Drug Therapy

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INTERACTIONS AMONG DRUGS FOR HIV AND OPPORTUNISTIC INFECTIONS

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DRUG interactions are an important factor in the treatment of patients with human immunodeficiency virus (HIV) infection. The complexity of current drug regimens for such patients requires that clinicians recognize and manage drug interactions. Antiretroviral drug regimens typically consist of three or four antiretroviral drugs but may include even more. In addition, patients may receive other drugs for supportive care, treatment of opportunistic infections, and immunomodulation, as well as alternative drugs obtained from health care providers other than their primary provider. Drug interactions are often unavoidable in HIV-infected patients because of the drug classes involved and the number of drugs prescribed. In this article we review the clinically important interactions among drugs used to treat HIV infection, provide an overview of the primary mechanisms of drug interactions, and discuss ways to prevent or minimize the adverse effects of such interactions on clinical care.

MECHANISMS OF DRUG INTERACTIONS

Drug interactions can be either pharmacokinetic or pharmacodynamic in nature. Pharmacokinetic interactions alter the absorption, transport, distribution, metabolism, or excretion of a drug. In therapy for HIV infection, pharmacokinetic interactions are often multifactorial. They may involve alterations in drug metabolism mediated by the cytochrome P-450 system, modulation of P-glycoprotein (a cellular transport protein), changes in renal elimination, changes in gastric pH and drug absorption, and fluctuations in intracellular drug concentrations (Table 1). These processes may take place at various sites in the body (Fig. 1). Pharmacodynamic interactions alter the pharmacologic response to a drug. The response can be additive, synergistic, or antagonistic. Pharmacodynamic interactions do not always modify a drug's concentration in tissue fluids.

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Metabolic Interactions

All HIV-protease inhibitors and non-nucleoside reverse-transcriptase inhibitors that have been approved by the Food and Drug Administration (FDA), as well as those that are investigational drugs, are metabolized by the cytochrome P-450 enzyme system, primarily by the 3A4 isoform (CYP3A4), and each of these drugs may alter the metabolism of other antiretroviral and concomitantly administered drugs.[15] The cytochrome P-450 system consists of at least 11 families of enzymes, classified by number, of which 3 (CYP1, CYP2, and CYP3) are important in humans.[16] The families are further divided into subfamilies, denoted by a capital letter (e.g., CYP3A). Individual proteins within a subfamily, called isozymes or isoenzymes, are identified by a second number (e.g., CYP3A4).[16]

Drugs can be classified as cytochrome P-450 substrates, inhibitors, or inducers. However, some drugs, such as ritonavir, nelfinavir, and efavirenz, may have properties of all three, depending on the specific combination (Table 2). Substrates are drugs metabolized through this enzyme system, and the plasma concentrations of such drugs may be increased or decreased by other drugs. Inhibition of cytochromes is usually reversible and competitive, in that the substrate and inhibitor compete for the same site on the enzyme. Inhibition also occurs by irreversible inactivation of the enzyme, leading to pharmacologic effects that are prolonged until new enzyme can be synthesized.[19] Drugs that inhibit cytochromes cause decreased clearance and increased plasma concentrations of substrate drugs, and the effects may be greater if inhibitory metabolites accumulate during multiple dosing.

Drugs that induce cytochromes increase the rate of hepatic metabolism of other drugs by increasing the transcription of cytochrome messenger RNA (mRNA), which in turn leads to the production of more enzyme and a corresponding decrease in plasma concentrations of drugs metabolized by the induced pathway. When a CYP3A4 inhibitor, such as ritonavir, is added to another protease inhibitor, such as saquinavir, plasma concentrations of the second protease inhibitor increase markedly (Fig. 2A), often allowing for more convenient dosing. Increased concentrations may also overcome viral resistance to the drug.[21] The addition of a CYP3A4 inducer, such as nevirapine, to indinavir or amprenavir results in a decrease in the area under the plasma concentration–time curve of the protease inhibitor (a measure of total exposure). A substantial decrease could reduce trough plasma concentrations of the protease inhibitor to a level below the in vitro concentration required to inhibit replication of 50 percent of viral strains (IC_{50}), with the subsequent development of resistance.

Intestinal Metabolism and P-Glycoprotein

The liver is the primary site of drug metabolism mediated by the cytochrome P-450 system, but CYP3A4

