HIV Protease Inhibitors: Advances in Therapy and Adverse Reactions, Including Metabolic Complications

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Protease inhibitors (PIs) effectively inhibit replication of the human immunodeficiency virus (HIV), and reduce mortality and prolong survival in patients with HIV infection. Newer PIs saquinavir (soft gelatin capsule) and amprenavir, as well as other PIs, may be effective when administered twice/day. Adverse reactions may occur, as well as metabolic complications and interactions between PIs and other drugs, including other PIs. The strategy of combining PIs is based on specific pharmacologic interactions among the agents.
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Summary

Human immunodeficiency virus (HIV) protease inhibitors (PIs), combined with nucleoside reverse transcriptase inhibitors (NRTIs), are potent inhibitors of viral replication that reduce morbidity and prolong survival in HIV-infected persons.[1–3] Consensus guidelines recommend that an antiretroviral regimen including a PI be given to all patients in whom a significant degree of viremia is present, even those in the early stages of HIV infection.[4–5]

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Mechanism of Action

The PIs inhibit HIV replication at the postintegrational level after the virus is integrated into the host genome in acutely and chronically infected cells. The target HIV protease enzyme, a 99-amino acid homodimer, cleaves pol-gag polypeptides on the viral envelope just as the virus buds form the plasma membrane of the infected host cell. Protease inhibitors, competitive inhibitors of this enzyme, result in the release from infected cells of immature, noninfectious viral particles.[6]

Efficacy

Indinavir, Nelfinavir, Ritonavir, and Saquinavir

The four approved HIV PIs—indinavir, nelfinavir, ritonavir, and saquinavir—are structurally related (Table 1). Nelfinavir, ritonavir, and indinavir in combination with two NRTIs have dramatic virologic potency, with 2–3 log reduction in plasma HIV RNA viral loads and improvement in immunologic parameters, and increases in CD4 counts between 50 and 250 cells/mm^3.[1, 2, 4, 7]

Table 1. Protease Inhibitors, Dosage, and Year Licensed

Agent	Brand Name	Dose	Year Licensed
Saquinavir	Invirase	600 mg t.i.d.	1995
Ritonavir	Norvir	600 mg b.i.d.	1996
Indinavir	Crixivan	800 mg t.i.d.	1996
Nelfinavir	Viracept	750 mg t.i.d.	1997
Saquinavir	Fortovase	1200 mg t.i.d.	1998
Amprenavir (141W94)	Agenerase	1200 mg b.i.d.	Investigational

The assumption that PI-associated suppression of viremia improves prognosis for patients in the early or middle stages of HIV infection is indirectly supported by several studies in which weak regimens accomplished only moderate reductions in viral loads.[8] These studies, with regimens that reduced plasma HIV RNA viral load by 1.0 log, reported a 56% reduction in the risk of disease progression at 1-year follow-up.[8, 9] The assertion that additional clinical benefit is associated with maximum reduction of viral load to undetectable levels remains to be documented. Nevertheless, the goal of achieving and maintaining an undetectable viral load is justified by the fact that disease progression is slowest in patients who have the lowest viral load.[10]

Clinical trials studying the efficacy of PIs in persons with later stages of acquired immunodeficiency syndrome (AIDS) directly showed a decrease in death and increased time to first AIDS-defining illness.[2, 3] Furthermore, studies in patients with AIDS identified a decline in mortality after PIs began to be administered in clinical practice. One study of 1255 patients reported a decline in mortality from 29.4/100 person-years in 1995 to 8.8/100 person-years in 1997, and a decrease in morbidity as evidenced by decline in frequency of three AIDS-associated opportunistic infections: *Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex infections, and cytomegalovirus retinitis.[11]

Saquinavir Soft Gelatin Caps

The absolute bioavailability of a 600-mg dose of saquinavir hard gelatin capsules (hgc; Invirase) is only 4% in healthy adults, which limits its effectiveness.[12] The soft gelatin capsule (sgc; Fortovase) has greater bioavailability. In one study, the relative bioavailability of saquinavir-sgc compared with saquinavir-hgc after a single 600-mg dose was 331% (95% CI 207–530).[12] At standard dosages, the area under the curve from zero to 8 hours at 3 weeks was 7249 ng hour/ml for saquinavir-sgc compared with 866 ng hour/ml for saquinavir-hgc.

The ability of both saquinavir preparations to achieve virologic suppression was compared in a randomized trial of 171 antiviral-naïve patients (mean baseline CD4 count 448 cells/mm^3, viral load 4.8 log copies/ml) who received either saquinavir-hgc or saquinavir-sgc with two NRTIs.[13] After 16 weeks of treatment, 80% of patients taking saquinavir-sgc had an undetectable viral load (< 400 copies/ml), compared with only 43% of those receiving saquinavir-hgc. Mean reductions in viral load were 2.0 and 1.6 log copies/ml, and mean increases in CD4 count were 97 and 115 cells/mm^3 in the two groups, respectively. Thus, saquinavir-hgc should never be the sole PI in a combination regimen.

Clinical studies found the efficacy of saquinavir-sgc to be similar to that of indinavir, nelfinavir, and ritonavir. In a randomized study of 62 antiretroviral-inexperienced patients (mean baseline CD4 count 310 cells/mm^3, viral load 4.9 log copies/ml), viral load was below 400 copies/ml at 24 weeks in 100% of patients taking saquinavir-sgc with two NRTIs and 100% taking indinavir with two NRTIs, and was below 50 copies/ml in 90%.[14] The mean reduction in viral load was 2.3 log copies/ml in both groups, and mean increases in CD4 count were 177 and 93 cells/mm^3 in the saquinavir-sgc and indinavir groups, respectively.

In 42 antiviral-naïve patients (mean baseline CD4 count 419 cells/mm^3, viral load 4.8 log copies/ml), 91% of those taking saquinavir-sgc with two NRTIs had undetectable viral loads (< 400 copies/ml).[15] At 32 weeks, the mean reduction was 3.34 log copies/ml, and mean increase in CD4 count was 209 cells/mm^3. Seventy percent of patients had viral loads below 20 copies/ml. Thus data support saquinavir-sgc as first-line PI as part of combination therapy.

