

HIV DRUG-DRUG INTERACTIONS

I. INTRODUCTION

GENERAL RECOMMENDATIONS:

The clinician should conduct a thorough medication history at each visit that includes prescription medications, including those prescribed by other providers, over-the-counter medications, recreational drugs, and herbal/alternative therapies.

The clinician should classify common substrates, inducers, and inhibitors of the CYP450 system used in HAART to accurately predict drugs that may lead to significant drug interactions (see Table 2 and Appendix A).

The clinician should identify dietary restrictions with ARV drugs so that food-drug interactions can be avoided.

Drug interactions have become an increasingly complex challenge for clinicians treating patients with HIV infection. Current treatment guidelines recommend the use of a combination of at least three ARV drugs for the treatment of HIV-infected patients. In addition to medications to treat HIV infection, patients are often receiving therapy for comorbid conditions and prophylaxis of opportunistic infections. Because of the number of drugs that the HIV-infected patient receives, clinicians often must rely on clinical judgment and are forced to predict drug interactions without supporting data.

Although no specific guidelines exist on how to prevent drug interactions, the most important strategy to successful prevention is to conduct a thorough medication history at each visit, including questions about prescription, over-the-counter, herbal, and recreational drugs and prescriptions received from other healthcare providers. Clinicians' self-education about drugs that are associated with clinically significant drug interactions with HAART is important for clinicians to avoid drug interactions or to monitor patients for virologic failure or toxicity.

Key Points:

- Clinicians should instruct their patients to notify them of any new medication the patient is taking.
- Providing patients with a detailed list of drugs that are contraindicated with HAART may help the patient to identify significant drug interactions.

This chapter provides an overview of known and potential drug interactions encountered with the use of HAART. Included is a description of common mechanisms of drug interactions, a review of the route of elimination for ARV drugs, an overview of common drug interactions encountered in this setting, and specific recommendations for management of drug interactions encountered with HAART.

II. CLASSIFICATION OF DRUG INTERACTIONS

Drug interactions can be classified into two broad categories: 1) interactions altering pharmacokinetics and 2) interactions affecting pharmacodynamics. Although both have the potential to be problematic in patients receiving HAART, pharmacokinetic interactions are more common and more difficult to predict due to the complex nature of drug metabolism. Clinically significant drug interactions are generally those that produce at least a 30% change in pharmacokinetic parameters, but this may vary. Table 1 outlines the classification of common drug interactions with supporting examples.

TABLE 1 DESCRIPTION AND EXAMPLES OF COMMON MECHANISMS OF DRUG INTERACTIONS		
Type of Interaction	Description	Example
Pharmacokinetic		
<i>Absorption</i>	Concurrent therapy or food results in increase or reduction in drug absorption, thereby increasing or decreasing bioavailability	Atazanavir taken with magnesium/aluminum-containing antacids can significantly reduce atazanavir absorption
<i>Distribution</i>	Concurrent therapy leads to protein-binding displacement, altering the activity of either drug	Sulfamethoxazole/trimethoprim can displace warfarin from its protein-binding sites, increasing INR
<i>Metabolism</i>	Therapy induces or inhibits CYP450 enzymes, thereby increasing or decreasing drug concentration	Rifampin can induce CYP3A4 and cause marked reductions in PI concentrations
<i>Excretion</i>	Concurrent therapy results in enhanced or decreased renal excretion of drug	Probenecid taken with penicillin can reduce renal elimination of penicillin
Pharmacodynamic		
<i>Additive</i>	Concurrent therapy results in additive drug effect	Additive bone marrow suppression with concurrent use of zidovudine and ganciclovir
<i>Synergistic</i>	Concurrent therapy results in an exponential increase in drug effect	Concurrent use of indinavir, lamivudine, and zidovudine results in their combined effect being greater than the sum of their individual effects
<i>Antagonistic</i>	Concurrent therapy leads to reduced drug effect for both drugs	Concurrent use of zidovudine and stavudine reduces antiviral effect

Data are from References 2-4.

A. Pharmacokinetic Interactions

Pharmacokinetic drug interactions can be classified according to whether they affect the absorption, distribution, metabolism, or elimination of other drugs. Most common drug interactions encountered in HIV infection involve those that affect metabolism or absorption.

Metabolism

Drug interactions involving metabolism are the most common and difficult to predict. Drugs used in HAART, especially NNRTIs and PIs, are metabolized via the cytochrome P450 enzyme system (CYP450). The CYP450 enzyme system is responsible for drug metabolism. The enzyme responsible for the majority of drug metabolism is CYP3A4, although 2C19 and 2D6 are also common and, to a lesser extent, CYP1A2. Drug therapy interacts with CYP450 enzymes in one of three ways: 1) through inhibition, 2) through induction, or 3) by acting as a substrate. Some medications may interact in more than one way and act as an inhibitor and inducer of different CYP450 enzymes. CYP450 enzymes are expressed both in the liver and in the enterocytes of the small intestine, also causing inhibition or induction of drug metabolism within the gastrointestinal (GI) tract. A common example of this type of interaction is concurrent use of saquinavir and grapefruit juice. As a result of CYP450 inhibition in the GI tract, grapefruit juice significantly increases the bioavailability of saquinavir.¹ Similarly, ritonavir may inhibit CYP3A4 in the intestine and liver, which is one of the proposed mechanisms that contributes to this drug acting as a pharmacokinetic “boost.”

Drugs that inhibit CYP450 enzymes generally lead to decreased metabolism of other drugs metabolized by the same enzyme. The decreased metabolism can result in higher drug levels and increased potential for toxicity. Although inhibition is usually reversible, irreversible inhibition of CYP450 can occur, requiring new CYP450 enzymes to be synthesized to overcome the inhibition. Inhibition of drug metabolism tends to occur quickly (based on drug half-life), with maximal effect occurring when highest concentrations of the inhibitor are reached.

Induction of the CYP450 system results in the increased clearance of concomitant medications metabolized by the same enzyme. When drugs that induce CYP450 enzymes are administered to a patient, the body responds by increasing the production of specific enzymes of the CYP450 system. The increased enzyme production can lead to increased metabolism and decreased concentrations of drugs metabolized via the same pathway.

Key Point:

Induction can be problematic during HAART due to concerns for virologic failure when PI and/or NNRTI drug concentrations are reduced.

