resources are some examples of tools they can use to enhance their drug-drug interaction assessment skills and patient counseling.

Key Concepts to Highlight When Teaching About HIV Drug Interactions

- ☑ The complexities of treating HIV and related illnesses increase the potential for significant drug-drug interactions.
- ☑ In the age of HAART (Highly Active Antiretroviral Therapy), patients are living longer and developing other medical problems requiring pharmacologic treatment.
- ☑ Complications and adverse effects of antiretroviral medications are being treated with additional medications.
- ☑ Assessment of drug interactions must be a routine part of HIV disease management.
- ☑ Pharmacists and other HIV care team members should develop and practice a consistent, step-wise approach to evaluating drug-drug interactions.

Tips for Leading Case-based Activity Discussions

Dates on the pharmacy profiles and prescriptions:

- Each case was designed to have "real time" dates in order to point out adherence issues and other drug-related problems. Please announce to the group prior to the start of their working sessions, "You can assume that the date is June 20th and that the dates listed on the pharmacy profiles are applicable."

Enhancing the activity based on skill level:

- Learners who are less familiar with HIV therapy and drug-drug interactions should concentrate on identifying and managing the interactions contained in their case. More experienced clinicians should review the drug interactions but should also be expected to identify larger picture issues present in the cases such as poor adherence, medication errors, patient counseling tips, and facilitating systems by which to communicate and manage drug interactions with providers.

Running out of time:

- Depending on the length of time allotted for the activity, some groups may be faced with just a few minutes to give their report back. **Skipping group report-backs is not recommended** because it makes the group feel the work they did was not valuable. If the session is running out of time, the remaining groups should (at minimum) be allowed to present the drug interactions they identified from the case and the recommended management for those drug interactions.

Drug Interactions Workshop Case Scenario #1

Directions for Small Groups:

1. On your paper, create a chart that looks similar to the diagram at right.
2. Choose one person to keep notes of the groups' discussion on the chart and report back to the whole group.
3. Choose one person to read through the case scenario and be the timekeeper for your group.
4. You are a pharmacist performing a dispensing shift at your local community or hospital outpatient pharmacy. You will have 15 minutes to analyze the following case scenario and fill in the chart with the pertinent information. We will then review your findings and care plans in the larger group.

Drug Interaction(s) 1) 2) 3)	Expected Outcome(s)
Pharmaceutical Care Plan	Patient Counseling Points

Dr's Office
12345 Medication Lane
San Francisco, CA 94143
(415) 911-4111

Patient: Homer Simpson

Date: 6/20/08

Rx:
Clarithromycin 500mg PO BID #60, 5 refills
Ethambutol 400mg, iii PO QD #90, 5 refills
Rifabutin 300mg, i po QD #30, 5 refills
Methadone 10mg ii PO BID #120, 0 refills

Signature: *Dr. Doe*

Conversation at the pharmacy counter:

"Hi! I'm here to refill my prescriptions. I think there are 7 of them. I also have these new ones (hands you the prescription) from Dr. Doe."

When you ask him how he has been lately he says . . . :

"I've been doing just OK. Dr. Doe keeps giving me all these medications. My back has been killing me – more than it has been in a long time. Especially over the last month. Maybe I should ask Dr. Payne if I can try a new medicine."

Drug Interactions Workshop Case Scenario #1

Patient	Homer J. Simpson
Address	128 Donut Lane, Springfield USA
Gender	Male
Insurance	Cover-all Insurance

PATIENT PROFILE

Drug Name	COMBIVIR 300mg/150mg TABS	*Original Rx*	3/18/08
Sig	Take one tablet by mouth twice daily	*Last Filled*	5/20/08
Quantity	60	*Physician*	Dr. Doe
Refills left	3		

Drug Name	INVIRASE 500mg TABS	*Original Rx*	3/18/08
Sig	Take two tablets by mouth twice daily	*Last Filled*	5/20/08
Quantity	120	*Physician*	Dr. Doe
Refills left	3		

Drug Name	NORVIR 100mg TABS	*Original Rx*	3/18/08
Sig	Take 1 capsule by mouth twice daily	*Last Filled*	5/20/08
Quantity	60	*Physician*	Dr. Doe
Refills left	3		

Drug Name	Buspirone 15mg TABS	*Original Rx*	2/20/08
Sig	Take 1 tablet by mouth daily	*Last Filled*	5/20/08
Quantity	30	*Physician*	Dr. Psych
Refills left	2		

Drug Name	Methadone 10mg TABS	*Original Rx*	5/20/08
Sig	Take 2 tablets by mouth twice daily	*Last Filled*	5/20/08
Quantity	120	*Physician*	Dr. Payne
Refills left	0		

Drug Name	Stavudine 30mg TABS	*Original Rx*	5/20/08
Sig	Take 1 capsule by mouth twice daily	*Last Filled*	5/20/08
Quantity	60	*Physician*	Dr. Newhouse
Refills left	4		

Drug Name	EPIVIR 150mg TABS	*Original Rx*	5/20/08
Sig	Take 1 tablet by mouth twice daily	*Last Filled*	5/20/08
Quantity	60	*Physician*	Dr. Newhouse
Refills left	4		

Drug Name	Digoxin 0.125mg TABS	*Original Rx*	3/20/08
Sig	Take 1 tablet by mouth twice daily	*Last Filled*	5/20/08
Quantity	60	*Physician*	Dr. Hart
Refills left	5		

Instructor's Notes — Case 1: Homer Simpson

Case Summary

- Patient arrives to pharmacy for refills on all his medicines (there are 8 total in his profile which have been filled in the last month)
- Patient has new prescriptions for mycobacterium avium complex
- Patient complaining of new pain

✓	Drug interaction	Expected Outcome	Recommended Management
	Zidovudine-stavudine	Antagonism at reverse transcriptase	Must discontinue one of the two drugs
	Rifabutin- saquinavir/ritonavir	Ritonavir ↑ rifabutin levels	Decrease rifabutin dose to 150mg every other day or consider removing rifabutin (MAC therapy OK with macrolide and ethambutol)
	Methadone - saquinavir/ritonavir	SQV/r ↓ methadone levels	Monitor for methadone efficacy and titrate to effect
	Clarithromycin – ritonavir	Ritonavir ↑ clarithromycin levels 77%	Monitor – adjust if renal or hepatic impairment. Alternatively, switch to azithromycin.
	Digoxin - saquinavir/ritonavir		Monitor digoxin levels

Pharmaceutical Care Plan

Contact MDs to…:

- Determine which is appropriate NRTI therapy (zidovudine/lamivudine or stavudine/lamivudine
- Approve new prescription of lower dose of rifabutin
- Alert provider of patient's complaint of pain and likely need for increase in methadone

Patient Counseling Notes

- Educate patient on fixed dose combinations containing same meds (Combivir® & lamivudine).

- Instruct patient to let his MD know about his increase in pain and likely cause of drug interactions between PI and methadone.
- Encourage patient to bring list of medications to all of his doctors' appointments – it appears that he has many providers caring for him and all may not be aware of the medications he is taking.
- Reinforce adherence to MAC therapy.

Drug Interactions Workshop Case Scenario #2

Directions for Small Groups:

1. On your paper, create a chart that looks similar to the diagram at right.
2. Choose one person to keep notes of the groups' discussion on the chart and report back to the whole group.
3. Choose one person to read through the case scenario and be the timekeeper for your group.
4. You are a pharmacist performing a dispensing shift at your local community or hospital outpatient pharmacy. You will have 15 minutes to analyze the following case scenario and fill in the chart with the pertinent information. We will then review your findings and care plans in the larger group.

Drug Interaction(s) 1) 2) 3)	Expected Outcome(s)
Pharmaceutical Care Plan	Patient Counseling Points

Dr's Office
12345 Medication Lane
San Francisco, CA 94143
(415) 911-4111

Patient: Marge Simpson

Date: 6/20/08

Rx:
Rifampin 300mg ii PO daily #60, 5 refills
Isoniazid 300mg PO daily #30, 5 refills
Pyrazinamide 500mg ii orally daily #60, 1 refill
Ethambutol 400mg, iii PO QD #90, 1 refills
Epivir HBV 100mg PO daily, #30, 5 refills

Signature: *Dr. I. Diseases*

Conversation at the pharmacy counter:

"I can't believe I got TB and hepatitis from my trip to Asia! Here are my prescriptions. I think I also need refills on my other meds too."

Drug Interactions Workshop Case Scenario #2

Patient	Marge Simpson
Address	128 Donut Lane, Springfield USA
Gender	Female
Insurance	Lotsa Insurance

PATIENT PROFILE

Drug Name	COMBIVIR 300mg/150mg TABS	*Original Rx*	2/18/08
Sig	Take one tablet by mouth twice daily	*Last Filled*	5/20/08
Quantity	60	*Physician*	Dr. Doe
Refills left	1		

Drug Name	KALETRA 200/50mg TABS	*Original Rx*	2/18/08
Sig	Take two tablets by mouth twice daily	*Last Filled*	5/20/08
Quantity	120	*Physician*	Dr. Doe
Refills left	1		

Drug Name	ADVAIR DISCUS 100/50mg	*Original Rx*	1/18/08
Sig	1 inhalation twice daily	*Last Filled*	5/20/08
Quantity	1	*Physician*	Dr. General
Refills left	0		

Drug Name	Phenytoin 300 CAPS	*Original Rx*	1/20/08
Sig	Take 1 capsule by mouth daily	*Last Filled*	5/20/08
Quantity	30	*Physician*	Dr. General
Refills left	1		

Drug Name	CRESTOR 5mg TABS	*Original Rx*	5/20/08
Sig	Take 1 tablets by mouth daily	*Last Filled*	5/20/08
Quantity	30	*Physician*	Dr. General
Refills left	2		

Instructor's Notes — Case 2: Marge Simpson

Case Summary

- Patient requests refills on all her meds and has new prescriptions for TB and hepatitis B therapy

✓	Drug interaction	Expected Outcome	Recommended Management
	Combivir® - Epivir HBV®	Therapy duplication but likely no outcome other than increased side effects	D/c Epivir HBV® – HIV doses are higher than what is needed for HBV treatment.
	lopinavir/ritonavir - rifampin	rifampin ↓ lopinavir levels	Contraindicated. Discuss options with MD: may include changing ARV therapy or d/c ARV during TB treatment.
	lopinavir/ritonavir - phenytoin	Bidirectional drug interactions where levels of both drugs are lowered	Could change anticonvulsant or monitor levels. Need to monitor viral suppression .
	lopinavir/ritonavir - fluticasone	lopinavir/ritonavir can ↑ systemic levels of fluticasone resulting in adrenal suppression	Change asthma therapy or just monitor for symptoms
	lopinavir/ritonavir - rosuvastatin	lopinavir/ritonavir ↑ levels of rosuvastatin	Initiate rosuvastatin at lower dose (5mg) and titrate slowly (as she already has been). Monitor for myopathy, signs of rhabdomyolysis.

Pharmaceutical Care Plan

Contact MDs to…

- Determine plan for TB therapy, given the rifampin-PI interaction.
- Alert provider of duplicate lamivudine therapy for HIV/HBV and suggest d/c Epivir® HBV. Suggest addition of another HBV active agent (tenofovir, or change to tenofovir/emtricitabine) for dual HBV coverage and protection against development of YMDD mutation.
- Alert provider about lopinavir/ritonavir –phenytoin interaction so that provider can draw levels or manage as appropriate

Patient Counseling Notes

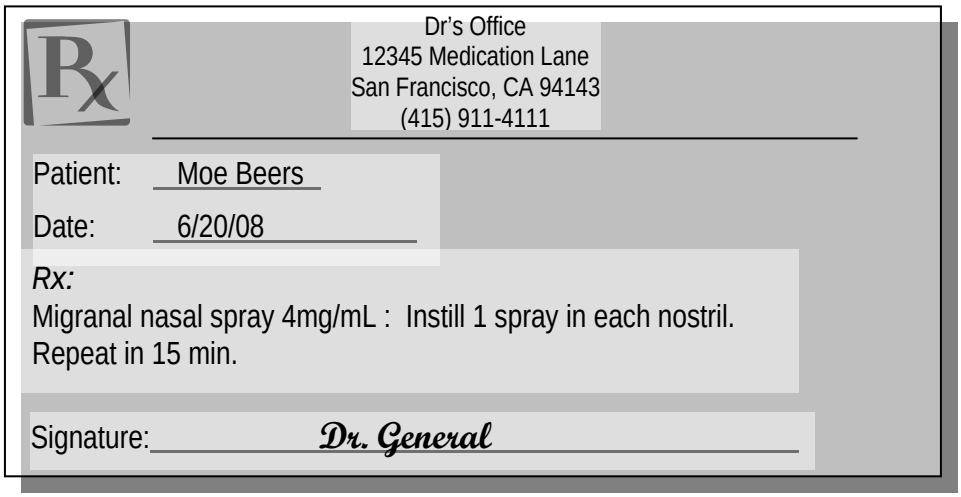
- Educate patient on fixed dose combinations containing same meds (Combivir® & Epivir® HBV) and why Epivir® HBV can be discontinued
- Inform patient about decisions that need to be made around TB and HIV therapy
- Counsel patient on signs and symptoms of Cushing's and adrenal suppression
- Counsel patient on signs and symptoms of rhabdomyolysis and myopathy (instruct to report any of these to her primary care provider)

Drug Interactions Workshop Case Scenario #3

Directions for Small Groups:

Drug Interaction(s)	Expected Outcome(s)
1) 2) 3)	
Pharmaceutical Care Plan	Patient Counseling Points

1. On your paper, create a chart that looks similar to the diagram at right.
2. Choose one person to keep notes of the groups' discussion on the chart and report back to the whole group.
3. Choose one person to read through the case scenario and be the timekeeper for your group.
4. You are a pharmacist performing a dispensing shift at your local community or hospital outpatient pharmacy. You will have 15 minutes to analyze the following case scenario and fill in the chart with the pertinent information. We will then review your findings and care plans in the larger group.



