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The Drug Advisor

COMPREHENSIVE ANALYSIS AND COMMENTARY

The HIV Protease Inhibitors

Atazanavir (Reyataz) is the first to be administered just once a day, but lopinavir/ritonavir (Kaletra) offers more

Atazanavir sulfate (*Reyataz*, Bristol-Myers Squibb) is the seventh human immunodeficiency virus (HIV) protease inhibitor to be marketed, joining amprenavir (*Agenerase*), indinavir (*Crixivan*), lopinavir/ritonavir (*Kaletra*), nelfinavir (*Viracept*), ritonavir (*Norvir*), and saquinavir (*Fortovase*, *Invirase*). The antiviral activity of the lopinavir/ritonavir combination is attributed to lopinavir; ritonavir is included in an amount that is only one sixth of its therapeutic dose for the purpose of inhibiting the metabolism and increasing the action of lopinavir.

Antiretroviral combination regimens are the treatment standard for HIV infection/acquired immunodeficiency syndrome (AIDS). An HIV protease inhibitor is often included in initial treatment regimens that also include two nucleoside reverse transcriptase inhibitors (NRTIs) (usually, lamivudine [*Epivir*] and zidovudine [*Retrovir*] that are also available in a combination formulation [*Combivir*]). None of the antiretroviral agents provide a cure for HIV infection; however, the combination regimens are more effective than monotherapy in prolonging survival and reducing the complications associated with HIV infection.

Like the other HIV protease inhibitors, atazanavir is administered orally. It is rapidly absorbed and should be administered with food to increase bioavailability and reduce pharmacokinetic variability. It is extensively metabolized, primarily via CYP3A pathways, and most of a dose is excreted in the feces in the form of metabolites. The drug's duration of action is long enough to allow once-a-day administration.

Selected characteristics and drug interactions of the seven HIV protease inhibitors are identified in Tables 1 and 2 and compared in the following discussion.

Indications/Efficacy

The development of the HIV protease inhibitors (the first of which, saquinavir, was marketed in late 1995) has represented an important advance in increasing the effectiveness of antiretroviral therapy and prolonging the survival of patients with HIV infection/AIDS. The most experience has been gained with the first agents in this class (saquinavir, ritonavir, indinavir), but good results have also been achieved with the newer agents.

All of the HIV protease inhibitors have the same indication—use in combination with other antiretroviral agents for the treatment of HIV-1 infection. In clinical studies, the regimens that included atazanavir (with two NRTIs) provided outcomes (eg, reduction of HIV viral load, increased CD4 cell counts) similar to those of nelfinavir and efavirenz (*Sustiva*) regimens with the same NRTIs, but not as good as those with a lopinavir/ritonavir plus two NRTIs regimen.

Because the HIV protease inhibitors are used in combination regimens in patients who are often using many other medications (some of which may interact), it is difficult to quantify the specific benefit the individual agents contribute to the

regimen's effectiveness. However, to the extent that studies permit a comparison of the protease inhibitors, lopinavir/ritonavir appears to exhibit the most potent antiretroviral action, and nelfinavir appears to be associated with a higher rate of virologic failure. The recently published (July 14, 2003) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents[1] recommend lopinavir/ritonavir plus lamivudine plus zidovudine *or* stavudine (*Zerit*) as the preferred protease inhibitor-based regimen for initiating therapy in previously untreated HIV-infected patients. The other recommended regimen for initial therapy (except in pregnant women) includes the nonnucleoside reverse transcriptase inhibitor (NNRTI) efavirenz plus lamivudine plus zidovudine *or* stavudine *or* tenofovir (*Viread*).

Varying degrees of cross-resistance have been observed among protease inhibitors. However, some agents have different resistance profiles than others, and resistance to one agent does not preclude the subsequent use of another protease inhibitor.

Safety

The primary challenge with the protease inhibitors is to prevent/address the numerous adverse events, drug interactions, and other risks associated with their use. All of the protease inhibitors may cause hyperglycemia/diabetes mellitus and redistribution/accumulation of body fat (eg, central obesity, "buffalo hump," peripheral and facial wasting, breast enlargement, "Cushingoid" appearance), and may increase the risk of bleeding in patients with hemophilia.