In general, the maximal effect of enzyme induction is apparent within 7 to 10 days, although with drugs with a relatively long half-life, such as methadone, the full effect of induction on the serum level of methadone may take longer. Drugs may also undergo a phenomenon termed auto-induction, whereby a drug has the capability of inducing its own metabolism. For example, because nevirapine undergoes auto-induction, it is dosed 200 mg daily for the first 14 days of treatment, then 200 mg twice daily thereafter.

A medication may act as a substrate by occupying the active site of a specific CYP450 enzyme. The medication's metabolism is then affected by other medications that either induce or inhibit the CYP450 enzyme system.

The major inhibitors, inducers, and substrates of CYP450 enzymes involved with drug metabolism are listed in Table 2.

TABLE 2				
SELECT CYP450 INDUCERS, INHIBITORS, AND SUBSTRATES				
	1A2	2C19	2D6	3A4
Inducers	ritonavir rifampin phenytoin omeprazole phenobarbital nicotine	rifampin carbamazepine ritonavir efavirenz	rifampin phenytoin phenobarbital carbamazepine	efavirenz, nevirapine, rifampin, phenytoin, phenobarbital, carbamazepine, glucocorticoids, St. John's Wort, ritonavir, etravirine
Inhibitors	fluoroquinolones cimetidine ticlopidine fluvoxamine amiodarone atazanavir	cimetidine ketoconazole omeprazole fluoxetine lansoprazole paroxetine etravirine	ritonavir paroxetine sertraline fluoxetine cimetidine celecoxib amiodarone quinidine methadone	PIs (in order of potency: ritonavir, indinavir, nelfinavir, amprenavir, atazanavir, saquinavir), delavirdine, fluconazole, ketaconazole, itraconazole, amiodarone, diltiazem, fluvoxamine, nefazodone, fluoxetine, clarithromycin, erythromycin, posaconazole, grapefruit juice, Seville orange juice
Substrates	haloperidol theophylline zileuton amitriptyline cyclobenzaprine olanzapine	nelfinavir lansoprazole omeprazole pantoprazole diazepam phenytoin voriconazole etravirine	metoprolol carvedilol codeine dextrometh- orphan tramadol venlafaxine	clarithromycin, cyclosporine, erythromycin, alprazolam, midazolam, triazolam, simvastatin, lovastatin, atorvastatin, nifedipine, nisoldipine, felodipine, PIs, nevirapine, efavirenz (2B6>3A4), delavirdine, sertraline, bepridil, propafenone, amiodarone, flecainide, irinotecan, pimozide, ergotamine, etravirine, maraviroc

Absorption

Drug interactions that affect absorption occur when one drug reduces the bioavailability of a second drug. Reduced absorption is caused by one of four mechanisms: 1) alterations related to the presence or absence of food; 2) alterations in gastric pH caused by antacids, H₂-blockers, or proton pump inhibitors; 3) chelation of drug caused by calcium, magnesium, or iron; or 4) inhibition of the P-glycoprotein or other transport pump. The last mechanism has not been conclusively established.

B. Pharmacodynamic Interactions

Pharmacodynamic interactions occur when one drug causes an alteration in the pharmacologic response (drug effect) of a second without a resultant change in drug concentrations or pharmacokinetic parameters. In this type of interaction, the pharmacologic response from the drug can be antagonistic, additive, or synergistic. Antagonistic effects result when a drug's pharmacologic effect is reduced due to concurrent therapy, such as when zidovudine and stavudine are co-administered.² Additive effects occur when the use of two drugs leads to enhanced pharmacologic activity. Synergy occurs when the use of two or more drugs concurrently results in an effect that is greater than the addition of all of the drugs together (i.e., the effect is exponential, not additive).

III. HAART-RELATED DRUG INTERACTIONS

This section reviews common drug interactions encountered with each class of medication used in HAART regimens. [Antiretroviral Therapy Appendix A](#) lists key interactions for each available ARV drug, and Appendix A outlines the route of metabolism for drugs used in HAART and their effect on the CYP450 system.

A. Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

Drug interactions involving metabolism for NRTIs are minimal because these drugs are excreted via renal elimination and are not metabolized by the CYP450 enzyme system. Two types of interactions predominate with this class of drugs are 1) pharmacokinetic interactions leading to impaired absorption or elimination and 2) pharmacodynamic interactions leading to antagonistic effects.

Specific Interactions:

Zidovudine and **stavudine** should not be co-administered because they have an antagonistic effect.²

Didanosine is formulated as an enteric-coated capsule and a buffered powder for oral solution (the buffered tablet containing calcium carbonate and magnesium hydroxide was discontinued at the end of 2006). Use of any buffered formulation can lead to drug interactions when co-administered with fluoroquinolones and tetracyclines. The buffer may reduce the fluoroquinolone antimicrobial activity by chelating with them and thereby impairing their absorption. Didanosine-buffered tablets have been shown to significantly impair the absorption

of ciprofloxacin when administered concurrently.^{3,4} Didanosine should be administered at least 2 hours after or 6 hours before the fluoroquinolone to minimize this interaction. Because the simultaneous administration of didanosine buffered tablet with the PI atazanavir lowers the absorption of atazanavir, patients should be instructed to take buffered didanosine 2 hours before or 1 hour after taking atazanavir. These interactions can be avoided by using the enteric-coated capsule formulation, which does not contain a buffer. However, the medications still should not be taken simultaneously because didanosine enteric coated capsules should be taken on an empty stomach and atazanavir needs to be taken with food.

Alterations in gastric pH, such as those that occur when taking buffered didanosine or antacid medications, can affect the absorption of azole antifungals, such as ketoconazole and itraconazole. Didanosine (buffered) has been shown to significantly impair the absorption of itraconazole.⁵ To manage this drug interaction, ketoconazole and itraconazole should be administered at least 2 hours prior to didanosine. No clinically significant interaction between didanosine and fluconazole has been demonstrated.⁶

Didanosine AUC can be increased significantly (up to 4-fold) when used concurrently with allopurinol in patients with concurrent renal impairment. Co-administration of these agents is not recommended due to the potential for didanosine toxicity.

