

CHAPTER 2B

HIV DRUG-DRUG INTERACTIONS

I. INTRODUCTION

GENERAL RECOMMENDATIONS:

The practitioner should conduct a thorough medication history at each visit that includes prescription medications, over-the-counter medications, and herbal/alternative therapies.

The practitioner should inquire about therapies prescribed by other health care providers.

The practitioner 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 Tables 3 and 4).

The practitioner should recognize drugs that should be avoided or used with caution during concurrent highly active antiretroviral therapy (HAART) (see Appendices A and B).

The practitioner should identify dietary restrictions with drugs used in HIV infection so that food-drug interactions can be avoided (see Table 2).

Drug interactions have become an increasingly complex challenge for providers treating patients with HIV infection. Current treatment guidelines recommend the use of a combination of at least three antiretroviral (ARV) drugs for the treatment of patients infected with HIV.^{1,2} In addition to medications to treat HIV infection, patients are often receiving therapy for co-morbid conditions and for prophylaxis of opportunistic infections.

Despite intense research in many areas of HIV infection, there is often a lack of formal drug interaction studies with HIV medications. Considering the number of drugs that the HIV-infected patient receives, providers often rely on clinical judgment and are forced to predict drug interactions without supporting data.

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.^{3,4} Although both have the potential to be problematic in patients receiving HAART, pharmacokinetic interactions are more common and most difficult to predict due to the complex nature of drug metabolism. Clinically significant drug interactions are generally those that produce at least a 25% to 30% change in pharmacokinetic parameters. 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	Indinavir taken with magnesium/aluminum-containing antacids can reduce indinavir 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 zalcitabine can reduce renal elimination of zalcitabine
Pharmacodynamic		
<i>Additive</i>	Concurrent therapy results in additive drug effect	Enhanced reduction in blood pressure when beta-blockers are added to ACE inhibitors
<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 Refs. 3-5.

A. Pharmacokinetic Interactions

Pharmacokinetic drug interactions can be further 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 absorption or metabolism.

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 latter mechanism has not been conclusively established. Table 2 outlines common drug interactions with HAART that lead to altered absorption with specific recommendations for management.

Drug interactions involving metabolism are most common and difficult to predict. Drugs used in HAART, especially the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the protease inhibitors (PIs), are metabolized via the cytochrome P450 enzyme system (CYP450). The CYP450 enzyme system is responsible for drug metabolism, with over 11 identified enzyme families.⁴ The enzyme responsible for the majority of drug metabolism is CYP3A4, although CYP1A2, 2C19, and 2D6 are also common. Drug therapy interacts with CYP450 enzymes in one of three ways: 1) through inhibition, 2) through induction, or 3) by acting as a substrate. 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

TABLE 2
CLINICALLY SIGNIFICANT INTERACTIONS AFFECTING THE ABSORPTION OF ARV THERAPY

Drug	Interaction	Comments
Didanosine (ddI, buffered)	ddI reduces AUC 55% when given within 2 hours of meal ddI reduces absorption of pH-dependent medications	Take ddI at least 30 minutes before or 2 hours after a meal Take ketoconazole, itraconazole, or dapsone at least 2 hours prior to ddI
Didanosine (ddI, enteric coated)	Food decreases absorption	Take 1 hour before meals or 2 hours after
Zalcitabine (ddC)	Aluminum/magnesium antacids reduces bioavailability 25%	Do not administer ddC with antacids
Tenofovir (TDF)	High fat meal increase AUC 40%, Cmax 14% Increases ddI AUC 40%	Take with meals Take ddI 2 hours before or 1 hour after TDF
Delavirdine (DLV)	Aluminum/magnesium antacids reduces AUC 41% ddI reduces systemic exposure of both drugs 20%	Separate antacids and DLV by at least 1 hour Separate ddI and DLV administration by at least 1 hour
Efavirenz (EFV)	High fat meals decreases absorption 50% Taking with food may increase central nervous system toxicity	Avoid high fat meals with EFV Take on an empty stomach
Saquinavir (SGC/HGC)	Food has been shown to enhance absorption	Take with a meal or up to 2 hours after a meal
Ritonavir (RTV)	Meal enhances absorption 13%	Take with a meal if possible
Indinavir (IDV)	High calorie meal has been shown to reduce AUC 77%	Take IDV 1 hour before or 2 hours after meal IDV may be taken with a light, low calorie snack
Nelfinavir (NFV)	AUC and Cmax were 2- to 3-fold higher when taken with food	Take with a meal or light snack
Amprenavir (APV)	High fat meals have been shown to reduce APV absorption	Avoid high fat meals with APV
Lopinavir/ritonavir (LPV/r)	Food increases AUC 48%, Cmax 23%	Take with food

AUC, area under the concentration versus time curve.

Data are from Refs. 5-24.

that either induce or inhibit the CYP450 enzyme system. Some medications may interact in more than one way and act as an inhibitor and inducer of different CYP450 enzymes. Table 3 lists the major inhibitors, inducers, and substrates of CYP450 enzymes involved with drug metabolism.

An understanding of the effect of CYP450 induction and inhibition is crucial to predicting drug interactions. Drugs that lead to inhibition of the CYP450 enzyme system lead to a decrease in clearance of other drugs metabolized by the same enzyme. The decrease in clearance 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 enzyme 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.³

TABLE 3
SELECT CYP450 INDUCERS, INHIBITORS, AND SUBSTRATES

	1A2	2C19	2D6	3A4
Inducers	Ritonavir, rifampin, phenytoin, omeprazole, phenobarbital, nicotine	Rifampin, carbamazepine	Rifampin, phenytoin, phenobarbital, carbamazepine	Efavirenz, nevirapine, rifampin, phenytoin, phenobarbital, carbamazepine, glucocorticoids, St. John's wort
Inhibitors	Fluoroquinolones, cimetidine, ticlopidine, fluvoxamine, amiodarone	Cimetidine, ketoconazole, omeprazole, fluoxetine, lansoprazole, paroxetine	Ritonavir, paroxetine, sertraline, fluoxetine, cimetidine, celecoxib, amiodarone, quinidine, methadone	PIs (in order of potency: ritonavir, indinavir, nelfinavir, amprenavir, saquinavir), delavirdine, fluconazole, ketoconazole, itraconazole, amiodarone, diltiazem, fluvoxamine, nefazodone, fluoxetine, clarithromycin, erythromycin, grapefruit juice, Seville orange juice
Substrates	Haloperidol, theophylline, zileuton, amitriptyline, cyclobenzaprine	Nelfinavir, lansoprazole, omeprazole, pantoprazole, diazepam, phenytoin	Metoprolol, carvedilol, codeine, dextromethorphan, tramadol, venlafaxine	Clarithromycin, cyclosporine, erythromycin, alprazolam, midazolam, triazolam, simvastatin, lovastatin, atorvastatin, nifedipine, nisoldipine, felodipine, protease inhibitors, sertraline

Data are from Ref. 25.

Induction of the CYP450 system results in the increased clearance of other drugs metabolized by the same enzyme system. When drugs that induce P450 enzymes are administered to a patient, the body responds by increasing the production of metabolic enzymes. The increased enzyme production can lead to increased metabolism and decreased drug levels of drugs metabolized via the same pathway. Induction can be problematic during HAART due to the concern for virologic failure if drug concentrations of PI and/or NNRTI are markedly reduced. The time to enzyme induction is much more prolonged compared with the onset of inhibition and is based on the half-life of the inducing drug and the time it takes to synthesize new enzyme.³ The maximal effect of enzyme induction is usually apparent within 7 days. Auto-induction is a phenomenon by which a drug induces its own metabolism. An example of auto-induction is the NNRTI, nevirapine. As a result, the dosing of nevirapine for the first 14 days is 200 mg daily, followed by 200 mg twice daily thereafter.

CYP450 enzymes are also found in the enterocytes of the small intestine, which can be involved with either inhibition or induction of drug metabolism in the gastrointestinal (GI) tract. A common example of this is the saquinavir/grapefruit juice drug interaction. As a result of CYP450 inhibition in the GI tract, grapefruit juice can significantly increase the bioavailability of saquinavir.²⁶ Similarly, ritonavir (a PI), may also inhibit CYP3A4 in the intestine, which is one of the proposed mechanisms that contributes to this drug acting as a pharmacokinetic “boost.”²⁷

B. Pharmacodynamic Interactions

Pharmacodynamic interactions involve alterations in the pharmacologic response of a particular drug without any change in drug concentrations (see Table 1). For example, when two drugs are used concurrently, the pharmacologic response can be antagonistic, additive, or synergistic, without necessarily altering plasma drug concentrations. An antagonistic effect results when a drug's pharmacologic effect is reduced due to concurrent therapy. A common example of an antagonistic drug interaction is the effect of concurrent zidovudine and stavu-

dine administration.²⁸ Additive effects occur when the use of two drugs leads to enhanced pharmacologic activity. Synergy occurs when two or more drugs used 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). Although pharmacodynamic interactions occur in clinical medicine, they usually do not result in serious adverse effects.³

III. HAART-RELATED DRUG INTERACTIONS

There are currently 16 drugs licensed in the United States for the treatment of HIV infection. These drugs belong to three distinct classes, which include nucleoside and nucleotide reverse transcriptase inhibitors (NRTI, NtRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI). This section reviews common drug interactions encountered with each class of medication used in HAART regimens. Appendix A lists key interactions by class. Table 4 outlines the route of metabolism for drugs used in HAART and their effect on the CYP450 system along with dose adjustments for patients with renal or hepatic impairment in Table 5. Table 6 lists drugs to avoid with PI-based regimens.