Dr's Office
12345 Medication Lane
San Francisco, CA 94143
(415) 911-4111

Patient: Moe Beers

Date: 6/20/08

Rx:
Migranal nasal spray 4mg/mL : Instill 1 spray in each nostril.
Repeat in 15 min.

Signature: *Dr. General*

Conversation at the pharmacy counter:

"Ugh. I thought I was supposed to be starting to feel better now! That's the whole reason I agreed to starting antivirals – to give me more energy. But I'm feeling awful! I've got this terrible headache, and my body and muscles really ache! I hope this migraine medicine does the trick. I never thought I had migraines before, but maybe it will at least get rid of my headache. Maybe some of these supplements will help too."

Brings to the counter for purchase:

A pack of gum, cigarettes, and a bottle of SAM-E and St. John's Wort.

Drug Interactions Workshop Case Scenario #3

Patient	Moe Beers
Address	911 Drinking Lane, Springfield USA
Gender	Male
Insurance	Kindasorta Insurance

PATIENT PROFILE

Drug Name	EPZICOM 300mg/600mg TABS	*Original Rx*	5/01/08
Sig	Take one tablet by mouth daily	*Last Filled*	5/01/08
Quantity	30	*Physician*	Dr. Infectious
Refills left	0		

Drug Name	EPZICOM 300mg/600mg TABS	*Original Rx*	6/01/08
Sig	Take one tablet by mouth daily	*Last Filled*	6/01/08
Quantity	30	*Physician*	Dr. Internal
Refills left	5		

Drug Name	LEXIVA 700mg TABS	*Original Rx*	5/01/08
Sig	Take one tablet by mouth twice daily	*Last Filled*	5/01/08
Quantity	60	*Physician*	Dr. Infectious
Refills left	0		

Drug Name	Famciclovir 500mg TABS	*Original Rx*	6/01/08
Sig	Take one tablet by mouth twice daily	*Last Filled*	6/01/08
Quantity	60	*Physician*	Dr. Internal
Refills left	5		

Drug Name	Simvastatin 40mg TABS	*Original Rx*	6/01/08
Sig	Take one tablet at bedtime	*Last Filled*	6/01/08
Quantity	30	*Physician*	Dr. General
Refills left	5		

Drug Name	WELLBUTRIN XL 300 TABS	*Original Rx*	1/20/08
Sig	Take 1 tablet by mouth daily	*Last Filled*	6/01/08
Quantity	30	*Physician*	Dr. General
Refills left	1		

Instructor's Notes — Case 3: Moe Beers

Case Summary

- Patient recently started ARV (8 weeks ago)
- Patient has new rx for migraine medicine but claims he has never had migraines before this
- Complaining of body and muscle aches
- Purchasing other dietary supplements and herbs to make him feel better

✓	Drug interaction	Expected Outcome	Recommended Management
	ergotamine - fosamprenavir	Protease inhibitor ↑ ergot	Alternative migraine treatment (if he needs migraine tx at all)
	St. John's Wort - fosamprenavir	St. John's Wort ↓ fosamprenavir	Contraindicated combination
	simvastatin -fosamprenavir	fosamprenavir ↑ simvastatin levels	Contraindicated combination

Pharmaceutical Care Plan

Contact MDs to…

- Change statin to pravastatin or atorvastatin
- Ask whether patient is supposed to be taking ritonavir (fosamprenavir dosing suggests it).
- Need to also check to see if there was a medication error – in May patient filled fosamprenavir, but in June patient filled Famvir® with similar dosing.
- Discuss care plan for migraine, given that ergot medications are contraindicated with patient's therapy.

Patient Counseling Notes

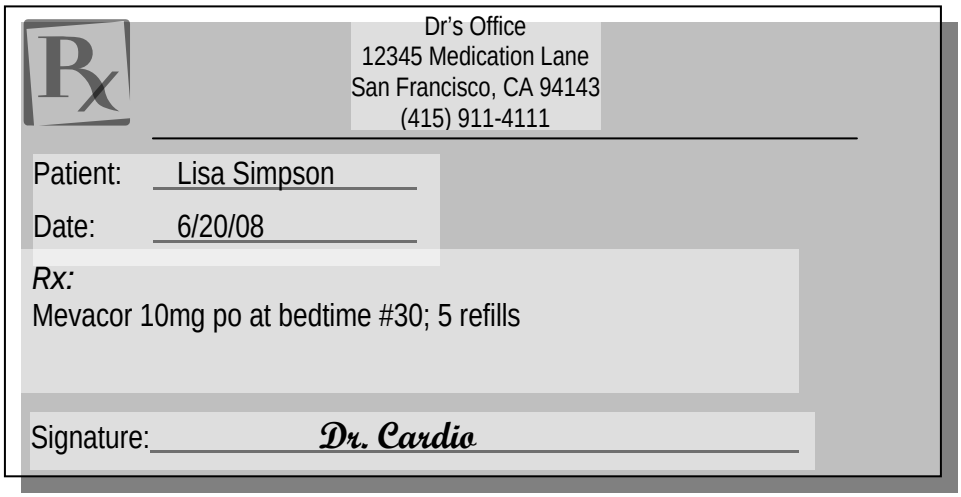
- Tell patient to see his MD right away; headache and body/muscle aches could be due to abacavir hypersensitivity reaction (patient started meds 8 weeks ago) or due to rhabdomyolysis from the simvastatin interaction. Both should be addressed immediately. Let patient know that these may be the source of his issues, and reassure him that sometimes finding the right antiretroviral combo takes time.
- Educate patient about contraindicated meds with his regimen – St. John's Wort and ergotamine medicines
- Ask patient about potential Famvir® /fosamprenavir mix up (did he take fosamprenavir somewhere else to be filled last month?)

Drug Interactions Workshop Case Scenario #4

Directions for Small Groups:

Drug Interaction(s)	Expected Outcome(s)
1) 2) 3)	
Pharmaceutical Care Plan	Patient Counseling Points

1. On your paper, create a chart that looks similar to the diagram at right.
2. Choose one person to keep notes of the groups' discussion on the chart and report back to the whole group.
3. Choose one person to read through the case scenario and be the timekeeper for your group.
4. You are a pharmacist performing a dispensing shift at your local community or hospital outpatient pharmacy. You will have 15 minutes to analyze the following case scenario and fill in the chart with the pertinent information. We will then review your findings and care plans in the larger group.



Conversation at the pharmacy counter:

"Sigh. Isn't San Francisco so grey in the summer? And now Dr. Cardio says I might have clogged arteries! It just figures that I have a broken heart. I thought I was doing so well, starting my meds and all. But I've been feeling so blah lately and I don't have any energy. Do I have to wait long for this prescription? I just want to go home, go back to bed, and stay there forever."

Drug Interactions Workshop Case Scenario #4

Patient	Lisa Simpson
Address	8220 Jazzy Lane
Gender	Female
Insurance	Smartypants Insurance

PATIENT PROFILE

Drug Name	EPZICOM 300mg/600mg TABS	*Original Rx*	2/01/08
Sig	Take one tablet by mouth daily	*Last Filled*	6/01/08
Quantity	30	*Physician*	Dr. Viral
Refills left	2		

Drug Name	PREZISTA 600mg TABS	*Original Rx*	2/01/08
Sig	Take one tablet by mouth twice daily	*Last Filled*	6/01/08
Quantity	60	*Physician*	Dr. Viral
Refills left	2		

Drug Name	NORVIR 100mg CAPS	*Original Rx*	2/01/08
Sig	Take one capsule by mouth twice daily	*Last Filled*	6/01/08
Quantity	60	*Physician*	Dr. Viral
Refills left	2		

Drug Name	ISENTRESS 400mg TABS	*Original Rx*	2/01/08
Sig	Take one tablet by mouth twice daily	*Last Filled*	6/01/08
Quantity	60	*Physician*	Dr. Viral
Refills left	2		

Drug Name	Lorazepam 1mg TABS	*Original Rx*	4/20/08
Sig	Take ½ - 1 tablet by mouth at bedtime as needed for sleep	*Last Filled*	6/01/08
Quantity	30	*Physician*	Dr. Psyche
Refills left	1		

Drug Name	Paroxetine 20mg TABS	*Original Rx*	12/20/08
Sig	Take 1 tablet by mouth daily	*Last Filled*	6/01/08
Quantity	30	*Physician*	Dr. Psyche
Refills left	6		

Drug Name	ORTHO CYCLEN 7/7/7 TABS	*Original Rx*	12/20/08
Sig	Take 1 tablet by mouth daily	*Last Filled*	6/01/08
Quantity	84	*Physician*	Dr. Baby
Refills left	1		

Drug Name	Vitamin C 500mg TABS	*Original Rx*	12/20/08
Sig	Take 1 tablet by mouth daily	*Last Filled*	6/01/08
Quantity	30	*Physician*	Dr. Baby
Refills left	1		

Instructor's Notes — Case 4: Lisa Simpson

Case Summary

- Patient filling new prescription to lower cholesterol
- Patient sounds very depressed, has been treated with paroxetine since 12/2007

✓	Drug interaction	Expected Outcome	Recommended Management
	lovastatin – darunavir/ritonavir	darunavir/ritonavir greatly ↑ lovastatin levels	Contraindicated combination – switch to another statin
	paroxetine – darunavir/ritonavir	darunavir/ritonavir ↓ paroxetine levels	Titrate paroxetine to effect or switch to another antidepressant
	ethinyl estradiol– darunavir/ritonavir	darunavir/ritonavir ↓ estradiol levels	Use back up method for prevention of partner transmission & pregnancy
	darunavir/ritonavir – vitamin C	Unknown, one study found that high dose (1000mg BID) vitamin C ↓ IDV levels	Monitor ARVs for efficacy

Pharmaceutical Care Plan

Contact MDs to…

- Change statin to pravastatin or atorvastatin
- Alert to potential lowering of previously steady SSRI levels by relatively new darunavir/ritonavir regimen.

Patient Counseling Notes

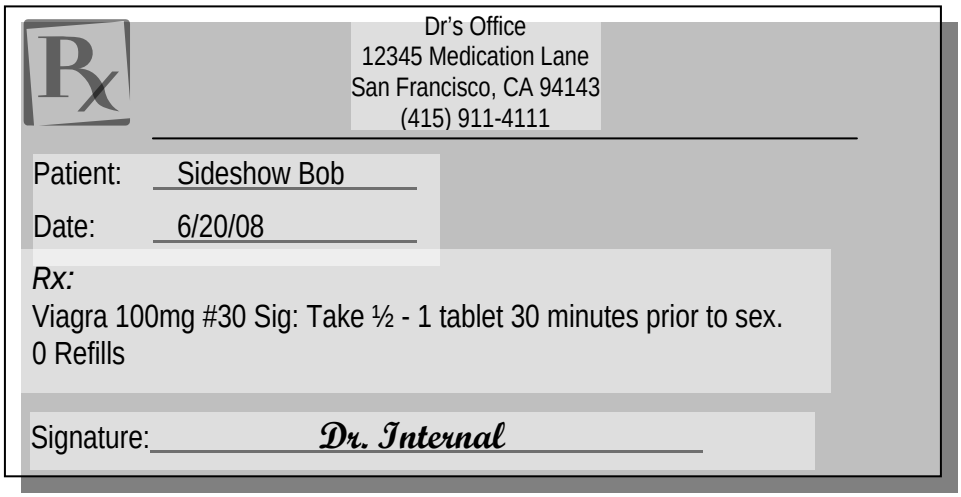
- Explain paroxetine drug interaction and encourage her to talk to her doctor about it
- Counsel patient on diet and exercise to lower her risk of heart disease
- Counsel patient about back up method for contraception and prevention of transmission
- Inform patient of (low) potential for Vitamin C to interact with her meds – advise her to continue taking no more than 500mg daily.

Drug Interactions Workshop Case Scenario #5

Directions for Small Groups:

1. On your paper, create a chart that looks similar to the diagram at right.
2. Choose one person to keep notes of the groups' discussion on the chart and report back to the whole group.
3. Choose one person to read through the case scenario and be the timekeeper for your group.
4. You are a pharmacist performing a dispensing shift at your local community or hospital outpatient pharmacy. You will have 15 minutes to analyze the following case scenario and fill in the chart with the pertinent information. We will then review your findings and care plans in the larger group.

Drug Interaction(s) 1) 2) 3)	Expected Outcome(s)
Pharmaceutical Care Plan	Patient Counseling Points



Dr's Office
12345 Medication Lane
San Francisco, CA 94143
(415) 911-4111

Patient: Sideshow Bob

Date: 6/20/08

Rx:
Viagra 100mg #30 Sig: Take ½ - 1 tablet 30 minutes prior to sex.
0 Refills

Signature: *Dr. Internal*

Conversation at the pharmacy counter

"I am just loving life! I need this prescription and refills on my Reyataz® and Truvada®, please."