TABLE 1. COMMON MECHANISMS FOR DRUG INTERACTIONS IN PATIENTS WITH HIV INFECTION.*

MECHANISM	EXAMPLES	EFFECT	CONSEQUENCES
Altered intracellular activation			
Impairment of phosphorylation	Ribavirin and zidovudine,[1] zidovudine and stavudine,[2] zalcitabine and lamivudine[3]	Interference with intracellular phosphorylation (in vitro)	Potential for decreased effectiveness and treatment failure
Altered drug absorption and tissue distribution			
Chelation	Fluoroquinolones with antacids[4,5]	Marked reduction in quinolone AUC from formation of insoluble complexes	Reduced antimicrobial effect
Change in gastric pH	Indinavir and didanosine[6]	Impaired absorption of indinavir due to increased pH	Low plasma indinavir concentrations may lead to viral resistance and treatment failure
Induction of efflux transporters	Rifampin and digoxin[7]	Decrease in digoxin AUC	Reduced therapeutic effect
Inhibition of efflux transporters	Ketoconazole with saquinavir and ritonavir[8]	Increased CSF concentrations of saquinavir and ritonavir in relation to unbound plasma concentrations	Combination being studied to target drug delivery to CSF; clinical relevance unknown
Altered drug metabolism			
Induction of cytochrome P-450	Rifabutin and saquinavir[9]	Saquinavir AUC reduced by 47 percent	Low plasma saquinavir concentrations may lead to viral resistance and treatment failure
Inhibition of cytochrome P-450 (hepatic and gastrointestinal)	Ritonavir and indinavir[10]	Marked increases in indinavir AUC and trough concentration	Combination under study to optimize therapy and develop more convenient regimens for patients
Inhibition of cytochrome P-450 (gastrointestinal only)	Grapefruit juice and saquinavir[11]	Saquinavir AUC increased by 50 to 150 percent	Increased plasma saquinavir concentrations, but the effect is highly variable
Increase in glucuronosyltransferase	Rifampin and zidovudine[12]	Zidovudine AUC decreased by 47 percent	Clinical relevance unknown but may lead to reduced antiviral effect if triphosphate concentrations are also decreased
Reduced renal excretion	TMP-SMX and lamivudine[13]	Lamivudine AUC increased by 44 percent due to inhibition of tubular secretion	Dosage alteration unnecessary, since increased lamivudine concentrations are unlikely to have toxic effects
Pharmacodynamic interactions			
Additive or synergistic interactions	Zidovudine and ganciclovir	Additive bone marrow suppression	May require discontinuation or reduced doses of one or both drugs or addition of G-CSF
	Combination HAART therapy	Sustained viral suppression	Potent therapy associated with long-term clinical and immunologic improvement
Antagonist or opposing interactions	Indinavir and saquinavir[14]	In vitro antagonism at high doses	Clinical consequences unclear

*AUC denotes the area under the concentration–time curve, CSF cerebrospinal fluid, TMP-SMX trimethoprim–sulfamethoxazole, G-CSF granulocyte colony-stimulating factor, and HAART highly active antiretroviral therapy.

is also present in the enterocytes of the small intestine.[22] Thus, drugs that inhibit CYP3A4 may alter intestinal or hepatic metabolism of other drugs. The 20-fold increase in plasma concentrations of saquinavir caused by ritonavir is probably produced by inhibition of CYP3A4 at both sites.[20] Grapefruit juice contains various substances that inhibit CYP3A4-mediated metabolism only in the wall of the gut, mainly by selective down-regulation of CYP3A4 protein in the small intestine.[23] The area under the curve for plasma saquinavir is increased by 50 to 150 percent during concomitant administration of grapefruit juice.[11] However, grapefruit juice should not be relied on to increase plasma concentrations of protease inhibitors, because the variations in the amounts of flavonoids and other potentially active substances among products can result in inconsistent effects.[24]

The enterocytes in the intestinal mucosa are also a major site of expression of P-glycoprotein, one of several membrane-bound proteins that increase the efflux of drugs from cells.[25] Several protease inhibitors are substrates for and inhibitors of P-glycoprotein[26,27]; ritonavir is the most potent inhibitor.[28,29] Both cytochrome P-450 enzymes and P-glycoprotein can present a barrier to the absorption of orally administered drugs and have a considerable effect on drug interactions. Figure 2B shows the effect of rifampin on plasma digoxin concentrations through the induction of intestinal P-glycoprotein.[7] Although the inhibition and induction of intestinal CYP3A enzymes from metabolic processes result in direct changes in drug absorption, the inhibition and induction of P-glycoprotein primarily affect the rate of drug absorption.[30] The overlap of tissue distribution and substrate specificity of CYP3A4 and P-glycoprotein in the gut wall makes it difficult to define the specific mechanisms of some