TABLE 4 ROUTES OF ELIMINATION OF HAART AND THE EFFECT ON CYP450		
Drug	Elimination	Effect on CYP450 System
Zidovudine (AZT, ZDV)	Hepatic metabolism with renal excretion	None
Didanosine (ddI)	Renal excretion 50%	None
Zalcitabine (ddC)	Renal excretion 70%	None
Stavudine (d4T)	Renal excretion 50%	None
Lamivudine (3TC)	Renal excretion 70%	None
Tenofovir (TFV)	Renal excretion 70-80%	None
Abacavir (ABC)	Hepatic	Insignificant
Nevirapine (NVP)	Hepatic	CYP3A4 inducer
Delavirdine (DLV)	Hepatic	CYP3A4 inhibitor
Efavirenz (EFV)	Hepatic	CYP3A4 inducer/inhibitor
Saquinavir (SQV)	Hepatic	CYP3A4 inhibitor
Ritonavir (RTV)	Hepatic	CYP3A4 inhibitor CYP2D6 inhibitor (3A4 inhibition >2D6) 3A4 and CYP1A2 inducer
Indinavir (IDV)	Hepatic	CYP3A4 inhibitor
Nelfinavir (NFV)	Hepatic	CYP3A4 inhibitor
Amprenavir (APV)	Hepatic	CYP3A4 inhibitor
Lopinavir/ritonavir (LPV/rtv)	Hepatic	CYP3A4 inhibitor CYP2D6 inhibitor (3A4 inhibition >2D6) 3A4 and CYP1A2 inducer

Data are from Refs. 6, 7, 14-24, 29-32.

TABLE 5			
HAART DRUGS REQUIRING DOSAGE ADJUSTMENT IN CASES OF RENAL OR HEPATIC FAILURE			
Drug	Dosage Adjustment Requirement	Dosage Recommendation	
Zidovudine	Renal impairment	100 mg q8h if patient on hemo/peritoneal dialysis	
Didanosine buffered tablets	Renal impairment	Creatinine Clearance (mL/min) 30-59 10-29 <10 Creatinine Clearance (mL/min) 30-59 10-29 <10	Dose (if >60kg) 100 mg bid or 200 mg qd 150 mg qd 100 mg qd Dose (if <60kg) 75 mg bid or 150 mg qd 100 mg qd 75 mg qd
Didanosine powder	Renal impairment	Creatinine Clearance (mL/min) 30-59 10-29 <10 Creatinine Clearance (mL/min) 30-59 10-29 <10	Dose (if >60kg) 100 mg bid 167 mg qd 100 mg qd Dose (if <60kg) 100 mg bid 100 mg qd 100 mg qd
Didanosine EC caps	Renal impairment	Creatinine Clearance (mL/min) 30-59 10-29 <10 Creatinine Clearance (mL/min) 30-59 10-29 <10	Dose (if >60kg) 200 mg qd 125 mg qd 125 mg qd Dose (if <60kg) 125 mg qd 125 mg qd Not recommended
Zalcitabine	Renal impairment	Creatinine Clearance (mL/min) 10-40 <10	Dose 0.75 mg q12h 0.75 mg q24h

AUC, area under the concentration versus time curve.

Data are from Refs. 5-24.

TABLE 5
HAART DRUGS REQUIRING DOSAGE ADJUSTMENT IN CASES OF
RENAL OR HEPATIC FAILURE (CONT'D.)

Drug	Dosage Adjustment Requirement	Dosage Recommendation	
Stavudine	Renal impairment	Creatinine Clearance (mL/min)	Dose (if >60kg)
		26-50	20 mg q12h
		10-26	20 mg q24h
		Dialysis	20 mg q24h
		Creatinine Clearance (mL/min)	Dose (if <60kg)
		26-50	15 mg q12h
10-26	15 mg q24h		
Dialysis	15mg q24h (post-dialysis)		
Lamivudine	Renal impairment	Creatinine Clearance (mL/min)	Dose
		30-49	150 mg qd
		15-29	150 mg once, then 100 mg qd
		5-14	150 mg once, then 50 mg qd
		<5	50 mg once, then 25 mg qd
		Dialysis	50 mg once, then 25 mg qd
Abacavir	Hepatic impairment	For patients with Childs-Pugh Scores of 5-6 and cirrhosis, consider 150 mg bid	
Tenofovir	Renal impairment	No published data to date evaluating the use of tenofovir in patients with creatinine clearance of <60 mL/min. Tenofovir elimination expected to be impaired in patients with renal dysfunction.	
Indinavir	Hepatic impairment	For patients with mild to moderate hepatic dysfunction, the dose of indinavir should be reduced to 600 mg q8h.	
Amprenavir	Hepatic impairment	Childs-Pugh Score	Dose
		5-8	450 mg bid
		9-12	300 mg bid

Data are from Refs. 6, 7, 14, 17, 22, 29-33.

A. Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

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.^{6,7,29-32} Two types of interactions predominate with this class of drugs: pharmacokinetic interactions leading to impaired absorption or elimination and pharmacodynamic interactions leading to antagonistic effects.

Concurrent use of zidovudine and stavudine has been shown to be antagonistic and is contraindicated.^{2,28-30} These drugs have been demonstrated to compete for the same enzyme that phosphorylates them to their active form.

Didanosine is formulated as an enteric-coated capsule, a buffered powder for oral solution, and a buffered tablet containing calcium carbonate and magnesium hydroxide. Because didanosine is unstable in acidic environments, the buffer is required to ensure adequate drug absorption in the GI tract. Patients taking the buffered tablet formulation should take at least two tablets at each dose to ensure that they receive adequate buffering. Use of the buffered powder or the buffered tablet formulations can lead to drug interactions when co-administered with fluoroquinolones and tetracyclines.⁶ The buffer may reduce the antimicrobial activity by chelating them and impairing their absorption. For example, didanosine-buffered tablets have been shown to significantly impair the absorption of ciprofloxacin when administered concurrently.^{8,9} To prevent this interaction, didanosine should be administered at least 2 hours after or 6 hours before the fluoroquinolone.⁶ This interaction can also be avoided by using the enteric-coated capsule formulation.

Alterations in gastric pH can also affect the absorption of the azole antifungals, ketoconazole and itraconazole. Concurrent antacid, H₂ antagonist, or proton-pump inhibitor has been shown to impair the absorption of ketoconazole.¹⁰ Didanosine has been shown to significantly impair the absorption of itraconazole.¹¹ Therefore, ketoconazole and itraconazole should be administered at least 2 hours prior to didanosine. Data evaluating concurrent didanosine and fluconazole have demonstrated no clinically significant interaction.¹²

Other documented drug interactions with didanosine include delavirdine, indinavir, tenofovir, and allopurinol. When didanosine was given concurrently with delavirdine or indinavir, the AUC of delavirdine and indinavir was reduced 20% and 84%, respectively.⁶ Delavirdine and indinavir should be given 1 hour prior to didanosine to maintain adequate AUC.^{13,34} When didanosine was co-administered with tenofovir, the AUC for didanosine was increased by 40%.

Although drug interactions associated with zalcitabine are minimal, there is evidence that concurrent use with probenecid or cimetidine can decrease the renal elimination of zalcitabine and increase its levels, leading to potential toxicity.^{7,35} When used concurrently with cimetidine or probenecid, clinicians should be aware of the potential for increased toxicity related to zalcitabine. Zalcitabine absorption can also be reduced in patients taking magnesium- or aluminum-containing antacids; avoiding concurrent administration or separating their use is an effective way to avoid this interaction.⁷ Drug interactions with stavudine, lamivudine, abacavir, and tenofovir are minimal.