Other documented drug interactions with didanosine buffered tablet include a reduction in the AUC of delavirdine and indinavir. Delavirdine and indinavir should be given 1 hour prior to didanosine to maintain adequate AUC.^{7,8}

When enteric-coated didanosine is co-administered with tenofovir, the didanosine AUC increases 60%; when given 2 hours before tenofovir, the didanosine AUC increases by 44%. Therefore, the enteric-coated didanosine dosage should be reduced to 250 mg daily in patients weighing ≥ 60 kg or to 200 mg in patients < 60 kg who take tenofovir and didanosine concurrently. The combination of didanosine and tenofovir, as initial therapy, is not recommended with an NNRTI due to the high virologic failure rate. If given, patients taking both tenofovir and enteric-coated didanosine should be monitored closely for didanosine-related toxicities. If signs or symptoms of pancreatitis, symptomatic hyperlactatemia, or lactic acidosis develop, the clinician should temporarily suspend the entire ARV regimen and should initiate a new regimen that does not combine tenofovir with didanosine.

B. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

NNRTIs are extensively metabolized via the CYP450 enzyme system: nevirapine is an inducer of CYP3A4; delavirdine is an inhibitor of CYP3A4; and efavirenz, *in vitro*, is a mixed inhibitor/inducer of CYP3A4, but in clinical studies, efavirenz is an inducer. Drug interactions with this class are expected if concurrent medications are also metabolized by CYP3A4. *In vitro* etravirine (ETR) is a CYP3A4, 2C19, and 2C9 substrate. ETR also undergoes glucuronidation. In addition, ETR inhibits 2C9 and 2C19 and is a mild inducer of CYP3A4, 2B6, and glucuronidation *in vitro*.

Specific Interactions:

Nevirapine is a potent inducer of CYP3A4, with maximal enzyme induction occurring approximately 2 to 4 weeks after beginning therapy. Because enzyme inducers generally lead to increased metabolism of co-administered drugs, reduced concentrations of co-administered drugs are expected. Concurrent nevirapine and oral contraceptives may lead to contraceptive failure; therefore, clinicians should recommend alternate methods of birth control in this setting.

Methadone withdrawal also has been reported in patients taking concurrent nevirapine due to increased methadone clearance.⁹⁻¹² Clinicians should closely monitor for signs and symptoms of methadone withdrawal when adding nevirapine to a regimen in patients taking methadone. The clinician should alert the methadone program that the patient's methadone requirement may increase. More detailed information regarding drug interactions with methadone and HAART is available at www.hivguidelines.org

Rifabutin and rifampin, also potent CYP3A4 inducers, have been shown to reduce nevirapine trough concentrations by 16% and 37%, respectively. In patients requiring treatment for *Mycobacterium avium* complex or *Mycobacterium tuberculosis*, rifabutin is the drug of choice to avoid significant reductions in nevirapine levels (see [Mycobacterial Infections](#)).

Efavirenz primarily induces CYP3A4 *in vivo*; however, *in vitro* data suggest that it can also inhibit CYP3A4, 2C9, and 2C19. All pharmacokinetic studies suggest that efavirenz induces CYP3A4, which can lead to reduced concentrations of concurrently administered drugs. Because of concerns with *in vitro* inhibition of CYP3A4 leading to enhanced drug toxicity, efavirenz is contraindicated with midazolam, triazolam, and ergotamine derivatives, although no published case reports to date have either proven or refuted the validity of these interactions.

Rifampin has been shown to reduce the AUC and C_{max} of efavirenz. The clinical significance of this interaction is unknown. However, guidelines suggest that clinicians may consider increasing the efavirenz dosage to 800 mg daily when prescribing rifampin to offset this interaction. When efavirenz is combined with rifabutin, current guidelines suggest that the rifabutin dose be increased to 450-600 mg qd or 600 mg 3x/week.

When selecting macrolide treatment in patients receiving efavirenz, it should be noted that concurrent use led to decreased AUC and C_{max} of clarithromycin 39% and 26%, respectively, while the AUC and C_{max} for the active metabolite of clarithromycin increased 34% and 49%, respectively. The clinical significance of this interaction is unknown; however, the incidence of rash was 46% in patients receiving these medications concurrently. It should be noted that 14-R-hydroxy clarithromycin is less active against MAC, but more active against *H influenzae*. Clarithromycin should be avoided in patients receiving efavirenz, if possible. Azithromycin should be considered as an alternative to clarithromycin.

Delavirdine is a potent inhibitor of CYP3A4; therefore, concurrent administration of drugs metabolized by this pathway can lead to increased drug levels and potential toxicity. Drugs metabolized by CYP3A4 include ergot alkaloid derivatives, sildenafil, simvastatin, lovastatin, and the following benzodiazepines: alprazolam, midazolam, and triazolam. Because their effect may be potentiated, these drugs should be avoided or used with caution in patients receiving delavirdine.

Other drugs known to induce CYP450 also have been shown to reduce the AUC for delavirdine. For example, rifampin and rifabutin have been shown to reduce the AUC for delavirdine by 96% and 80%, respectively. Based on these data, rifampin and rifabutin are contraindicated in patients receiving delavirdine due to the concern for virologic failure.^{13,14}

Population pharmacokinetics suggest that delavirdine trough concentration may increase by 50% when used concurrently with ketoconazole or fluoxetine. Combination therapy with either of these drugs should be avoided.

Due to their ability to induce the CYP450 system, anticonvulsants (carbamazepine, phenobarbital, phenytoin) may significantly reduce **delavirdine, efavirenz, nevirapine, and etravirine** serum concentrations, thus these drugs should be avoided with NNRTI-based regimens if possible. Alternative anticonvulsants are valproic acid and levetiracetam.

Etravirine is a mild CYP3A4 inducer and an inhibitor of CYP2C9 and CYP2C19. The co-administration of unboosted protease inhibitors should be avoided due to significant decrease in PI serum concentrations by ETR. Additionally, co-administration with boosted tipranavir, fosamprenavir, and atazanavir is not recommended by the manufacturer due to a significant increase in ETR serum concentrations; however, the clinical implications of concomitant FPV/r and ATV/r are unclear.

With DRV/r co-administration, DRV AUC increased by 15%, but etravirine AUC and C_{min} decreased by 37% and 49%, respectively. Despite a significant reduction in ETR serum concentrations, good virologic response was observed in clinical trials when standard doses were used. Other non-nucleoside inhibitors should be avoided because they can decrease (i.e., efavirenz, nevirapine) or increase (i.e., delavirdine) ETR serum concentrations leading to decreased efficacy or increase in toxicity.