Drug Interactions Workshop Case Scenario #5

Patient	Sideshow Bob
Address	1092 Bigtop Lane
Gender	Male
Insurance	CircusCircus Insurance

PATIENT PROFILE

Drug Name	TRUVADA 300mg/200mg TABS	*Original Rx*	1/01/08
Sig	Take one tablet by mouth daily	*Last Filled*	3/01/08
Quantity	30	*Physician*	Dr. NT Viral
Refills left	2		

Drug Name	Didanosine 400mg CAPS	*Original Rx*	1/01/08
Sig	Take one capsule by mouth daily	*Last Filled*	3/01/08
Quantity	30	*Physician*	Dr. NT Viral
Refills left	2		

Drug Name	NORVIR 100mg CAPS	*Original Rx*	1/01/08
Sig	Take one capsule by mouth daily	*Last Filled*	3/01/08
Quantity	30	*Physician*	Dr. NT Viral
Refills left	2		

Drug Name	REYATAZ 300mg CAPS	*Original Rx*	1/01/08
Sig	Take one capsule by mouth daily	*Last Filled*	3/01/08
Quantity	30	*Physician*	Dr. NT Viral
Refills left	2		

Drug Name	COMBIVENT INH	*Original Rx*	1/20/08
Sig	2 inhalations four times daily	*Last Filled*	2/01/08
Quantity	1	*Physician*	Dr. Internal
Refills left	3		

Drug Name	Albuterol MDI	*Original Rx*	1/20/08
Sig	1-2 inhalations every 4-6 hours as needed for shortness of breath	*Last Filled*	6/01/08
Quantity	1	*Physician*	Dr. Internal
Refills left	0		

Drug Name	Esomeprazole 40mg CAPS	*Original Rx*	4/01/08
Sig	Take 1 capsule by mouth daily	*Last Filled*	6/01/08
Quantity	30	*Physician*	Dr. Internal
Refills left	3		

Drug Name	CARDIZEM CD 120mg CAPS	*Original Rx*	4/01/08
Sig	Take one capsule by mouth daily	*Last Filled*	6/01/08
Quantity	30	*Physician*	Dr. Internal
Refills left	1		

Instructor's Notes — Case 5: Sideshow Bob

Case Summary

- Patient filling new prescription for sildenafil and asks for Reyataz® and Truvada® refills
- Last pick up of ARVs and other meds was >3 months ago
- Patient picks up albuterol regularly

✓	Drug interaction	Expected Outcome	Recommended Management
	sildenafil – atazanavir/ritonavir	atazanavir/ritonavir greatly ↑ sildenafil levels	Restrict dose to 25mg every 72 hours
	didanosine - tenofovir	tenofovir ↑ didanosine levels	Reduce dose of didanosine to 250mg daily (200mg if patient weighs < 60 kg)
	esomeprazole– atazanavir/ritonavir	esomeprazole ↓ atazanavir/ritonavir absorption	If patient is tx naïve, can separate by 12 hours (needs to be ritonavir-boosted atazanavir)
	diltiazem – atazanavir/ritonavir	atazanavir/ritonavir ↑ diltiazem AUC 125%	↓ diltiazem dose by 50% and monitor EKGs

Pharmaceutical Care Plan

Contact MDs to…

- Change didanosine, sildenafil, and diltiazem doses

Patient Counseling Notes

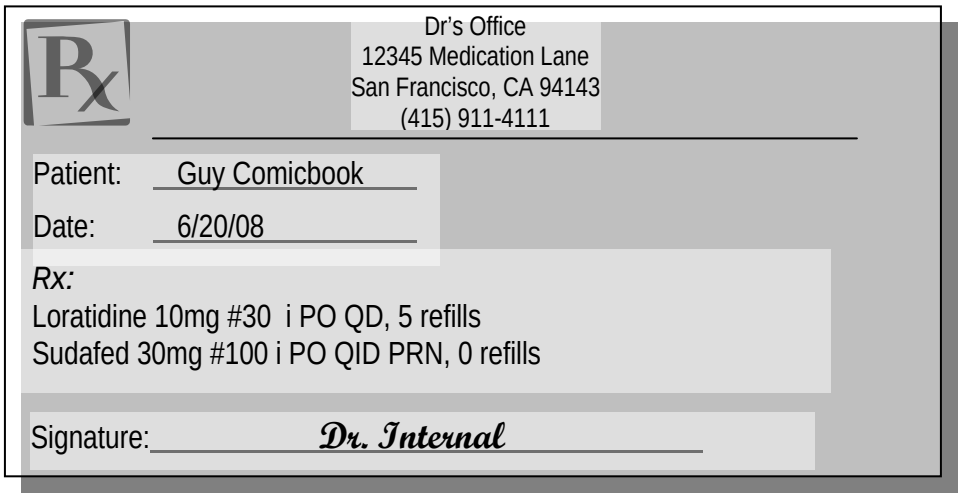
- Ask why patient is only picking up part of his ARV regimen – was he having side effects?
- Discuss adherence and potential link with resistance; encourage patient to restart all of his prescribed ARVs.
- Explain difference between maintenance asthma meds and "controller" asthma meds; encourage adherence to maintenance med. Inquire about smoking, refer to quitting sources if ready.
- Instruct patient to take esomeprazole or other H2 blockers 12 hours apart from his ARV regimen.
- Encourage safe sex with condoms.

Drug Interactions Workshop Case Scenario #6

Directions for Small Groups:

1. On your paper, create a chart that looks similar to the diagram at right.
2. Choose one person to keep notes of the groups' discussion on the chart and report back to the whole group.
3. Choose one person to read through the case scenario and be the timekeeper for your group.
4. You are a pharmacist performing a dispensing shift at your local community or hospital outpatient pharmacy. You will have 15 minutes to analyze the following case scenario and fill in the chart with the pertinent information. We will then review your findings and care plans in the larger group.

Drug Interaction(s) 1) 2) 3)	Expected Outcome(s)
Pharmaceutical Care Plan	Patient Counseling Points



Dr's Office
12345 Medication Lane
San Francisco, CA 94143
(415) 911-4111

Patient: Guy Comicbook

Date: 6/20/08

Rx:
Loratidine 10mg #30 i PO QD, 5 refills
Sudafed 30mg #100 i PO QID PRN, 0 refills

Signature: *Dr. Internal*

Conversation at the pharmacy counter:

"I need refills on my Septra®. I'm already behind by a week. My doctor said it's going to prevent me from getting sick – I don't want to get that sick again. Here, I'll buy this can of grapefruit juice to wash my meds down with. And, by the way, I know it's a little early, but can I also pick up my other meds? Not the methadone – I know I need a special prescription for that one. I have an appointment coming up with Dr. Payne and Dr. Specialist on June 30th."

Drug Interactions Workshop Case Scenario #6

Patient	Guy Comicbook
Address	28346 Fantasy Island Street
Gender	Male
Insurance	Trekkie Insurance

PATIENT PROFILE

Drug Name	TRUVADA 300mg/200mg TABS	*Original Rx*	5/30/08
Sig	Take one tablet by mouth daily	*Last Filled*	5/30/08
Quantity	30	*Physician*	Dr. Specialist
Refills left	3		

Drug Name	VIRAMUNE 200mg TABS	*Original Rx*	5/30/08
Sig	Take one tablet by mouth daily x 21 days then increase to one tablet twice daily	*Last Filled*	5/30/08
Quantity	60	*Physician*	Dr. Specialist
Refills left	3		

Drug Name	Methadone 10mg TABS	*Original Rx*	5/30/08
Sig	Take 3 tablets orally three times daily	*Last Filled*	5/30/08
Quantity	270	*Physician*	Dr. Payne
Refills left	0		

Drug Name	BACTRIM DS 800/160mg TABS	*Original Rx*	5/26/08
Sig	Take 2 tablets by mouth three times daily	*Last Filled*	5/26/08
Quantity	126	*Physician*	Dr. Specialist
Refills left	0		

Drug Name	Azithromycin 600 mg TABS	*Original Rx*	5/30/08
Sig	Take two tablets by mouth once weekly	*Last Filled*	5/30/08
Quantity	8	*Physician*	Dr. Specialist
Refills left	3		

Drug Name	VFEND 200 mg TABS	*Original Rx*	5/26/08
Sig	Take one tablets by mouth twice daily	*Last Filled*	5/26/08
Quantity	60	*Physician*	Dr. Specialist
Refills left	2		

Instructor's Notes — Case 6: Guy Comicbook

Case Summary

- Patient filling new prescription for antihistamine and pseudoephedrine
- Requesting refills on Septra (prescription was only for 21 days) as well as his other meds (except methadone)

✓	Drug interaction	Expected Outcome	Recommended Management
	nevirapine – methadone	nevirapine ↓ methadone	Monitor pain and titrate methadone to effect
	nevirapine – voriconazole	nevirapine ↓ voriconazole; voriconazole ↑ nevirapine	Change antifungal OR monitor for antifungal efficacy and NNRTI toxicity
	grapefruit juice – nevirapine	Potential ↑ nevirapine levels	Need larger and consistent amounts of grapefruit juice, but can monitor for any ↑ NVP side effects

Pharmaceutical Care Plan

Contact MDs to…

- Alert provider regarding possible decrease in voriconazole efficacy
- See if patient needs secondary prophylaxis (1 double strength tablet by mouth daily) for pneumocystis pneumonia

Patient Counseling Notes

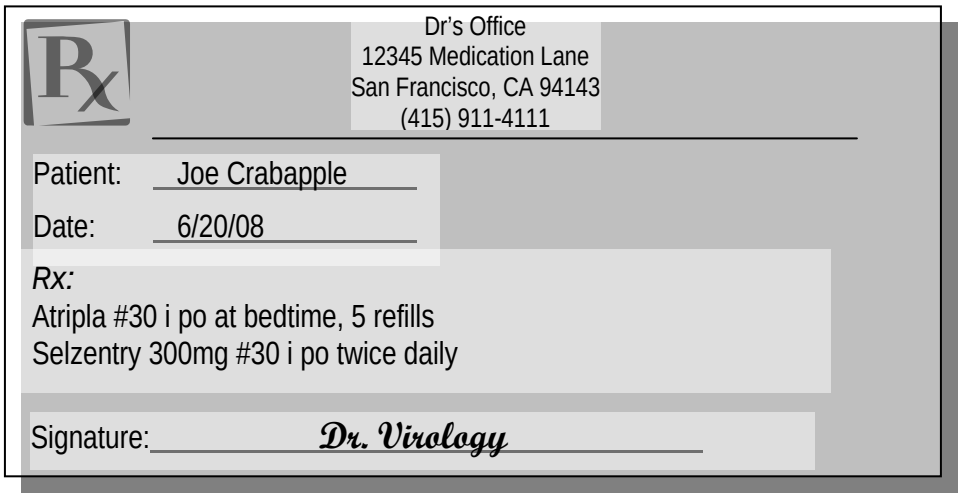
- Explain difference between PCP treatment and PCP prophylaxis; encourage adherence to PCP and MAC prophylaxis (which will help him "not get this sick again")
- Educate patient to report any changes in pain levels to his providers
- Inform patient about antifungal potentially decreased efficacy
- Counsel patient on potential interaction with grapefruit juice

Drug Interactions Workshop Case Scenario #7

Directions for Small Groups:

Drug Interaction(s)	Expected Outcome(s)
1) 2) 3)	
Pharmaceutical Care Plan	Patient Counseling Points

1. On your paper, create a chart that looks similar to the diagram at right.
2. Choose one person to keep notes of the groups' discussion on the chart and report back to the whole group.
3. Choose one person to read through the case scenario and be the timekeeper for your group.
4. You are a pharmacist performing a dispensing shift at your local community or hospital outpatient pharmacy. You will have 15 minutes to analyze the following case scenario and fill in the chart with the pertinent information. We will then review your findings and care plans in the larger group.



Dr's Office
12345 Medication Lane
San Francisco, CA 94143
(415) 911-4111

Patient: Joe Crabapple

Date: 6/20/08

Rx:
Atripla #30 i po at bedtime, 5 refills
Selzentry 300mg #30 i po twice daily

Signature: *Dr. Virology*

Conversation at the pharmacy counter:

"Time to start these meds, huh? I guess things could be worse – I'm feeling pretty good, so I think I'm up to it."

Drug Interactions Workshop Case Scenario #7

Patient	Joe Crabapple
Address	6253 Schoolhouse Street
Gender	Male
Insurance	University Insurance

PATIENT PROFILE

Drug Name	Risperdal 1mg TABS	*Original Rx*	2/30/08
Sig	Take one tablet by mouth twice daily	*Last Filled*	5/30/08
Quantity	60	*Physician*	Dr. Hed Case
Refills left	1		

Drug Name	Doxycycline 100mg CAPS	*Original Rx*	3/30/08
Sig	Take one capsule by mouth twice daily until gone	*Last Filled*	3/30/08
Quantity	20	*Physician*	Dr. General
Refills left	0		

Drug Name	Itraconazole 200mg CAPS	*Original Rx*	3/30/08
Sig	Take one capsule by mouth daily x 12 weeks for toenails	*Last Filled*	5/30/08
Quantity	30	*Physician*	Dr. General
Refills left	0		

Drug Name	CIALIS 10mg TABS	*Original Rx*	3/30/08
Sig	Take one tablet by mouth 30 minutes prior to sex	*Last Filled*	3/30/08
Quantity	30	*Physician*	Dr. General
Refills left	0		

Drug Name	Atorvastatin 20 mg TABS	*Original Rx*	3/30/08
Sig	Take one tablet by mouth at bedtime	*Last Filled*	5/30/08
Quantity	30	*Physician*	Dr. Hearty
Refills left	3		

Drug Name	Lorazepam 1mg TABS	*Original Rx*	4/20/08
Sig	Take ½ - 1 tablet by mouth at bedtime as needed for sleep	*Last Filled*	6/01/08
Quantity	30	*Physician*	Dr. Hed Case
Refills left	1		

Instructor's Notes — Case 7: Joe Crabapple

Case Summary

- Patient filling first new prescriptions for ARV therapy

✓	Drug interaction	Expected Outcome	Recommended Management
	maraviroc – itraconazole	itraconazole ↑ maraviroc	Reduce maraviroc dose to 150mg BID
	maraviroc – efavirenz	efavirenz ↓ maraviroc levels 45%	↑ maraviroc dose to 600mg twice daily

Pharmaceutical Care Plan

Contact MDs to…

- Discuss using maraviroc in patient's regimen. Conflicting interactions give two different dosing schemes for maraviroc. It is unclear what the right dosing is for this patient as there are not any studies of this specific combination or drugs. One plan would be to contact MD to determine whether patient actually needs maraviroc as part of first line regimen (not typical initial therapy by treatment guidelines - perhaps there is some strange transmitted resistance pattern) or whether patient can avoid itraconazole and use alternate therapy for onchomycosis .