The only available drug in the nucleotide reverse transcriptase inhibitor class is tenofovir, which was approved in October 2001. This drug is primarily eliminated via the kidney, thus minimal drug interactions involving metabolism are expected. Although limited drug interaction data exist with this drug, tenofovir has been shown to increase the concentrations of didanosine. When used concurrently, didanosine concentrations were increased by 40%; however, the clinical significance of this interaction is unknown.¹⁴

B. Non-Nucleoside Reverse Transcriptase Inhibitors

There are currently three licensed NNRTIs available in the United States: nevirapine, delavirdine, and efavirenz. Drugs in this class are extensively metabolized via the CYP450 enzyme system: nevirapine is an inducer of CYP3A4; delavirdine is an inhibitor of CYP3A4; and efavirenz is a mixed inhibitor/inducer of CYP3A4.^{15,16,23} Therefore, drug interactions with this class are expected if concomitant medications are also metabolized by CYP3A4.

Nevirapine is a potent inducer of the CYP3A4 isoenzyme, with maximal enzyme induction occurring approximately 2 to 4 weeks after beginning therapy.¹⁵ Because enzyme inducers often lead to an increased metabolism of co-administered drugs, reduced concentrations of co-administered drugs are expected. For example, when nevirapine was used concurrently with ketoconazole, the AUC and maximum concentration (C_{max}) of ketoconazole decreased 63% and 40%, respectively.¹⁵ If nevirapine is co-administered with oral contraceptives, clinicians should be aware of the potential for contraceptive failure, and alternative methods of birth control should be employed. Similarly, methadone withdrawal also has been reported in patients taking concurrent nevirapine due to increased methadone clearance.³⁶⁻³⁹ Clinicians should be cautious when adding nevirapine to a regimen in patients taking methadone and should closely monitor for signs and symptoms of methadone withdrawal. The clinician should alert the methadone program that the patient's methadone requirement may increase.

Rifabutin and rifampin, also potent CYP3A4 inducers, have been shown to reduce nevirapine trough concentrations by 16% and 37%, respectively.¹⁵ In patients requiring treatment for *Mycobacterium avium* complex or *Mycobacterium tuberculosis*, rifabutin is the preferred drug to be used to avoid significant reductions in nevirapine levels (see Appendix D).

Efavirenz has been demonstrated to induce CYP3A4 in vivo, although in vitro data suggest that it can also inhibit CYP3A4, 2C9, and 2C19.²³ Although this drug may induce or inhibit metabolic enzymes, it more prominently induces CYP3A4, leading to reduced concentrations of concurrently administered drugs. Because of concerns with in vitro inhibition of CYP3A4, efavirenz should be avoided with midazolam, triazolam, and the ergot derivatives, although no published case reports to date have either proven or refuted the validity of these interactions.²³

Rifampin has been shown to reduce the AUC and C_{max} of efavirenz by 26% and 20%, respectively.²³ The clinical significance of this interaction is unknown, and no dosage reduction is recommended by the manufacturer when these drugs are used concurrently.²³ When efavirenz is combined with rifabutin, rifabutin levels are reduced, necessitating an increase in dose to 450 mg daily.

When selecting macrolide treatment in patients receiving efavirenz, it should be noted that, when concurrent use of these drugs was studied, the AUC and C_{max} of clarithromycin was decreased 39% and 26%, respectively, while the AUC and C_{max} for the active metabolite of clarithromycin increased 34% and 49%, respectively.²³ Although the clinical significance of this interaction is unknown, it is important to note that the incidence of rash was 46% in patients receiving these drugs concurrently. Therefore, it is recommended to avoid clarithromycin-based regimens in patients receiving efavirenz.²³

Delavirdine is a potent inhibitor of CYP3A4; therefore, concurrent administration of drugs metabolized by the same isoenzyme can lead to increased drug levels and potential toxicity.¹⁶ Other drugs that are metabolized by CYP3A4 include ergot alkaloid derivatives, nifedipine, sildenafil, and the following benzodiazepines: alprazolam, midazolam, and triazolam.¹⁶ Administration of these drugs with delavirdine can potentiate their effect, leading to drug toxicity, and should be avoided or used with caution in patients receiving delavirdine.

Due to their ability to induce the CYP450 system, the anticonvulsants (phenytoin, carbamazepine, and phenobarbital) may significantly reduce delavirdine, efavirenz, and nevirapine levels, thus these drugs should be avoided with NNRTI-based regimens if possible.¹⁶ Other drugs known to induce CYP450, also have been shown to reduce the AUC for delavirdine.^{16,40,41}

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.⁴²

Other potential interactions with delavirdine include ketoconazole and fluoxetine. Population pharmacokinetics suggest that trough delavirdine concentration may increase by 50% when used concurrently with these drugs.¹⁶ Combination therapy with either of these drugs should be avoided.

C. Protease Inhibitors

PI therapy is often complicated by drug interactions because each is a potent inhibitor of the CYP3A4.⁴ Because many other drugs available on the market are also metabolized by CYP3A4, the potential for drug interactions is a major concern for clinicians treating patients with HIV infection.

The most potent inhibitor of CYP3A4 is ritonavir, whereas the least potent is saquinavir (CYP3A4 inhibition from the PIs, indinavir, nelfinavir, and amprenavir, tends to be greater than saquinavir).⁴ In addition to its inhibitory effect on CYP3A4, ritonavir also exhibits inhibition of CYP2D6 (to a lesser extent than CYP3A4) and induction of CYP1A2 and possibly CYP2C9. The effect of ritonavir on multiple CYP450 enzymes further complicates and increases the number and severity of interactions associated with this drug; however, its ability to inhibit the metabolism of other PIs can be exploited when used as a boosting drug for other PIs.

Enterocytes of the GI tract express P-glycoprotein, a complex protein that increases efflux of drugs from cells into the GI tract, thereby reducing absorption. PIs have been shown to inhibit P-glycoprotein transport in the GI tract, with resultant increases in drug absorption in animal models. Although ritonavir is the most potent inhibitor, other PIs have been shown to inhibit P-glycoprotein as well.^{43,44}

Numerous drugs should be avoided during concurrent PI therapy because of CYP450 inhibition and the potential for increased toxicity or reduced efficacy. These drugs are listed in Table 6.

D. Antifungal Drugs

Antifungal drugs are recommended in the treatment of HIV infection either for oral candidiasis or for maintenance therapy of cryptococcal meningitis.⁴⁷ Data evaluating interactions with fluconazole and concurrent PI therapy have demonstrated drug interactions of minimal clinical significance.^{48,49} Ketoconazole is a potent CYP3A4 inhibitor and has been shown to increase the AUC of saquinavir and amprenavir 190% and 31%, respectively, and increase indinavir levels by 68%.^{1,2,50,51} During concurrent use of ketoconazole with saquinavir or amprenavir, the standard dose for each drug should be used, whereas when used with indinavir, the manufacturer recommends a dosage reduction to 600 mg every 8 hours.¹⁷ Conversely, ritonavir and lopinavir/ritonavir have demonstrated three-fold increase in ketoconazole levels when used concurrently, and doses >200 mg/day of ketoconazole are not recommended when using either of these drugs.^{1,2,18,24}

E. Anticonvulsants

There are limited data regarding drug interactions with anticonvulsants. Phenytoin, phenobarbital, and carbamazepine are of concern due to their ability to induce metabolic enzymes. Despite this concern, these drugs are often required for treatment of seizure disorders. One case report in the literature describes ARV therapy failure related to carbamazepine therapy.⁵² In this case, 200 mg of carbamazepine was taken with 800 mg of indinavir every 8 hours, with subsequent reduction in indinavir levels. Therefore, concurrent use of these drugs with PIs should be avoided, and a different anticonvulsant should be considered. In general, a patient's therapy should be monitored for proper drug levels of anticonvulsants and for virologic failure.

TABLE 6 DRUGS TO AVOID WITH PI-BASED HAART REGIMENS		
Drug	Interaction	Recommendation
Ergot alkaloids	Impaired hepatic metabolism from PI reported to increase risk of ergotism	Avoid concurrent use with PI therapy. Consider alternative drugs.
Simvastatin, lovastatin	Significant increase in levels of statins	Use pravastatin or low dose atorvastatin during concurrent PI therapy.
Phenytoin, carbamazepine, phenobarbital	Potential for increased metabolism of PI, leading to virologic failure	Avoid concurrent use if possible. Consider alternative anticonvulsant during PI therapy.
Alprazolam, midazolam, triazolam	Potential for prolonged or increased sedation or respiratory depression	Avoid concurrent use. Consider zolpidem or lorazepam.
St. John's wort	Significant decrease in PI (IDV studied) levels, potentially leading to virologic failure	Avoid concurrent use during PI therapy.
Garlic	Significant decrease in PI (SQV studied) levels, potentially leading to virologic failure	Avoid concurrent use with PI therapy.
Pimozide	Potential increased risk of cardiac toxicity with concurrent ritonavir use	Avoid concurrent use with ritonavir-based regimens, including lopinavir/ritonavir.
Rifampin	Significant decrease in PI concentrations, potentially leading to virologic failure	Consider rifabutin. See Appendix A for dosing recommendations.
Amiodarone, propafenone, bepridil, quinidine, flecainide	Potential increased risk for severe cardiac arrhythmias with concurrent ritonavir use	Avoid concurrent use with ritonavir-based regimens, including lopinavir/ritonavir.