All of the protease inhibitors often cause gastrointestinal adverse events (eg, nausea, diarrhea). Other adverse events occur less commonly, and some are primarily associated with the use of just one or several of the seven agents. Atazanavir causes asymptomatic hyperbilirubinemia, which may be accompanied by yellowing of the skin (jaundice) and/or whites of the eyes (scleral icterus) in many patients, although it is reversible upon discontinuation of treatment. If this response is a concern for the patient, alternative antiretroviral therapy should be considered because the efficacy of lower dosages of atazanavir has not been evaluated. Because indinavir may also cause hyperbilirubinemia, concurrent use with atazanavir is not recommended.

Atazanavir has been reported to prolong the PR interval of the electrocardiogram, which is associated, with rare exceptions, with asymptomatic abnormalities in atrioventricular (AV) conduction (first-degree AV block). Caution should be exercised when the new agent is used in patients with preexisting conduction system disease and when other drugs that prolong the PR interval (eg, most beta-blockers, digoxin, verapamil [eg, *Calan*]) are administered concurrently.

There are also other important adverse events/risks that have been associated with the use of one or several of the protease inhibitors, but not with the others. Nephrolithiasis/urolithiasis (eg, flank pain, hematuria, pyelonephritis, renal insufficiency) has been expe-

[1]Developed by the Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services. (Atazanavir was not available at the time this revision of the guidelines was developed).

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rienced by numerous patients treated with indinavir, and it is recommended that adults drink at least 1.5 liters of liquids per day to ensure adequate hydration. Indinavir has also been infrequently associated with the occurrence of acute hemolytic anemia.

The use of ritonavir and lopinavir/ritonavir has been associated with large increases in total cholesterol and triglyceride concentrations, and, in some cases, pancreatitis. Some patients treated with amprenavir have experienced severe and life-threatening skin reactions, including Stevens-Johnson syndrome. Because amprenavir is a sulfonamide, a potential for cross-sensitivity exists in patients known to be allergic to sulfonamides (eg, sulfamethoxazole).

Some potential problems are related to components in the formulations other than the active drug. To improve stability, the formulations of amprenavir contain vitamin E in an amount that far exceeds the recommended daily allowance; patients should be advised not to take supplemental vitamin E. The oral solution formulation of amprenavir contains a large amount of propylene glycol to increase its solubility, and the propylene glycol content introduces additional contraindications and other risks with this formulation (see Table 1). The oral powder formulation of nelfinavir contains 11.2 mg of phenylalanine per gram of powder, an important consideration for patients with phenylketonuria.

All of the protease inhibitors undergo extensive hepatic metabolism, primarily via CYP3A pathways, and are primarily eliminated in the feces in the form of metabolites. They must be used with caution in patients with hepatic impairment, and the labeling for amprenavir, atazanavir, and indinavir includes specific recommendations for dosage reductions in these patients. In addition to being a substrate for CYP3A, all of the protease inhibitors inhibit CYP3A metabolic pathways and ritonavir also induces them. Therefore, a potential exists for interactions with a large number of other therapeutic agents, including other antiretroviral agents, that are metabolized by CYP3A or inhibit or induce these metabolic pathways (see Table 2).

Because the protease inhibitors inhibit CYP3A, they may markedly increase the concentrations and actions of the CYP3A substrates midazolam (eg, *Versed*), triazolam (eg, *Halcion*), ergot derivatives, pimozide (eg, *Orap*), and cisapride (withdrawn from the market but available on a special need basis). The concurrent use of any of these agents with a protease inhibitor is contraindicated. For the same reason, the concurrent use of lovastatin (eg, *Mevacor*) or simvastatin (*Zocor*) with a protease inhibitor is not recommended. St. John's wort induces CYP3A pathways and may cause marked reductions in the concentrations and action of the protease inhibitors; therefore, its use should be avoided in patients treated with any of the protease inhibitors. The potent enzyme inducer rifampin (eg, *Rifadin*) may also markedly reduce the action of the protease inhibitors; concurrent use with most of these agents is not recommended.

Numerous other documented and potential interactions involving the protease inhibitors are identified in Table 2. In many situations, concurrent use is appropriate, but caution must be exercised and dosage adjustments may be necessary. For example, the protease inhibitors may markedly increase the concentrations and incidence of adverse events of sildenafil (*Viagra*). The dosage of sildenafil should be reduced so that it does not exceed 25 mg every 48 hours.