Patient Counseling Notes

- Encourage adherence
- Explain conflicting drug interactions
- Discuss potential side effects of his regimen

Drug Interactions Workshop Case Study Worksheet

Case: _____

Drug Interactions	Expected Outcome of Interactions
Pharmaceutical Care Plan	Patient Counseling Points

Notes

Systematic Approach to HIV Drug Interaction Evaluation

1 Complete and Accurate Medication History

- ☑ Check for OTC, herbal/non-traditional medications; illicit drugs
- ☑ Medications from other providers
- ☑ All medications medically necessary?
- ☑ Address adherence: patient taking all medications?
- ☑ Any relevant medication schedule issues:
  - ➲ Food interactions
  - ➲ Drug administration

2 Check for Documented (Probable) Interactions

DOCUMENTED = interaction data exist

- ☑ Check at least 2 references for documented drug interactions! See other side for resources and references:
  - ➲ Primary literature
  - ➲ PUBMED
  - ➲ Online databases
  - ➲ Drug interaction texts
  - ➲ Package inserts

"Red Flag" (Potentially Interacting) Drugs:

- PI- or NNRTI-containing regimens
- Maraviroc-containing regimens
- Drug classes metabolized by liver: psychoactives, anticonvulsants, OCPs, statins
- Tenofovir-containing regimens
- PPI

3 Consider Possible (Theoretical) Interactions

Consider undocumented but possible interactions:

- ☑ Focus on PK section of drug monographs
- ☑ Consider clearance route, metabolic pathways, P450 isoenzyme systems
- ☑ Drugs may interact by acting as precipitant (inhibitors/inducers) or object (substrates) drugs or both
- ☑ Expect interactions if P450 inhibitor or inducer used w/ P450 substrate
- ☑ Package insert & drug references contain information on hepatic metabolism & isoenzymes involved

4 Assess Clinical Significance / Consequences

- ? What is the consequence of the interaction?
- ? Which drug level is affected?
- ? Onset of interaction?
  - ▪ Inhibition usually occurs quickly
  - ▪ Induction may take days or weeks
- ? Is interaction bi-directional?
- ? What is a clinically significant change in drug levels?
- ? At what point does toxicity occur? Can toxicity be monitored?
- ? If drug levels decline, when does risk of resistance develop?

5 Management and Monitoring of Interactions

- ? Are there therapeutically acceptable alternatives? (e.g. rifabutin instead of rifampin)
- ? Are there recommended dose adjustments?
  Dosage Form Modifications and Renal/Hepatic Dosing of Antiretrovirals:
  http://www.nccc.ucsf.edu/Clinical_Resources/Pharmacy/ARV%20dosage%20table%202008.pdf
- ? Empiric dose adjustments

Monitor for toxicities or subtherapeutic responses.

OCTOBER 2008

Handout prepared by Cristina Gruta, PharmD and Robert Teague, MSSW
Pacific AIDS Education and Training Center – University of California, San Francisco

Selected Antiretroviral Drug Interaction Resources

National HIV/AIDS Clinicians' Consultation Center

CALL FOR EXPERT CONSULTATION!

National HIV Telephone Consultation Service: 1-800-933-3413
National Clinician's Post-Exposure Prophylaxis Hotline: 1-888-448-4911
National Perinatal HIV Hotline: 1-888-448-8765

HIV-Specific References

DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents:
http://aidsinfo.nih.gov/Guidelines/Default.aspx?MenuItem=Guidelines
Includes downloadable drug interaction tables

HIV InSite Database of Antiretroviral Drug Interactions:
http://hivinsite.ucsf.edu/insite?page=ar-00-02
Fully referenced searchable database of ARV drug interactions

AIDSinfo Drug Database:
http://aidsinfo.nih.gov/DrugsNew/Default.aspx?MenuItem=Drugs&Search=On
Fact sheets on ARVs describing use, pharmacology, side effects, and more

HIV-druginteractions.org (Liverpool Pharmacology Group)
http://www.hiv-druginteractions.org/
Includes downloadable drug interaction tables

Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis
http://www.cdc.gov/TB/TB_HIV_Drugs/default.htm
Updated CDC recommendations for managing drug-drug interactions between ARVs and rifamycins for treatment of tuberculosis

Toronto General Hospital Immunodeficiency Clinic
http://www.tthhivclinic.com/interact_tables.html
Includes downloadable drug interaction tables

General Drug Interaction References

AHFS Drug Information
http://www.ashp.org/ahfs/index.cfm
Online drug reference portal from American Society of Health-System Pharmacists, including access to Lexi-Comp ONLINE

Cytochrome P450 Drug Interaction table
http://medicine.iupui.edu/flockhart/table.htm
List of CYP450 enzyme substrates, inhibitors and inducers

Facts and Comparisons
http://online.factsandcomparisons.com/index.aspx
(requires subscription)

RxList Internet Drug Index
http://www.rxlist.com/
Current brand and generic pharmaceutical drug information from WebMD

Patient Education Resources

AIDS InfoNet
http://www.aidsinfonet.org/
HIV/AIDS treatment and drug information single-topic Fact Sheets in English and Spanish

AIDSmeds.com
http://www.aidsmeds.com/cmm/
Includes "Check My Meds" searchable drug interactions database; checks for food interactions

The Body – HIV Drug-Drug Interactions
http://www.thebody.com/index/treat/interactions.html
Comprehensive list and links to HIV drug interactions information and education resources

Project Inform
http://www.projinf.org/
Extensive HIV/AIDS treatment information and drug interactions tables

Provider Training & Clinical Resources

AETC *Clinical Manual for Management of the HIV-Infected Adult*
http://www.aids-etc.org/aidsetc?page=cm-00-00
Includes chapters on Antiretroviral Medications and Oral Contraceptives; Drug-Drug Interactions with HIV-Related Medications; Recreational Drugs and Antiretroviral therapy

Clinical Care Options: Drug-Drug Interactions in the Treatment of HIV
http://www.clinicaloptions.com/HIV/Treatment%20Updates/Drug-Drug%20Interactions.aspx
(requires registration)
Includes downloadable interactive drug-drug interactions calculator tool

HIV Web Study
http://depts.washington.edu/hivaids/drug/index.html
Interactive case-based clinical training modules

Drug-Drug Interactions with HIV-Related Medications

Background

Drug-drug interactions are common concerns of both patients with HIV and their health care providers. The issues involved in evaluating and drug interactions are complex. Although many questions can be articulated simply (eg, "What antidepressant is least likely to have drug interactions with HIV medications?"), the responses to these questions involve more complex concerns (eg, "In choosing an antidepressant for my patient with HIV, I must consider efficacy, adverse effects, and tolerability as well as drug interactions.").

This complexity is increased because antiretroviral agents, particularly protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), can cause and be affected by alterations in the activity of the cytochrome P450 enzymes in the liver. These enzymes are responsible for metabolizing many medications. Understanding the relevance of the influence of P450 enzymes is challenging because of several factors, including the following:

- Different drugs affect different P450 enzymes.
- Some medications have dosage-related responses that influence their effects on P450 enzymes.
- Formal pharmacokinetic studies on drug combinations are limited.
- Even when pharmacokinetic data exist for specific drug combinations, the clinical significance of any changes in pharmacokinetic parameters may not be clear.
- Patients taking HIV medications often have complex drug regimens. The interaction of only 2 drugs is rarely the concern; more often, patients are taking 3 or more medications that could influence interactions. Pharmacokinetic studies that evaluate the clinical significance of drug interactions involving more than 2 medications are less likely to be available.
- The P450 system is not the only influence on medication activity. Other influences include absorption, food-drug interactions, protein binding, altered activation of medications intracellularly, and altered efflux-pump activity.

Information on various drug-drug interactions is available in guidelines and via the Internet (see "Resources" below). Such resources can provide data regarding 2-drug combinations, but rarely consider all the complexities outlined above. What follows, therefore, is a suggested approach to considering drug-drug interactions in the management of HIV-infected patients and making patient-specific decisions.

S: Subjective

A new patient arrives for his clinic intake appointment. The patient receives his medical care from a local infectious-disease physician who has only a handful of HIV-infected patients in her practice. The patient was recently released from the hospital with a discharge diagnosis of pneumonia and *Mycobacterium avium* complex (MAC). He is not yet taking HIV medications, but is likely to start them in the next several weeks after the establishment of care and adherence support programs. Other problems include hyperlipidemia, erectile dysfunction, diabetes, depression, and herpes. The clinician wants to review the patient's medication list to check for any potential drug-drug interactions.

O: Objective

Review the patient's pharmacy records for current medications. As requested, the patient has brought in all his medications from home for review. His current medication list includes the following:

- Clarithromycin 500 mg twice daily
- Ethambutol 1,000 mg daily
- Rifabutin 300 mg daily
- TMP-SMX (Septra, Bactrim) DS 1 tablet daily
- Lovastatin 20 mg daily
- Metformin 500 mg twice daily
- Bupropion 150 mg daily
- Acyclovir 400 mg twice daily
- Milk thistle *(silymarin)*
  (patient takes as needed for energy and liver health)

A: Assessment

Step 1: Identify interactions and classify them as follows:

- Definite interactions
- Probable interactions
- Possible interactions

Definite Drug Interactions

A drug interaction is definite if a high level of evidence is available regarding the drug combination, the clinical significance of the interaction is well understood, and consensus exists regarding the management strategy (eg, dosage adjustments). Common definite interactions for HIV patients include:

- Certain combinations of HIV agents (eg, boosted PIs, NNRTI + PI combinations)
- Rifamycins and PIs or NNRTIs
- Statins and PIs + NNRTIs
- Erectile dysfunction agents and PIs
- Methadone and PIs

Probable Drug Interactions

A drug interaction is probable if the limited available evidence suggests that an interaction may occur, even if the clinical outcome or significance may not be clearly established. Effective management of a probable interaction is based on assessment and clinical judgment about the risks and benefits of a particular combination for that patient. Examples of probable interactions with HIV-related medications include:

- Antidepressants and PIs or NNRTIs
- Oral contraceptives and PIs
- Warfarin and PIs or NNRTIs
- Proton pump inhibitors or H-2 blockers and atazanavir

Possible Drug Interactions

Possible drug interactions may be difficult to distinguish from probable drug interactions, but in these cases, only theoretical evidence is available. The proper management of such an interaction requires weighing the risks and benefits of the combination and making sound clinical judgments. Examples of possible drug interactions with HIV medications include:

- Herbal products and PIs or NNRTIs (except in the case of St. John's wort, for which definite information on interactions is available)
- Antidiabetic medications and PIs or NNRTIs
- Antifungal agents and PIs or NNRTIs (except in the case of voriconazole, for which definite information on interactions is available)
- Antiseizure medications and PIs or NNRTIs
- Antipsychotic agents and PIs or NNRTIs

Memorizing all the potential drug interactions is impossible. It is possible, however, to remember a few commonly used drug combinations with the potential for clinically significant interactions. The above examples of definite, probable, and possible interactions are reasonable "red flag" drug combinations that can be recalled easily. In addition, certain Internet resources allow you to submit all of a patient's current medications and planned additions (eg, lopinavir/ritonavir as part of a new antiretroviral regimen) and receive feedback on potential interactions (see "Resources" below). Finally, consultation with clinical pharmacists can aid in identifying and classifying potential interactions.

P: Plan

Step 2: The patient described above will start an antiretroviral regimen of lopinavir/ritonavir + zidovudine + lamivudine. The PI may cause problematic drug-drug interactions with some of his other medications. Develop a plan for management when lopinavir/ritonavir is added to this regimen.

For this patient, the following definite interactions should be of concern:

- Rifabutin and lopinavir/ritonavir
- Lovastatin and lopinavir/ritonavir

Refer to available references for management suggestions. Such references include:

- DHHS Adult and Adolescent Antiretroviral Treatment Guidelines *http://www.aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?MenuItem=Guidelines&GuidelineID=7*
- HIV InSite Database of Antiretroviral Drug Interactions: *http://hivinsite.ucsf.edu/arvdb?page=ar-00-02*

- Toronto General Hospital Drug Interaction Tables *http://tthhivclinic.com/interact_tables.html*
- Discover Drug Interaction Checker *http://health.discovery.com/encyclopedias/checker/checker.jsp*
- Check my Meds on AIDSMeds.com *http://aidsmeds.com/cmm/DrugsNewContent.asp*

Most of these sites include specific dosage adjustments or alternative agents to consider when managing these drug combinations. The following are suggestions for the above interactions:

- The rifabutin dosage should be 150 mg every other day with standard lopinavir/ritonavir dosing. Alternatively, discuss with the patient's primary care provider whether rifabutin is important to the current MAC regimen or whether the patient could be treated adequately with just clarithromycin + ethambutol to avoid the above interactions.
- Lovastatin should be discontinued in this patient when lopinavir/ritonavir is begun. To manage hyperlipidemia, the patient should be switched to safer statins such as pravastatin or low-dose atorvastatin.

Although this patient's current medication list does not contain an erectile dysfunction agent, the patient should be educated about the definite interactions and dosage adjustments recommended for patients using those agents with PIs. Some patients may obtain erectile dysfunction agents outside the care of their physician and, if unaware of the interactions and suggested dosage adjustments, may be at risk for life-threatening consequences.

Some additional probable or possible interactions should be considered if PIs are begun, including:

- Bupropion with lopinavir/ritonavir
- Milk thistle with lopinavir/ritonavir

The Web sites and references listed above include some information about these potential interactions, but no specific management or dosage adjustments are given. This patient should be monitored for increased effects of bupropion and educated about potential interactions with milk thistle. Clinical judgment and decision making with the primary care provider and other subspecialists (eg, psychiatrists) may be required. Consultation with clinical pharmacy services also may assist in evaluating the potential significance of an interaction and developing management strategies.