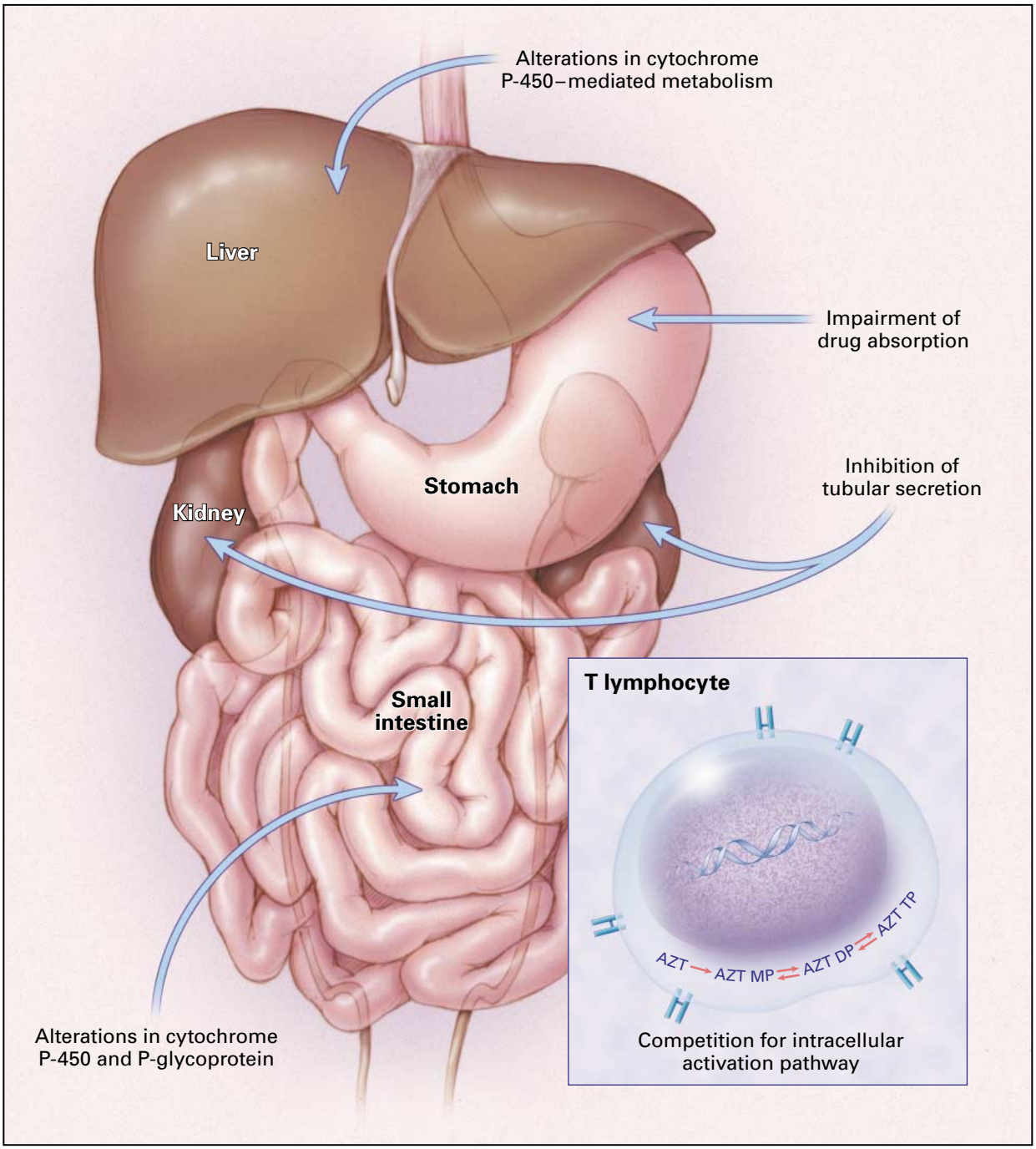

Figure 1. Various Sites in the Body in Which Drug Interactions Occur.

The inset shows a T lymphocyte in which nucleoside-analogue reverse-transcriptase inhibitors are undergoing intracellular conversion to their active forms. AZT denotes zidovudine, MP monophosphate, DP diphosphate, and TP triphosphate.

TABLE 2. CYTOCHROME P-450 ISOFORMS AND SELECTED DRUGS USED FOR THE TREATMENT OF HIV INFECTION.*

CYP3A4 substrates	CYP3A4 inhibitors	CYP3A4 inducers
Astemizole	Amprenavir	Carbamazepine
Clarithromycin	Clarithromycin	Efavirenz
Cyclosporine	Delavirdine	Nevirapine
Dapsone	Efavirenz	Phenytoin
Efavirenz	Erythromycin	Phenobarbital
Erythromycin	Fluconazole	Rifampin
Estrogens	Fluoxetine	Rifabutin
Etoposide	Grapefruit juice	Ritonavir
Fentanyl	Indinavir	Troglitazone
Midazolam	Itraconazole	
Nefazodone	Ketoconazole	
Prednisone	Lopinavir	
Protease inhibitors	Nelfinavir	
	Ritonavir	
Sertraline	Saquinavir	
Testosterone		
Triazolam		
CYP2D6 substrates	**CYP2D6 inhibitors**	
Codeine	Fluoxetine	
Desipramine	Paroxetine	
Fluoxetine	Quinidine	
Haloperidol	Ritonavir	
Methadone	Sertraline	
Morphine		
Paroxetine		
Risperidone		
CYP2C19 substrates	**CYP2C19 inhibitors**	**CYP2C19 inducers**
Nelfinavir	Fluconazole	Rifampin
Omeprazole	Omeprazole	
Diazepam	Fluoxetine	
CYP1A2 substrates	**CYP1A2 inhibitors**	**CYP1A2 inducers**
Haloperidol	Ciprofloxacin	Carbamazepine
Theophylline	Clarithromycin	Phenytoin
Zileuton	Erythromycin	Phenobarbital
	Fluvoxamine	Ritonavir
	Paroxetine	Cigarette smoke

*Data are from Flockhart[17] and Michalets.[18]

drug interactions and predict the plasma concentrations of certain drug combinations. Morover, the involvement of CYP3A4 and P-glycoprotein in drug interactions is not always complementary. For example, plasma indinavir concentrations either do not change or are decreased by the ingestion of grapefruit juice, suggesting that the activation of P-glycoprotein may compensate for the inhibition of CYP3A4,[6,31,32] but P-glycoprotein has little effect on the absorption of saquinavir.[33] The specific contribution of CYP3A4 inhibition and P-glycoprotein activation to interactions within the gastrointestinal tract remains unclear because most drugs that modulate P-glycoprotein also inhibit CYP3A4.[34] In any case, the inhibition of CYP3A4, P-glycoprotein, or both in the gut wall may have a substantial effect on plasma concentrations of many anti-HIV drugs.

P-glycoprotein is present at numerous other sites in the body.[35] Its presence in the renal tubular cells and hepatocytes results in increased drug excretion in urine and bile. P-glycoprotein in the endothelial cells of the blood–brain barrier prevents the entry of certain drugs into the central nervous system.[36] Ketoconazole, an inhibitor of both CYP3A4 and P-glycoprotein, causes a larger increase in cerebrospinal fluid concentrations of saquinavir and ritonavir than in unbound plasma concentrations, suggesting that the inhibition of efflux transporters can be used to target therapy in the central nervous system.

Drug Absorption

Interactions that alter the absorption of drugs often lead to dramatic changes in plasma drug concentrations. The concomitant administration of a fluoroquinolone with divalent and trivalent cations can reduce the area under the curve for plasma quinolone by more than 90 percent.[4] A didanosine formulation containing an aluminum–magnesium antacid buffer decreases the area under the curve for plasma ciprofloxacin by 80 percent (Fig. 2C).[5] These interactions can easily be avoided by administering the fluoroquinolone at least two hours before or six hours after the antacid, or by using the new, enteric-coated formulation of didanosine.