Ritonavir and lopinavir/ritonavir are implicated in an even larger number of interactions than the other protease inhibitors because, in addition to being a substrate for and inhibiting and inducing CYP3A, ritonavir is also a substrate for and inhibits CYP2D6. Atazanavir may inhibit the pathway involved in the metabolism of irinotecan (*Camptosar*) and increase the risk of toxicity of the antineoplastic agent. Accordingly, concurrent use is not recommended. It is also recommended that proton pump inhibitors (esomeprazole [*Nexium*], lansoprazole [*Prevacid*], omeprazole [*Prilosec*], pantoprazole [*Protonix*], rabeprazole [*Aciphex*]) not be used in patients treated with atazanavir because concentrations of the antiviral agent may be substantially reduced. Antacids and histamine H_2-receptor antagonists (cimetidine [eg, *Tagamet*], famotidine [eg, *Pepcid*], nizatidine [eg, *Axid*], ranitidine [eg, *Zantac*]) may also reduce the absorption of atazanavir. Doses of the medications should be separated by the recommended intervals (see Table 2).

Atazanavir, nelfinavir, and ritonavir are classified in Pregnancy Category B, whereas the other protease inhibitors are in Category C. There has been more extensive, and safe, experience in pregnant women with the use of nelfinavir than with the other protease inhibitors. The efficacy and safety of use in younger children has been demonstrated for lopinavir/ritonavir (6 months of age), nelfinavir (2 years of age), ritonavir (2 years of age), and amprenavir (4 years of age).

Administration

Atazanavir is the first protease inhibitor for which effectiveness has been demonstrated with once-a-day

administration. This represents an advantage over the other agents in the class, especially in patients in whom the "pill burden" of so many antiretroviral and other medications at multiple times during the day makes it difficult to comply with dosage instructions. Amprenavir, nelfinavir, lopinavir/ritonavir, and ritonavir are administered twice a day, whereas indinavir and saquinavir are administered three times a day, although twice-a-day regimens for these latter agents are being evaluated. The number of capsules/tablets administered per dose contributes to the "pill burden" for some patients. For example, eight capsules (150 mg) are needed for each adult dose of amprenavir, and six capsules (200 mg) for each dose of saquinavir (*Fortovase* formulation). In contrast, only two atazanavir capsules (200 mg) are needed to provide the single daily dose. The recent approval of a higher potency formulation of nelfinavir (625 mg tablets) facilitates administration (two tablets twice a day) of this agent.

Most of the protease inhibitors should be administered with food, or soon after a meal (saquinavir), to increase bioavailability. Amprenavir may be administered with or without food, but should not be administered with a high-fat meal because it may reduce absorption. Indinavir should be administered at least one hour before or two hours after a meal to achieve optimum absorption.

Oral solution formulations of amprenavir, lopinavir/ritonavir, and ritonavir are marketed, as is an oral powder formulation of nelfinavir, to facilitate administration of the drugs in pediatric patients or in adults who have difficulty swallowing capsules/tablets.

Formulations of amprenavir, atazanavir, indinavir, and nelfinavir may be stored at room temperature, although precautions must be taken to protect indinavir against exposure to moisture. Some of the lopinavir/ritonavir, ritonavir, and saquinavir formulations should be refrigerated until dispensed.

The *Invirase* formulation (hard gelatin capsules) of saquinavir was the first marketed, but the more recently marketed *Fortovase* formulation (soft gelatin capsules) provides greater bioavailability of the drug, and is the one recommended in most situations in which this protease inhibitor is used.

Comparisons/Conclusions

Although most of the protease inhibitors are generally similar in their antiviral activity, lopinavir/ritonavir appears to exhibit the most potent antiretroviral action, and nelfinavir may be associated with a higher rate of virologic failure. The potential for greater effectiveness with lopinavir/ritonavir provides an advantage over the other protease inhibitors, as does the demonstration of its effectiveness and safety in younger patients (6 months and older) than has been demonstrated with the other agents. These advantages outweigh the disadvantages of a less favorable safety profile (eg, lipid elevations/risk of pancreatitis, interactions with a larger number of drugs) than agents such as nelfinavir and the need for more frequent administration (twice a day) than atazanavir (once a day). Accordingly, lopinavir/ritonavir should be considered the preferred protease inhibitor for inclusion in a combination antiretroviral regimen.

Atazanavir has an advantage over the other agents in being administered just once a day, but it causes hyperbilirubinemia in many patients, is the only agent in the class (to date) to be associated with prolongation of the PR interval, is implicated in certain drug interactions (irinotecan, proton pump inhibitors) not observed with other protease inhibitors, and is not indicated for pediatric use.

Amprenavir appears to have the highest risk of serious skin reactions and may cause hypersensitivity reactions in patients who are allergic to sulfonamides. The usual adult dose requires the administration of eight capsules. The large amount of propylene glycol in the oral solution formulation adds contraindications/risks beyond those of the drug itself.