Data are from Refs. 1, 2, 17-22, 24, 45, 46.

F. Antimycobacterial Drugs

Drug interactions are well documented with the antimycobacterial drugs, rifampin, rifabutin, and clarithromycin, during concurrent 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.^{1,2,17-22,24,52,53} Information regarding the management of HAART during concomitant therapy with rifabutin are published elsewhere (see Appendix D).⁴² Alterations in clarithromycin levels have been reported during concurrent therapy with PIs, and guidelines for dosing of antimycobacterial drugs during concurrent HAART are summarized in Appendix A.

G. Erectile Dysfunction

Sildenafil is used for erectile dysfunction and has also been evaluated for drug interactions with PIs. When this drug was given concurrently with indinavir, saquinavir, or ritonavir, the AUC for sildenafil was significantly increased by a factor of 2- to 11-fold.^{54,55} Based on these data, it is generally recommended that initial doses of sildenafil should be no more than 25 mg during concurrent PI therapy, and the dose should not be repeated for 48 hours.^{1,2}

H. Ergot Alkaloids

The ergot alkaloids are contraindicated with PIs because of their potential ergotism due to enhanced levels caused by CYP450 inhibition. Although the majority of case reports from the literature have described this event during therapy with ritonavir, other drugs associated with this interaction include indinavir and nelfinavir.⁵⁶⁻⁶² When treating migraine headaches, the ergot derivatives should be avoided in patients receiving concurrent PI therapy.

I. Herbal/Alternative Therapy

Herbal therapy use has become more frequent in both the general population and the HIV-infected population.⁶³⁻⁶⁶ Data from one hospital in New York State regarding herbal therapy use demonstrate that 34% of patients on HAART use herbal therapy on a regular basis⁶⁷; however, only 54% of these patients tell their providers that they are using herbal therapy, and 62% of the time, providers are unable to predict which patients are using herbal therapy.⁶⁷ Significant interactions occur when PIs are used with St. John's wort and garlic supplements. In a study of concurrent St. John's wort and indinavir use in healthy volunteers, researchers found that the AUC for indinavir was reduced 57%, demonstrating that St. John's wort, given with concurrent herbal therapy, may lead to virologic failure.⁴⁵ A recently published study also demonstrated that concurrent saquinavir and garlic supplements can reduce saquinavir plasma concentrations by 51%.⁴⁶ After a 10-day washout period, the saquinavir AUC, trough, and Cmax were only 60% to 70% of baseline levels. In the setting of HAART, supplemental garlic and St. John's wort are considered contraindicated, and all herbal products should be used with caution until further data are available regarding its effect on HAART *in vivo*.

J. HMG-CoA Reductase Inhibitors

Dyslipidemia occurs in approximately 70% of patients taking PIs, often requiring the use of HMG Co-A reductase inhibitors for treatment.⁶⁸ Studies have been conducted evaluating the potential interaction between PIs and the "statins," pravastatin, atorvastatin, and simvastatin.⁶⁹ 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.⁷⁰ 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.⁷¹ The results of these studies provide evidence that pravastatin is the safest drug for treating hyperlipidemia during concurrent PI therapy and that atorvastatin can be used cautiously at lower doses (5-10 mg) and with slow titration. The large increases in AUC associated with concurrent ritonavir/saquinavir and simvastatin administration demonstrates that simvastatin should not be used during PI therapy.^{1,2} 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.^{1,2}

K. Oral Contraceptives

Oral contraceptives should be used with caution in patients receiving HAART due to the varied effect on ethinyl estradiol levels with different PIs. One published study evaluated the effect of ritonavir on ethinyl estradiol levels.⁷² Researchers found that the AUC and Cmax of ethinyl estradiol was reduced 41% and 32%, respectively. Similar results have been reported with nelfinavir and lopinavir/ritonavir.²⁰ With these drugs, it is recommended to use alternate forms of birth control. Conversely, data with indinavir demonstrate an increase in the AUC for both ethinyl estradiol and norethindrone.¹⁸ Based on these data, contraceptive failure with indinavir is not expected when used concurrently with oral contraceptives.

L. Sedative/Hypnotics

Ritonavir has been shown to significantly impair the oral clearance of alprazolam and triazolam in healthy volunteers.^{73,74} As a result, there is a potential for increased benzodiazepine levels, which would lead to potentiation of the sedation and respiratory depression associated with these compounds. Although data describing this interaction are primarily with ritonavir, these drugs should not be administered with any of the PIs. Although no formal drug interactions studies evaluating the combination of clonazepam and PIs exist, levels of clonazepam may be elevated as it is also metabolized by CYP3A4. Acceptable sedative/hypnotic drugs, including zolpidem, lorazepam, or temazepam, may be used.^{1,2,74}

IV. DOSE ADJUSTMENTS DURING HAART REGIMENS

Clinicians should be cognizant of the multiple dosing adjustments 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 that may require 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 35% and 28%, respectively.^{75,76} Similar results were also found when efavirenz or nevirapine was co-administered with lopinavir/ritonavir.²⁴ 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 1,000 mg every 8 hours; lopinavir/ritonavir should be increased to 533 mg/133 mg twice daily.^{17,24} 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.^{21,77}

The NNRTI, delavirdine, has been shown to be a potent inhibitor of CYP3A4, and preliminary results suggest that, when used concurrently with indinavir, nevirapine 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.^{17,78}

B. Dual 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 adherence with reduced dosing frequency and reduced pill burden, to overcome enzyme induction related to nevirapine or efavirenz, and to increase efficacy of HAART against resistant viral strains. 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 and its inhibition of the P-glycoprotein system. To date, numerous dual-PI combinations have been evaluated, including lopinavir/ritonavir, saquinavir/ritonavir, indinavir/ritonavir, and amprenavir/ritonavir. In addition, multiple dosing strategies have been used. The most common regimens used are listed in Table 7.

Dosing of HAART is complex and becomes increasingly difficult in patients receiving drugs from multiple classes. Table 8 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.

TABLE 7
DRUG INTERACTIONS: COMBINING PROTEASE INHIBITORS POSSIBLE DOSE COMBINATIONS*†

Saquinavir

Saquinavir + Indinavir: not recommended
 Saquinavir + Nelfinavir: 1,200 mg bid + 1,250 mg bid
 Saquinavir + Ritonavir: 400 mg bid + 400 mg bid
 Saquinavir + Amprenavir: no recommendation
 Saquinavir + Lopinavir/Ritonavir: 800 mg bid + 3 capsules bid

Indinavir

Indinavir + Ritonavir: 800 mg bid + 100 mg bid or 200 mg bid; 400 mg bid + 400 mg bid
 Indinavir + Saquinavir: not recommended
 Indinavir + Nelfinavir: 1,200 mg bid + 1,250 mg bid
 Indinavir + Amprenavir: no recommendation
 Indinavir + Lopinavir/Ritonavir: 600 mg bid + 3 caps bid

Amprenavir

Amprenavir + Ritonavir: 600 mg bid + 100 mg bid; 1,200 mg qd + 200 mg qd
 Amprenavir + Saquinavir: no recommendation
 Amprenavir + Indinavir: no recommendation
 Amprenavir + Lopinavir/Ritonavir: 750 mg bid + 3 caps bid
 Amprenavir + Nelfinavir: no recommendation

Nelfinavir

Nelfinavir + Saquinavir: 1,250 mg bid + 1,200 mg bid
 Nelfinavir + Indinavir: 1,250 mg bid + 1,200 mg bid
 Nelfinavir + Ritonavir: 500-750 mg bid + 400 mg bid
 Nelfinavir + Amprenavir: no recommendation
 Nelfinavir + Lopinavir/Ritonavir: no recommendation

Lopinavir/Ritonavir

Lopinavir/Ritonavir + Indinavir: 3 caps bid + 600 mg bid
 Lopinavir/Ritonavir + Amprenavir: 3 caps bid + 750 mg bid
 Lopinavir/Ritonavir + Saquinavir: 3 caps bid + 800 mg bid
 Lopinavir/Ritonavir + Ritonavir: no recommendation
 Lopinavir/Ritonavir + Nelfinavir: no recommendation

* When adding an NNRTI to any of the combinations, further dose changes may be necessary as a result of induction or inhibition of the cytochrome P450 system.

† Generally based on pharmacokinetic studies rather than randomized clinical trials.