Patient Education

- Instruct patients that HIV medications, in particular PIs and NNRTIs, have a high potential for significant drug interactions.
- Tell patients to take all their medicines, including any herbal supplements and over-the-counter remedies, with them to all medical appointments. If they cannot take the actual bottles with them, they should make a list of current prescribed medications, supplements, and over-the-counter medications.
- Patients should have their primary care provider or pharmacist review any newly prescribed medications along with their current list of medicines. This is especially important if another physician prescribes a new medication.
- Patients should not "borrow" medications from friends or family. Assure patients that if they have a problem that needs medical treatment, their primary care provider will discuss it and choose the safest treatments for them.
- Tell patients that if they are considering buying a new nutritional or herbal supplement or an over-the-counter product, they should consult their pharmacist or primary care provider about interactions with drugs on their current medication list.
- Not all drug interactions are cause for alarm. Some drug combinations are safe for certain people, but less safe for others. Warn patients not to stop taking any medicines without the advice of their primary care provider.

References

- Liedtke MD, Lockhart SM, Rathbun RC. *Anticonvulsant and antiretroviral interactions.* Ann Pharmacother. 2004 Mar;38(3):482-9.
- Rainey PM. *HIV drug interactions: the good, the bad, and the other.* Ther Drug Monit. 2002 Feb;24(1):26-31.
- Piscitelli SC, Gallicano KD. *Interactions among drugs for HIV and opportunistic infections.* N Engl J Med. 2001 Mar 29;344(13):984-96.
- Sheehan NL, Kelly DV, Tseng AL, et al. *Evaluation of HIV drug interaction web sites.* Ann Pharmacother. 2003 Nov;37(11):1577-86.
- U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.* October 10, 2006. Available online at aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7. Accessed July 7, 2007.

Resources

- *HIV InSite Database of Antiretroviral Drug Interactions:* http://hivinsite.ucsf.edu/arvdb?page=ar-00-02
- *Toronto General Hospital Drug Interaction Tables:* http://tthhivclinic.com/interact_tables.html
- *Discover Drug Interaction Checker:* http://health.discovery.com/encyclopedias/checker/checker.jsp
- *Check my Meds on* AIDSMeds.com*:* http://aidsmeds.com/cmm/DrugsNewContent.asp

Dosage Adjustments for ARV-ARV Drug Interactions

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Many antiretroviral medications used to treat HIV infection, particularly certain protease inhibitors and nonnucleoside reverse transcriptase inhibitors, interact with other antiretroviral agents. These interactions are usually due to effects on hepatic drug metabolism and can cause clinically significant alterations in serum drug concentrations. Certain antiretroviral agents require dosage adjustment (or pharmacokinetic enhancement) when coadministered, and some combinations are contraindicated. This table shows evidence-based adult dosage adjustments for interacting antiretroviral medications. Not all are approved by the U.S. Food and Drug Administration.

For further information, see the Database of Antiretroviral Drug Interactions (http://hivinsite.ucsf.edu/InSite?page=ar-00-02). For information about pharmacokinetic enhancement ("boosting") of protease inhibitors by ritonavir, see Dosing for Ritonavir-Boosted Protease Inhibitors (http://hivinsite.ucsf.edu/InSite?page=md-rr-23).

Drug	Coadministered Drug	Dosage Adjustment
Amprenavir	As of June 2005, no longer manufactured for adult dosing; consider fosamprenavir.	
Atazanavir	Efavirenz	• Atazanavir 300 mg QD + ritonavir 100 mg QD; efavirenz 600 mg QD
	Nevirapine	• Dosage adjustment of atazanavir not established; consider atazanavir 300 mg QD + ritonavir 100 mg QD; nevirapine 200 mg BID
	Maraviroc	• Atazanavir 300 mg QD + ritonavir 100 mg QD; maraviroc 150 mg BID OR • Atazanavir 400 mg QD; maraviroc 150 mg BID
	Saquinavir	• Dosage adjustment not established; consider atazanavir 300 mg QD + ritonavir 100 mg QD; saquinavir 1,600-2,000 mg QD
	Tenofovir	• Atazanavir 300 mg QD + ritonavir 100 mg QD; tenofovir 300 mg QD
	Tipranavir	• Not recommended
Delavirdine	Indinavir	• Delavirdine 400 mg TID; indinavir 600 mg Q8H
	Saquinavir	• Delavirdine 400 mg TID; saquinavir 800 mg TID (monitor LFTs)
Didanosine	Tenofovir	• For body weight ≥60 kg, didanosine 250 mg QD; tenofovir 300 mg QD • For body weight <60 kg, didanosine 200 mg QD; tenofovir 300 mg QD
Efavirenz	Atazanavir	• Efavirenz 600 mg QD; atazanavir 300 mg QD + ritonavir 100 mg QD
	Fosamprenavir	• Efavirenz 600 mg QD; fosamprenavir 700 mg BID + ritonavir 100 mg BID OR • Efavirenz 600 mg QD; fosamprenavir 1,400 mg QD + ritonavir 300 mg QD (QD dosing of fosamprenavir is not recommended for protease inhibitor-experienced patients)
	Indinavir	• Efavirenz 600 mg QD; indinavir 800-1,000 mg BID + ritonavir 100-200 mg BID

Drug	Coadministered Drug	Dosage Adjustment
	Lopinavir/ritonavir	• Efavirenz 600 mg QD; lopinavir/ritonavir 400/100 mg (2 tablets) BID (for ARV-naive patients) or 600/150 (3 tablets) BID (for ARV-experienced patients)
	Maraviroc	• Efavirenz 600 mg QD; maraviroc 600 mg BID
	Saquinavir	• Dosage adjustment of saquinavir not established; consider efavirenz 600 mg QD; saquinavir 1,000 mg BID + ritonavir 200 mg BID
	Tipranavir	• Dosage adjustment not necessary
Fosamprenavir	Efavirenz	• Fosamprenavir 700 mg BID + ritonavir 100 mg BID; efavirenz 600 mg QD OR • Fosamprenavir 1,400 mg QD + ritonavir 300 mg QD; efavirenz 600 mg QD (QD dosing of fosamprenavir is not recommended for protease inhibitor-experienced patients)
	Lopinavir/ritonavir	• Dosage adjustment of fosamprenavir and lopinavir/ritonavir not established; consider fosamprenavir 1,400 mg BID; lopinavir/ritonavir 600/150 mg (3 tablets) BID
	Maraviroc	• Fosamprenavir 1,400 mg BID; maraviroc 150 mg BID OR • Fosamprenavir 700 mg BID + ritonavir 100 mg BID; maraviroc 150 mg BID OR • Fosamprenavir 1,400 mg QD + ritonavir 200 mg QD; maraviroc 150 mg BID
	Nevirapine	• Dosage adjustment of fosamprenavir not established; consider fosamprenavir 700 mg BID + ritonavir 100 mg BID; nevirapine 200 mg BID OR • Fosamprenavir 1,400 mg QD + ritonavir 300 mg QD; nevirapine 200 mg BID (QD dosing of fosamprenavir is not recommended for protease inhibitor-experienced patients)
	Saquinavir	• Dosage adjustment not established; consider fosamprenavir 700 mg BID + ritonavir 100-200 mg BID; saquinavir 1,000 mg BID
	Tipranavir	• Not recommended
Indinavir	Delavirdine	• Indinavir 600 mg Q8H; delavirdine 400 mg TID
	Efavirenz	• Indinavir 800-1,000 mg BID + ritonavir 100-200 mg BID; efavirenz 600 mg QD
	Lopinavir/ritonavir	• Indinavir 600-800 mg BID; lopinavir/ritonavir 400/100 mg (2 tablets) BID
	Maraviroc	• Indinavir 800 mg BID + ritonavir 100 mg BID; maraviroc 150 mg BID OR • Indinavir 800 mg Q8H; maraviroc 150 mg BID
	Nelfinavir	• Indinavir 1,200 mg BID; nelfinavir 1,250 mg BID
	Nevirapine	• Consider indinavir 800-1,000 mg BID + ritonavir 100-200 mg BID; nevirapine 200 mg BID
	Tipranavir	• Not recommended
Lopinavir/ ritonavir	Efavirenz	• Lopinavir/ritonavir 400/100 mg (2 tablets) BID (for ARV-naive patients) or 600/150 (3 tablets) BID (for ARV-experienced patients); efavirenz 600 mg QD
	Fosamprenavir	• Dosage adjustment of fosamprenavir and lopinavir/ritonavir not established; consider lopinavir/ritonavir 600/150 mg (3 tablets)

Drug	Coadministered Drug	Dosage Adjustment
		BID; fosamprenavir 1,400 mg BID
	Indinavir	• Lopinavir/ritonavir 400/100 mg (2 tablets) BID; indinavir 600-800 mg BID
	Maraviroc	• Lopinavir/ritonavir 400/100 mg (2 tablets) BID; maraviroc 150 mg BID
	Nevirapine	• Lopinavir/ritonavir 400/100 mg (2 tablets) BID (ARV-naive patients) or 600/150 (3 tablets) BID (for ARV-experienced patients); nevirapine 200 mg BID
	Saquinavir	• Lopinavir/ritonavir 400/100 mg (2 tablets) BID; saquinavir 1,000 mg BID
	Tipranavir	• Not recommended
Maraviroc	Amprenavir Atazanavir Darunavir Fosamprenavir Indinavir Lopinavir/ritonavir Saquinavir	• Maraviroc 150 mg BID; protease inhibitor at usual dose
	Efavirenz Etravirine* (if used without PIs listed above or other strong CYP3A inhibitor)	• Maraviroc 600 mg BID, efavirenz 600 mg QD
	Nevirapine	• Maraviroc 300 mg BID (dosage adjustment not necessary); nevirapine 200 mg BID
	Tipranavir	• Maraviroc 300 mg BID (dosage adjustment not necessary); tipranavir 500 mg BID + ritonavir 200 mg BID
Nelfinavir	Indinavir	• Nelfinavir 1,250 mg BID; indinavir 1,200 mg BID
	Maraviroc	• Nelfinavir 1,250 mg BID; maraviroc 150 mg BID
Nevirapine	Atazanavir	• Dosage adjustment of atazanavir not studied; consider nevirapine 200 mg BID; atazanavir 300 mg QD + ritonavir 100 mg QD
	Fosamprenavir	• Dosage adjustment of fosamprenavir not established; consider nevirapine 200 mg BID; fosamprenavir 700 mg BID + ritonavir 100 mg BID OR • Nevirapine 200 mg BID; fosamprenavir 1,400 mg QD + ritonavir 300 mg QD (QD dosing of fosamprenavir is not recommended for protease inhibitor-experienced patients)
	Indinavir	• Consider nevirapine 200 mg BID; indinavir 800-1,000 mg BID + ritonavir 100-200 mg BID
	Lopinavir/ritonavir	• Nevirapine 200 mg BID; lopinavir/ritonavir 400/100 mg (2 tablets) BID (for ARV-naive patients), 600/150 mg (3 tablets) BID (for ARV-experienced patients)
	Maraviroc	• Nevirapine 200 mg BID; maraviroc 300 mg BID (dosage adjustment not necessary)
	Saquinavir	• Dosage adjustment of saquinavir not established; consider nevirapine 200 mg BID; saquinavir 400 mg BID + ritonavir 400 mg BID
	Tipranavir	• Dosage adjustment not established
Saquinavir	Atazanavir	• Dosage adjustment not established; consider saquinavir 1,600-2,000 mg QD + atazanavir 300 mg QD + ritonavir 100 mg QD
	Delavirdine	• Saquinavir 800 mg TID; delavirdine 400 mg TID (monitor LFTs)

Drug	Coadministered Drug	Dosage Adjustment
	Efavirenz	• Dosage adjustment of saquinavir not established; consider saquinavir 1,000 mg BID + ritonavir 200 mg BID; efavirenz 600 mg QD
	Fosamprenavir	• Dosage adjustment not established; consider saquinavir 1,000 mg BID + ritonavir 100-200 mg BID; fosamprenavir 700 mg BID
	Lopinavir/ritonavir	• Saquinavir 1,000 mg BID; lopinavir/ritonavir 400/100 mg (2 tablets) BID
	Maraviroc	• Saquinavir 1,000 mg BID + ritonavir 100-200 mg BID; maraviroc 150 mg BID
	Nevirapine	• Dosage adjustment of saquinavir not established; consider saquinavir 400 mg BID + ritonavir 400 mg BID; nevirapine 200 mg BID
	Tipranavir	• Not recommended
Tenofovir	Atazanavir	• Tenofovir 300 mg QD; atazanavir 300 mg QD + ritonavir 100 mg QD
	Didanosine	• Tenofovir 300 mg QD; didanosine 250 mg QD (for body weight ≥60 kg) • Tenofovir 300 mg QD; didanosine 200 mg QD (for body weight <60 kg)
Tipranavir	Atazanavir Fosamprenavir Lopinavir/ritonavir Saquinavir	• Combination of tipranavir and other protease inhibitors is not currently recommended
	Maraviroc	• Tipranavir 500 mg BID + ritonavir 200 mg BID; maraviroc 300 mg BID (dosage adjustment not necessary)
	Efavirenz Nevirapine	• Dosage adjustment not necessary

Abbreviations: ARV = antiretroviral; BID = 2 times daily; LFTs = liver function tests; PI = protease inhibitor; Q8H = every 8 hours; QD = once daily; TID = 3 times daily

* Etravirine is an investigational nonnucleoside reverse transcriptase inhibitor.