Indinavir may cause nephrolithiasis/urolithiasis that requires attention to adequate hydration, may cause hyperbilirubinemia, is not indicated for use in children, and is administered in an inconvenient regimen of three times a day apart from meals. Also, the drug must be protected against exposure to moisture.

Nelfinavir has the most favorable safety profile but may be associated with a higher rate of virologic failure than with certain other protease inhibitors. It may be administered twice a day in adults but is administered three times a day in children (ages 2 to 13).

Ritonavir is more likely than the other agents to cause elevated lipid concentrations and pancreatitis. It is also likely to interact with a larger number of other medications than the other protease inhibitors.

Saquinavir is administered three times a day and the usual dose requires the administration of six *Fortovase* capsules. It is not indicated for pediatric use.

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Table 1. Selected Characteristics of the HIV Protease Inhibitors

Generic name	Amprenavir	Atazanavir sulfate	Indinavir sulfate	Lopinavir/ ritonavir	Nelfinavir mesylate	Ritonavir	Saquinavir/ Saquinavir mesylate
Trade name (Manufacturer)	*Agenerase* (GlaxoSmithKline)	*Reyataz* (Bristol-Myers Squibb)	*Crixivan* (Merck)	*Kaletra* (Abbott)	*Viracept* (Agouron)	*Norvir* (Abbott)	*Fortovase, Invirase* (Roche)
Labeled indication							
In combination with other antiretroviral agents for the treatment of HIV-1 infection	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Contraindications							
Hypersensitivity to the drug	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Concurrent use with							
Amiodarone	No	No	No	No	Yes	Yes	No
Bepridil	No	No	No	No	No	Yes	No
Cisapride[a]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Disulfiram	Yes (oral solution)	No	No	No	No	No	No
Ergot derivatives (ergotamine, dihydroergotamine, ergonovine, methylergonovine)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Flecainide	No	No	No	Yes	No	Yes	No
Metronidazole	Yes (oral solution)	No	No	No	No	No	No
Midazolam	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pimozide	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Propafenone	No	No	No	Yes	No	Yes	No
Quinidine	No	No	No	No	Yes	Yes	No
Triazolam	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Children younger than 4 years of age	Yes (oral solution)	No	No	No	No	No	No
Pregnant women	Yes (oral solution)	No	No	No	No	No	No
Patients with hepatic failure	Yes (oral solution)	No	No	No	No	No	No

continues

Table 1. Selected Characteristics of the HIV Protease Inhibitors

Generic name	Amprenavir	Atazanavir sulfate	Indinavir sulfate	Lopinavir/ ritonavir	Nelfinavir mesylate	Ritonavir	Saquinavir/ Saquinavir mesylate
Contraindications (cont'd.)							
Patients with renal failure	Yes (oral solution)	No	No	No	No	No	No
Selected warnings/ precautions/risks							
Diabetes/hyperglycemia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fat redistribution (eg, central obesity, "buffalo hump," breast enlargement)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Patients with hemophilia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Patients with hepatic impairment	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hepatic reactions	No	No	Yes	Yes	No	Yes	Yes
Lipid elevations	Yes	No	No	Yes	No	Yes	No
Pancreatitis	No	No	No	Yes	No	Yes	No
Nephrolithiasis/ urolithiasis	No	No	Yes (hydration is recommended)	No	No	No	No
Hemolytic anemia	Yes	No	Yes	No	No	No	No
Serious skin reactions (eg, Stevens-Johnson syndrome)	Yes	No	No	No	No	No	No
Cross-sensitivity in sulfonamide-allergic patients	Yes	No	No	No	No	No	No
Allergic reactions	No	No	No	No	No	Yes	No
Hyperbilirubinemia	No	Yes	Yes	No	No	No	No
PR interval prolongation	No	Yes	No	No	No	No	No
Patients with phenylketonuria	No	No	No	No	Yes (powder formulation)	No	No