Amprenavir

Amprenavir, an investigational PI currently available on an expanded-access basis, appears to have potent antiretroviral activity. In an early

dose-escalation study of amprenavir monotherapy, at 4 weeks a dosage of 1200 mg twice/day reduced viral load 1.95 log copies/ml.[16] Amprenavir also was tested in combination with nucleoside agents. In 41 antiretroviral-naïve patients (median CD4 count 756 cells/mm^3, viral load 4.43 log copies/ml) receiving amprenavir 1200 mg twice/day plus abacavir 300 mg twice/day, viral load was less than 500 copies/ml in 79% and less than 5 copies/ml in 60% at 24 weeks.[17] The mean CD4 count increase was 187 cells/mm^3. In 20 PI- and lamivudine-naïve patients (median CD4 count 405 cells/mm^3, viral load 4.88 log copies/ml), the combination of zidovudine, lamivudine, and amprenavir 1200 mg twice/day resulted in a reduction of viral load of 2.35 log copies/ml and increase in CD4 count of 177 cells/mm^3.[18]

Amprenavir was tested in dual-PI combinations. Twenty-seven antiviral naïve patients (mean baseline CD4 count 420 cells/mm^3, viral load 4.09 log copies/ml) received one of four regimens: group A, amprenavir 800 mg 3 times/day alone; group B. amprenavir 800 mg 3 times/day plus saquinavir-sgc 800 mg 3 times/day; group C, amprenavir 800 mg 3 times/day plus indinavir 800 mg 3 times/day; and group D, amprenavir 800 mg 3 times/day plus nelfinavir 750 mg 3 times/day.[19] After 4 weeks of treatment 13/16 patients had undetectable viral loads (< 400 copies/ml) with median decreases of 1.74, 2.53, 2.57, and 3.18 log copies/ml, respectively, in the four groups.

The drug selects for mutations at codon 50 (unique to amprenavir), as well as codons 46 and 47. In vitro data show that whereas amprenavir-resistant mutants have decreased sensitivity to ritonavir, they have increased sensitivity to saquinavir and indinavir.[20] The clinical significance of this is not known.

Twice/Day Dosing

Studies with twice/day dosing of PIs originally licensed for 3 times/day dosing were conducted to improve patient compliance by eliminating the midday dose.[21–28] In a preliminary study, 87 lamivudine- and PI-naïve patients were randomized to indinavir either standard 3 times/day dosing or 1000 or 1200 mg twice/day.[21] At 20 weeks, reductions in viral loads were comparable. In a larger trial of 374 patients, interim analysis at 24 weeks revealed that 91% and 64%, respectively, of patients receiving indinavir 3 times/day versus twice/day had plasma viral loads below 400 copies/ml. Crixivan is rapidly absorbed (time to maximum concentration [T_{max}] 0.8 ± 0.3 hrs) and cleared (half-life 0.8 ± 0.4 hrs).[23] The observation that the low trough may lead to failure of antiretroviral therapy[24] could explain the superiority of dosing the agent 2 rather than 3 times/day.

Nelfinavir is absorbed more slowly (T_{max} 2–4 hrs) and has a longer half-life (3.5–5 hrs) than indinavir,[25] and is thus more likely to be effective with less frequent dosing. Two studies evaluated twice/day dosing of nelfinavir. Thirty-six treatment-naïve HIV-infected patients (mean baseline CD4 count 342 cells/mm^3, viral load 5.14 log copies/ml) were randomized to nelfinavir 1250 mg and 10 to 1000 mg twice/day, each in combination with two NRTIs.[26] After 24 weeks of therapy, 96% of patients in each group had an undetectable viral load (< 400 copies/ml, mean reduction 2.2 log copies/ml). The mean increase in CD4 count at 24 weeks in the combined groups was 125 cells/mm^3.

Nelfinavir 1250 mg twice/day was compared with nelfinavir 750 mg 3 times/day, both in combination with two NRTIs, in 279 PI-naïve patients (mean baseline CD4 count 388 cells/mm^3, viral load 5.3 log copies/ml).[27] After 32 weeks of treatment, 93% of patients in both groups had undetectable viral loads (< 400 copies/ml) and mean decreases of 2.2 and 2.4 log copies/ml, respectively. Mean increases in CD4 counts were 181 and 155 cells/mm^3, respectively.

Preliminary results of twice/day therapy of saquinavir-sgc-based regimens are available. One hundred eighty-six patients were randomized to saquinavir-sgc 1200 mg 3 times/day or 1600 mg twice/day in combination with two NRTIs.[28] Baseline CD4 count was 337 cells/mm^3 and viral load 4.7 log copies/ml. At 16 weeks, viral load reductions and CD4 increases were similar in the two study arms.

Although these results are preliminary, twice/day dosing of nelfinavir or saquinavir-sgc is an option for patients who cannot tolerate a midday dose. More long-term data are available for nelfinavir than for saquinavir-sgc. Indinavir should not be dosed twice/day. Dual-PI therapy is another option for these patients.

Adverse Reactions

General

Adverse reactions to PIs are not uncommon (Table 2). Headache, gastrointestinal complaints,

Table 2. Common Adverse Reactions to Protease Inhibitors

Adverse Event	Amprenavir[20]	Indinavir[23] (%)	Ritonavir[29] Naïve/experienced (%)	Saquinavir (sgc)[12] Naive/experienced (%)	Nelfinavir[25] Naive/experienced (%)
Symptoms					
Diarrhea	+	4.6	12.8/18.3	15.6/19.9	20.0/32.0
Nausea	+	11.7	23.1/26.2	17.8/10.6	7.0/2.0
Emesis	+	4.1	12.8/15.2	4.4/2.9	–/–
Abdominal pain	–	8.7	3.4/7.0	13.3/8.6	–/4.0
Taste perversion	–	–	10.3/5.4	–/–	–/–
Asthenia	+	3.6	9.4/14.2	6.7/4.8	1.0/1.0
Circumoral paresthesia	+	–	2.6/5.9	–/–	
Peripheral paresthesia	–	–	6.0/5.0	–/–	–/–
Nephrolithiasis	–	4.0	–/–	–/–	–/–
Rash	18	–	–/–	–/–	–/–
Laboratory abnormalities					
↑ Aspartate aminotransferase	–	2.1	6.5/3.8	–/3.0	–/3.0
↑ Alanine aminotransferase	–	3.1	5.6/6.1	1.0/4.0	1.0/2.0
Hyperbilirubinemia	–	7.8	–/–	–/–	–/–
Hypertriglyceridemia	+	–	1.4/7.9	–/–	–/–

+ = Reported, frequency not available; – = frequency less than 2% or not reported.

and fatigue occasionally occur during the first week of treatment, but are transient and usually resolve within 3 weeks. To reduce early side effects, many clinicians give agents individually in a stepwise fashion. Resistant viral strains are unlikely to emerge if the entire combination regimen is introduced within 1 week.