When used in conjunction with HMG-CoA reductase inhibitors, the dose of atorvastatin may need to be increased while rosuvastatin and pravastatin are unlikely to interact and are preferred over lovastatin, simvastatin, and fluvastatin. For patients who required macrolide antibiotics, concurrent use of clarithromycin lead to a 42% increase in ETR AUC and clarithromycin AUC decreased by 39%. Azithromycin is preferred in patients requiring a macrolide for the treatment of MAC while taking etravirine

Rifabutin decreases the AUC and C_{min} of ETR by 37% and 35%, respectively. Although the standard dose of 300 mg daily is appropriate, co-administration with darunavir/ritonavir or saquinavir/ritonavir should be avoided due to the potential additive decrease in ETR exposure.

C. Protease Inhibitors (PIs)

PI therapy is often complicated by drug interactions because they are potent inhibitors of CYP3A4. Because the majority of other drugs available on the market are also metabolized by CYP3A4, the potential for drug interactions is a major concern for clinicians treating HIV-infected patients. Numerous drugs should be avoided during concurrent PI therapy because of CYP450 inhibition and the potential for increased toxicity or reduced efficacy (see [Antiretroviral Therapy Appendix A](#)).

Lopinavir/ritonavir

Lopinavir is essentially completely metabolized by CYP3A. Ritonavir inhibits the metabolism of lopinavir, thereby increasing the plasma concentrations of lopinavir; therefore, the antiviral activity of LPV/r is due to lopinavir. Use caution with co-administration of LPV/r with other drugs that prolong the PR interval (e.g., beta-blocker, calcium channel blocker, digoxin, atazanavir), especially if the drug is metabolized by CYP3A.

Ritonavir is the most potent inhibitor of CYP3A4 among the PIs (saquinavir is the least potent). Ritonavir also inhibits CYP2D6 to a lesser extent than CYP3A4 and may induce CYP1A2, CYP2C9, CYP2C19, and CYP3A4. The effect of ritonavir on multiple CYP450 enzymes complicates and increases the number and severity of interactions associated with this drug. Its ability to inhibit the metabolism of other PIs can be exploited to enhance the pharmacokinetic parameters of co-administered PIs.

Ritonavir has been shown to inhibit P-glycoprotein transport in the GI tract, with resultant increases in drug absorption in animal models, adding to its ability to act as a boosting medication. Other PIs have been shown to inhibit P-glycoprotein, although ritonavir is the most potent.

D. CCR5 Co-Receptor Antagonist

Maraviroc is a substrate of CYP3A and P-glycoprotein. Drug-drug interactions are unlikely to occur with NRTIs and enfuvirtide. A dose reduction to 150 mg bid is recommended when maraviroc is used concurrently with CYP3A inhibitors (with or without a CYP3A inducer). These include protease inhibitors (except tipranavir/ritonavir), delavirdine, ketoconazole, itraconazole, clarithromycin, and other strong CYP3A inhibitors (i.e., nefazodone, telithromycin). This dose reduction is also recommended for concomitant use with lopinavir/ritonavir plus efavirenz or saquinavir/ritonavir plus efavirenz.

A dose increase to 600 mg bid is recommended when maraviroc is used in combination with CYP3A inducers (without a strong CYP3A inhibitor). Examples include efavirenz, etravirine, rifampin, carbamazepine, phenobarbital, and phenytoin.

E. HIV-1 Integrase Inhibitor

Raltegravir is metabolized via UGT-1A1-mediated glucuronidation. It is not a substrate of, nor does it induce/inhibit, the CYP pathway. As a strong UGT1A1 inducer, rifampin reduces raltegravir AUC and C_{min} by 40% and 61%, respectively; co-administration should be avoided due to the lack of clinical data. Similarly, co-administration with phenobarbital and phenytoin may significantly decrease raltegravir serum concentration; co-administration should be avoided

or used with caution when these are used concomitantly. Conversely, atazanavir (with and without ritonavir), is a strong inhibitor of UGT1A1. Although plasma levels of raltegravir are increased with atazanavir co-administration, no dose adjustments of raltegravir are necessary.

F. Anticonvulsants

RECOMMENDATIONS:

Clinicians should monitor anticonvulsant levels in patients taking concurrent HAART and anticonvulsant therapy.

Clinicians should avoid prescribing carbamazepine, phenobarbital, and phenytoin for patients receiving NNRTIs or PIs. Levetiracetam may be considered.

There are limited data regarding drug interactions with anticonvulsants. Because of the capacity of phenytoin, phenobarbital, and carbamazepine to induce metabolic enzymes, these drugs should be avoided in patients receiving NNRTIs or PIs. Phenytoin and phenobarbital should be avoided or used with caution with raltegravir due to potential for significant reduction of raltegravir serum concentrations. Use of an alternative anticonvulsant, such as levetiracetam, should be considered. Anticonvulsant drug concentrations should be monitored frequently in patients taking concurrent HAART and anticonvulsant therapy. Clinicians may also consider obtaining drug levels of ARV agents.

G. Antifungal Drugs

RECOMMENDATION:

Clinicians should not prescribe voriconazole for patients taking ritonavir (400 mg q12h). Clinicians should avoid or use caution when combining voriconazole with the other NNRTIs or unboosted PIs.

The management of HIV infection includes antifungal drugs that are used for the treatment of oral candidiasis or for maintenance therapy of cryptococcal meningitis. Data evaluating interactions with fluconazole and concurrent PI therapy have demonstrated drug interactions of minimal clinical significance.^{15,16} Ketoconazole is a potent CYP3A4 inhibitor and has been shown to increase saquinavir, amprenavir, and indinavir levels. When ketoconazole is used with saquinavir or amprenavir, the standard dose for each drug should be used, whereas when used with indinavir, the manufacturer recommends that the indinavir dose be reduced to 600 mg tid. Conversely, ritonavir and lopinavir/ritonavir increase ketoconazole levels 3-fold when used concurrently; thus, doses >200 mg/day of ketoconazole are not recommended when using either of these drugs.