Table 21. Drugs That Should Not Be Used With PI, NNRTI, or CCR5 Antagonist Antiretrovirals

(Updated January 29, 2008)

Drug Category[#]	Calcium channel blocker	Cardiac	Lipid Lowering Agents	Anti-Mycobacterial[‡]	Anti-histamine[∂]	Gastro-intestinal drugs[∂]	Neuro-leptic	Psychotropic	Ergot Alkaloids (vasoconstrictor)	Herbs	Other
Atazanavir	Bepridil	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	fluticasone indinavir irinotecan
Darunavir/ ritonavir	(none)	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	as above	St. John's wort	carbamazepine phenobarbital phenytoin fluticasone[⊗]
Fosamprenavir	Bepridil	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	as above	St. John's wort	Delavirdine fluticasone oral contraceptives
Indinavir	(none)	amiodarone	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	as above	St. John's wort	Atazanavir
Lopinavir/ Ritonavir	(none)	flecainide propafenone	simvastatin lovastatin	rifampin[∫] rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	as above	St. John's wort	fluticasone[⊗]
Nelfinavir	(none)	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	as above	St. John's wort	
Ritonavir	Bepridil	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	as above	St. John's wort	voriconazole (with RTV ≥ 400mg BID) fluticasone[⊗] alfuzosin
Saquinavir/ ritonavir	(none)	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam [Σ] triazolam	as above	St. John's wort garlic supplements	fluticasone
Tipranavir/ ritonavir	Bepridil	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam [Σ] triazolam	as above	St. John's wort	fluticasone[⊗]
Delavirdine	(none)	(none)	simvastatin lovastatin	rifampin rifapentine[‡‡] rifabutin	astemizole terfenadine	cisapride H2 blockers proton pump inhibitors	(none)	alprazolam midazolam[Σ] triazolam	as above	St. John's wort	amprenavir fosamprenavir carbamazepine phenobarbital phenytoin
Efavirenz	(none)	(none)	(none)	rifapentine[‡‡]	astemizole terfenadine	cisapride	(none)	midazolam[Σ] triazolam	as above	St. John's wort	voriconazole
Etravirine	(none)	(none)	(none)	rifampin rifapentine[‡‡]	(none)	(none)	(none)	(none)	(none)	St John's wort	Unboosted PI, ritonavir-boostted atazanavir, fosamprenavir, or tipranavir, other NNRTIs, Carbamazepine, phenobarbital, phenytoin
Nevirapine	(none)	(none)	(none)	rifampin rifapentine[‡‡]	(none)	(none)	(none)	(none)	(none)	St. John's wort	
Maraviroc	•	•	•	rifampin rifapentine[‡‡]	•	•	•	•	•	St. John's wort	•

[#] Certain listed drugs are contraindicated based on theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with P450–3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur among patients.

[‡‡] HIV patients treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens; an alternative agent is recommended.

[∫] In one small study, higher doses of RTV (additional 300mg BID) or a double dose of LPV/RTV offset rifampin-inducing activity of LPV. Of note, 28% of subjects discontinued because of increases in LFTs. The safety of this combination is still under evaluation. Further studies are needed.

[Σ] Midazolam can be used with caution as a single dose and given in a monitored situation for procedural sedation.

[†] This is likely a class effect.

[∂] Astemizole and terfenadine are not marketed in the United States. The manufacturer of cisapride has a limited-access protocol for patients meeting specific clinical eligibility criteria.

[⊗] Concomitant use of fluticasone and ritonavir results in significantly reduced serum cortisol concentrations. Coadministration of fluticasone and ritonavir or any ritonavir-boosted PI regimen is not recommended unless potential benefit outweighs risk of systemic corticosteroid side effects. Fluticasone should be used with caution and alternatives considered if given with an unboosted PI regimen.

Suggested Alternatives:

Cerivastatin (no longer marketed in the United States), simvastatin, lovastatin: Pravastatin and fluvastatin have the least potential for drug-drug interactions (except for pravastatin with darunavir/ritonavir, see Table 22a); atorvastatin should be used with caution, using the lowest possible starting dose and monitor closely; no pharmacokinetic data or safety data are available for coadministration of rosuvastatin with the antiretroviral agents.

Rifabutin: clarithromycin, azithromycin (MAI prophylaxis); clarithromycin, azithromycin, ethambutol (MAI treatment)

Astemizole, terfenadine (no longer marketed in the United States): desloratadine, loratadine, fexofenadine, cetirizine

Midazolam, triazolam: temazepam, lorazepam

Table 22a. Drug Interactions Among Antiretrovirals and Other Drugs: PIs and Maraviroc

 (Updated January 29, 2008)

Drug Interactions Requiring Dose Modifications or Cautious Use		
Drugs Affected	**Atazanavir (ATV)**	**Fosamprenavir (FPV)**
ANTIFUNGALS		
Itraconazole	No data, but potential for bi-directional inhibition between itraconazole and PIs, monitor for toxicities.	No data, but potential for bi-directional inhibition between itraconazole and PIs, monitor for toxicities. Dose: Dose adjustment for patients receiving >400mg/day may be needed.
Ketoconazole	Unboosted: No dosage adjustment necessary. RTV boosted: See RTV recommendations.	No data, but presumably similar interaction as seen with APV with an increase in both APV and ketoconazole levels (APV ↑ 31%; ketoconazole ↑ 44%). Dose: Consider ketoconazole dose reduction if dose is >400mg/day. If FPV/r: Use with caution; do not exceed 200mg ketoconazole daily.
Voriconazole	RTV boosted: No data, but potential for bi-directional inhibition between voriconazole and PIs exists; monitor for toxicities. See RTV recommendations if boosted with RTV.	No data, but potential for bi-directional inhibition between voriconazole and PIs; monitor for toxicities. See RTV recommendations if boosted with RTV.
ANTI-MYCOBACTERIALS		
Clarithromycin	Levels: clarithromycin AUC ↑ 94% and may cause QTc prolongation. Clarithromycin active metabolite concentrations are significantly reduced. Dose: ↓ clarithromycin dose by 50%. Consider alternative therapy.	Presumably similar interaction and recommendation as APV. Levels: APV AUC ↑ 18%. No change in clarithromycin AUC. No dose adjustment.
Rifabutin	Levels: Rifabutin AUC ↑ 2.5-fold Dose: ↓ rifabutin dose to 150mg QOD or 3x/week[¢]	Rifabutin 150mg QOD + FPV 700/100mg BID, rifabutin unchanged. No data on FPV level. Dose: No change in FPV dose; decrease rifabutin to 150mg QD or 300mg 3x/week[¢]. If RTV-boosted FPV, reduce rifabutin dose to 150mg QOD or 3x/week[¢].
Rifampin	Should not be coadministered.	A substantial decrease in APV AUC (≈ ↓ 82%) is expected based on the interaction with APV. Should not be coadministered.
HORMONAL CONTRACEPTIVES		
	Levels: Ethinyl estradiol AUC ↑ 48%, norethindrone AUC ↑ 110% Dose: use lowest effective dose or alternative methods.	An increase in ethinyl estradiol and norethindrone levels occurred with APV, and APV levels ↓ 20%. Do not coadminister; alternative methods of contraception are recommended.
LIPID-LOWERING AGENTS		
Atorvastatin	Atorvastatin levels have potential for large increase. Use lowest possible starting dose of atorvastatin with careful monitoring.	Atorvastatin AUC ↑ 150% - use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	No data.	No data.
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use
ANTICONVULSANTS		
Carbamazepine **Phenobarbital** **Phenytoin**	Unknown, but may decrease ATV levels substantially. Monitor anticonvulsant level and virologic response. Consider using alternative anticonvulsant or monitoring ATV level and boosting with RTV if necessary.	Unknown, but may decrease APV levels substantially. Monitor anticonvulsant levels and virologic response, or consider alternative anticonvulsant. Consider monitoring APV levels and boosting with RTV if necessary.
Methadone	No change in methadone or ATV levels.	With APV, R-methadone levels ↓ 13%, and APV Cmin ↓ 25%. The interaction with FPV is presumed to be similar. Monitor and titrate methadone if needed.

[¢] Rifabutin: At least 3x/week is recommended if CD4 cell count is <100/mm^3

Table 22a. Drug Interactions Among Antiretrovirals and Other Drugs: PIs and Maraviroc

 (Updated January 29, 2008)

Drug Interactions Requiring Dose Modifications or Cautious Use		
Drugs Affected	**Atazanavir (ATV)**	**Fosamprenavir (FPV)**
ERECTILE DYSFUNCTION AGENTS		
Sildenafil	Sildenafil levels have potential for increase. Start with reduced dose of 25mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 2- to 11-fold with APV. Use cautiously. Start with reduced dose of 25mg every 48 hours and monitor for adverse effects.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal=17.5h). Start with a 5mg dose, and do not exceed a single dose of 10mg every 72 hours.	No data, but concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5 mgdose, and do not exceed a single dose of 10mg every 72 hours.
Vardenafil	No data, but vardenafil AUC may be substantially increased. Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. Do not exceed 2.5mg in 72 hours if administered with RTV.	No data, but vardenafil AUC may be substantially increased. Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. Do not exceed 2.5mg in 72 hours if administered with RTV.
MISCELLANEOUS	Diltiazem: AUC ↑ 125%, ↓ diltiazem dose by 50%; ECG monitoring is recommended. Other calcium channel blockers: caution is warranted; dose titration should be considered; ECG monitoring is recommended. Irinotecan: ATV inhibits UGT and may interfere with irinotecan metabolism; avoid concomitant use. H_2-receptor antagonists: • Not recommended with unboosted ATV. • H_2-receptor antagonist dose should not exceed a 40mg dose equivalent of famotidine BID. ATV 300mg + RTV 100mg should be administered simultaneously with, and/or >10 hours after the H_2-receptor antagonist. • In treatment experienced patients, if TDF is used with H_2-receptor antagonists, ATV 400mg + RTV 100mg should be used. Proton-Pump Inhibitors (PPI): • PPIs are not recommended for patients receiving unboosted ATV or in treatment-experienced patients. • For treatment-naïve patients, PPI dose not exceeding a 20mg dose equivalent of omeprazole may be taken approximately 12 hours prior to ATV 300mg + RTV 100mg. Antacids and buffered medications: Reduced ATV concentrations are expected with simultaneous administration; give ATV 2 hrs before or 1 hr after these medications.	H2 Blockers: Coadministration of ranitidine with FPV decreases (↓) APV AUC 30%; Cmin unchanged. Separate administration if coadministration is necessary. Monitor closely for desired virologic response. Consider boosting with RTV. Proton-Pump Inhibitors: No effect of esomeprazole 20mg on APV AUC, C_{max}, or C_{min}, regardless of whether FPV was given with or without ritonavir.

Table 22a. Drug Interactions Among Antiretrovirals and Other Drugs: PIs and Maraviroc

 (Updated January 29, 2008)