TABLE 8
DRUG INTERACTIONS: PROTEASE INHIBITORS—EFFECT OF DRUG ON LEVELS (AUCs)/DOSE

Drug Affected	Ritonavir	Saquinavir*	Nelfinavir
Indinavir (IDV)	Levels: IDV ↑ 2-5x Dose: IDV 400 mg bid + RTV 400 mg bid, or IDV 800 mg bid + RTV 100 or 200 mg bid	Levels: IDV no effect, SQV ↑ 4-7x † Dose: Insufficient data	Levels: IDV ↑ 50%, NFV ↑ 80% Dose: Limited data for IDV 1,200 mg bid + NFV 1,250 mg bid
Ritonavir (RTV)	–	Levels: RTV no effect SQV ↑ 20x ‡ Dose: Invirase or Fortovase 400 mg bid + RTV 400 mg bid	Levels: RTV no effect NFV ↑ 1.5x Dose: RTV 400 mg bid + NFV 500-750 mg bid
Saquinavir (SQV)	–	–	Levels: SQV ↑ 3-5x, NFV ↑ 20% † Dose: Standard NFV Fortovase 800 mg tid or 1,200 mg bid
Nelfinavir (NFV)	–	–	–
Amprenavir (APV)	–	–	–
Drug Affected	Amprenavir	Lopinavir + Ritonavir	
Indinavir (IDV)	Levels: APV AUC ↑ 33% Dose: no change	Levels: IDV AUC and Cmin increased. Dose: IDV 600 mg bid	
Ritonavir (RTV)	Levels: APV AUC ↑ 2.5-fold Dose: Limited data for APV 600-1,200 mg bid + RTV 100-200 mg bid	Lopinavir is co-formulated with ritonavir as Kaletra.	
Saquinavir (SQV)	Levels: APV AUC ↓ 32% Dose: insufficient data	Levels: SQV † AUC and Cmin increased Dose: SQV 800 mg bid, LPV/r standard	
Nelfinavir (NFV)	Levels: APV AUC ↑ 1.5-fold Dose: insufficient data	No data	
Amprenavir (APV)	–	Levels: APV AUC and Cmin increased Dose: APV 600-750 mg bid, LPV/r standard	

Reprinted from the Department of Health and Human Services and Henry J. Kaiser Family Foundation: *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents* (2001).

* Several drug interaction studies have been completed with saquinavir given as Invirase or Fortovase. Results from studies conducted with Invirase may not be applicable to Fortovase.

† Conducted with Fortovase.

‡ Conducted with Invirase.

TABLE 8
DRUG INTERACTIONS: PROTEASE INHIBITORS AND NON-NUCLEOSIDE REVERSE
TRANSCRIPTASE INHIBITORS—EFFECT OF DRUG ON LEVELS (AUCs)/DOSE (CONT'D.)

Drug Affected	Nevirapine	Delavirdine	Efavirenz
Indinavir (IDV)	Levels: IDV ↓28% NVP no effect Dose: IDV 1,000 mg q8h NVP standard	Levels: IDV ↑>40% DLV no effect Dose: IDV 600 mg q 8h DLV: standard	Levels: IDV ↓31% Dose: IDV 1,000 mg q8h EFV standard
Ritonavir (RTV)	Levels: RTV ↓11% NVP no effect Dose: Standard	Levels: RTV ↑70% DLV: no effect Dose: DLV: standard RTV: no data	Levels: RTV ↑18% EFV ↑21% Dose: RTV 600 mg bid (500 mg bid for intolerance) EFV standard
Saquinavir (SQV)	Levels: SQV ↓25% NVP no effect Dose: No data	Levels: SQV ↑5x‡ DLV no effect Dose: Fortovase 800 mg tid, DLV standard (monitor transaminase levels)	Levels: SQV ↓62%‡ EFV ↓12% Co-administration not recommended
Nelfinavir (NFV)	Levels: NFV ↑10% NVP no effect Dose: Standard	Levels: NFV ↑2x DLV ↓50% Dose: No data (monitor for neutropenic complications)	Levels: NFV ↑20% Dose: Standard
Amprenavir (APV)	No data	No data	Levels: APV AUC ↓36% Dose: APV 1,200 mg tid as single PI, or 1,200 mg bid + RTV 200 mg bid EFV standard
Lopinavir/ Ritonavir (LPV/RTV)	Levels: LPV Cmin ↓55% Dose: Consider LPV/r 533/133 mg bid in PI- experienced patients NVP standard	Levels: LPV levels expected to increase. Dose: Insufficient data	Levels: LPV AUC ↓40% EFV no change Dose: Consider LPV/r 533/133 mg bid in PI-experienced patients EFV standard
Nevirapine (NVP)	–	No data	Levels: NVP: No effect EFV: AUC ↓22%
Delavirdine (DLV)	No data	–	No data

Reprinted from the Department of Health and Human Services and Henry J. Kaiser Family Foundation: *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents* (2000).

‡ Conducted with Invirase.

V. RESOURCES FOR CONSULTATION

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

<http://www.hivatis.org/druginteractions.html>

<http://www.hiv-druginteractions.org>

VI. CONCLUSIONS

Drug interactions often complicate the treatment of HIV infection unless they are recognized, anticipated, and avoided. 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 that includes inquiry regarding prescription, over-the-counter medications, and herbal/alternative therapies. Patients need to be questioned regarding therapies that are received from other health care providers. Clinicians practicing in HIV medicine should be diligent in self-education regarding drugs that are commonly associated with clinically significant drug interactions with concurrent HAART and either avoid the use of these drugs or monitor patients for virologic failure or toxicity. Providing patients with a detailed list of contraindicated drugs with HAART may help to educate the patient to identify significant drug interactions. Finally, clinicians should be aware of dietary restrictions with drugs used in HIV infection so that food-drug interactions can be avoided.

The risk of drug interactions occurring with HIV therapy is likely; however, with education and diligence, the HIV clinician can identify these interactions and proactively prevent them from occurring.

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APPENDIX A
DRUG INTERACTIONS BETWEEN ANTIRETROVIRALS AND OTHER DRUGS

TABLE A-1			
DRUG INTERACTIONS BETWEEN PIs AND OTHER DRUGS THAT REQUIRE DOSE MODIFICATIONS OR CAUTIOUS USE			
Drugs Affected	Indinavir (IDV)	Ritonavir* (RTV)	Saquinavir† (SQV)
ANTIFUNGALS			
Ketoconazole	Levels: IDV ↑68% Dose: IDV 600 mg tid	Levels: Keto. ↑3X Dose: Use with caution; do not exceed 200 mg ketoconazole daily.	Levels: SQV ↑3X Dose: Standard
ANTI-MYCOBACTERIALS			
Rifampin	Levels: IDV ↓89% Contraindicated	Levels: RTV ↓35% Dose: No data Increased liver toxicity possible.	Levels: SQV ↓84% Contraindicated, unless using RTV+SQV, then use rifampin 600 mg qd or 2-3x/week.
Rifabutin	Levels: IDV ↓32%; rifabutin ↑2X Dose: ↓rifabutin to 150 mg qd or 300 mg 2-3x/week. IDV 1000 mg tid	Levels: Rifabutin ↑4X Dose: ↓rifabutin to 150 mg qod, or dose 3x per week. RTV: Standard	Levels: SQV ↓40% No dose adjustment unless using RTV+SQV, then use rifabutin 150 mg 2-3x/week SQV: Use with RTV enhancement.
Clarithromycin	Levels: Clarithromycin ↑53% No dose adjustment	Levels: Clarithromycin ↑77% Dose: adjust for renal insufficiency.	Levels: Clarithromycin ↑45% SQV ↑177% No dose adjustment
ORAL CONTRACEPTIVES	Levels: Norethindrone ↑26% ethinyl estradiol ↑24% No dose adjustment	Levels: ethinyl estradiol ↓40% Use alternative or additional method.	No data
LIPID-LOWERING AGENTS			
Simvastatin Lovastatin	Levels: Potential for large increase in statin levels. Do not use these agents.	Levels: Potential for large increase in statin levels. Do not use these agents.	Levels: Potential for large increase in statin levels. Do not use these agents.
ANTICONSULSANTS			
Phenobarbital Phenytoin Carbamazepine	Carbamazepine markedly ↓IDV AUC. Consider alternative agent.	Unknown Use with caution. Monitor anticonvulsant levels.	Unknown but may decrease SQV levels substantially. Monitor anticonvulsant levels.
Methadone	No change in methadone levels.	Methadone ↓37%. Monitor and titrate dose if needed. May require ↑methadone dose.	No data
Miscellaneous	Grapefruit juice ↓IDV levels by 26%. Sildenafil AUC ↑2- to 11-fold. Do not exceed 25 mg in a 48-hr period.	Desipramine ↑145%, reduce dose. Theophylline ↓47%, monitor theo. levels. Sildenafil AUC ↑2- to 11-fold. Do not exceed 25 mg in a 48-hr period. Many possible interactions (see package insert).	Grapefruit juice increases SQV levels. Dexamethasone decreases SQV levels. Sildenafil AUC ↑2- to 11-fold. Use a 25-mg starting dose of sildenafil.