Voriconazole has also been used to treat fungal infections in HIV-infected patients. Data from the manufacturer demonstrate that when used concurrently with the PI indinavir, no clinically significant interaction occurred. When ritonavir 400 mg q12h or 100 mg q12h was combined with voriconazole, it decreased the voriconazole AUC by 82% and 39%, respectively; the concentrations of ritonavir were not affected. Ritonavir at this dose should not be co-administered with voriconazole. Smaller boosting doses of ritonavir (100 mg bid) resulted in a

39% decrease in voriconazole AUC. Monitor voriconazole serum concentrations when co-administered with boosted PIs or consider using an alternative antifungal agent. Efavirenz decreases voriconazole AUC by 77%, and efavirenz AUC was increased by 44%; however, there was no significant change in voriconazole and EFV AUC with voriconazole 400 mg q12h plus EFV 300 mg qhs. Therefore, if efavirenz and voriconazole are co-administered, dose adjustment is required. Caution should be used when combining voriconazole with other NNRTIs.

H. Antimycobacterial Drugs

RECOMMENDATION:

Clinicians should not use rifampin with any PI. Consider rifabutin with proper dose adjustment.

Drug interactions are well documented between the antimycobacterial drugs (rifampin, rifabutin, and clarithromycin) and HAART. The greatest concern is with rifamycin-based regimens because of the risk of significant reductions in PI concentrations caused by enzyme induction related to the rifamycin. In general, rifampin should be avoided during concurrent therapy with PIs, due to marked reductions in PI levels. Alterations in clarithromycin levels have been reported during concurrent therapy with PIs. See [Antiretroviral Therapy Appendix A](#) and [Mycobacterial Infections](#) for guidelines on dosing and management of HAART during concomitant antimycobacterial therapy.

With proper dose adjustments, rifampin can be safely used with the following drugs:	
NtRTIs Enfuvirtide Maraviroc	Efavirenz <i>and</i> NRTIs or NtRTIs (No clinical data; monitor closely)
With proper dose adjustments, rifabutin can be safely used with the following drugs:	
NRTIs NtRTIs Atazanavir/r Darunavir/r Enfuvirtide Etravirine Fosamprenavir/r Indinavir/r	Lopinavir/r * Maraviroc Nelfinavir Raltegravir (no interaction) Ritonavir Efavirenz when used with 2 NRTIs Nevirapine when used with 2 NRTIs Saquinavir + ritonavir Tipranavir/r

* Consider therapeutic drug monitoring of rifabutin.

I. Erectile Dysfunction Agents

Sildenafil, vardenafil, and tadalafil are all extensively metabolized by CYP3A4. When sildenafil was given concurrently with indinavir, saquinavir, or ritonavir, the AUC for sildenafil was increased by a factor of 2- to 11-fold. The AUCs of vardenafil and tadalafil were increased when given with ritonavir.

Based on these data, the following is generally recommended when erectile dysfunction agents are combined with PIs:

Sildenafil - use reduced initial dose of 25 mg q48h and monitor for adverse effects

Tadalafil - use initial dose of 5 mg, and do not exceed a single dose of 10 mg in 72 hours

Vardenafil - use initial dose of 2.5 mg, and do not exceed a single 2.5-mg dose in 72 hours

J. Ergot Alkaloids

RECOMMENDATION:

Clinicians should not prescribe ergotamine derivatives in patients receiving concurrent PI therapy. Alternative medications should be considered.

Ergotamine derivatives are contraindicated with all PIs because of potential ergotism due to enhanced levels caused by CYP450 inhibition. Although the majority of case reports have described this event during therapy with ritonavir, other drugs associated with this interaction include indinavir and nelfinavir.¹⁷⁻²³

K. Herbal Therapy

RECOMMENDATIONS:

In the setting of PI- or NNRTI-based HAART, supplemental garlic and St. John's Wort are contraindicated.

All herbal products should be used with caution until further data are available regarding their effects with concurrent HAART.

Herbal therapy use has become more frequent in both the general population and the HIV-infected population.²⁴

Key Point:

Because most providers cannot accurately predict which patients use herbal therapy, it is important to discuss ARV/herbal therapy drug interactions with all patients.

Data from one hospital in New York State indicate that 34% of patients receiving HAART use herbal therapy on a regular basis. However, only 54% of patients told their clinicians that they were using herbal therapy, and 62% of the time, clinicians were unable to predict which patients used herbal therapy.²⁴ Drug interactions are known to occur when PIs are used concurrently with St. John's Wort or garlic supplementation. Concurrent use of St. John's Wort and unboosted indinavir resulted in a 57% reduction in indinavir AUC.²⁵ Data also demonstrated that concurrent saquinavir soft-gel capsule and garlic supplementation reduced saquinavir plasma concentrations by 51%.²⁶ After a 10-day washout period, the saquinavir AUC, trough, and C_{max} were only 60% to 70% of baseline levels, suggesting an ongoing effect. In the setting of PI- or NNRTI-based

HAART, supplemental garlic and St. John's Wort are contraindicated. All herbal products should be used with caution until further data are available regarding their effects on concurrent HAART.

Data suggest that the use of milk thistle with indinavir does not cause a clinically significant interaction.²⁷

L. HMG-CoA Reductase Inhibitors

RECOMMENDATION:

Clinicians should not prescribe simvastatin or lovastatin for patients taking PIs.

Dyslipidemia occurs in approximately 70% of patients taking PIs, often requiring the use of HMG Co-A reductase inhibitors for treatment.²⁸ Studies have been conducted evaluating the potential interaction between PIs and the HMG-CoA reductase inhibitors, commonly referred to as "statins" (pravastatin, atorvastatin, lovastatin, rosuvastatin, and simvastatin). When these drugs were studied with concurrent ritonavir/saquinavir, the AUC of simvastatin increased by a factor of 32 and atorvastatin by a factor of 4.5, whereas the AUC for pravastatin was reduced by a factor of 0.5. Significant drug interactions have also been reported with lopinavir/ritonavir when given concurrently with simvastatin or atorvastatin. After co-administration, the AUC increased by 5.9-fold for atorvastatin, whereas the pravastatin levels increased 0.3-fold. Similar results have also been reported with co-administration of nelfinavir with atorvastatin or simvastatin.²⁹

Key Points:

- *Lovastatin and simvastatin are contraindicated with all PIs and DLV.*
- Pravastatin is the safest drug for treating hyperlipidemia during concurrent PI therapy.
- Atorvastatin can be used cautiously at lower doses (5-10 mg) with careful titration.
- Rosuvastatin can be used at lower doses (5mg) with careful titration.