Because several PIs are therapeutically equivalent, selection of one must take the toxicity profile as well as the patient's symptoms into account. For example, nelfinavir should be avoided in patients who have chronic diarrhea, a symptom caused more commonly by this agent than by other PIs.[25] The drug also may be avoided in those who have difficulty swallowing pills, since it dissolves quickly in saliva. In contrast, it would be a rational selection for patients with preexisting nausea or those about to undergo chemotherapy, since nausea occurs less frequently with nelfinavir than with saquinavir, ritonavir, or indinavir.[12, 23, 25, 29]

Indinavir may crystallize in the urinary tract and result in nephrolithiasis.[23] Consequently, it should be avoided in individuals who are unable to maintain adequate hydration, have congestive cardiac failure, or have had episodes of nephrolithiasis. It also may cause asymptomatic hyperbilirubinemia.[23]

Ritonavir may cause circumoral or peripheral paresthesias and taste perversion.[29] Amprenavir may cause a macular or maculopapular rash, occurring within 7–12 days of starting therapy, in 18% of patients. Rash may be more common in patients concurrently treated with other antiretrovirals (NRTIs) that also cause rash. Cessation of therapy was required in 33% of patients, but rechallenge with a gradually escalating or full dose was successful.[20] The rash may be serious in 3% of patients and result in Stevens-Johnson syndrome. Headache, fatigue, nausea, vomiting, diarrhea, and circumoral paresthesia also occur with amprenavir.[20]

Complications

Several complications of PIs, such as hyperglycemia,[30–36] altered fat distribution,[34–42] hyperlipidemia,[34, 36, 43–47] renal abnormalities associated with indinavir,[48, 49] and increased bleeding in hemophiliacs,[50–54] were described after these agents were licensed for use. Management of these complications is crucial to allow continued therapy.

Hyperglycemia

Several reports described new-onset hyperglycemia associated with PIs, in addition to worsening of existing diabetes mellitus.[30–36] In 1997, reports of 83 cases of diabetes mellitus prompted a labeling revision of PIs to include the warning of hyperglycemia. The disorder was serious in several patients; 27 patients required hospitalization and 5 developed ketoacidosis. New-onset or exacerbation of existing hyperglycemia developed an average of 76 days after PI treatment was begun.[30] In six patients (3 taking saquinavir, 1 ritonavir, 2 nelfinavir), blood glucose levels were elevated from 300 to 1000 mg/dl. Five patients achieved control of diabetes with continued PI therapy.[31]

Data on long-term management and consequences of PI-induced hyperglycemia are sparse. In a series of seven patients (6 indinavir, 1 ritonavir), one was free of symptoms without requiring hypoglycemic treatment, one was well controlled with oral hypoglycemic agents, two were well controlled with insulin, and one was poorly controlled with oral agents.[32] In two others, the PI was discontinued with resolution of hyperglycemia within 6 weeks. Ketonuria did not occur, and one patient was briefly hospitalized for hyperglycemia.

Three studies found the incidence of new-onset hyperglycemia in patients receiving PIs to be low.[32–34] In one trial conducted from January 1996–January 1997, the frequency was 0.35/100 person-months (95% CI 0.09–0.90) in a cohort of 290 patients.[33] Others calculated a rate of 1% in 1050 patients.[32] The incidence of of new or worsening diabetes mellitus was 2% in 116 patients.[34]

One study compared the relative effects of PIs and other antiretroviral agents on serum glucose levels.[35] Glucose and insulin levels were measured before and after start of antiretroviral therapy in 24 patients. In 16 patients the regimen contained a PI and in 8 it did not. The control group consisted of 16 HIV-infected patients who were untreated or receiving stable therapy. Glucose and insulin levels increased 14 ± 4 mg/dl and 18.6 ± 9.5 IU/ml, respectively, in patients receiving the PI, whereas no change in levels was observed in patients not receiving a PI and controls. Cortisol and dihydroepiandosterone levels did not change in any group. The authors did not determine whether changes in insulin and glucose levels were direct effects of PIs or secondary to unknown metabolic changes associated with the more effective viral suppression achieved with that regimen.

It was suggested that peripheral insulin resistance may be the mechanism underlying PI-associated hyperglycemia.[36] Intravenous glucose tolerance tests were performed in 27 patients treated with a PI, 7 treatment-naïve patients, and 18 uninfected controls. Eleven PI-treated patients had impaired glucose tolerance. The test was normal in HIV-negative controls and HIV-infected, treatment-naïve patients.

Patients receiving PIs should have blood glucose levels measured periodically and be instructed to notify a physician if hyperglycemic symptoms occur. In our clinic, we measure fasting blood glucose levels before and 8 weeks after starting treatment, and every 4 months thereafter. This should be done more often when indicated; for example, in patients with existing glucose intolerance or those receiving agents that cause dysglycemias, such as didanosine, pentamidine, corticosteroids, and megestrol acetate.[55]

Due to the importance of PIs in the management of HIV infection, administering hypoglycemic agents while continuing PIs is the preferred strategy. Treatment of PI-induced hyperglycemia is similar to that for non-HIV-infected persons with type II diabetes mellitus. The goal is a normal glycated hemoglobin. Nutrition counseling is indicated for all patients. Those with mild symptoms who do not require hospitalization should be treated with an oral hypoglycemic drug. Interactions between these agents and PIs occur, however. Glyburide and glipizide are metabolized by the cytochrome P450 (CYP) 2C9/19 isoenzyme and may have moderate (1.5–3 x) increases or decreases in AUCs when coadministered with ritonavir.[29] If ritonavir is given with either of these drugs, the sulfonylurea should be taken at half the usual starting dosage, and monitoring for hypoglycemia is appropriate. Significant interactions between sulfonylureas and other PIs are unlikely to occur, but have not been specifically evaluated.[12, 23, 25]

Metformin decreases hepatic glucose production and increases insulin sensitivity; hypoglycemia does not occur when it is given as monotherapy. The drug is excreted unchanged in urine, does not undergo hepatic metabolism, and does not interact with PIs.[56] Because of the risk of lactic acidosis, serum creatinine above 1.5 mg/dl, significant liver disease, and preexisting acidosis are contraindications to metformin. The agent should be discontinued in patients who develop hypoxia or dehydration, and should be withheld for at least 48 hours after administration of iodinated contrast material and restarted after serum creatinine has returned to baseline value.[56]

Acarbose inhibits intestinal and pancreatic enzymes responsible for hydrolysis of carbohydrates, resulting in delayed glucose absorption and lower postprandial serum glucose levels.[57] It is metabolized in the gastrointestinal tract, and significant interactions with PIs are unlikely to occur. Flatulence and diarrhea are the main side effects,[57] and the drug should be avoided in patients with diarrhea, wasting syndrome, or other gastrointestinal tract pathology. Troglitazone decreases insulin resistance and induces CYP3A4.[58] It may consequently lower PI

levels[12, 23, 25, 29] and should not be administered to patients receiving PIs.