Vitamin E supplementation	Yes (supplementation should be avoided)	No	No	No	No	No	No
Most common adverse events (as reported in noncomparative clinical trials)	(with lamivudine and zidovudine) Nausea (74%) Diarrhea (39%) Vomiting (34%) Rash (27%) Paresthesia, oral/perioral (26%) Hyperglycemia (45%) Hypertriglyceridemia (41%)	(with lamivudine and zidovudine) (moderate or severe intensity) Nausea (16%) Headache (14%) Hyperbilirubinemia (35%)	(moderate or severe intensity) Abdominal pain (17%) Nausea (12%) Nephrolithiasis/urolithiasis (9%) Vomiting (8%) Back pain (8%) Hyperbilirubinemia (12%)	(with lamivudine and stavudine) (moderate or severe intensity) Diarrhea (16%) Nausea (7%) Hypercholesterolemia (9%) Hypertriglyceridemia (9%)	(with lamivudine and zidovudine) (moderate or severe intensity) Diarrhea (20%) Nausea (7%)	(moderate or severe intensity) Nausea (26%) Diarrhea (15%) Vomiting (14%) Taste perversion (11%) Asthemia (10%) Hypercholesterolemia Hypertriglyceridemia	[*Fortovase* formulation with other antiretroviral(s)] (moderate or severe intensity) Diarrhea (20%) Nausea (11%) Abdominal discomfort (9%) Dyspepsia (8%)
Pregnancy category	C	B	C	C	B	B	C
Pediatric use (minimum age for which use is indicated)	4 years	16 years	18 years	6 months	2 years	2 years	16 years
Metabolism	Primarily via CYP3A4	Primarily via CYP3A	Primarily via CYP3A4	Primarily via CYP3A	Primarily via CYP3A	Primarily via CYP3A and to a lesser extent via CYP2D6	Primarily via CYP3A4
Excretion	Primarily in the feces as metabolites	Primarily in the feces as metabolites	Primarily in the feces as metabolites	Primarily in the feces as metabolites	Primarily in the feces as metabolites	Primarily in the feces as both metabolites and unchanged drug	Primarily in the feces as metabolites
Drug interactions (see Contraindications and also Table 2)							
Administration with food	May be administered with or without food, but should not be taken with a high-fat meal (which would decrease absorption)	Should be administered with food to increase bioavailability	Should be administered at least 1 hour before or 2 hours after a meal with water for optimum absorption; alternatively, may be administered with another liquid or a light meal	Should be administered with food to increase bioavailability	Should be administered with a meal or light snack to increase bioavailability	Should be administered with a meal	*Fortovase* formulation should be administered with a meal or up to 2 hours after a meal; *Invirase* formulation should be administered within 2 hours after a full meal

continues

Table 1. Selected Characteristics of the HIV Protease Inhibitors

Generic name	Amprenavir	Atazanavir sulfate	Indinavir sulfate	Lopinavir/ ritonavir	Nelfinavir mesylate	Ritonavir	Saquinavir/ Saquinavir mesylate
Usual dosage							
Adults	capsules—1200 mg twice a day; oral solution—1400 mg twice a day	400 mg once daily with food	800 mg every 8 hours at least 1 hour before or 2 hours after a meal for optimal absorption	400 mg/100 mg twice a day with food	1250 mg twice a day or 750 mg 3 times a day with a meal or light snack	600 mg twice a day with a meal	*Fortovase*—1200 mg 3 times a day with a meal or up to 2 hours after a meal; *Invirase*—600 mg 3 times a day within 2 hours after a full meal
Children	Ages 13–16 years: capsules—1200 mg twice a day; oral solution—1400 mg twice a day; Ages 4–12 years (or 13–16 years with weight of less than 50 kg): capsules—20 mg/kg twice a day or 15 mg/kg 3 times a day; oral solution—22.5 mg/kg twice a day or 17 mg/kg 3 times a day	—	—	Ages 6 months to 12 years: 12 mg/3 mg/kg for patients weighing 7 kg to less than 15 kg and 10 mg/2.5 mg/kg for patients weighing 15 to 40 kg twice a day with food	Ages 2–13 years: 20–30 mg/kg 3 times a day with a meal or light snack	Ages 2 years and above: 400 mg/m^2 twice a day with a meal	—
Recommended dosage adjustments/precautions in special populations							
Hepatic impairment	450 mg (capsules) twice a day in patients with moderate impairment; 300 mg twice a day in patients with severe impairment	300 mg once a day in patients with moderate impairment; should not be used in patients with severe impairment	600 mg every 8 hours in patients with mild to moderate impairment due to cirrhosis	Lopinavir concentrations may be increased	Has not been studied in patients with hepatic impairment	Dosage does not need to be adjusted in patients with mild impairment; caution should be exercised in patients with moderate or severe impairment	Has not been studied in patients with hepatic impairment