The large increases in AUC associated with concurrent ritonavir/saquinavir and simvastatin administration demonstrates that simvastatin should not be used during PI therapy. In fact, one case report in the literature describes a patient who received concurrent simvastatin with nelfinavir therapy that resulted in death from acute rhabdomyolysis. Similar cases have also been reported with concurrent statin and lopinavir/ritonavir use. Lovastatin is also extensively metabolized by CYP3A4, thus this drug would be expected to have its levels markedly reduced by PI therapy and should also be avoided. Rosuvastatin AUC was increased by 110% and 37% with LPV/r and TPV/r co-administration, respectively. If rosuvastatin is co-administered with LPV/r or TPV/r, the lower dose rosuvastatin (5mg) should be considered with careful dose titration.

M. Oral Contraceptives

RECOMMENDATIONS:

Clinicians should use caution when prescribing oral contraceptives for patients receiving HAART because of the variations in effect on ethinyl estradiol levels.

Clinicians should advise women who are taking efavirenz, nevirapine, lopinavir/ ritonavir, nelfinavir, ritonavir, tipranavir/ritonavir, darunavir/ritonavir or saquinavir to use alternate or additional forms of birth control.

One published study found that the AUC and Cmax of ethinyl estradiol levels were reduced in patients concurrently taking ritonavir. Similar results have been reported with nelfinavir, darunavir/ritonavir, and lopinavir/ritonavir. Women receiving these drugs should use alternate forms of birth control. In contrast, data for indinavir and unboosted atazanavir demonstrated an increase in the AUC for both ethinyl estradiol and norethindrone. Therefore, when co-administered with unboosted atazanavir, oral contraceptive should contain no more than 30 mcg ethinyl estradiol. However, when co-administered with atazanavir/ritonavir, oral contraceptive should contain at least 35 mcg ethinyl estradiol. Based on these data, indinavir and atazanavir should not cause contraceptive failure when taken concurrently with oral contraceptives; however, the manufacturer recommends use of an alternative form of contraception.

With etravirine co-administration, ethinyl estradiol AUC increased by 22%, but norethindrone AUC decreased by 5%. Maraviroc did not affect the serum concentration of Levonorgestrel. Interaction between oral contraceptives and raltegravir is unlikely.

N. Psychotropic Therapies

Drug interactions with most psychotropic therapies are summarized in Table 3.

TABLE 3
SIGNIFICANT INTERACTIONS BETWEEN ANTIRETROVIRAL THERAPY AND
PSYCHOTROPIC MEDICATIONS: CONTRAINDICATED COMBINATIONS AND
AGENTS TO BE USED WITH CAUTION*

Medication	Contraindicated	Use With Caution	Comments
Atazanavir (Reyataz)	Midazolam Triazolam Pimozide	Carbamazepine Phenobarbital Phenytoin	<ul style="list-style-type: none"> • Midazolam and triazolam levels may be significantly increased with concurrent PI use. • Carbamazepine, phenobarbital, and phenytoin may reduce PI drug concentrations due to induction of the CYP450 system; consider alternative anticonvulsant.
Darunavir (Prezista)	Midazolam Triazolam Pimozide	Carbamazepine Phenobarbital Phenytoin	<ul style="list-style-type: none"> • Midazolam and triazolam levels may be significantly increased with concurrent PI use. • Carbamazepine, phenobarbital, and phenytoin may reduce PI drug concentrations due to induction of the CYP450 system; consider alternative anticonvulsant.
Delavirdine (Rescriptor)	Midazolam Triazolam Pimozide	Carbamazepine Phenobarbital Phenytoin	<ul style="list-style-type: none"> • Midazolam and triazolam levels may be significantly increased with concurrent use; avoid combination.
Efavirenz (Sustiva)	Midazolam Triazolam	Pimozide Carbamazepine Phenobarbital Phenytoin	<ul style="list-style-type: none"> • Based on <i>in vitro</i> data, midazolam and triazolam concentrations may be significantly increased with co-administration, but <i>in vivo</i>, a reduction in midazolam is expected; avoid combination. • Efavirenz may increase pimozide levels; monitor closely for toxicity. • Carbamazepine, phenobarbital, and phenytoin may reduce EFV drug concentrations due to induction of the CYP450 system; consider alternative anticonvulsant.
Etravirine (Intelence)	Carbamazepine Phenobarbital Phenytoin		<ul style="list-style-type: none"> • Carbamazepine, phenobarbital, and phenytoin may significantly reduce ETR drug concentrations due to induction of the CYP450 system; do not use.
Fosamprenavir (Lexiva)	Midazolam Triazolam Pimozide	Tricyclic antidepressants Carbamazepine Phenobarbital Phenytoin	<ul style="list-style-type: none"> • Midazolam, triazolam, and pimozide levels may be significantly increased with concurrent PI use. • Monitor tricyclic antidepressant therapy closely for toxicity.

			<ul style="list-style-type: none"> • Carbamazepine, phenobarbital, and phenytoin may reduce PI drug concentrations due to induction of the CYP450 system; consider alternative anticonvulsant.
Indinavir (Crixivan)	Midazolam Triazolam Pimozide	Carbamazepine Phenobarbital Phenytoin	<ul style="list-style-type: none"> • Midazolam, triazolam, and pimozide levels may be significantly increased with concurrent PI use. • Carbamazepine, phenobarbital, and phenytoin may reduce PI drug concentrations due to induction of the CYP450 system; consider alternative anticonvulsant.
Lopinavir/ritonavir (Kaletra)	Midazolam Triazolam Pimozide	Carbamazepine Olanzapine Phenobarbital Phenytoin	<ul style="list-style-type: none"> • Midazolam, triazolam, and pimozide levels may be significantly increased with concurrent PI use. • Lopinavir/ritonavir may reduce olanzapine levels. • Carbamazepine, phenobarbital, and phenytoin may reduce PI drug concentrations due to induction of the CYP450 system; consider alternative anticonvulsant.
Maraviroc (Selzentry)	None	Carbamazepine Phenobarbital Phenytoin	<ul style="list-style-type: none"> • Carbamazepine and phenobarbital may increase maraviroc metabolism, leading to loss of virologic response, and possible resistance to maraviroc. Increase maraviroc dose to 600 mg twice daily with co-administration.
Nelfinavir (Viracept)	Midazolam Triazolam Pimozide	Carbamazepine Phenobarbital Phenytoin	<ul style="list-style-type: none"> • Midazolam and triazolam levels may be significantly increased with concurrent PI use. • Carbamazepine, phenobarbital, and phenytoin may reduce PI drug concentrations due to induction of the CYP450 system; consider alternative anticonvulsant.
Nevirapine (Viramune)	None	Carbamazepine Phenobarbital Phenytoin	<ul style="list-style-type: none"> • Potential for interaction with carbamazepine is unknown. Use with caution and consider monitoring carbamazepine levels.
Raltegravir (Isentress)	None	Phenobarbital Phenytoin	<ul style="list-style-type: none"> • Phenobarbital and phenytoin co-administration may significantly decrease raltegravir serum concentrations.