Adapted from the Department of Health and Human Services and Henry J. Kaiser Family Foundation: *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents* (2001).

* Drugs in which plasma concentrations may be decreased by co-administration with Norvir: anticoagulants (warfarin), anticonvulsants (phenytoin, divaproex, lamotrigine), antiparasitics (atovaquone).

† Some drug interaction studies were conducted with Invirase. May not necessarily apply to use with Fortovase.

TABLE A-1
DRUG INTERACTIONS BETWEEN PIS AND OTHER DRUGS THAT REQUIRE
DOSE MODIFICATIONS OR CAUTIOUS USE (CONT'D.)

Drugs Affected	Nelfinavir (NFV)	Amprenavir (APV)	Lopinavir (LPV)
ANTIFUNGALS			
Ketoconazole	No dose adjustment necessary.	Levels: APV ↑31% Ketoconazole ↑44% Combination under investigation.	Levels: LPV AUC ↓13% Ketoconazole ↑3-fold
ANTI-MYCOBACTERIALS			
Rifampin	Levels ↓82% Contraindicated	Levels: APV AUC ↓82% No change in rifampin AUC. Avoid concomitant use.	Levels: LPV AUC ↓75% Avoid concomitant use.
Rifabutin	Levels: NFV ↓32% Rifabutin ↑2X Dose: ↓rifabutin to 150 mg qd OR 300 mg 2-3x/week. ↑NFV dose to 1000 mg tid.	Levels: APV AUC ↓15% Rifabutin ↑193% Dose: No change in APV dose; Decrease rifabutin to 150 mg qd or 300 mg 2-3x/week.	Levels: Rifabutin AUC ↑3-fold 25-O-desacetyl metabolite ↑47.5-fold. Decrease rifabutin dose to 150 mg qod. LPV/r: Standard
Clarithromycin	No data	Levels: APV AUC ↑18%. No change in Clarithromycin AUC. No dose adjustment	No data
ORAL CONTRACEPTIVES	Levels: Norethindrone ↓18% ethinyl estradiol ↓47% Use alternative or additional method.	Levels: Potential for metabolic interactions; use alternative or additional method.	Levels: ethinyl estradiol ↓42% Use alternative method.
LIPID-LOWERING AGENTS			
Simvastatin Lovastatin Atorvastatin Pravastatin	Levels: Potential for large increase in statin levels. Do not use these agents.	Levels: Potential for large increase in statin levels. Do not use these agents.	Levels: Potential for large increase in statin levels. Do not use these agents. Atorvastatin AUC ↑5.88-fold. Use with caution and monitor. Pravastatin AUC ↑33%; no dosage adjustment necessary.
ANTICONVULSANTS			
Phenobarbital Phenytoin Carbamazepine	Unknown but may decrease NFV levels substantially. Monitor anticonvulsant levels.	Unknown but may decrease APV levels substantially. Monitor anticonvulsant levels.	Unknown, but may decrease LPV levels substantially. Monitor anticonvulsant levels.
Methadone	NFV may decrease methadone levels, but minimal effect on maintenance dose. Monitor and titrate dose if needed. May require ↑methadone dose.	No data	Methadone AUC ↓53%. Monitor and titrate dose if needed. May require ↑methadone dose.
Miscellaneous	Sildenafil AUC ↑2- to 11-fold. Do not exceed 25 mg in a 48-hr period	Sildenafil AUC ↑2- to 11-fold. Do not exceed 25 mg in a 48-hr period.	Probable substantial ↑ in sildenafil AUC. Do not exceed 25 mg in a 48-hr period.

Adapted from the Department of Health and Human Services and Henry J. Kaiser Family Foundation: *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents* (2001).

TABLE A-2
DRUG INTERACTIONS BETWEEN NNRTIS AND OTHER DRUGS THAT REQUIRE
DOSE MODIFICATIONS OR CAUTIOUS USE

Drugs Affected	Nevirapine (NVP)	Delavirdine (DLV)	Efavirenz (EFV)
ANTIFUNGALS			
Ketoconazole	Levels: Ketoconazole ↓63% NVP ↑15-30%	No data	No data
ANTI-MYCOBACTERIALS			
Rifampin	Dose: Not recommended	Levels: DLV ↓96% Contraindicated	Levels: EFV ↓25% No dose adjustment
Rifabutin	Levels: NVP ↓37% Not recommended Levels: NVP ↓16% No dose adjustment.*	Levels: DLV ↓80% Rifabutin ↑100% Not recommended	Levels: EFV unchanged; Rifabutin ↓35% Dose: ↑rifabutin dose to 450-600 mg 2-3x/week.* EFV: standard
Clarithromycin	Levels: NVP ↑26%, Clarithromycin ↓30%. No dose adjustment.	Levels: Clarithromycin ↑100%, DLV ↑44% Dose adjust for renal failure.	Levels: Clarithromycin ↓39% Alternative recommended
ORAL CONTRACEPTIVES	Levels: Ethinyl estradiol ↓ approx 20%. Use alternative or additional methods.	No data	Levels: Ethinyl estradiol ↑37% No data on other component. Use alternative or additional methods.
LIPID-LOWERING AGENTS			
Simvastatin Lovastatin	No data	Levels: Potential for large increase in statin levels. Avoid concomi- tant use.	No data
ANTICONSULSANTS			
Phenobarbital Phenytoin Carbamazepine	Unknown Use with caution. Monitor anticonvulsant levels.	Unknown but may decrease DLV levels substantially Monitor anticonvulsant levels.	Unknown Use with caution Monitor anticonvulsant levels.
Methadone	Levels: NVP unchanged, methadone ↓significantly. Monitor and titrate dose if needed.	No data	Levels: methadone ↓ significantly. Titrate methadone dose to effect.
Miscellaneous	No data	May increase levels of dapson, warfarin and quinidine. Sildenafil: potential for increased concentrations and adverse effects. Do not exceed 25 mg in a 48-hr period.	Monitor warfarin when used concomitantly.

Adapted from the Department of Health and Human Services and Henry J. Kaiser Family Foundation: *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents* (2001).

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

TABLE A-3
DRUG INTERACTIONS BETWEEN NRTIs AND OTHER DRUGS THAT REQUIRE
DOSE MODIFICATIONS OR CAUTIOUS USE

Drugs Affected	Zidovudine (ZDV)	Stavudine (d4T)	Didanosine (ddI)
Methadone	No data	Levels: d4T ↓27%, methadone unchanged. No dose adjustment.	Levels: ddI ↓41%, methadone unchanged. Consider ddI dose increase.
Miscellaneous	Ribavirin inhibits phosphorylation of ZDV; this combination should be avoided if possible.	No data	No data

Adapted from the Department of Health and Human Services and Henry J. Kaiser Family Foundation: *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents* (2001).

**INTERACTIONS BETWEEN HIV-RELATED MEDICATIONS AND PSYCHOTROPIC MEDICATIONS:
INDICATIONS AND CONTRAINDICATIONS**

RECOMMENDATION:

Practitioners should refer to the full prescribing information of all medications their patients are taking. Doing so is particularly important when changes in mental status or the onset of psychiatric symptoms seem to be linked chronologically to changes in medication or dosage.

Most patients tolerate HIV-related medications without psychiatric or central nervous system side effects. However, when a change in mental status or the onset of psychiatric symptoms seems to be linked chronologically to changes in medications or dosage, it may be helpful to review the side effects described in the prescription literature.

Few psychiatric drugs are fully contraindicated for concomitant use with HIV-related medications. Consultation with a psychiatrist experienced in the treatment of HIV-infected patients is warranted when implementing combinations that suggest use with caution or when possible dose adjustment is recommended.

TABLE A-4 INTERACTIONS BETWEEN HIV-RELATED MEDICATIONS AND PSYCHOTROPIC MEDICATIONS: INDICATIONS AND CONTRAINDICATIONS			
Medication	Contraindicated	Use With Caution	Possible Dose Adjustment
Amprenavir	Alprazolam, diazepam, midazolam, triazolam, zolpidem	Fluoxetine and fluvoxamine may increase PI concentration and toxicity. Carbamazepine, phenobarbital, phenytoin, primidone, St. John's wort reduce level of PI, and concurrent use should be avoided. Avoid pimoziide if possible.	Carbamazepine, phenobarbital, phenytoin levels rise: monitor levels and adjust prn.
Clarithromycin	None identified	St. John's wort may decrease level of clarithromycin.	Carbamazepine level rises: monitor level and adjust prn. Initial dose of benzodiazepines (i.e., alprazolam, midazolam) should be reduced, as clarithromycin may increase levels.
Delavirdine	Alprazolam, midazolam, triazolam	Fluoxetine, fluvoxamine and nefazodone may increase NNRTI level and increase toxicity. Carbamazepine, phenobarbital, phenytoin, St. John's wort can lower delavirdine levels: avoid concurrent use if possible. Avoid pimoziide if possible.	Carbamazepine levels may rise: monitor and adjust prn.
Didanosine (ddI)	None identified	Gabapentin levels decreased by antacid: ddI should be given 2 hours before or after.	Methadone decreases ddI: consider increased dose.
Efavirenz	Alprazolam, diazepam, midazolam, pimoziide, triazolam	Fluoxetine, fluvoxamine, and nefazodone may increase NNRTI level and increase toxicity. St. John's wort may decrease efavirenz levels and should be avoided.	Methadone levels decreased: may need to increase dose. Carbamazepine levels may rise: monitor and adjust prn.