Potential drug interactions (see Table 2)							
Products	Capsules—50 mg, 150 mg; Oral solution—15 mg/mL	Capsules—100 mg, 150 mg, 200 mg	Capsules—100 mg, 200 mg, 333 mg, 400 mg	Capsules—133.3 mg lopinavir/33.3 mg ritonavir; Oral solution—80 mg lopinavir/20 mg ritonavir/mL	Tablets—250 mg, 625 mg; Oral powder—50 mg/gram (one level scoopful)	Capsules—100 mg; Oral solution—80 mg/mL	*Fortovase* capsules—200 mg; *Invirase* capsules—200 mg
Administration considerations	Capsules and solution are not interchangeable on a mg/mg basis; oral solution contains a large amount of propylene glycol that contraindicates its use in some patients	—	Should be dispensed and stored in the original container, which includes desiccant to protect against moisture	—	Oral powder may be mixed with a small amount of water, milk, formula, soy formula, or soy milk; should not be mixed or used in conjunction with acidic foods or juices (orange, apple)	—	*Fortovase* and *Invirase* capsules are not bioequivalent and cannot be used interchangeably
Storage	May be stored at room temperature	May be stored at room temperature	May be stored at room temperature; protect against moisture	Should be refrigerated until dispensed; following dispensing, formulation kept at room temperature should be used within 2 months	May be stored at room temperature	Oral solution should be stored at room temperature. Capsules should be refrigerated until dispensed; following dispensing, capsules kept at room temperature should be used within 30 days	*Invirase* capsules may be stored at room temperature. *Fortovase* capsules should be refrigerated until dispensed; following dispensing, capsules kept at room temperature should be used within 3 months

[a]No longer marketed but available to selected patients on a special need basis

Table 2. Selected Drug Interactions Involving the HIV Protease Inhibitors[a]

Generic name	Amprenavir	Atazanavir sulfate	Indinavir sulfate	Lopinavir/ ritonavir	Nelfinavir mesylate	Ritonavir	Saquinavir
Trade name	*Agenerase*	*Reyataz*	*Crixivan*	*Kaletra*	*Viracept*	*Norvir*	*Fortovase*
Metabolized by	CYP3A4	CYP3A	CYP3A4	CYP3A	CYP3A	CYP3A CYP2D6	CYP3A4
Inhibits	CYP3A4	CYP3A CYP1A2 CYP2C9	CYP3A4	CYP3A CYP2D6	CYP3A	CYP3A CYP2D6	CYP3A4
Induces	—	—	—	CYP3A	—	CYP3A	—
I. Interactions in which concurrent use is *contraindicated*							
Interactions in which the action of the interacting drug is *increased*							
Amiodarone	See section III	See section III	—	See section III	Yes	Yes	—
Bepridil	See section III	See section III	__	See section III	—	Yes	—
Cisapride[b]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ergot derivatives	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Flecainide	—	—	—	Yes	—	Yes	—
Midazolam	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pimozide	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Propafenone	—	—	—	Yes	—	Yes	—
Quinidine	See section III	See section III	—	See section III	Yes	Yes	—
Triazolam	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Interactions in which toxicity may result from large amounts of propylene glycol in formulation							
Disulfiram	Yes (oral solution)	—	—	—	—	—	—
Metronidazole	Yes (oral solution)	—	—	—	—	—	—
II. Interactions in which concurrent use is *not recommended*							
Interactions in which the action of the interacting drug is *increased*							
Bepridil	See section III	Yes	—	See section III	—	Contraindicated	—

Irinotecan	—	Yes	—	—	—	—	—
Lovastatin	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Simvastatin	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Interactions in which the action of the HIV protease inhibitor is *increased*							
Indinavir	—	Yes (increased risk of hyperbilirubinemia)	—	—	—	—	—
Ritonavir (oral solution)	Yes (oral solution)	—	—	—	—	—	—
Interactions in which the action of the HIV protease inhibitor is *decreased*							
Proton pump inhibitors (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)	—	Yes	—	—	—	—	—
Rifampin	Yes	Yes	Yes	Yes	Yes	—	See section III
St. John's wort	Yes	Yes	Yes	Yes	Yes	Yes	Yes
III. Interactions in which the medications may be used concurrently with appropriate precautions							
Interactions with other HIV protease inhibitors							
Amprenavir	—	—	Increased action of amprenavir	Increased action of amprenavir	Increased action of amprenavir	Dosage of amprenavir should be reduced by one-half	Decreased action of saquinavir
Atazanavir	—	—	Not recommended	—	—	Increased action of atazanavir	Increased action of saquinavir
Indinavir	Increased action of amprenavir	Not recommended	—	Increased action of indinavir	Increased action of nelfinavir and indinavir	Increased action of indinavir	Increased action of saquinavir
Lopinavir/ritonavir	Increased action of amprenavir	—	Increased action of indinavir	—	—	Increased action of lopinavir	Increased action of saquinavir
Nelfinavir	Increased action of amprenavir	—	Increased action of indinavir and nelfinavir	—	—	Increased action of nelfinavir	Increased action of saquinavir

continues

Table 2. Selected Drug Interactions Involving the HIV Protease Inhibitors[a]