The absorption of other drugs may be altered by changes in gastric pH. For example, because ketoconazole is best absorbed when the gastric pH is low, concomitant administration of ketoconazole and H_2-antagonists, antacids, or proton-pump inhibitors results in marked impairment of the absorption of ketoconazole.[37] Itraconazole is also best absorbed when the gastric pH is low, but its administration with food is more important for achieving high plasma concentrations.[38] The absorption of fluconazole is unaffected by variations in gastric pH.[39]

Renal Elimination

Probenecid and trimethoprim are competitive inhibitors of renal tubular secretion of other drugs that are primarily eliminated through this pathway. Although probenecid increases plasma acyclovir concentrations and trimethoprim–sulfamethoxazole increases plasma lamivudine concentrations (Fig. 2D), these interactions are not clinically important and do not warrant a change in dose, because high concentrations of these drugs are not associated with adverse effects.[13,40] Probenecid also inhibits hepatic glucuronidation of zidovudine and increases plasma zidovudine concentrations by 80 percent.[41] The clinical importance of this increase is unknown.

PREDICTING DRUG INTERACTIONS

The multiple metabolic pathways of some drugs make it difficult to predict the outcome of drug interactions. Although in vitro systems have been de-

Figure 2. Mechanisms of Drug Interactions.

Inhibition of intestinal and hepatic CYP3A4 by ritonavir markedly increases plasma saquinavir concentrations when saquinavir is given at a dose of 400 mg and ritonavir at a dose of 600 mg (Panel A; bars denote standard errors).[20] Induction of intestinal P-glycoprotein by rifampin decreases plasma digoxin concentrations (Panel B; I bars denote standard deviations).[7] The combination of ciprofloxacin and didanosine results in decreased plasma ciprofloxacin concentrations, because absorption of the drug is decreased by chelation with divalent cations in the antacid buffer of didanosine (Panel C; bars denote standard deviations).[5] When lamivudine is combined with trimethoprim–sulfamethoxazole (TMP-SMX), plasma lamivudine c0z pamUzkn-Z08pc-Z0zFpentr-8:zFpati-0 z8pons -Z:Fz8apr-8/z1ps -Z

veloped to test the effects of certain drugs on the metabolism of other drugs, these systems may not accurately predict the effect in patients receiving drugs with complex metabolism, and induction interactions may not be detected if the system can assess only inhibition.[42] For example, initial in vitro data from human liver microsomes suggested that plasma methadone concentrations would be increased by the inhibitory effects of ritonavir on CYP3A4.[43] In a clinical study, however, plasma methadone concentrations were decreased by the administration of ritonavir.[44] Subsequently, ritonavir was found to displace methadone from plasma protein–binding sites and to increase its metabolism by inducing CYP2B6, which degrades methadone.[45,46] Studies in hepatocytes revealed no effect of rifampin on glucuronidation of zidovudine, but rifampin-induced glucuronidation of zidovudine was demonstrated in vivo.[12,47,48]

Even clinical studies may not accurately predict changes if the interaction is dependent on time. Ritonavir inhibits the metabolism of alprazolam during a short-term regimen of ritonavir but induces the metabolism of alprazolam when it is given for 10 days.[49] Furthermore, most in vivo and in vitro studies of drug interactions evaluate two-drug regimens, and the results may not apply to the multi-drug regimens often used clinically. This is especially true for a regimen consisting of three or more drugs with opposing ef-

fects on CYP3A4 metabolism. The lack of multidrug interaction studies provides little assistance to the clinician, who is left to rely on adverse effects or treatment failure to demonstrate whether an interaction occurred.

NUCLEOSIDE-ANALOGUE REVERSE-TRANSCRIPTASE INHIBITORS

Because nucleoside-analogue reverse-transcriptase inhibitors are primarily eliminated by the kidneys, they do not interact with other drugs through the cytochrome P-450 system. These drugs can be given with protease inhibitors and non-nucleoside reverse-transcriptase inhibitors without dosage adjustments.

Nucleoside reverse-transcriptase inhibitors are prodrugs that require intracellular phosphorylation to the active moiety, and they may therefore interact with drugs that compete for the intracellular activation pathway. Ribavirin decreases the phosphorylation of zidovudine and stavudine in vitro, resulting in decreased concentrations of the active compound.[50,51] Patients who have HIV infection and hepatitis C may be treated with regimens that contain ribavirin, which may reduce the efficacy of zidovudine. Similarly, zidovudine may impair the intracellular phosphorylation of stavudine,[1] and this combination is associated with a less favorable outcome than other regimens containing two nucleoside reverse-transcriptase inhibitors.[2] Also, lamivudine inhibits phosphorylation of zalcitabine.[3]

Other intracellular interactions may increase the activity of nucleoside reverse-transcriptase inhibitors. Hydroxyurea, an inhibitor of the enzyme ribonucleotide reductase, which is involved in the formation of deoxynucleotides, increases the antiviral action of didanosine.[52] One possible mechanism for this effect involves a decrease in the intracellular pool of 2′-deoxyadenosine-5′-triphosphate (dATP), which competes with 2′,3′-dideoxyadenosine-5′-triphosphate (ddATP), the active metabolite of didanosine, for incorporation into viral DNA. As a result, the intracellular ratio of ddATP to dATP is increased, improving the antiviral potency of didanosine. However, the long-term clinical benefits of hydroxyurea-containing combinations are unclear, because hydroxyurea blunts the increase in CD4 cells that occurs in response to antiretroviral therapy and has numerous adverse effects, including hepatitis, pancreatitis, and bone marrow toxicity.[53]