Lipid Changes in HIV-Infected Patients

These patients have higher triglyceride levels than uninfected persons. In addition, triglyceride levels are higher in later stages of HIV infection than in earlier asymptomatic stage.[59–61] Triglyceride levels in 32 patients with AIDS, 8 asymptomatic HIV-infected patients, and 17 HIV-negative controls were elevated in 30%, 20%, and less than 5%, respectively.[59] Respective mean triglyceride levels were 231 ± 27, 166 ± 36, and 91 ± 10 mg/dl. Hypertriglyceridemia (triglyceride > 150 mg/dl) occurred in 27/58 HIV-infected patients,[61] and similar findings were reported by others.[60] The mean level was 159 ± 80 mg/dl in HIV-infected patients, compared with 79 ± 53 mg/dl in age- and gender-matched controls.

There are several possible mechanisms of hypertriglyceridemia in HIV infected patients.[62, 63] Cytokines are associated with hyperlipidemia,[64, 65] and a correlation exists between elevated α-interferon levels in patients with AIDS and hypertriglyceridemia.[62] α-Interferon may act by decreasing lipoprotein lipase levels with resulting hypertriglyceridemia.[62] In addition, the low-density lipoprotein B phenotype, which is associated with hypertriglyceridemia, is 2.5 times more common in patients with AIDS than in matched controls[63]; this may be an additional mechanism of hypertriglyceridemia.

Hyperlipidemia. Protease inhibitor therapy is a risk factor for developing significant hyperlipidemia.[34, 36, 43–47] Both hypertriglyceridemia and hypercholesterolemia have been reported. In one study, lipid concentrations were increased in 41 (33%) of 124 patients receiving PIs, and mean fasting cholesterol and triglyceride levels were 310 and 1194 mg/dl, respectively.[44] Cholesterol levels of 166 patients treated with PIs, 32 HIV-infected patients who did not receive PIs, and 47 age- and sex-matched controls were 228 ± 7.7, 174 ± 15.4, and 189 ± 15.4 mg/dl, respectively; respective triglyceride levels were 292 ± 35.4, 142 ± 17.7, and 106.2 ± 8.85 mg/dl. Both levels were significantly higher in patients treated with ritonavir plus saquinavir than in those receiving indinavir alone (469.1 ± 70.8 and 274.1 ± 23.2 mg/dl vs 221 ± 26.6 and 212.4 ± 23.2 mg/dl).[34] In a cohort of 94 patients receiving combination therapy including a PI, serum triglyceride levels were more than 95% of the normal range in 66%. Seventeen of 20 patients treated with ritonavir and 10/11 treated with ritonavir and saquinavir had triglyceride levels more than 95% of the normal range.[46]

Additional studies suggest that hyperlipidemia is more common with ritonavir or ritonavir plus saquinavir than with other PIs. In premarketing studies of ritonavir, severe hypertriglyceridemia (> 1500 mg/dl) occurred in 7.9% of patients with advanced disease.[29] In a trial of combination therapy with ritonavir and saquinavir, triglyceride elevations to this level occurred in 11% of patients.[43] In premarketing studies, severe hypertriglyceridemia occurred in less than 2% of patients treated with a PI other than ritonavir.[12, 23, 25]

A prospective study identified that abnormalities in lipid profiles develop soon after PI treatment begins. Serum lipid analysis were performed in 10 antiretroviral-naïve patients after combination therapy with two NRTIs and indinavir was begun.[45] Within 1 month of therapy cholesterol baseline levels of 145.8 ± 24.9 mg/dl increased to 172.5 ± 36 mg/dl, and triglyceride baseline levels of 95.5 ± 39.2 increased to 142.1 ± 54.4. In phase III clinical trials of ritonavir, increases in triglyceride levels of 70–110 mg/dl in naïve patients and 240 mg/dl in experienced patients were first noted on day 15 and persisted throughout the 16-week evaluation (Abbott Laboratories, personal communication, 1998).

To determine whether these changes in lipid profiles are due to PIs or are a consequence of viral suppression, changes in metabolic parameters were assessed before and after start of a regimen containing either PI or lamivudine, and in a control group receiving stable therapy.[35] Although overall weight gain did not differ among the groups, glucose, triglyceride, and cholesterol levels increased in patients treated with a PI (14 ± 4 mg/dl, p=0.03; 75 ± 35 mg/dl, p=0.002; + 51 ± 10 mg/dl, respectively, p<0.001) but not in the lamivudine-treated or control group. Viral suppression was more effective with PI, and the authors suggested that this is a possible cause of lipid changes.

Pancreatitis and vascular disease are the major clinical sequelae of hyperlipidemia. Whereas their frequency in patients receiving long-term PI therapy is unknown, isolated cases have been reported. Pancreatitis secondary to hyperlipidemia was not identified as an adverse event in phase III trials of ritonavir or in a trial of ritonavir-saquinavir that lasted less than 90 weeks (Abbott Laboratories, personal communication,

1998). Pancreatitis, however, was reported in postmarketing surveillance trials in hyperlipidemic patients taking ritonavir and saquinavir in combination. The duration of PI therapy before the onset of pancreatitis has not been reported (Abbott Laboratories, personal communication, 1998).

Two patients receiving PIs developed premature coronary artery disease.[44] One, a 26-year-old with a history of tobacco and cocaine use and late-stage HIV infection (CD4 count < 10 cells/mm^3), developed an occlusive thrombus in the right coronary artery after beginning ritonavir and saquinavir. Lipid profiles were not reported. The second patient, a 35-year-old man with a 2-year history of diabetes mellitus and family history of heart disease (CD4 count 14 cells/mm^3), developed hypercholesterolemia (475 mg/dl), hypertriglyceridemia (1959 mg/dl), and a right-sided cervical fat pad after beginning an antiretroviral regimen containing indinavir. Occlusion of the left anterior descending and atherosclerosis of the right coronary artery were noted on coronary angiogram performed after chest pain developed. The long-term risk of vascular disease and pancreatitis may increase as PIs are administered for prolonged periods of time.

Management of Lipid Abnormalities. Management of PI-induced hypertriglyceridemia and hypercholesterolemia in HIV-infected persons is the same as in the general population. Patients with persistent fasting hyper-triglyceridemia greater than 1000–1500 mg/dl after dietary intervention should take lipid-lowering agents to avoid pancreatitis and vascular disease, even though the true risk for developing these complications with a given triglyceride level is not known.