Generic name	Amprenavir	Atazanavir sulfate	Indinavir sulfate	Lopinavir/ ritonavir	Nelfinavir mesylate	Ritonavir	Saquinavir
III. Interactions in which the medications may be used concurrently with appropriate precautions (cont'd.)							
Interactions with other HIV protease inhibitors (cont'd.)							
Ritonavir	Dosage of amprenavir should be reduced by one-half	Increased action of atazanavir; use 300 mg with 100 mg of ritonavir once daily	Increased action of indinavir	Increased action of lopinavir	Increased action of nelfinavir	—	Increased action of saquinavir
Saquinavir	Decreased action of saquinavir	Increased action of saquinavir	Increased action of saquinavir	Increased action of saquinavir	Increased action of saquinavir	Increased action of saquinavir	—
Interactions with other antiretroviral agents							
Interactions in which the action of the HIV protease inhibitor is *increased*							
Delavirdine	Yes	—	Yes (a dosage reduction of indinavir to 600 mg every 8 hours should be considered)	—	—	—	—
Interactions in which the action of the HIV protease inhibitor is *decreased*							
Didanosine	Yes (should be given at least 1 hour before or after didanosine buffered formulations)	Yes (should be given 2 hours before or 1 hour after didanosine buffered formulations)	See below	See below	—	See below	—
Efavirenz	Yes	Yes (a dose of 300 mg should be used with 600 mg efavirenz and 100 mg of ritonavir once a day)	Yes (dosage of indinavir should be increased to 1000 mg every 8 hours)	Yes (dosage increase to 533 mg/133 mg of lopinavir/ ritonavir should be considered)	—	—	Yes

Nevirapine	Yes	—	—	Yes (dosage increase to 533 mg/133 mg of lopinavir/ ritonavir should be considered)	—	—	Yes
Interactions in which the action of the interacting drug is *decreased*							
Didanosine	—	—	Yes (should be administered at least 1 hour apart)	Yes (should be given at least 2 hours before or 1 hour after didanosine)	—	Yes (should be administered 2½ hours apart)	—
Interactions with other medications in which the action of the HIV protease inhibitor is *increased*							
Clarithromycin	—	Yes	—	—	—	—	Yes
Itraconazole	—	—	Yes (dosage of indinavir should be reduced to 600 mg every 8 hours)	—	—	—	—
Ketoconazole	—	—	Yes (dosage of indinavir should be reduced to 600 mg every 8 hours)	—	—	—	Yes
Interactions with other medications in which the action of the HIV protease inhibitor is *decreased*							
Antacids	Yes (should be administered at least 1 hour before or after antacid)	Yes (should be administered 2 hours before or 1 hour after antacid)	—	—	—	—	—

continues

Table 2. Selected Drug Interactions Involving the HIV Protease Inhibitors[a]

Generic name	Amprenavir	Atazanavir sulfate	Indinavir sulfate	Lopinavir/ ritonavir	Nelfinavir mesylate	Ritonavir	Saquinavir
III. Interactions in which the medications may be used concurrently with appropriate precautions (cont'd.) Interactions with other medications in which the action of the HIV protease inhibitor is *decreased* (cont'd.)							
Carbamazepine	Yes	—	—	Yes	Yes	—	Yes
Dexamethasone	Yes	—	—	Yes	—	—	Yes
Histamine H_2-receptor antagonists (cimetidine, famotidine, nizatidine, ranitidine)	—	Yes (should preferably be administered 12 hours apart)	—	—	—	—	—
Phenobarbital	Yes	—	—	Yes	Yes	—	Yes
Phenytoin	Yes	—	—	Yes	Yes	—	Yes
Rifabutin	—	—	Yes (dosage of indinavir should be increased to 1000 mg every 8 hours)	—	—	—	Yes
Rifampin	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	—	Yes
Interactions with other medications in which the action of the interacting medication (noted below) is *increased*							
Amiodarone	Yes	Yes	—	Yes	Contraindicated	Contraindicated	—
Atorvastatin	Yes	Yes	—	Yes	Yes	Yes	—
Benzodiazepines (midazolam, triazolam)	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Benzodiazepines (alprazolam, clorazepate, diazepam, flurazepam)	Yes (dosage of benzodiazepine may need to be reduced)	—	—	—	—	Yes	—
Bepridil	Yes	Not recommended	—	Yes	—	Contraindicated	—