NON-NUCLEOSIDE REVERSE-TRANSCRIPTASE INHIBITORS

The three non-nucleoside reverse-transcriptase inhibitors that have been approved by the FDA can inhibit or induce cytochrome P-450 activity, depending on the specific drug. Nevirapine and efavirenz are moderate inducers of CYP3A4. Nevirapine decreases plasma concentrations of indinavir and saquinavir (Table 3) but does not have clinically important effects on nelfinavir and ritonavir, because these drugs are not exclusively metabolized by CYP3A4, and they induce their own metabolism, minimizing the effects of further induction.[58,60,63] Efavirenz inhibits or induces cytochrome P-450 activity, depending on the concomitantly administered drug. Efavirenz decreases plasma concentrations of indinavir, lopinavir, saquinavir, and amprenavir[55,57,59,64] but increases plasma concentrations of ritonavir and nelfinavir by approximately 20 percent, possibly through inhibition of the CYP2C9 or CYP2C19 pathway.[65,66] Since efavirenz causes large decreases in plasma saquinavir concentrations, this combination should be avoided, unless given concomitantly with ritonavir.[67]

Of particular concern is the effect of nevirapine or efavirenz on plasma methadone concentrations. Both drugs can reduce plasma methadone concentrations by about 50 percent in patients receiving methadone maintenance therapy,[68,69] and many patients have symptoms consistent with methadone withdrawal, requiring an increase in the dose of methadone. Patients receiving methadone should be monitored closely when given efavirenz or nevirapine, with the expectation that the methadone dose will need to be increased.

Delavirdine is a potent inhibitor of cytochrome P-450. Because of its effect on CYP3A4, serious toxic effects may occur if delavirdine is administered with antiarrhythmic drugs, calcium-channel blockers, sedative or hypnotic drugs, or quinidine.[70] The administration of delavirdine with vasoconstrictor drugs such as ergotamine can lead to peripheral ischemia and can increase the toxicity of certain chemotherapeutic drugs, such as etoposide and paclitaxel. Clinicians need to be aware of and avoid these combinations.

HIV-PROTEASE INHIBITORS

HIV-protease inhibitors are associated with numerous drug interactions, many of which are clinically important (Table 3). These drugs are inhibitors of CYP3A4 enzymes and are contraindicated in combination with certain antiarrhythmic drugs, sedative and hypnotic drugs, ergot derivatives, cisapride, and the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors lovastatin and simvastatin. Ritonavir is the most potent inhibitor of cytochrome activity and is therefore most likely to interact with other drugs. Indinavir, amprenavir, and nelfinavir have a moderate probability of causing interactions, and saquinavir has the lowest probability. The newer, soft-gel formulation of saquinavir is similar to the original formulation in this respect.[9] The combination of lopinavir and ritonavir is likely to have interactions that are similar to those of full-dose ritonavir alone, but the magnitude of the interactions may be smaller.[57]

In addition to inhibiting enzymes, ritonavir has enzyme-inducing properties, even inducing its own metabolism in a dose-dependent manner during the

TABLE 3. SELECTED INTERACTIONS AMONG ANTIRETROVIRAL DRUGS AND BETWEEN ANTIRETROVIRAL AND OTHER DRUGS.*

DRUG	INTERACTING DRUG	RESULT*	RECOMMENDATION
Amprenavir	Rifampin	Amprenavir AUC decreased by 81%[54]	Avoid combinations of rifampin and protease inhibitor except possibly for rifampin and ritonavir; use rifabutin at adjusted dose with nelfinavir, amprenavir, indinavir, and ritonavir
Indinavir	Rifampin	Indinavir AUC decreased by 92%[54]	
Ritonavir	Rifampin	Ritonavir AUC decreased by 35%[54]	
Saquinavir (hard or soft gel capsules)	Rifampin	Saquinavir AUC decreased by 70–80%[9,54]	
Nelfinavir	Rifampin	Nelfinavir AUC decreased by 82%[54]	
Amprenavir	Efavirenz	Amprenavir AUC decreased by 36%[55]	Increase amprenavir dose to 1200 mg 3 times a day or add ritonavir (200 mg twice a day)
HMG CoA reductase inhibitors			
Simvastatin	Ritonavir with saquinavir (soft gel capsules)	Simvastatin AUC increased by a factor of 32[56]	Do not use simvastatin with ritonavir
Atorvastatin	Ritonavir with saquinavir (soft gel capsules)	Atorvastatin AUC increased by a factor of 4.5[56]	Use atorvastatin with slow dose titration and close monitoring
Pravastatin	Ritonavir with saquinavir (soft gel capsules)	Pravastatin AUC decreased by a factor of 0.5[56]	Adjustment of pravastatin dose not required
Atorvastatin	Lopinavir–ritonavir	Atorvastatin AUC increased by a factor of 5.9[57]	Use atorvastatin with slow dose titration and close monitoring
Pravastatin	Lopinavir–ritonavir	Pravastatin AUC increased by 30%[57]	Pravastatin does not require dose adjustment
Indinavir	Nevirapine	Indinavir AUC decreased by 28%[58]	Increase indinavir dose to 1000 mg every 8 hours
Indinavir	Efavirenz	Indinavir AUC decreased by 35%[59]	Increase indinavir dose to 1000 mg every 8 hours
Lopinavir–ritonavir	Efavirenz	Lopinavir trough concentration decreased by 40%[57]	Consider increasing lopinavir dose to 533 mg and ritonavir dose to 133 mg
Rifabutin	Amprenavir	Rifabutin increased by a factor of 2 to 3[54]	Decrease rifabutin dose to 150 mg/day
	Indinavir		Decrease rifabutin dose to 150 mg/day, increase indinavir dose to 1000 mg 3 times a day
	Nelfinavir		
Rifabutin	Ritonavir	Rifabutin AUC increased by a factor of 4[54]	Decrease rifabutin dose to 150 mg every 2 or 3 days or 2 or 3 times a week
Rifabutin	Lopinavir–ritonavir	Rifabutin AUC increased by a factor of 3[57]	Decrease rifabutin dose to 150 mg every 2 or 3 days or 2 or 3 times a week
Saquinavir	Nevirapine	Saquinavir AUC decreased by 62%[60]	Avoid combination unless ritonavir is used concomitantly
Saquinavir (hard or soft gel capsules)	Rifabutin	Saquinavir AUC decreased by 45% (hard gel capsules) or 47% (soft gel capsules)[9,54]	Avoid combination unless ritonavir is administered concomitantly
Sildenafil	Indinavir, saquinavir, or ritonavir	Sildenafil AUC increased by a factor of 2 with indinavir, a factor of 3 with saquinavir, and a factor of 11 with ritonavir[61,62]	Start with 25 mg of sildenafil; with ritonavir, do not repeat the sildenafil dose for 48 hours