Data are from 1) Klein R, Struble K. *The Protease Inhibitors: Backgrounder*. Food and Drug Administration, September 1996. 2) Preston SL, Stein DS. Drug interactions and adverse drug reactions with protease inhibitors. *Primary Psychiatry*. 1997;64:69. 3) *Physicians' Desk Reference*. Oradell, NJ: Medical Economics Company, Inc.; 1997.

TABLE A-4
INTERACTIONS BETWEEN HIV-RELATED MEDICATIONS AND PSYCHOTROPIC MEDICATIONS:
INDICATIONS AND CONTRAINDICATIONS (CONT'D.)

Medication	Contraindicated	Use With Caution	Possible Dose Adjustment
Fluconazole	None identified	None identified	Carbamazepine and phenytoin levels rise: monitor level and decrease dose prn. Because of CNS effects, may need to decrease dose of benzodiazepines (i.e., alprazolam, midazolam, triazolam), methadone, or zolpidem. Levels of amitriptyline and nortriptyline may rise: monitor and adjust prn.
Indinavir	Diazepam, midazolam, St. John's wort, triazolam, zolpidem	Fluoxetine, fluvoxamine, and nefazodone increase PI level and increase toxicity. Carbamazepine, phenobarbital, phenytoin, and primidone reduce indinavir level. Avoid pimozone if possible.	Carbamazepine level rises: monitor and lower dose prn.
Ketoconazole	Alprazolam, clonazepam, diazepam, midazolam, triazolam	None identified	Carbamazepine and ethosuximide levels rise: monitor toxicity and lower dose if necessary.
Lamivudine	None identified	None identified	None identified
Lopinavir/ Ritonavir*	Alprazolam, bupropion, clorazepate, clozapine, diazepam, estazolam, flurazepam, midazolam, pimozone, St. John's wort, triazolam, zolpidem	Fluoxetine, fluvoxamine, and PI levels may increase. Mexiletine levels rise and may cause greater cardiac/neurologic toxicity: use with caution. Phenobarbital and primidone levels may rise and PI level fall: avoid concurrent use if possible.	Desipramine levels may rise significantly: consider 50% lower dose. Meperidine and methadone levels decrease: may need increased dose. Carbamazepine, clonazepam, nefazodone, and sertraline: initial dose should be reduced 70%. Trazodone levels may increase: start low. Phenothiazines, SSRIs, and TCAs should have initial dose reduced by 50% and be monitored closely for toxicity. Valproic acid, phenytoin doses may need to be higher. Ethosuximide level rises: may need to lower dose.
Nelfinavir	Diazepam, midazolam, St. John's wort, triazolam, zolpidem	Fluoxetine and fluvoxamine may increase PI level. Carbamazepine, phenobarbital, phenytoin, primidone may decrease PI: avoid concurrent use if possible.	None identified
Nevirapine	St. John's wort	Avoid pimozone if possible. Fluoxetine and fluvoxamine may increase NNRTI level.	Methadone levels lowered: may need higher dose. Carbamazepine levels rise, PI level may drop: avoid concurrent use if possible.

Data are from 1) Klein R, Struble K. *The Protease Inhibitors: Backgrounder*. Food and Drug Administration, September 1996. 2) Preston SL, Stein DS. Drug interactions and adverse drug reactions with protease inhibitors. *Primary Psychiatry*. 1997;64:69. 3) *Physicians' Desk Reference*. Oradell, NJ: Medical Economics Company, Inc.; 1997.

* Dose of ritonavir is lower than when used as a single PI, and the drug-drug impact of ritonavir may be less significant. However, as pharmacologic data are limited, at this time the same cautions and contraindications as with full-dose ritonavir are repeated.

TABLE A-4
INTERACTIONS BETWEEN HIV-RELATED MEDICATIONS AND PSYCHOTROPIC MEDICATIONS:
INDICATIONS AND CONTRAINDICATIONS (CONT'D.)

Medication	Contraindicated	Use With Caution	Possible Dose Adjustment
Pyrimethamine	Lorazepam increases risk of hepatic toxicity (monitor LFTs).	None identified	None identified
Rifabutin and Rifampin	None identified	None identified	Methadone level decreases, and higher dose may be needed. Carbamazepine, phenytoin, valproic acid levels may decrease: may need to increase dose based upon levels.
Ritonavir	Alprazolam, bupropion, clorazepate, clozapine, diazepam, estazolam, flurazepam, midazolam, pimozone, St. John's wort, triazolam, zolpidem	Fluoxetine, fluvoxamine, and PI levels may increase. Mexiletine levels rise and may cause greater cardiac/neurologic toxicity: use with caution.	Desipramine levels may rise significantly: consider 50% lower dose. Meperidine and methadone levels decrease: may need increased dose. Carbamazepine, clonazepam, nefazadone, and sertraline: initial dose should be reduced 70%. Trazodone levels may increase: start low. Phenothiazines, SSRIs, and TCAs should have initial dose reduced by 50% and be monitored closely for toxicity. Valproic acid, phenytoin doses may need to be higher. Ethosuximide level rises: may need to lower dose.
Saquinavir	Diazepam, midazolam, St. John's wort, triazolam, zolpidem	Phenobarbital and primidone levels may rise and PI level fall: avoid concurrent use if possible. Fluoxetine and fluvoxamine may increase PI level and toxicity. Phenobarbital and primidone can lower PI: avoid concurrent use if possible. Avoid pimozone if possible.	Carbamazepine level rises (may need to lower dose prn) and PI falls when co-administered.
Stavudine	None identified	None identified	None identified
Zalcitabine (ddC)	None identified	Disulfiram and phenytoin may increase risk for peripheral neuropathy.	None identified
Zidovudine	None identified	Methadone and valproic acid increase zidovudine levels: monitor for toxicity.	None identified

Data are from 1) Klein R, Struble K. *The Protease Inhibitors: Background*. Food and Drug Administration, September 1996. 2) Preston SL, Stein DS. Drug interactions and adverse drug reactions with protease inhibitors. *Primary Psychiatry*. 1997;64:69. 3) *Physicians' Desk Reference*. Oradell, NJ: Medical Economics Company, Inc.; 1997.

APPENDIX B
DRUGS THAT SHOULD NOT BE USED WITH ANTIRETROVIRALS

TABLE B-1
DRUGS THAT SHOULD NOT BE USED WITH PI ANTIRETROVIRALS

Drug Category	Indinavir	Ritonavir*	Saquinavir	Nelfinavir	Amprenavir	Lopinavir + Ritonavir*
Ca++ channel blocker	(none)	bepidil	(none)	(none)	bepidil	(none)
Cardiac	(none)	amiodarone flecainide propafenone quinidine	(none)	(none)	(none)	flecainide propafenone
Lipid lowering agents	simvastatin lovastatin	simvastatin lovastatin	simvastatin lovastatin	simvastatin lovastatin	simvastatin lovastatin	simvastatin lovastatin
Anti-mycobacterial	rifampin	(none)	rifampin rifabutin	rifampin	rifampin	rifampin
Gastrointestinal drugs	cisapride	cisapride	cisapride	cisapride	cisapride	cisapride
Neuroleptic	(none)	clozapine pimozide	(none)	(none)	(none)	pimozide
Psychotropic	midazolam triazolam	midazolam triazolam	midazolam triazolam	midazolam triazolam	midazolam triazolam	midazolam triazolam
Ergot alkaloids (vasoconstrictor)	dihydro-ergotamine (D.H.E. 45) ergotamine† (various forms)	dihydro-ergotamine (D.H.E. 45) ergotamine† (various forms)	dihydro-ergotamine (D.H.E. 45) ergotamine† (various forms)	dihydro-ergotamine (D.H.E. 45) ergotamine† (various forms)	dihydro-ergotamine (D.H.E. 45) ergotamine† (various forms)	dihydro-ergotamine (D.H.E. 45) ergotamine† (various forms)
Herbs	St. John's wort garlic	St. John's wort garlic	St. John's wort garlic	St. John's wort garlic	St. John's wort garlic	St. John's wort garlic

Adapted from the Department of Health and Human Services and Henry J. Kaiser Family Foundation: *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents* (2001).