Ritonavir (Norvir)	Midazolam Triazolam Pimozide	Alprazolam, carbamazepine, clorazepate, diazepam, estazolam, flurazepam, methamphetamine, nefazodone, olanzapine, perphenazine, phenobarital, phenytoin, risperidone, trazadone, selective serotonin re-uptake inhibitors (SSRIs), thioridazine, zolpidem	<ul style="list-style-type: none"> • Midazolam, triazolam, and pimozide levels may be significantly increased with concurrent PI use. • Due to the complex nature of ritonavir metabolism, increased or decreased levels of psychotropic agents may occur. Monitor patients closely when changing psychotropic agents or adding ritonavir. • Monitor desipramine levels when used with ritonavir. • Ritonavir may reduce olanzapine levels. • Carbamazepine, phenobarbital, and phenytoin may reduce PI drug concentrations due to induction of the CYP450 system; consider alternative anticonvulsant.
Saquinavir (Invirase)	Midazolam Triazolam Pimozide	Carbamazepine Phenobarbital Phenytoin	<ul style="list-style-type: none"> • Midazolam and triazolam levels may be significantly increased with concurrent PI use. • Carbamazepine, phenobarbital, and phenytoin may reduce PI drug concentrations due to induction of the CYP450 system; consider alternative anticonvulsant.
Tipranavir (Aptivus)	Midazolam Triazolam Pimozide	Olanzapine Mirtazapine Nefazadone Carbamazepine Phenobarbital Phenytoin	<ul style="list-style-type: none"> • Midazolam and triazolam levels may be significantly increased with concurrent PI use. • Carbamazepine, phenobarbital, and phenytoin may reduce PI drug concentrations due to induction of the CYP450 system; consider alternative anticonvulsant.

* Tricyclic antidepressants should be used with caution with all boosted PIs.

O. Sedative/Hypnotics

RECOMMENDATION:

Clinicians should not prescribe midazolam or triazolam for patients receiving PIs. Lorazepam or oxazepam may be considered.

Ritonavir has been shown to significantly impair the oral clearance of alprazolam and triazolam in healthy volunteers.³⁰ This potential for increased benzodiazepine levels would lead to potentiation of the sedation and respiratory depression associated with these compounds. Although data describing this interaction are primarily based on ritonavir use, these drugs should not be administered with any of the PIs. Although no formal studies of drug interactions evaluating the combination of clonazepam and PIs exist, levels of clonazepam may be elevated because it is also metabolized by CYP3A4. Acceptable sedative/hypnotic drugs, including zolpidem, lorazepam, or temazepam, may be used.

IV. DOSE ADJUSTMENTS DURING HAART REGIMENS

Multiple dosing adjustments may be necessary during treatment with PI-based and NNRTI-based regimens. These regimens may contain an NNRTI and a PI or may be dual-PI regimens requiring dose adjustment of either drug.

A. PI + NNRTI Combinations

The NNRTIs efavirenz and nevirapine are known to induce the CYP3A4 system, resulting in clinically significant reductions in PI levels when used concurrently. When efavirenz or nevirapine were co-administered with indinavir, the AUC of indinavir was reduced 31% and 28%, respectively. Similar results were also found when efavirenz or nevirapine was co-administered with lopinavir/ritonavir. Based on these data, the dose of indinavir or lopinavir/ritonavir needs to be increased during concurrent nevirapine or efavirenz therapy: indinavir should be increased to 1000 mg every 8 hours (or consider IDV 800/RTV 100-200 mg bid); lopinavir/ritonavir should be increased to 600 mg/150 mg twice daily. Other research has demonstrated similar interactions with nevirapine and saquinavir co-administration, whereas the combination of nelfinavir and efavirenz resulted in no significant pharmacokinetic changes in either drug.³¹

The NNRTI delavirdine has been shown to be a potent inhibitor of CYP3A4, and preliminary results suggest that, when used concurrently with indinavir, delavirdine leads to marked increases in the AUC for indinavir. To offset this interaction, the manufacturer recommends reducing the indinavir dosage to 600 mg every 8 hours during co-administration with delavirdine.

When using concurrent atazanavir and efavirenz, atazanavir AUC is reduced by 74%. Therefore, when using these two agents together, it is necessary to reduce the atazanavir dosage to 300 mg po qd and add ritonavir 100 mg po qd to offset the interaction. An observational study suggests using atazanavir 300 mg qd with ritonavir 100 mg qd when co-administered (boosted) used with nevirapine.³²

B. Boosted PI Regimens

Pharmacokinetically enhanced regimens using two or more PIs concurrently have become increasingly common in the era of HAART. The main reasons for using dual-PI regimens have been to improve pharmacokinetics, to improve adherence with reduced dosing frequency and reduced pill burden, to overcome enzyme induction related to nevirapine or efavirenz, and to increase the barrier to protease inhibitor resistance. Most commonly, the PI ritonavir is used in this setting because of its potent inhibition of the CYP3A4 system in the liver and GI tract. To date, numerous boosted-PI combinations have been evaluated, including atazanavir/ritonavir, lopinavir/ritonavir, saquinavir/ritonavir, indinavir/ritonavir, darunavir/ritonavir, tipranavir/ritonavir, fosamprenavir/ritonavir, with multiple dosing strategies employed.