*AUC denotes area under the concentration–time curve, and HMG CoA 3-hydroxy-3-methylglutaryl coenzyme A.

first 14 days of therapy.[71] Ritonavir decreases plasma concentrations of theophylline, probably through the induction of CYP1A2.[72] Ritonavir and nelfinavir also increase glucuronosyltransferase activity, which may partly explain the substantial decreases in plasma ethinyl estradiol concentrations during concurrent therapy with these protease inhibitors.[73,74] Alternative or additional methods of contraception are recommended in women taking ritonavir or nelfinavir.

Not only do HIV-protease inhibitors affect the metabolism of certain drugs, but their own metabolism is also altered by other inducers or inhibitors of cytochrome activity. Potent enzyme-inducing drugs can cause clinically important decreases in plasma concentrations of protease inhibitors. For example, rifampin decreases plasma saquinavir concentrations by 70 to 80 percent.[9,54] The resulting low plasma concentrations may promote viral resistance and result in treatment failure. With the possible exception of ritonavir, protease inhibitors should not be given to patients receiving rifampin.[75] Patients with tuberculosis who are already receiving a protease inhibitor should be treated with a four-drug regimen that includes rifabutin instead of rifampin.[54] For patients receiving indinavir, nelfinavir, or amprenavir, the dose of rifabutin should be reduced from 300 to 150 mg per day to compensate for the inhibition of rifabutin clearance by these drugs. Increasing the dose of indinavir from 800 to 1000 mg every eight hours, in addition to reducing the dose of rifabutin, is also an

option.[76] Ritonavir increases the area under the curve for plasma rifabutin by a factor of four, which may lead to clinically important adverse effects.[77,78] However, intermittent administration of rifabutin, either 150 mg every three days or 300 mg every seven days, is safe and tolerable over a two-month period with a combination of ritonavir and saquinavir (400 mg of each drug every 12 hours).[79] Updated guidelines for using rifabutin and rifampin in patients receiving antiretroviral drugs have recently been issued by the Centers for Disease Control and Prevention.[79]

Other potent enzyme inducers, such as phenytoin, phenobarbital, and carbamazepine, can cause similar reductions in plasma concentrations of protease inhibitors.[80] Although standard doses of carbamazepine and phenobarbital may have to be decreased in the presence of protease inhibitors, standard doses of phenytoin may have to be increased in the presence of nelfinavir or ritonavir.[81] For example, plasma phenytoin concentrations were decreased by nelfinavir, perhaps through the induction of its CYP2C9-mediated metabolism.[82] Ritonavir may either inhibit or induce the metabolism of phenytoin, as it does with alprazolam, depending on the duration of ritonavir therapy.[49] Interactions between anticonvulsant drugs and protease inhibitors are complex because of their two-way nature. It is best to avoid these combinations, and close monitoring is required when they must be used.

Patients who are taking protease inhibitors and who require prophylaxis against *Mycobacterium avium* complex infection can be given azithromycin or clarithromycin. The area under the curve for plasma clarithromycin is moderately increased by ritonavir and indinavir, but dosage adjustments are not necessary in patients with normal renal function.[83,84] Azithromycin is excreted primarily by the biliary route and does not interact with protease inhibitors or delavirdine.[85]

The concept of using drug interactions to the patient's benefit has been the focus of much research. The administration of cytochrome P-450 inhibitors with other drugs can reduce the pill burden, increase plasma concentrations, simplify the dosing schedule, and circumvent drug interactions. Table 4 lists combinations that improve the pharmacokinetic profile of protease inhibitors. The bioavailability of saquinavir is less than 20 percent, and up to 18 capsules per day must be given to achieve effective plasma concentrations. When ritonavir is given with saquinavir, however, steady-state plasma concentrations of saquinavir increase by a factor of 20 or more, dramatically improving the oral bioavailability of the drug.[22] With ritonavir 400 mg twice daily, the dose of saquinavir can be reduced from 1200 mg every eight hours to 400 mg twice daily, decreasing the number of saquinavir capsules that must be taken from 18 to 4 per day. Similarly, nelfinavir raises plasma saquinavir concentrations by a factor of about 12, allowing the dose of saquinavir to be reduced to 1000 mg twice daily.[87]