* Some of the contraindicated drugs listed are based on theoretical considerations. Thus, drugs with low therapeutic indices yet with suspected major metabolic contribution from cytochrome P450 3A, CYP2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

† This is likely a class effect.

Suggested Alternatives

Simvastatin, lovastatin: atorvastatin, pravastatin, fluvastatin, cerivastatin (alternatives should be used with caution).

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

Astemizole, terfenadine: loratidine, fexofenadine, cetirizine.

Midazolam, triazolam: temazepam, lorazepam.

TABLE B-2
DRUGS THAT SHOULD NOT BE USED WITH NNRTI ANTIRETROVIRALS

Drug Category	Nevirapine	Delavirdine	Efavirenz
Ca++ channel blocker	(none)	(none)	(none)
Cardiac	(none)	(none)	(none)
Lipid lowering agents	(none)	simvastatin lovastatin	(none)
Anti-mycobacterial	(none)	rifampin rifabutin	(none)
Gastrointestinal drugs	(none)	cisapride H-2 blockers Proton pump inhibitors	cisapride
Neuroleptic	(none)	(none)	(none)
Psychotropic	(none)	midazolam triazolam	midazolam triazolam
Ergot alkaloids (vasoconstrictor)	(none)	dihydroergotamine (D.H.E. 45) ergotamine† (various forms)	dihydroergotamine (D.H.E. 45) ergotamine† (various forms)

Adapted from the Department of Health and Human Services and Henry J. Kaiser Family Foundation: *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents* (2001).

* Some of the contraindicated drugs listed are based on theoretical considerations. Thus, drugs with low therapeutic indices yet with suspected major metabolic contribution from cytochrome P450 3A, CYP2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

† This is likely a class effect.

Suggested Alternatives

Simvastatin, lovastatin: atorvastatin, pravastatin, fluvastatin, cerivastatin (alternatives should be used with caution).

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

Astemizole, terfenadine: loratidine, fexofenadine, cetirizine.

Midazolam, triazolam: temazepam, lorazepam.

APPENDIX C
HIV-RELATED DRUGS WITH OVERLAPPING TOXICITIES

Bone Marrow Suppression	cidofovir, cotrimoxazole, cytotoxic, chemotherapy, dapsone, flucytosine, ganciclovir, hydrox-yurea, interferon- α , primaquine, pyrimethamine, ribavirin, sulfadiazine, trimetrexate, zidovudine
Peripheral Neuropathy	didanosine, isoniazid, stavudine, zalcitabine
Pancreatitis	cotrimoxazole, didanosine, lamivudine (children), pentamidine, ritonavir, stavudine
Nephrotoxicity	adefovir, aminoglycosides, amphotericin B, cidofovir, foscarnet, indinavir, pentamidine, ritonavir
Hepatotoxicity	delavirdine, efavirenz, fluconazole, isoniazid, itraconazole, ketoconazole, nevirapine, NRTIs, protease inhibitors, rifabutin, rifampin
Rash	abacavir, amprenavir, cotrimoxazole, dapsone, NNRTIs, protease inhibitors, sulfadiazine
Diarrhea	didanosine, clindamycin, nelfinavir, ritonavir, lopinavir/ritonavir
Ocular Effects	didanosine, ethambutol, rifabutin, cidofovir

Adapted from the Department of Health and Human Services and Henry J. Kaiser Family Foundation: *Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents* (2001).

APPENDIX D

**RECOMMENDATIONS FOR CO-ADMINISTERING DIFFERENT ANTIRETROVIRAL DRUGS WITH THE
ANTIMYCOBACTERIAL DRUGS RIFABUTIN AND RIFAMPIN – UNITED STATES, 2000**

TABLE D-1			
RECOMMENDATIONS FOR CO-ADMINISTERING DIFFERENT ANTIRETROVIRAL DRUGS WITH THE ANTIMYCOBACTERIAL DRUGS RIFABUTIN AND RIFAMPIN – UNITED STATES, 2000			
Antiretroviral Drug	Use in combination with rifabutin	Use in combination with rifampin	Comments
Saquinavir*			
Hard-gel capsules (HGC)	Possibly†, if ARV regimen also includes ritonavir	Possibly, if ARV regimen also includes ritonavir	Co-administration of saquinavir SGC with usual-dose rifabutin (300 mg daily or two or three times per week) is a possibility. However, the pharmacokinetic data and clinical experience for this combination are limited.
Soft-gel capsules (SGC)	Probably‡	Possibly, if ARV regimen also includes ritonavir	The combination of saquinavir SGC or saquinavir HGC and ritonavir, co-administered with 1) usual-dose rifampin (600 mg daily or 2 or 3 times per week), or 2) reduced-dose rifabutin (160 mg 2 or 3 times per week) is a possibility. However, the pharmacokinetic data and clinical experience for these combinations are limited. Co-administration of saquinavir HGC or saquinavir SGC with rifampin (in the absence of ritonavir) is not recommended because rifampin markedly decreases concentrations of saquinavir.
Ritonavir	Probably	Probably	If the combination of ritonavir and rifabutin is used, then a substantially reduced-dose rifabutin regimen (160 mg 2 or 3 times per week) is recommended. Co-administration of ritonavir with usual-dose rifampin (600 mg daily or 2 or 3 times per week) is a possibility, although pharmacokinetic data and clinical experience are limited.
Indinavir	Yes	No	There is limited, but favorable, clinical experience with co-administration of indinavir§ with a reduced daily dose of rifabutin (150 mg) or with the usual dose of rifabutin (300 mg 2 or 3 times per week). Co-administration of indinavir with rifampin is not recommended because rifampin markedly decreases concentrations of indinavir.
Nelfinavir	Yes	No	There is limited, but favorable, clinical experience with co-administration of nelfinavir with a reduced daily dose of rifabutin (160 mg) or with the usual dose of rifabutin (300 mg 2 or 3 times per week). Co-administration of nelfinavir with rifampin is not recommended because rifampin markedly decreases concentrations of nelfinavir.
Amprenavir	Yes	No	Co-administration of amprenavir with a reduced daily dose of rifabutin (150 mg) or with the usual dose of rifabutin (300 mg 2 or 3 times per week) is a possibility, but there is no published clinical experience. Co-administration of amprenavir with rifampin is not recommended because rifampin markedly decreases concentrations of amprenavir.

TABLE D-1
RECOMMENDATIONS FOR CO-ADMINISTERING DIFFERENT ANTIRETROVIRAL DRUGS WITH THE
ANTIMYCOBACTERIAL DRUGS RIFABUTIN AND RIFAMPIN – UNITED STATES, 2000 (CONT'D.)

Antiretroviral Drug	Use in combination with rifabutin	Use in combination with rifampin	Comments
Nevirapine	Yes	Possibly	Co-administration of nevirapine with usual-dose rifabutin (300 mg daily or 2 or 3 times per week) is a possibility based on pharmacokinetic study data. However, there is no published clinical experience for this combination. Data are insufficient to assess whether dose adjustments are necessary when rifampin is co-administered with nevirapine. Therefore, rifampin and nevirapine should be used only in combination if clearly indicated and with careful monitoring.
Delavirdine	No	No	Contraindicated because of the marked decrease in concentrations of delavirdine when administered with either rifabutin or rifampin.
Efavirenz	Probably	Probably	Co-administration of efavirenz with increased-dose rifabutin (450 mg or 600 mg daily, or 600 mg 2 or 3 times per week) is a possibility, although there is no published clinical experience. Co-administration of efavirenz¶ with usual-dose rifampin (600 mg daily or 2 or 3 times per week) is a possibility, although there is no published clinical experience.

Reprinted from Centers for Disease Control and Prevention. Updated guidelines for the use of rifampin or rifabutin for the treatment of prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *Morb Mortal Wkly Rev MMWR* 2000;49:185-189.

* Usual recommended doses are 400 mg 2 times per day for each of these protease inhibitors and 400 mg of ritonavir.

† Despite limited data and clinical experience, the use of this combination is potentially successful.

‡ Based on available data and clinical experience, the successful use of this combination is likely.

§ Usual recommended dose is 800 mg every 8 hours. Some experts recommend increasing the indinavir dose to 1,000 mg every 8 hours if indinavir is used in combination with rifabutin.

|| Usual recommended dose is 750 mg 3 times per day or 1,250 mg twice daily. Some experts recommend increasing the nelfinavir dose to 1,000 mg if the 3x/day dosing is used and nelfinavir is used in combination with rifabutin.

¶ Usual recommended dose is 600 mg daily. Some experts recommend increasing the efavirenz dose to 800 mg daily if efavirenz is used in combination with rifampin.