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Darunavir + Ritonavir (DRV/RTV)†**	**Indinavir (IDV)**	**Lopinavir + Ritonavir (LPV/r)**
ANTIFUNGALS			
Itraconazole	Level: No data. Dose: Use with caution; do not exceed 200mg itraconazole daily.	Level: IDV 600mg Q8H given with itraconazole 200mg BID: AUC similar to IDV 800mg Q8H. Dose: IDV 600mg Q8H; Itraconazole: Do not exceed 200mg BID.	Levels: Itraconazole ↑ when administered with LPV/r. Dose: Itraconazole – consider not exceeding 200mg/day, or monitor level and toxicity.
Ketoconazole	Levels: DRV AUC □ 42%. Azole AUC □ 3-fold. Dose: Use with caution; do not exceed 200mg ketoconazole QD.	Levels: IDV ↑ 68%. Dose: IDV 600mg Q8H.	Levels: LPV AUC ↓ 13%. Azole ↑ 3-fold. Dose: Use with caution; do not exceed 200mg ketoconazole daily.
Voriconazole	Levels: No data with DRV/r. Voriconazole AUC □ 39% with RTV 100mg BID; coadministration not recommended unless benefit outweighs risk.	Levels: No significant changes in AUC of azole or IDV (healthy subjects). See RTV recommendations if boosted with RTV. Dose: Standard.	Voriconazole AUC ↓ 39% with RTV 100mg BID; Coadministration is not recommended unless the benefit outweighs the risk.
ANTI-MYCOBACTERIALS			
Clarithro-mycin	Levels: Clarithromycin AUC ↑ 57%. DRV:No significant effect. Dose: Adjust clarithromycin dose for moderate & severe renal impairment.	Levels: Clarithromycin ↑ 53%.No dose adjustment.	Levels: ↑ Clarithromycin AUC 77%. Dose: Adjust clarithromycin dose for moderate and severe renal impairment.
Rifabutin	Levels: No data Dose: Decrease rifabutin to 150mg QOD.	Levels: IDV ↓ 32%. Rifabutin ↑ 2X. Dose: ↓ rif to 150mg/d or 300mg 3x/week.[¢] IDV 1,000mg Q8H. If RTV boosted, rif 150mg QOD or 3x/week[¢] continue current dose of boosted IDV.	Levels: Rifabutin AUC ↑ 3-fold. 25-O-desacetyl metabolite ↑ 47.5-fold. Dose: Decrease rifabutin dose to 150mg QOD or 3x/week[¢]; LPV/r: Standard.
Rifampin	Levels: No data, but a significant decrease in DRV concs is expected. **Should not be coadministered.**	Levels: IDV (unboosted) ↓ 89%; IDV (boosted) ↓ 87%; **Should not be coadministered.**	Levels: LPV AUC ↓ 75%.* **Should not be coadministered.**
HORMONAL CONTRACEPTIVES			
	Levels: Potential for ↓ ethinyl estradiol from RTV. Use alternative or additional method with DRV/r.	Levels: Norethindrone ↑ 26%. Ethinylestradiol ↑ 24%. .No dose adjustment.	Levels: Ethinyl estradiol ↓ 42%. Use alternative or additional method.
LIPID-LOWERING AGENTS			
Atorvastatin	Statin exposure from 10mg QD with DRV/r gives similar exposure to 40mg QD alone. Use lowest possible statin starting dose w/careful monitoring.	Levels: Potential for increase in atorvastatin levels. Use lowest possible starting dose of atorvastatin with careful monitoring.	Atorvastatin AUC ↑ 5.88-fold. Use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	Levels: Mean ↑ in statin AUC was 81% with DRV/r. However, statin AUC increased by up to 5-fold in some subjects. Start at lowest dose and titrate up, monitor for toxicities.	No data.	Pravastatin AUC ↑ 33%; no dosage adjustment necessary.
Simvastatin Lovastatin	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.
ANTICONVULSANTS			
Carbamazepine Phenobarbital Phenytoin	Coadministration is expected to result in significant decrease in DRV concentrations. Avoid concomitant use.	Carbamazepine markedly ↓ IDV AUC. Consider alternative anticonvulsant, RTV boosting, and/or monitoring IDV level.	Many possible interactions: carbamazepine: ↑ levels when co-administered with RTV. Use with caution. Monitor anticonvulsant levels. Phenytoin: ↓ levels of LPV, RTV, and of phenytoin when given together. Avoid concomitant use or monitor LPV level.
Methadone	Levels: No data with DRV/r. However, RTV is a known inducer of methadone metabolism. Monitor closely; increase methadone as clinically indicated.	No change in methadone levels.	Methadone AUC ↓ 53%. Opiate withdrawal may occur. Monitor and titrate dose if needed. May require ↑ methadone dose.
ERECTILE DYSFUNCTCION AGENTS			
Sildenafil	Sildenafil AUC from a 25 mg single dose given w/ DRV/r was similar to 100mg given alone. Do not exceed 25 mg q48h; monitor for adverse effects.	Sildenafil AUC ↑ 3-fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 11-fold in combination with RTV. Do not exceed 25mg every 48 hours.
Tadalafil	No data, but concomitant administration is expected to result in substantial increase in tadalafil AUC and half-life (normal = 17.5h). Do not exceed a single dose of 10mg in 72h.	Concomitant administration will result in substantial increase in tadalafil AUC & half-life (normal=17.5h). Start with 5mg dose; do not exceed a single dose of 10mg q72h.	Tadalafil AUC ↑ 124% when coadministered with RTV. Do not exceed a single dose of 10mg every 72 hours.
Vardenafil	No data, but a substantial increase in vardenafil AUC is expected. Do not exceed a single dose of 2.5 mg in 72 hours.	Vardenafil AUC ↑ 16-fold. IDV (unboosted) AUC ↓ 30%. Dose: Consider sildenafil instead of vardenafil if IDV unboosted. Do not exceed vardenafil 2.5mg in 72h if administered w/RTV.	No data, but vardenafil AUC may be substantially increased. Do not exceed a single 2.5mg dose in 72 hours.
Miscellaneous	Paroxetine and Sertraline AUC's ↓ 39% and 49%, respectively. Patients initiated on DRV/r should be monitored closely for antidepressant response. Carefully titrate SSRI dose based on clincal assessment. DRV levels unchanged when DRV/r is administered with omeprazole or ranitidine.	Grapefruit juice ↓ IDV levels by 26%. Vitamin C ≥1 gram/day ↓ IDV AUC by 14% and Cmin by 32%.Amlodipine: Amlodipine AUC ↑ 90% when coadministered with IDV/RTV. No change in IDV/RTV levels. Monitor closely.	LPV/r levels unchanged when tablets are given with omeprazole or ranitidine.

† Darunavir interaction studies were conducted with RTV 100mg BID and mostly with darunavir doses of 300–400mg BID instead of the FDA approved dose of DRV 600mg BID

¢ Rifabutin: At least 3x/week is recommended if CD4 cell count is <100/mm^3.

* In one small study, higher doses of RTV (an additional 300mg BID) or a double dose of LPV/RTV offset rifampin-inducing activity of LPV. Of note, 28% of subjects discontinued treatment because of increases in LFTs. The safety of this combination is still under evaluation. Further studies are needed.

Table 22a. Drug Interactions Among Antiretrovirals and Other Drugs: PIs and Maraviroc

 (Updated January 29, 2008)

	Drug Interactions Requiring Dose Modifications or Cautious Use	
Drugs Affected	**Nelfinavir (NFV)**	**Ritonavir* (RTV)**
ANTIFUNGALS		
Itraconazole	No data, but potential for bi-directional inhibition between itraconazole and PIs; monitor for toxicities.	No data, but potential for bi-directional inhibition between itraconazole and RTV; monitor for toxicities. Dose: Dose adjustment for patients receiving >400mg itraconazole may be needed, or consider monitoring itraconazole level.
Ketoconazole	No dose adjustment necessary.	Levels: ketoconazole ↑ 3X. Dose: Use with caution; do not exceed 200mg ketoconazole daily.
Voriconazole	No data, but potential for bi-directional inhibition between voriconazole and PIs exists; monitor for toxicities.	Levels: voriconazole AUC ↓ 82% when coadministered with 400mg BID of RTV, and concomitant therapy of voriconazole with RTV 400mg BID or higher is contraindicated. Voriconazole AUC ↓ 39% with RTV 100mg BID; administration of voriconazole and RTV 100mg is not recommended unless benefit outweighs risk.
ANTI-MYCOBACTERIALS		
Clarithromycin	No data.	Levels: Clarithromycin ↑ 77%. Dose: Adjust clarithromycin dose for moderate and severe renal impairment.
Rifabutin	Levels: NFV ↓ 32% if 750mg Q8H dose given; no change if 1,250mg Q12H dose used. Rifabutin ↑ 2X. Dose: ↓ rifabutin to 150mg QD or 300mg 3x/wk.[¢] NFV 1,250mg BID.	Levels: Rifabutin ↑ 4X. Dose: ↓ rifabutin to 150mg QOD or dose 3x/week.[¢] RTV: Maintain current dose.
Rifampin	Levels: NFV ↓ 82%. **Should not be coadministered.**	Levels: RTV ↓ 35%. Increased liver toxicity possible. Coadministration may lead to loss of virologic response if RTV sole PI. Alternative antimycobacterial agents, such as rifabutin, should be considered. **Should not be coadministered.**
HORMONAL CONTRACEPTIVES		
	Levels: Norethindrone ↓ 18%. Ethinyl estradiol ↓ 47%. Use alternative or additional method.	Levels: Ethinyl estradiol ↓ 40%. Use alternative or additional method.
LIPID-LOWERING AGENTS		
Atorvastatin	Atorvastatin AUC ↑ 74%. Use lowest possible starting dose of atorvastatin with careful monitoring.	Levels: 450% ↑ when administered with SQV/RTV combination. Use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	No data.	Levels: 50% ↓ when administered with SQV/RTV combination. Dose: Pravastatin dosage adjustment based on lipid response.
Simvastatin **Lovastatin**	Simvastatin AUC ↑ 505%. Potential for large increase in lovastatin AUC. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.
ANTICONVULSANTS		
Carbamazepine **Phenobarbital** **Phenytoin**	Unknown, but may decrease NFV levels substantially. Monitor anticonvulsant levels and virologic response. Consider alternative anticonvulsant or NFV levels.	Carbamazepine: ↑ serum levels when coadministered with RTV. Use with caution. Monitor anticonvulsant levels.
METHADONE	NFV may decrease methadone levels, but opiate withdrawal rarely occurs. Monitor and titrate dose if needed. May require ↑ methadone dose.	Methadone ↓ 37%. Monitor and titrate dose if needed. May require ↑ methadone dose.
ERECTILE DYSFUNCTION AGENTS		
Sildenafil	Sildenafil AUC ↑ 2- to 11-fold. Use cautiously. Start with reduced dose of 25mg every 48 hours; monitor for adverse effects.	Sildenafil AUC ↑ 11-fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5mg dose, and do not exceed a single dose of 10mg every 72 hours.	Tadalafil AUC ↑ 124%. Start with a 5mg dose, and do not exceed a single dose of 10mg every 72 hours.
Vardenafil	No data, but vardenafil AUC may be substantially increased. Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. Do not exceed 2.5mg in 72 hours if administered with RTV.	Vardenafil AUC ↑ 49-fold. RTV AUC ↓ 20%. Dose: Vafdenafil: Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 72 hours. RTV: Maintain current dose.
Miscellaneous		Many possible interactions. Desipramine ↑ 145%; reduce dose. Trazodone AUC ↑ 2.4-fold when given with RTV 200mg BID. Use lowest dose of trazodone and monitor for CNS and CV adverse effects. Theophylline ↓ 47%; monitor theophylline levels. RTV 100mg BID significantly increases systemic exposure of inhaled (oral or nasal) fluticasone and may predispose patients to systemic corticosteroid effects. Coadministration not recommended unless benefit of fluticasone outweighs the risk.

* Drugs for which plasma concentrations may be decreased by coadministration with ritonavir: anticoagulants (warfarin), anticonvulsants (phenytoin, divaproex, lamotrigine), antiparasitics (atovaquone).

¢ Rifabutin: At least 3x/week is recommended if CD4 cell count is <100/mm^3.

Table 22a. Drug Interactions Among Antiretrovirals and Other Drugs: PIs and Maraviroc

 (Updated January 29, 2008)

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Saquinavir[†] (SQV)**	**Tipranavir + Ritonavir (TPV/RTV)**	**Maraviroc (MVC)**
ANTIFUNGALS			
Itraconazole	Bi-directional interaction between itraconazole & SQV has been observed. Dose: Not established, but decreased itraconazole dosage may be warranted. Consider therapeutic drug monitoring for both SQV (if unboosted) and itraconazole.	No data. Use with caution; do not exceed 200mg itraconazole daily.	Possible increase in maraviroc concentration. Dose: 150mg BID.
Ketoconazole	Levels: SQV ↑ 3X. Dose: No dosage adjustment necessary.	No data. Use with caution; do not exceed 200mg ketoconazole daily.	Levels: MVC AUC ↑ 5x. Dose: 150mg BID.
Voriconazole	No data, but potential for bi-directional inhibition between voriconazole and PIs, monitor for toxicities	Potential for bi-directional inhibition between voriconazole and PIs exists. Voriconazole AUC ↓ 39% with RTV 100mg BID; interaction between TPV and voriconazole unknown. Coadministration is not recommended unless the benefit outweighs the risk.	No data, monitor for toxicities.
ANTI-MYCOBACTERIALS			
Clarithromycin	Levels: Clarithromycin ↑ 45%. SQV ↑ 177%. Dose: No dose adjustment.	Levels: TPV ↑ 66%, Clarithromycin ↑ 19%, 14-hydroxy-clarithromycin metabolite ↓ 97%. Dose: No adjustment for patients with normal renal function; reduce clarithromycin dose by 50% for CrCl 30–60 mL/min; reduce clarithromycin dose by 75% for CrCl <30 mL/min.	Possible increase in maraviroc concentration. Dose: 150mg BID.
Rifampin	Levels: SQV ↓ 84%. Marked elevation of transaminases was seen in a pharmacokinetic study, where healthy volunteers received a combination of rifampin 600mg QD + RTV/SQV 100/1,000mg BID. This combination should not be used.	No data; should not be coadministered.	Levels: MVC AUC ↓ 64%. Dose: 600mg BID or use rifabutin instead of rifampin.
Rifabutin	Levels: SQV ↓ 40%. Contraindicated unless SQV/RTV. Dose: Rifabutin 150mg QOD or 3x/week.[ɛ]	Levels: Rifabutin AUC ↑ 2.9-fold. 25-O-desacetyl metabolite ↑ 20.7-fold. Dose: Decrease rifabutin dose to 150mg QOD or 3x/week.[ɛ] Single-dose study, thus the effect of multiple doses of rifabutin on TPV/r PK was not assessed.	No data, potential for induction of MVC metabolism. If used without a strong CYP3A inducer or inhibitor: 300mg BID. Monitor for virologic response. If used with a strong CYP3A inhibitor: 150mg BID.
HORMONAL CONTRACEPTIVES			
	No data.	Levels: Ethinyl estradiol Cmax and AUC ↓ ~ 50%.[a] Use alternative or additional method. Women on estrogen may have increased risk of nonserious rash. Used as hormone replacement therapy, monitor clinically for signs of estrogen deficiency.	No significant interaction, safe to use in combination.
LIPID-LOWERING AGENTS			
Atorvastatin	Levels: 450% ↑ when administered with SQV/RTV combination. Use lowest possible starting dose of atorvastatin with careful monitoring.	Levels: Atorvastatin AUC ↑ 9-fold. Dose: Use lowest possible starting dose of atorvastatin with careful monitoring.	No data, potentially safe to use in combination.
Pravastatin	Levels: 50% ↓ when administered with SQV/RTV combination. No dose adjustment needed. Dose: Pravastatin dosage adjustment based on lipid response.	No data.	No data, potentially safe to use in combination.
Simvastatin Lovastatin	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Potential for large increase in statin levels. Avoid concomitant use.	No data, potentially safe to use in combination.
ANTICONVULSANTS			
Carbamazepine Phenobarbital Phenytoin	Unknown, but may markedly ↓ SQV levels. Consider alternative anticonvulsant. Monitor anticonvulsant levels and consider monitoring SQV level.	No data. Consider alternative anticonvulsant. Monitor anticonvulsant levels and consider obtaining TPV level.	Possible decrease in maraviroc concentration Dose: 600mg BID or use alternative antiepileptic agent.
Methadone	Methadone AUC ↓ 19% when coadministered with SQV/RTV 1,000/100mg BID. Dose: No adjustment for this PI regimen, but monitor and titrate to methadone response as necessary.	No data. Dosage of methadone may need to be increased when coadministered with TPV/r.	No data, potentially safe to use in combination.

[a] Study conducted with TPV/r dose(s) other than FDA-approved dose of 500/200mg BID.

[†] Some drug interaction studies were conducted with Invirase® soft gel capsule. May not necessarily apply to use with Fortovase.