Options for therapy include the fibric acid derivative gemfibrozil, the HMG coenzyme A (CoA) reductase inhibitor atorvastatin, and niacin. In the Helsinki heart study,[66] gemfibrozil decreased triglyceride levels by 41.4% in middle-aged men with elevated cholesterol levels. The drug's metabolism has not been well studied, but may involve the CYP system, and thus plasma levels of this agent may be increased by PIs, particularly ritonavir.[29] Gemfibrozil has not been described as an inducer of the CYP system and thus would not be expected to lower PI levels.[67] In a study of 15 PI-treated patients with hyperlipidemia (mean serum cholesterol 357 mg/dl, mean serum triglyceride 1879 mg/dl), gemfibrozil 600 mg twice/day resulted in decreases in mean serum cholesterol to 261 mg/dl and mean serum triglyceride to 1244 mg/dl.[47] Six patients failed to respond.

Atorvastatin is more potent in reducing triglycerides than any other HMG CoA reductase inhibitor. The highest reduction noted with fluvastatin, simvastatin, and lovastatin is 27% (lovastatin 40 mg twice/day).[68] In patients with primary hypercholesterolemia, atorvastatin reduced triglycerides by 19% at 10 mg/day, 26% at 20 mg/day, 29% at 40 mg/day, and 37% at 80 mg/day.[69] Atorvastatin is a substrate of CYP3A4 isoenzyme, but has not been described as an inducer, and thus would not be expected to reduce PI levels (Warner-Lambert Co., personal communication, 1998). Atorvastatin levels are increased by the CYP3A4 inhibitor erythromycin.[70] Protease inhibitors, particularly ritonavir, may be expected to increase atorvastatin levels.[29] No direct data on the interaction between atorvastatin and protease inhibitors are available (Warner-Lambert, personal communication, 1998). Niacin, which may achieve a triglyceride reduction of up to 40%, should be considered a third-line agent.

Adverse reactions to lipid-lowering agents should be evaluated periodically. Elevations of serum transaminase levels greater than 3 times the upper limit of normal occurred in 0.7% of patients taking atorvastatin in clinical trials.[69] The frequency may be higher in HIV-infected patients taking other hepatotoxic drugs, and hepatic transaminase levels should be monitored before starting therapy, at 6 and 12 weeks, and at least biannually thereafter.[69] Rhabdomyolysis was associated with HMG CoA reductase inhibitors.[69] Treatment with zidovudine and HIV infection itself may cause myopathy.[71] Thus, patients should be monitored for myalgias or weakness, and creatine phosphokinase should be measured if symptoms occur. The dosage of niacin should be titrated slowly to 1 g 3 times/day, with flushing common after each dose. Glucose intolerance is a contraindication to niacin, and transaminase levels should be checked, as with atorvastatin.

Patients with hypercholesterolemia should be managed according to the National Cholesterol Education Program Adult Treatment Panel II, which stratifies treatment decisions and sets treatment goals based on low-density lipoprotein levels and risk factors for cardiac disease.[72] The HMG CoA reductase inhibitors are preferred first-line agents. Both lovastatin and pravastatin are metabolized by the CYP3A4 isoenzyme, and large (> 3 x) increases in their AUCs may occur when administered with ritonavir.[29] The CYP

isoenzyme responsible for the metabolism of fluvastatin and simvastatin is unknown, and their AUCs may be increased by ritonavir.[29] Interactions with other PIs would be predicted to be less, but have not been tested. As with atorvastatin, transaminase values should be routinely monitored and clinical monitoring for rhabdomyolysis is required. In patients with both hypercholesterolemia and hypertriglyceridemia, atorvastatin is the drug of choice.[68]

As lipid abnormalities have been reported frequently with ritonavir and ritonavir-saquinavir,[43] changing to an alternative PI may be required. In one study, 21 patients with hyperlipidemia taking indinavir or ritonavir-saquinavir were switched to nelfinavir. After 3 months the median triglyceride level decreased from 328 to 248 mg/dl. Serum cholesterol levels did not change.[73] In patients with severe or recurrent pancreatitis or active coronary artery disease who are refractory to drug therapy or switching protease inhibitors, It may be necessary to discontinue PI therapy.

Fat Redistribution. Anecdotal reports of abnormal fat distribution in patients treated with PIs were followed by systematic investigations. Peripheral lipodystrophy characterized by facial and extremity wasting with or without central adiposity, lipomatosis (dorsocervical fat pad or other localized collection of fat), and increased visceral adiposity were reported.[34–42] Seven patients developed dorsocervical fat pad enlargement 4–61 weeks after starting PI therapy.[37] No correlation was seen between a particular PI and this complication. Based on 24-hour urine cortisol and dexamethasone suppression testing, Cushing's disease was excluded in all patients. Histopathologic analysis of a biopsy specimen from one patient demonstrated unencapsulated fat.

Other reports described increased abnormal fat distribution due to PIs. It occurred in three patients taking indinavir in a large urban clinic.[38] Metabolic and body composition analyses were performed by dual energy x-ray absorptiometry (DEXA) in eight patients who developed a dorsocervical fat pad while receiving antiretroviral treatment; half were receiving a PI.[39] Patients had a higher trunk fat to total fat ratio than HIV-infected matched controls. Cushing's disease was excluded.

Lipodystrophy was reported in eight patients 2–12 months after indinavir was begun.[40] Six patients experienced facial fat loss that created a cachectic appearance, and two others noted onset of central adiposity and loss of fat in the extremities. Another study suggested that PIs may cause increased storage of visceral adipose tissue compared with total body fat. This abnormal distribution may have clinical consequences, such as abdominal fullness or bloating. Visceral adipose tissue was assessed by computerized tomography (CT) in 10 patients receiving indinavir who had abdominal fullness, distention, or bloating, and compared with patients receiving indinavir who did not have abdominal symptoms and with HIV-positive controls.[41] The mean ratio of visceral to total abdominal tissue in the three groups were 0.70 (SD 0.20), 0.59 (0.18), and 0.40 (0.15, $p<0.05$), respectively. Mean triglyceride levels in both indinavir-treated groups correlated with visceral to total abdominal tissue ratios ($r=0.57$, $p=0.01$); however, the mean body mass index of the three groups was similar.

The frequency of abnormalities in lipid distribution was investigated in a cross-sectional study in 116 PI-treated patients, 32 PI-naïve, and 47 HIV-negative subjects.[34] Extremity and facial fat wasting with relative central adiposity was observed in 64% of PI-treated patients and 3% of PI-naïve HIV infected subjects based on DEXA, physical examination, and patient history. Patient reports of fat wasting in the face or extremities were accepted as evidence of lipodystrophy, and data were collected retrospectively from questionnaires in which patients described events over the previous 12 months. By the more objective criteria of regional DEXA, performed in 45 PI-treated and 16 PI-naïve subjects, the former had significantly less fat mass in the arms, legs, and trunk than the latter. Central abdominal fat did not differ. Lipodystrophy occurred in 26/28 patients treated with combination ritonavir-saquinavir developed lipodystrophy, compared with 41/77 indinavir-treated patients and 7/11 patients treated with other PIs. The relative risk for developing lipodystrophy associated with ritonavir-saquinavir was 1.70 (1.03–2.80) compared with indinavir. The mean duration of PI therapy was 15.2 months for patients with lipodystrophy compared with 10.9 months for untreated subjects. Affected patients actually had weight loss compared with PI-treated subjects without lipodystrophy, in addition to significantly higher triglyceride, cholesterol, insulin, and C-peptide levels, and insulin resistance scores.