Calcium channel blockers (diltiazem; verapamil; nifedipine and other dihydropyridines)	Yes	Yes (a dose reduction of diltiazem by 50% should be considered)	Yes	Yes	—	Yes	—
Clarithromycin	—	Yes (a dose reduction of clarithromycin by 50% should be considered)	—	Yes	—	Yes	—
Cyclosporine	Yes	Yes	—	Yes	Yes	Yes	—
Itraconazole	Yes (a dose reduction of itraconazole may be needed)	—	—	Yes (dosage of itraconazole should not exceed 200 mg a day)	—	Yes	—
Ketoconazole	Yes (a dosage reduction of ketoconazole may be needed)	—	—	Yes (dosage of ketoconazole should not exceed 200 mg a day)	—	Yes (dosage of ketoconazole should not exceed 200 mg a day)	—
Lidocaine (systemic)	Yes	Yes	—	Yes	—	Yes	—
Meperidine	—	—	—	—	—	Yes (increased concentrations of meperidine metabolite are formed)	—
Oral contraceptives	—	Yes	—	—	—	—	—
Quinidine	Yes	Yes	—	Yes	Contraindicated	Contraindicated	—
Rifabutin	Yes (dosage of rifabutin should be reduced by at least 50%)	Yes (dosage of rifabutin should be reduced by up to 75%)	Yes (dosage of rifabutin should be reduced by 50%)	Yes (dosage of rifabutin should be reduced by at least 75%)	Yes (dosage of rifabutin should be reduced by 50%; nelfinavir regimen should be 1250 mg twice a day)	Yes (dosage of rifabutin should be reduced by at least 75%)	—

continues

Table 2. Selected Drug Interactions Involving the HIV Protease Inhibitors[a]

Generic name	Amprenavir	Atazanavir sulfate	Indinavir sulfate	Lopinavir/ ritonavir	Nelfinavir mesylate	Ritonavir	Saquinavir
III. Interactions in which the medications may be used concurrently with appropriate precautions (cont'd.) Interactions with other medications in which the action of the interacting medication (noted below) is *increased* (cont'd.)							
Sildenafil	Yes (dosage of sildenafil should be reduced to no more than 25 mg every 48 hours)	Yes (dosage of sildenafil should be reduced to no more than 25 mg every 48 hours)	Yes (dosage of sildenafil should be reduced to no more than 25 mg every 48 hours)	Yes (dosage of sildenafil should be reduced to no more than 25 mg every 48 hours)	Yes (dosage of sildenafil should be reduced to no more than 25 mg every 48 hours)	Yes (dosage of sildenafil should be reduced to no more than 25 mg every 48 hours)	Yes (initial dose of sildenafil should be 25 mg)
Sirolimus	Yes	Yes	—	Yes	Yes	Yes	—
Tacrolimus	Yes	Yes	—	Yes	Yes	Yes	—
Tricyclic antidepressants (eg, amitriptyline, imipramine)	Yes	Yes	—	—	—	Yes	—
Warfarin	INR should be monitored	Yes (INR should be monitored)	—	INR should be monitored	—	—	—
Interactions with other medications in which the action of the interacting medication (noted below) is *decreased*							
Atovaquone	—	—	—	Yes	—	Yes	—
Methadone	—	—	—	Yes	—	Yes	—
Oral contraceptives (ethinyl estradiol)	Additional or alternative contraceptive measures should be used	—	—	Additional or alternative contraceptive measures should be used	Additional or alternative contraceptive measures should be used	Additional or alternative contraceptive measures should be used	—
Theophylline	—	—	—	—	—	Yes	—

[a]The interactions included are primarily those identified in the labeling for the HIV protease inhibitors. The interactions are grouped in 3 sections:
I. Interactions in which concurrent use is contraindicated;
II. Interactions in which concurrent use is not recommended;
III. Interactions in which the medications may be used concurrently with appropriate precautions (eg, a dosage adjustment)
When consulting the table regarding a particular interaction, all 3 sections should be checked. Because all of the protease inhibitors are substrates for and inhibit CYP3A, interactions that involve inhibition or induction of this metabolic pathway should be anticipated with all the protease inhibitors, even though they have been reported (and identified in the table) for only certain individual protease inhibitors.

[b]No longer marketed but available to selected patients on a special need basis