Table 22a. Drug Interactions Among Antiretrovirals and Other Drugs: PIs and Maraviroc

 (Updated January 29, 2008)

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Saquinavir[†] (SQV)**	**Tipranavir + Ritonavir (TPV/RTV)**	**Maraviroc (MVC)**
ERECTILE DYSFUNCTION AGENTS			
Sildenafil	Sildenafil AUC ↑ 2-fold. Use a 25mg starting dose of sildenafil.	No data. Starting dose should not exceed 25 mg sildenafil within 48 hours.	No data, potentially safe to use in combination.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5mg dose, and do not exceed a single dose of 10mg every 72 hours.	No data. Starting dose should not exceed 10mg tadalafil every 72 hours.	No data, potentially safe to use in combination.
Vardenafil	No data, but vardenafil AUC may be substantially increased. Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. Do not exceed a single 2.5mg dose in 72 hours if administered with RTV.	No data. Starting dose should not exceed 2.5mg vardenafil every 72 hours.	No data, potentially safe to use in combination.
Miscellaneous	Grapefruit juice ↑ SQV levels. Dexamethasone ↓ SQV levels.	Abacavir ↓ 35%–44%.[a] Appropriate doses for the combination of ABC and TPV/r have not been established. Zidovudine ↓ 31%–43%. Appropriate doses for the combination of ZDV and TPV/r have not been established. Loperamide ↓ 51%.[a] TPV Cmin ↓ 26% with loperamide. Antacids ↓ TPV ~30%, TPV should be administered 2 hrs before or 1 hr after these medications. Fluconazole: Doses >200mg/day are not recommended to be given with TPV. TPV capsules contain alcohol. Avoid use of disulfiram and metronidazole.	No data.

[a] Study conducted with TPV/r dose(s) other than FDA-approved dose of 500/200mg BID.
[†] Some drug interaction studies were conducted with Invirase® soft gel capsule. May not necessarily apply to use with Fortovase.

Table 22b. Drug Interactions Among Antiretrovirals and Other Drugs: NNRTIs (Updated January 29, 2008)

Drug Interactions Requiring Dose Modifications or Cautious Use				
Drugs Affected	**Delavirdine (DLV)**	**Efavirenz (EFV)**	**Etravirine (ETV)**	**Nevirapine (NVP)**
ANTIFUNGALS				
Fluconazole	No clinically significant changes in DLV or fluconazole concentrations.	No clinically significant changes in EFV or fluconazole concentrations.	↑ ETV, ↔ fluconazole Dose: standard	Levels: NVP: Cmax, AUC, and Cmin ↑ 100%. Fluconazole: No change. Risk of hepatotoxicity may ↑ with this combination. If coadministered, monitor NVP toxicity.
Itraconazole			↑ ETV, ↓ itraconazole Dose adjustments for itraconazole, may be necessary depending on other coadministered drugs, monitor itraconazole level.	
Ketoconazole	DLV: Cmin ↑ 50%. Ketoconazole: No data. Dose: Standard.	No data.	↑ ETV, ↓ ketoconazole Dose adjustments for ketoconazole may be necessary depending on other coadministered drugs.	Levels: Keto ↓ 63%. NVP ↑ 15%–30%. Dose: Not recommended.
Posaconazole			↑ ETV, ↔ posaconazole Dose: standard	
Voriconazole	Metabolism of voriconazole may be inhibited by DLV. Voriconazole may inhibit NNRTI metabolism. Frequently monitor for NNRTI toxicity and antifungal outcome.	Levels: EFV ↑ 44%. Voriconazole ↓ 77%. This combination is not recommended.	↑ ETV, ↑ voriconazole Dose adjustments for voriconazole may be necessary depending on other coadministered drugs, consider monitoring voriconazole level	Metabolism of voriconazole may be induced by NVP. Voriconazole may inhibit NNRTI metabolism. Carefully monitor for NNRTI toxicity and antifungal outcome.
ANTI-MYCOBACTERIALS				
Clarithromycin	Levels: Clarithromycin ↑ 100%. DLV ↑ 44%. Adjust dosage for renal failure.	Levels: Clarithromycin ↓ 39%. Monitor for efficacy or use alternative agent.	↑ ETV AUC 42%, ↓ clarithromycin AUC 39%, Cmin 53%, ↑ 14-OH-clarithromycin AUC 21% Alternatives to clarithromycin, such as azithromycin, should be considered for the treatment of MAC	Levels: NVP ↑ 26%. Clarithromycin ↓ 30%. Monitor for efficacy or use alternative agent.
Rifabutin	Levels: DLV ↓ 80%. Rifabutin ↑ 100%. Not recommended.	Levels: EFV unchanged. Rif ↓ 35%. Dose: ↑ rifabutin dose to 450–600mg QD or 600mg 3x/week.* EFV: Standard.	↓ ETV AUC 37% and Cmin 35%, ↓ rifabutin AUC 17% Cmin 24%, ↓ 25-O-desacetylrifabutin AUC 17% Cmin 22% Rifabutin dose of 300 mg daily if ETV is NOT coadministered with a RTV boosted PI If ETV is coadministered with DRV/RTV or SQV/RTV, and rifabutin is needed, consider alternative antiretroviral agent to ETV	Levels: NVP ↓ 16%. No dose adjustment.*
Rifampin/ Rifapentine	Levels: DLV ↓ 96%. Contraindicated.	Levels: EFV ↓ 25%. Dose: Maintain EFV dose at 600mg QD in patients weighing <60 kg or consider ↑ EFV to 800mg QD.	Potential for significant ↓ ETV Do not coadminister ETV with rifampin or rifapentine	Levels: NVP ↓ 20%–58%. Virologic consequences are uncertain; the potential for additive hepatotoxicity exists. If used, coadministration should be done with careful monitoring of virologic responses and toxicities.
HORMONAL CONTRACEPTIVES				
	Levels of ethinyl estradiol may increase. Clinical significance is unknown.	Levels: Ethinyl estradiol ↑ 37%. No data on other component. Use alternative or additional methods.	↑ ethinylestradiol AUC 22%, ↔ Norethindrone Dose: standard	Levels: Ethinyl estradiol ↓ approx 20%. Use alternative or additional methods.

* These recommendations apply to regimens that do not include PIs, which can substantially increase rifabutin levels.

Table 22b. Drug Interactions Among Antiretrovirals and Other Drugs: NNRTIs (Updated January 29, 2008)

Drug Interactions Requiring Dose Modifications or Cautious Use				
Drugs Affected	**Delavirdine (DLV)**	**Efavirenz (EFV)**	**Etravirine (ETV)**	**Nevirapine (NVP)**
LIPID-LOWERING AGENTS				
Atorvastatin	Potential for inhibition of atorvastatin metabolism. Use lowest possible dose and monitor for toxicity.	Levels: Atorvastatin AUC ↓ 43%; EFV unchanged. Dose: Adjust atorvastatin dose according to lipid responses, not to exceed the maximum recommended dose.	↔ ETV, ↓ atorvastatin AUC 37%, ↑ 2-OH-atorvastatin AUC 27% Cmax 76% Dose: standard; adjust atorvastatin dose based on response	No data.
Fluvastatin			↔ ETV, ↑ fluvastatin Dose adjustments for these HMG-CoA reductase inhibitors may be necessary	
Pravastatin **Rosuvastatin**	No data.	No data.	↔ ETV, ↔ pravastatin, ↔ rosuvastatin Dose: standard	No data.
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Simvastatin AUC ↓ by 58%; EFV unchanged. Dose: Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose.	↔ ETV, ↓ lovastatin, ↓ simvastatin Dose adjustments for these HMG-CoA reductase inhibitors may be necessary. If used with ritonavir-boosted PI, simvastatin and lovastatin should be avoided.	No data.
ANTICONVULSANTS				
Carbamazepine **Phenobarbital** **Phenytoin**	Levels: DLV Cmin ↓ 90% when coadministered with phenytoin, phenobarbital, or carbamazepine. Contraindicated.	Use with caution. CBZ and EFV AUCs ↓ 27% and 36%, respectively, when combined. One case report showed low EFV concs with phenytoin. Monitor anticonvulsant and EFV levels. If possible, use alternative anticonvulsant.	Potential for ↓ ETV & Anticonvulsant concentrations Do not coadminister ETV with carbamazepine, phenobarbital or phenytoin. Consider alternative anticonvulsants.	
Methadone	Levels: DLV unchanged; no data on methadone levels but potential for increased levels. Monitor for methadone toxicity; may require a dose reduction.	Levels: Methadone ↓ 60%. Opiate withdrawal common; increased methadone dose often necessary. Titrate methadone dose to effect.	↔ ETV, ↔ methadone Dose: standard; however, monitor for methadone withdrawal symptoms and adjust methadone as needed	Levels: NVP unchanged. Methadone ↓ significantly. Opiate withdrawal common when this combination is used; increased methadone dose often necessary. Titrate methadone dose to effect.
Miscellaneous	May increase levels of dapsone, warfarin, and quinidine. Sildenafil: Potential for increased concentrations and adverse effects. Use cautiously. Start with reduced dose of 25mg every 48 hours and monitor for adverse effects. Vardenafil: No data, but vardenafil AUC may be substantially increased.Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. Tadalafil: No data, but concomitant administration will likely result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5mg dose and do not exceed a single dose of 10mg every 72 hours. Coadministration of fluoxetine increases DLV Cmin 50%.	Monitor warfarin when used concomitantly.	↓ antiarrhythmics Dose: use with caution with antiarrhythmics concentration monitoring if available ↑ warfarin, Monitor INR ↑ diazepam - a decrease in diazepam may be needed dexamethasone (systemic) ↓ ETV Use with caution or alternative corticosteroid particularly for long term use ↓ cyclosporine, sirolimus, tacrolimus – monitor immunosuppressant levels ↓ sildenafil AUC 57% Dose: standard, may need to alter sildenafil dose based on clinical effect	No data.

Table 22c. Drug Interactions Among Antiretrovirals and Other Drugs: NRTIs (Updated October 10, 2006)

Drug Interactions Requiring Dose Modifications or Cautious Use				
Drugs Affected	**Didanosine (ddI)**	**Stavudine (d4T)**	**Tenofovir (TDF)**	**Zidovudine (ZDV)**
Atazanavir (ATV)	Levels: Simultaneous EC ddI + ATV (with food): ↓ AUC of ddI 34%. ATV no change. Administer separately; ATV should be taken with food and ddI-EC on an empty stomach.	No data.	ATV 400mg + TDF 300mg - Levels: ATV AUC ↓ 25% and Cmin ↓ 40%. TDF AUC ↑ 24%. Avoid concomitant use without RTV. ATV + RTV 300/100mg QD + TDF 300mg QD - Levels: ATV AUC ↓ 25% and Cmin ↓23%; ATV Cmin higher with RTV than without . TDF AUC ↑ 30%; monitor for toxicities. Dose: ATV + RTV 300/100mg QD coadministered with TDF 300mg QD.	ZDV: No change in AUC but 30% ↓ in Cmin. Significance unknown.
Cidofovir, Ganciclovir, Valganciclovir	Buffered ddI + ganciclovir (GCV): ddI AUC ↑ 50%–111%; GCV AUC ↓ 21% when ddI administered 2 hours prior to oral GCV; no change in IV GCV concentrations. Appropriate doses for the combination of ddI and GCV have not been established.	No data.	Serum concentration of these drugs and/or tenofovir may be increased. Monitor for dose-related toxicities.	Ganciclovir + ZDV: No significant changes in levels for either drug. Potential increase in hematologic toxicities.
Darunavir (DRV)	No data.	No data.	Levels: Tenofovir AUC ↑ 22%, Cmax ↑ 24% and Cmin ↑ 37%. Clinical significance unknown; monitor for tenofovir toxicity.	No data.
Didanosine	•	Peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination; should be avoided unless potential benefit far outweighs potential risks.	Levels: ddI EC AUC ↑ by 48%–60%, Cmax ↑ by 48%–64% For patients >60 kg, 250mg/day of ddI EC is recommended; for patients <60 kg, 200mg EC ddI is recommended; the ddI doses apply to patients with creatinine clearanace >60 mL/min. Monitor for ddI-associated toxicities.	No significant interactions.
Indinavir (IDV)	EC ddI can be taken together with IDV.	No significant PK interaction.	Levels: IDV Cmax ↑ 14%. Dose: Standard.	No significant PK interaction.
Lopinavir/ritonavir (LPV/r)	No data.	No data.	LPV/r 400/100mg AUC ↓ 15%; TDF AUC ↑ 34%; clinical significance of interaction is unknown; monitor for tenofovir toxicities.	No data.
Methadone	Levels: EC ddI unchanged. Dose: No change EC ddI.	Levels: d4T ↓ 27%; methadone unchanged. Dose: No dose adjustment.	No change in methadone or TDF levels.	ZDV AUC ↑ 43%. Monitor for ZDV-related adverse effects.
Ribavirin	Coadministration not recommended. Ribavirin increases the intracellular levels of the active metabolite of ddI and may cause serious toxicities.	No data.	Level: Ribavirin unchanged; no data on TDF level.	Ribavirin inhibits phosphorylation of ZDV; this combination should be avoided if possible, or closely monitor virologic response.
Tipranavir/ ritonavir	Levels: EC ddI ↓ 10%.[a] TPV Cmin ↓ 34% with EC ddI.[a] Dose: EC ddI and TPV/r should be separated by at least 2 hours.	No significant PK interaction.	TPV AUC and Cmin ↓ 9%–18% and 12%–21%, respectively[a]; clinical significance is unknown.	Levels: ZDV AUC and Cmax ↓ 31%–42% and 46%–51%, respectively.[a] Appropriate doses for the combination of ZDV and TPV/r have not been established.

[a] Study conducted with TPV/r dose(s) other than FDA-approved dose of 500/200mg BID.

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