Dosing of HAART is complex and becomes increasingly difficult in patients receiving drugs from multiple classes. [Antiretroviral Therapy Appendix A](#) provides a complete summary of the pharmacokinetic effects when combining different PIs and when combining PIs with NNRTIs. Included are specific dosing recommendations based on current guidelines.

V. RESOURCES FOR CONSULTATION

Clinicians who need additional information concerning ARV drug interactions can refer to the following websites:

www.aidsinfo.nih.gov

www.hiv-druginteractions.org

www.hopkins-hivguide.org

Antiretroviral Package Inserts:

Single antiretrovirals

- Abacavir (Ziagen): http://us.gsk.com/products/assets/us_ziagen.pdf
- Amprenavir (Agenerase): (not currently available online)
- Atazanavir (Reyataz): http://packageinserts.bms.com/pi/pi_reyataz.pdf
- Darunavir (Prezista): http://www.prezista.com/prezista/documents/us_package_insert.pdf
- Delavirdine (Rescriptor): http://media.pfizer.com/files/products/uspi_rescriptor.pdf
- Didanosine (Videx), enteric coated (Videx EC):
http://packageinserts.bms.com/pi/pi_videx_ec.pdf
- Efavirenz (Sustiva): http://packageinserts.bms.com/pi/pi_sustiva.pdf
- Emtricitabine (Emtriva): http://www.gilead.com/pdf/emtriva_pi.pdf
- Enfuvirtide (Fuzeon): <http://www.rocheusa.com/products/fuzeon/pi.pdf>
- Etravirine (Intelence): http://www.intelence-info.com/intelence/assets/pdf/INTELENCE_PI.pdf
- Fosamprenavir (Lexiva): http://us.gsk.com/products/assets/us_lexiva.pdf
- Indinavir (Crixivan):
http://www.merck.com/product/usa/pi_circulars/c/crixivan/crixivan_pi.pdf
- Lamivudine (Epivir): http://us.gsk.com/products/assets/us_epivir.pdf
- Lopinavir/ritonavir (Kaletra): <http://rxabbott.com/pdf/kaletratabpi.pdf>

- Maraviroc (Selzentry): http://media.pfizer.com/files/products/uspi_maraviroc.pdf
- Nevirapine (Viramune): <http://us.viramune.com/index.jsp>
- Nelfinavir (Viracept): http://us.gsk.com/products/assets/us_viracept.pdf
- Raltegravir (Isentress):
http://www.merck.com/product/usa/pi_circulars/i/isentress/isentress_pi.pdf
- Ritonavir (Norvir): <http://www.rxabbott.com/pdf/norpi2a.pdf>
- Saquinavir (Invirase): <http://www.gene.com/gene/products/information/invirase/pdf/pi.pdf>
- Stavudine (Zerit): http://packageinserts.bms.com/pi/pi_zerit.pdf
- Tenofovir (Viread): http://www.viread.com/common/Viread_FPI.pdf
- Tipranavir (Aptivus): <http://www.aptivus.us/hcp/index.jsp>
- Zidovudine (Retrovir): http://us.gsk.com/products/assets/us_retrovir.pdf

Combination antiretrovirals

- Atripla – Efavirenz + Emtricitabine + Tenofovir: http://www.gilead.com/pdf/atripla_pi.pdf
- Combivir – Lamivudine + Zidovudine: http://us.gsk.com/products/assets/us_combivir.pdf
- Epzicom – Abacavir + Lamivudine: http://us.gsk.com/products/assets/us_epzicom.pdf
- Trizivir – Abacavir + Lamivudine + Zidovudine:
http://us.gsk.com/products/assets/us_trizivir.pdf
- Truvada – Tenofovir + Emtricitabine: <http://www.truvada.com/pdf/fpi.pdf>

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APPENDIX A

ROUTES OF ELIMINATION OF HAART AND THE EFFECT ON CYP450

TABLE 1 ROUTES OF ELIMINATION OF HAART AND THE EFFECT ON CYP450		
Drug	Elimination	Effect on CYP450 System
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors		
Abacavir (ABC)	Hepatic	Insignificant
Didanosine (ddI)	Renal excretion 50%	None
Emtricitabine (FTC)	Renal excretion 86%	None
Lamivudine (3TC)	Renal excretion 70%	None
Stavudine (d4T)	Renal excretion 50%	None
Tenofovir (TDF)	Renal excretion 70-80%	None
Zalcitabine (ddC)	Renal excretion 70%	None
Zidovudine (AZT, ZDV)	Hepatic metabolism with renal excretion	None
Non-Nucleoside Reverse Transcriptase Inhibitors		
Delavirdine (DLV)	Hepatic	CYP3A4 inhibitor
Efavirenz (EFV)	Hepatic	CYP3A4 inducer (inhibitor <i>in vitro</i>)
Etravirine (ETR)	Hepatic	CYP3A4 Inducer, CYP2C9 and CYP2C19 inhibitor
Nevirapine (NVP)	Hepatic	CYP3A4 inducer
Protease Inhibitors		
Amprenavir (APV), Fosamprenavir (FPV)	Hepatic	CYP3A4 inhibitor/inducer
Atazanavir (ATZ)	Hepatic	CYP3A4 inhibitor, CYP1A2, CYP2C9 inhibitor
Darunavir/r (DRV/r)	Hepatic	CYP3A4 inhibitor
Indinavir (IDV)	Hepatic	CYP3A4 inhibitor
Lopinavir/ritonavir (LPV/r)	Hepatic	CYP3A4 inhibitor CYP2D6 inhibitor (3A4 inhibition >2D6) 3A4 and CYP1A2 inducer

Nelfinavir (NFV)	Hepatic	CYP3A4 inhibitor/inducer
Ritonavir (RTV)	Hepatic	CYP3A4 inhibitor CYP2D6 inhibitor (3A4 inhibition >2D6) 3A4 and CYP1A2 inducer
Saquinavir (SQV)	Hepatic	Weak CYP3A4 inhibitor
Tipranavir/ritonavir (TPV/r)	Hepatic	CYP3A4 inhibitor Potent P-gp inducer
Fusion Inhibitors		
Enfuvirtide (T-20)	Hepatic	None
CCR5 Co-receptor Antagonists		
Maraviroc (MVC)	Hepatic (3A4 substrate)	None
Integrase Inhibitor		
Raltegravir (RAL)	Hepatic (Phase 2)	None