Of 118 HIV-infected women treated with a PI,

19 reported changes in body habitus.[42] With the exception of increased breast size, alterations in fat distribution were similar to those in men.

The pathogenesis of lipodystrophy and hyperlipidemia in PI treated patients is unknown. One group searched for amino acid homology to a 12-amino acid sequence in the catalytic region of the HIV-1 protease inhibitor. They found a 63% amino acid homology to a region of the low-density lipoprotein-receptor-related protein (LRP) and a 58% homology with the carboxy terminal region of the cytoplasmic retinoic acid-binding protein type 1 (CRABP-1). The protein is involved in production of *cis*-9-retinoic acid, which in turn is a regulator of adipocyte function. The LRP functions to increase hepatic clearance of serum lipids. The authors hypothesized that protease inhibitor-mediated alterations in functions of CRABP-1 and LRP may explain metabolic changes observed with PI therapy. These intriguing theories require further investigation.[74]

Management of Fat Redistribution. Management of lipodystrophy is challenging. Options include changing the PI, growth hormone therapy, surgery, and exercise.[34, 42, 73, 75] To evaluate the effect of changing protease inhibitors, 21 patients with hyperlipidemia and lipodystrophy by visual criteria taking either indinavir or the combination of ritonavir and saquinavir were changed to a nelfinavir-based regimen.[73] Visual inspection for lipodystrophy was performed at 1- to 3-month intervals. Most patients (57%) had no change at 3 months, 33% had partial improvement, and 10% worsened. A more objective measurement (DEXA, CT scan) was not performed, and switched patients were not compared with patients with lipodystrophy who continued indinavir or ritonavir-saquinavir. Another patient experienced improvement but not resolution of lipodystrophy when ritonavir-saquinavir was changed to indinavir.[34] Human growth hormone 6 mg/kg/day subcutaneously was administered to two PI-treated patients with dorsocervical fat pads, truncal obesity, and peripheral muscle wasting.[75] After 12 weeks of treatment, the fat pad regressed completely in one patient, and partially after 6 weeks in the other. In two patients, neither exercise nor weight training resulted in a significant change in body habitus.[42]

Metabolic side effects possibly associated with PIs have generated interest in combination antiretroviral regimens that achieve durable viral suppression without PIs. The combination of zidovudine, didanosine, and nevirapine, a nonnucleoside reverse transcriptase inhibitor (NNRTI), achieved undetectable viral loads (< 400 copies/ml) in 51% of patients at 1 year.[76] Patients in this trial, however, were naïve to all antiretrovirals and had relatively high CD4 counts (median 395 cells/mm^3) and relatively low viral loads (median 4.25 log copies/ml). Two preliminary studies of other protease-sparing regimens showed promising results. The combination of zidovudine, lamivudine, and indinavir was compared with zidovudine, lamivudine, and efavirenz, an NNRTI, in 450 patients naïve to PIs, lamivudine, and NNRTIs.[77] Baseline CD4 count was 345 cells/mm^3 and plasma HIV RNA viral load was 4.77 log copies/ml. At 24 weeks, in an intention-to-treat analysis, 74.7% of patients in the efavirenz arm versus 56.2% in the indinavir group had plasma HIV RNA below 400 copies/ml.

Therapy with three nucleoside agents was investigated as a possible PI-sparing regimen in 173 treatment-naïve patients with CD4 counts of 438 cells/mm^3 and plasma HIV RNA levels of 4.50 log copies/ml. Patients were randomized to zidovudine and lamivudine or zidovudine, lamivudine, and abacavir, an investigational NRTI.[78] At 16 weeks, 75% of patients in the abacavir-containing arm and 35% in the dual-therapy arm had plasma HIV RNA levels below 400 copies/ml. The durability of protease-sparing regimens is unknown, but preliminary data are promising.

Patients often experience discomfort with fat redistribution and may find these changes cosmetically unacceptable. Furthermore, visceral adiposity has been associated with insulin resistance, dyslipidemia, glucose intolerance, hypertension, and atherosclerosis.[79] Long-term effects of peripheral lipodystrophy are unknown.

Renal Abnormalities Associated with Indinavir Crystallization

Early studies estimated the frequency of indinavir-induced nephrolithiasis to be 4%.[23] Nephrolithiasis is a distinct feature of indinavir, and is caused by crystallization of this agent in the urinary tract.[47] Twelve percent of the drug is excreted unchanged in urine, and its solubility is greater than 100 mg/ml at pH below 3.5, but only 0.03 mg/ml at pH 6.0.[80, 81] In addition to nephrolithiasis, indinavir may crystallize in other locations in the urinary tract; dysuria may occur

Table 3. Drug Interactions: Effect of Selected Drugs on Protease Inhibitor Serum Levels

Drug	Indinavir (substrate of 3A4 inhibitor of 3A4)	Saquinavir (substrate of 3A4, inhibitor of 3A4) Invirase	Saquinavir (substrate of 3A4, inhibitor of 3A4) Fortovase	Ritonavir (substrate of[a], inhibitor of 3A4, 2D6)	Nelfinavir (substrate of 3A4[b], inhibitor of 3A4)	Amprenavir (substrate of 3A4, inhibitor of 3A4)
Nevirapine	↓ AUC 28%[c]	↓ AUC 27%[c]	NA	↓ AUC 11%[c]	↓ AUC 46%[87] ↓ AUC 8%[88]	NA
Delavirdine	↑ AUC 40%[89]	↑ AUC 5x[89]	NA	↑ AUC 60%[90]	↑ AUC 92%[91] ↓ metab 50%[91]	NA
Efavirenz	↓ AUC 35%[92] ↑ ind 1 g q8h[d]	NA	↓ AUC 60%[d, e]	↓ AUC 20%[d]	↑ AUC 20%[93] ↓ metab 37%[93]	↓ AUC 37%[98]
Rifampin	↓ AUC 89%[23] Contraindicated	↓ AUC 80%[95] Contraindicated	↓ AUC 84%[17] Contraindicated	↓ AUC 35%[29] Contraindicated	↓ AUC 82%[25] Contraindicated	↓ AUC 81%[24] Contraindicated
Rifabutin	↓ AUC 32%[23] ↓ 50% dose rif[23]	↓ AUC 40%[95] Avoid	↓ AUC 43%[12] Avoid	Contraindicated[29, f]	↓ AUC 32%[25] ↓ 50% dose rif[25]	↓ AUC 14%[82] ↓ 50% dose rif[82]
Isoniazid	No effect[10]	NA	NA	NA	NA	NA
Ketoconazole	↑ AUC 68%[23] ↓ ind 600 mg q8h[23]	↑ AUC 130%[12]	NA	NA	↑ AUC 35%[25,e]	↑ AUC 32%[96]
Fluconazole	↓ AUC 19%[23]	NA	NA	↑ AUC 12%[29]	NA	NA
Cimetidine, ranitidine	No effect[23]	↑ AUC 67%[12]	NA	NA	NA	NA
Grapefruit juice	↓ AUC 26%[23]	NA	NA	NA	NA	NA
TMP-SMX	No effect[23]	NA	NA	NA	NA	NA
Clarithro-mycin	↑ AUC 29%[23]	NA	↑ AUC 177%[12]	↑ AUC 12%[29]	NA	NA
Fluoxetine	NA	NA	NA	↑ AUC 19%[29, g]	NA	NA