The combination of ritonavir and indinavir can overcome the unfavorable pharmacokinetic properties of indinavir. Indinavir must be taken every eight hours on an empty stomach or with a meal that is low in fat (<2 g). The trough plasma concentrations of indinavir are highly variable, and in some patients the concentrations at the end of the dosing interval may be below the in vitro concentration needed to inhibit the replication of 90 percent of HIV isolates (IC_{90}). Concomitant administration of ritonavir increases the area under the curve by a factor of up to three and increases the trough plasma concentration by a factor of three to seven.[10,86] This allows for a decrease in dosing from three times daily without food to twice daily with food. Twice-daily regimens of indinavir and ritonavir (800 mg of indinavir and 100 mg of ritonavir, 800 mg of indinavir and 200 mg of ritonavir, and 400 mg of each) are being evaluated in patients with HIV infection.[88,89] All three regimens result in higher plasma indinavir concentrations, although the lower doses of ritonavir may be better tolerated. In one study, the incidence of renal complications was low among patients who were given 400 mg of each drug twice a day, and there were no cases of nephrolithiasis among the 89 patients who received this regimen for a mean period of 40 weeks.[89]

Similarly, the reduction in plasma amprenavir or saquinavir concentrations produced by efavirenz can be circumvented by the addition of ritonavir. Efavirenz markedly decreases the area under the curve for amprenavir and saquinavir.[55,64] The addition of ritonavir (200 mg twice daily) to amprenavir and efavirenz not only prevents the efavirenz-induced reduction, but also increases the area under the curve for plasma amprenavir by a factor of two and increases the trough plasma concentration by a factor of four.[90] Plasma saquinavir concentrations are not affected by efavirenz in patients who are also taking 400 mg of ritonavir twice daily.[91]

Lopinavir, a recently approved protease inhibitor, relies on the inhibitory effects of ritonavir to achieve plasma concentrations well above the IC_{90} value for wild-type HIV. Low doses of ritonavir increase the area under the curve for plasma lopinavir by a factor of 20.[92] The trough plasma concentration of tipranavir, an investigational protease inhibitor, is increased in a dose-dependent fashion by ritonavir.[93]

Delavirdine is also an inhibitor of CYP3A4 and can be given to increase plasma concentrations of protease inhibitors.[94,95] Recent improvement in the formulation (a 200-mg tablet) and studies of twice-daily dosing make it a possible alternative to ritonavir as a means of increasing the concentrations of protease inhibitors.

DRUGS FOR OPPORTUNISTIC INFECTIONS

Azole antifungal drugs, macrolide antibiotics, and rifamycins have important interactions with other

TABLE 4. COMBINATIONS OF DRUGS THAT CAN BE GIVEN TO ACHIEVE OPTIMAL PLASMA CONCENTRATIONS OF ANTIRETROVIRAL DRUGS.

AFFECTED DRUG	INTERACTING DRUG	RESULTS*	RECOMMENDATION
Amprenavir	Lopinavir–ritonavir	Amprenavir AUC increased[57]	Consider giving amprenavir at a dose of 750 mg twice a day
Indinavir	Ritonavir	Indinavir AUC increased by a factor of up to 3 and trough concentration increased by a factor of 3 to 7[10,86]	Regimens under evaluation: 800 mg of indinavir and 100 mg of ritonavir twice a day, 800 and 200 mg twice a day, and 400 and 400 mg twice a day
Indinavir	Delavirdine	Indinavir AUC increased by a factor of 3[94]	Consider decreasing indinavir dose to 600 mg three times a day
Indinavir	Lopinavir–ritonavir	Increased indinavir AUC[57]	Consider giving indinavir at a dose of 600 mg twice a day
Saquinavir	Lopinavir–ritonavir	Increased saquinavir AUC[57]	Consider giving saquinavir at a dose of 800 mg twice a day
Saquinavir	Nelfinavir	Saquinavir AUC increased by a factor of 5 (soft gel capsules) or 12 (hard gel capsules)[87]	Decrease saquinavir dose to 800 mg three times a day or 1000 mg twice a day
Saquinavir	Ritonavir	Saquinavir C_{ss} increased by a factor of 20 or more[22]	Give both drugs at a dose of 400 mg twice a day; regimens under evaluation: 200 mg of ritonavir and 800 mg of saquinavir twice a day, 100 and 1000 mg twice a day
Saquinavir	Delavirdine	Saquinavir AUC increased by a factor of 5[95]	Consider decreasing the saquinavir dose to 800 mg three times a day

*AUC denotes area under the concentration–time curve, and C_{ss} plasma concentration in steady state.

drugs, complicating the prophylaxis and treatment of opportunistic infections (Table 3). Ketoconazole and itraconazole, which are potent inhibitors of CYP3A4 and moderate inhibitors of P-glycoprotein, can be given to increase plasma concentrations of protease inhibitors.[34] For example, ketoconazole increases the area under the curve for plasma saquinavir by 150 percent.[96] However, this combination is rarely given because of concern about the toxicity of ketoconazole and the development of resistant fungal infections. Fluconazole can also inhibit CYP3A4, although the extent of inhibition and the magnitude of interactions are dose-dependent. Doses of less than 200 mg per day are not associated with important interactions, whereas higher doses can increase plasma concentrations of substrates of CYP3A4,[97] as well as glucuronidated drugs such as zidovudine.[98] Fluconazole also inhibits CYP2C9, as evidenced by its potential to increase the risk of bleeding in patients also taking warfarin.[99]

Erythromycin and clarithromycin are substrates of CYP3A4 and inhibitors of both CYP3A4 and P-glycoprotein.[34] Rifampin and rifabutin can substantially decrease plasma clarithromycin concentrations, but the clinical importance of the decrease is unknown because intracellular concentrations of macrolides are much higher than plasma concentrations.[100,101] Decreased effectiveness against pathogens such as *M. avium* complex is a potential concern, but no studies have specifically addressed the clinical effect of the combination.