Recommended dosage adjustments are included. The table does not include all clinically relevant drug interactions.
NA = not available; ind = indinavir; TMP-SMX = trimethoprim-sulfamethoxazole; rif = rifabutin.
[a]Ritonavir is a substrate of 3A4 > 2D6 > 2C9, 2C19 > > 1A2, 2A6, 2E1. It is an inducer of glucuronosyl transferases and CYP1A2.
[b]A4 is responsible for 52% of the metabolism of nelfinavir.
[c]Personal communication, Roxane Laboratories, 1998.
[d]Personal communication, DuPont Merck, 1998.
[e]The manufacturer recommends avoiding saquinavir as sole PI with efavirenz.
[f]Rifabutin 150 mg every other day was suggested in patients taking ritonavir.[85]
[g]Increased adverse events in postmarketing experience.

if it develops in the bladder[47] and chronic renal insufficiency if it develops in the renal parenchyma.[48, 49]

One patient developed azotemia, pyuria, proteinuria, and hypertension 28 weeks after beginning monotherapy with indinavir. Renal biopsy revealed interstitial fibrosis with tubular atrophy and chronic inflammation, with indinavir-appearing crystals and inflammatory cells in the collecting ducts. Hypertension and pyuria resolved after indinavir was discontinued, but serum creatinine did not return to baseline.[49] In a series of seven indinavir-treated patients without nephrolithiasis but with flank or back pain and crystalluria, CT scan of the abdomen showed bilateral renal parenchymal defects consistent with indinavir crystallization in the distal renal tubules.[48] In three of these patients the abnormalities resolved with discontinuation of therapy. Urinalysis showed crystalluria (asymptomatic) in 20% of patients treated with indinavir; renal biopsies were not performed. It is possible that the frequency of chronic renal insufficiency is uncommon with short-term therapy, but may increase as these agents are administered for longer treatment courses.

The decision to discontinue indinavir must be made on an individual basis. Hydration, pain control, and temporary discontinuation of the drug may be considered as a first approach. If this fails, invasive procedures to remove the calculi are indicated. In early studies, only 9% of patients with nephrolithiasis required permanent discontinuation of therapy.[23] If rechallenge with indinavir is attempted, at least 1.5 L of fluid/day must be consumed to reduce the risk of renal calculi.[23] Patients with a history of nephrolithiasis secondary to indinavir should not be

Table 4. Drug Interactions: Effect of Protease Inhibitors on Serum Levels of Selected Drugs

Drug	Indinavir (substrate of 3A4, inhibitor of 3A4)	Saquinavir (substrate of 3A4, inhibitor of 3A4) Invirase	Saquinavir (substrate of 3A4, inhibitor of 3A4) Fortovase	Ritonavir (substrate of[a], inhibitor of 3A4,) 2D6	Nelfinavir (substrate of 3A4,[b] inhibitor of 3A4)	Amprenavir (substrate of 3A4, inhibitor of 3A4)
Nevirapine	↓ < 10% C_{min}[c]	↓ AUC 3%[c]	NA	No effect[c]	No effect[88]	NA
Delavirdine	No effect[89]	↓ 15% AUC[89]	NA	No effect	↓ 42% AUC[91]	NA
Efavirenz (investigational)	No effect[92]	NA	NA	NA	NA	NA
Rifampin	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Contraindicated	Contraindicated
Rifabutin	↑ AUC 204%[23] ↓ 50% dose rif[23]	NA, ↓ 50% dose rif[12] Avoid	NA, ↓ 50% dose rif[12] Avoid	↑ AUC 4x[83] Contra-indicated[29, d]	↑ AUC 207%[25] ↓ 50% dose rif[25]	↑ C_{min} 3–6 x[82] ↓ 50% dose rif[82]
Norethindrone	↑ AUC 26%[23, e]	NA	NA	↓ AUC 40%[29, e]	↓ AUC 18%[25, e]	NA
Ethinyl estradiol	↑ AUC 24%[23, e]				↓ AUC 47%[25, e]	
TMP-SMX	↑ AUC 19%[23] No change[23]	NA	NA	↓ AUC 20%[29] ↓ AUC 20%[29]	NA	NA
Ketoconazole	NA	No effect[95]	NA	NA	NA	↑ AUC 44%[96]
Fluconazole	No effect[23]	NA	NA	NA	NA	NA
Isoniazid	↑ AUC 13%[23]	NA	NA	NA	NA	NA
Clarithromycin 14-OH metabolite	↑ AUC 53%[23]	NA	↑ AUC 45%[12] ↓ AUC 22%[12]	↑ AUC 77%[29, f] ↓ AUC 100%[29]	NA	NA
Theophylline	NA	NA	NA	↓ AUC 43%[29]	NA	NA
Desipramine	NA	NA	NA	↑ AUC 145%[29] Consider ↓ dose[29]	NA	NA

Recommended dosage adjustments are included. The table does not include all clinically relevant drug interactions.
NA = not available; rif = rifabutin; TMP-SMX = trimethoprim-sulfamethoxazole.
[a]Ritonavir is a substrate of 3A4 > 2D6 > 2C9, 2C19 > > 1A2, 2A6, 2E1. It is an inducer of glucuronosyl transferases and CYP1A2.
[b]3A4 is responsible for 52% of the metabolism of nelfinavir.
[c]Personal communication, Roxane Laboratories, 1998.
[d]Rifabutin 150 mg every other day was suggested in patients taking ritonavir.[85]
[e]Alternative or additional method of contraception is recommended.
[f]Adjust clarithromycin dosage for patients with renal impairment.

treated with the drug if they are unable to maintain adequate hydration or if nephrolithiasis recurs. Exclusion of indinavir, however, diminishes remaining options for future treatment with PIs.