Fluconazole increases the area under the curve for plasma rifabutin by 75 percent.[102] This combination of drugs is more effective in preventing *M. avium* complex bacteremia than rifabutin alone, although there is an increased risk of rifabutin-associated toxic effects, such as uveitis and arthralgias.[103]

SPECIAL ISSUES

Alternative Therapies

Alternative therapies, including herbal remedies and nutritional supplements, have long been considered harmless. However, certain alternative therapies may interact with drugs used in the treatment of HIV infection. St. John's wort decreases the area under the curve for plasma indinavir by more than 50 percent

in normal subjects, an effect that is due to the induction of CYP3A4 or P-glycoprotein.[104-106] Use of this herb should be avoided in patients taking protease inhibitors and non-nucleoside reverse-transcriptase inhibitors, because of the risk of viral resistance to these drugs.

Raw garlic and garlic supplements inhibit the activity of CYP3A4 in vitro and in animals.[107,108] Severe gastrointestinal toxicity was reported in two persons after they ingested garlic supplements with ritonavir.[109] Other herbs with reported in vitro effects on cytochrome P-450–mediated drug metabolism include silymarin (milk thistle), ginseng, and skullcap.[110] Clinicians should be aware of these potential interactions, because alternative therapies are not usually evaluated as a cause of treatment failure or toxicity.

Drug–Cytokine Interactions

Cytochrome P-450 drug metabolism can be altered by certain proinflammatory cytokines such as interleukin-6, interleukin-1, and tumor necrosis factor α (TNF-α).[111] These cytokines are released during periods of stress, trauma, or infection. In several in vitro studies, interleukin-6 and TNF-α inhibited cytochrome P-450–mediated metabolism through a metabolic interaction at the level of transcription of cytochrome mRNA.[112]

The administration of immunomodulators such as interleukin-2 results in a profound release of these cytokines.[113,114] In a study of HIV-infected patients who were receiving a five-day infusion of interleukin-2, the area under the curve for plasma indinavir was increased by 75 percent.[115]

ROLE OF THERAPEUTIC DRUG MONITORING

Several studies have established associations between plasma concentrations of protease inhibitors and their antiviral effects,[116-118] suggesting a role for therapeutic monitoring of these drugs. Although there is considerable debate regarding the value of drug monitoring,[119-121] determination of plasma drug concentrations may have a role in the evaluation of drug interactions, provided that the limitations in the use of plasma drug measurements to evaluate individual patients are recognized. These limitations include the large variability in pharmacokinetic characteristics within individual patients, lack of information on specific therapeutic ranges and target concentrations (i.e., data on the concentrations that cause 50 percent inhibition), variations in drug binding to α1-acid glycoprotein and albumin, slow viral responses to changes in plasma drug concentrations, and clinical interpretations of measurements.

The clinical utility of therapeutic monitoring of antiretroviral drugs has yet to be proved, but trials are ongoing. Adjustments of doses on the basis of plasma drug measurements in cases of drug interactions should be made with caution pending the outcome of trials examining the correlations between such measurements and virologic and clinical end points. Any decision to adjust a dose, whether because of low plasma drug concentrations or drug toxicity, must take into consideration the wide variability in plasma drug concentrations in an individual patient, both on a single day and from one day to the next due to diurnal and food effects, the stage of the disease, and changes in adherence to the treatment regimen.

MANAGEMENT OF DRUG INTERACTIONS

New information about drug interactions in patients with HIV infection becomes available almost weekly. The increasing number of documented and theoretical drug interactions can be overwhelming for the practicing clinician. Fortunately, extensive tables and product information are available to aid in the recognition and management of drug interactions (Table 5). A thorough drug history, including over-the-counter drugs and alternative therapies, should be obtained at each clinic visit. Clinicians should have a high index of suspicion for a drug interaction in patients receiving antiretroviral therapy who have an increased viral load or clinical progression, if other factors, including adherence, can be ruled out. Interactions should also be suspected in patients with serious toxic effects of antiretroviral or supportive drugs. Regimens containing many drugs and drugs with a high potential for interactions (rifamycin, protease inhibitors, and antifungal drugs) should be reviewed and assessed for drug interactions. The selection of a drug that is less likely to interact with other drugs should be considered if warranted by the clinical circumstances. For example, azithromycin is not metabolized by cytochrome P-450 and does not have the interactions associated with other macrolide antibiotics. Similarly, fluconazole at low doses is less likely to interact with other drugs than are ketoconazole

TABLE 5. WEB SITES WITH INFORMATION ABOUT DRUG INTERACTIONS.

www.dml.georgetown.edu/depts/pharmacology (Department of Pharmacology, Georgetown University Medical Center)
www.foodmedinteractions.com (food and drug interactions)
www.hivatis.org (HIV/AIDS Treatment Information Service)
www.hivdent.org (dental information)
hivinsite.ucsf.edu
www.hiv.net (in German)
www.hopkins-aids.edu (Johns Hopkins AIDS Service)
www.iapac.org (International Association of Physicians in AIDS Care)
www.hiv-druginteractions.org (Liverpool HIV Pharmacology Group)
www.medscape.com

and itraconazole. Therapeutic use of pharmacokinetic interactions should be considered to simplify complex regimens and reduce the pill burden.

With so many new drugs in clinical development, drug interactions will continue to be an important aspect of the treatment of patients with HIV infection. It is essential that clinicians understand the main mechanisms and concepts underlying these interactions, so that they can choose regimens for their patients that are potent, safe, and convenient.

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