Exacerbation of Bleeding in Hemophiliac Patients

Clinicians caring for these patients should be aware of a number of case reports that link PIs to increased episodes of spontaneous bleeding.[50–54] The Food and Drug Administration (FDA) sent letters to health care providers in July 1996 regarding this possibility.[52] Spontaneous subcutaneous and joint bleeding occurred in a number of patients with previously stable bleeding histories soon after starting ritonavir or indinavir. In one patient bleeding recurred after withdrawal and resumption of ritonavir, but did not occur after indinavir was begun.[50]

The Canadian Adverse Drug Reaction Newsletter reported 55 cases of increased episodes of spontaneous bleeding worldwide.[51] No serious or life-threatening episodes of bleeding have occurred, and most hemophiliacs are able to receive PIs.[52] Nonetheless, they should be alerted to the possibility of increased bleeding.

Drug Interactions

General

All PIs are substrates of and metabolized by the CYP3A4 isoenzyme.[12, 20, 23, 25, 29] Ritonavir has a high affinity for additional CYP isoforms (3A > 2D6 > 2C9, 2C19 > > 2A6, 1A2, 2E1).[29] Theoretically, drugs that induce CYP3A4 should lower PI serum levels and thus promote viral resistance to the agent. In fact, pharmacokinetic studies demonstrated that rifampin and rifabutin, agents that induce CYP, significantly reduce PI levels (Table 3).[82–86] In addition, serum levels of both drugs are increased by PIs (Table 4).[86]

Thus, rifampin is contraindicated with all PIs. The dosage of rifabutin, which does not induce CYP as strongly as rifampin,[85] should be reduced if administered with PIs. As rifabutin lowers saquinavir levels more than it does those of other PIs, this combination should be avoided if at all possible.[12, 23, 25, 29, 83]

Recommendations are available for tuberculosis therapy in patients treated with PIs.[84] The CYP inducers carbamazepine, phenobarbital, phenytoin, and dexamethasone should be avoided in patients receiving PIs. Pharmacokinetic studies with these agents have not been conducted.

Protease inhibitors, in addition to being metabolized by CYP3A4, may inhibit this enzyme; this is accomplished most avidly by ritonavir, less so by indinavir, nelfinavir, and amprenavir; saquinavir is the least efficient inhibitor.[20] Thus, drugs that are extensively metabolized by CYP3A4, such as nonsedating antihistamines terfenadine and astemizole and others such as cisapride, may have significant increases in plasma concentrations when coadministered with PIs.[12] To avoid life-threatening arrhythmias, these drugs should not be coadministered with PIs.[12, 25, 29]

Inhibition of many CYP isoenzymes by ritonavir accounts for the greater number of clinically significant drug interactions associated with this PI. In addition, the drug may increase the activity of glucuronosyl transferases, resulting in loss of therapeutic effect from directly glucuronidated agents. A list of predicted drug interactions with ritonavir is beyond the scope of this article and is available from the manufacturer.[29]

The NNRTIs such as nevirapine and efavirenz may induce CYP3A4, whereas others, such as delavirdine, may inhibit this enzyme. Consequently, PI plasma levels may be influenced by NNRTIs. Combinations of these agents, although not currently recommended as first-line therapy, are prescribed with increasing frequency in clinical practice in several situations. Examples are treatment of those who fail a PI-containing regimen and PI-naive patients heavily pretreated with NRTIs.

Although efficacy data on combination NNRTI-PI therapy are not available to guide dosage adjustments, pharmacokinetic studies have been conducted for many such combinations. The dosage of indinavir should be increased to 1 g 3 times/day when given in combination with efavirenz; saquinavir should not be the sole PI in combination with efavirenz. Data are conflicting regarding the interaction of nelfinavir and nevirapine. A pharmacokinetic study of eight HIV-positive patients showed a 46% reduction in nelfinavir AUC when nevirapine was added.[87] A similar study of 12 patients treated with stavudine and nelfinavir showed an insignificant 8% decrease in AUC when nevirapine was added.[88] The conflicting results in these two studies may be explained by the institution of nevirapine in the first study 2 days after nelfinavir was begun. Nelfinavir levels decline 20–30% in the first week of therapy as a result of autoinduction of CYP3A4 (Roxane Laboratories, personal communication, 1998).

Indinavir levels are decreased when the drug is coadministered with nevirapine, and subjects with higher baseline levels tend to have a larger reduction. Thus, the manufacturer does not currently recommend increasing the dosage of indinavir (Roxane Laboratories, personal communication, 1998). Delavirdine significantly increases nelfinavir levels and decreases the levels of an active metabolite.[91] In a pharmacokinetic study in 24 healthy volunteers, 4 subjects developed neutropenia. Two subjects had grade 3 or 4 neutropenia, and all resolved within a few days of stopping the agent.[91] If this combination is prescribed, monitoring for neutropenia is appropriate. In a study of patients treated with delavirdine and saquinavir in combination, hepatocellular enzyme were elevated in 13% (6% grade III-IV).[95]

The only clinically significant drug interaction identified between NRTIs and PIs is impairment of indinavir's absorption by the buffer contained in didanosine. If administered together, the two should be taken at least 1 hour apart on an empty stomach.[23] As nelfinavir, ritonavir, and saquinavir all should be taken with food,[12, 25, 29] they should not be taken with didanosine, which must be taken one half-hour before or 2 hours after eating.

Interactions Between PIs

Because ritonavir is a potent inhibitor of the CYP3A4 system, the plasma concentration of saquinavir increases 20-fold when the two agents are given in combination (Table 5).[97, 98] When saquinavir-sgc 1200 mg 3 times/day is combined with nelfinavir or indinavir, saquinavir AUCs are increased 392% and 620%, respectively.[99] Efficacy data for dual-PI combinations are outlined below.

Table 5. Dual-Protease Inhibitor Interactions (effect of drug in first column on drug in each column heading)

		Saquinavir				
Drug	Indinavir	Invirase	Fortovase	Ritonavir	Nelfinavir	Amprenavir
Indinavir	—	NA	↑ AUC 620%[99]	No effect[100, a]	↑ AUC 83%[23, 27, b]	↑ AUC 64%[20]
Invirase	NA	—	—	No effect	NA	NA
Fortovase	No effect[5]	—	—	No effect[12, c]	↑ AUC 18%[12, d]	NA
Ritonavir	↑ AUC up to 480%[100, a]	↑ AUC 1587%[12]	↑ AUC 20x[99, c]	—	↑ 1.5x[25]	NA
Nelfinavir	↑ AUC 53%[25, 27, b]	↑ AUC 5–30x[101, 102]	↑ AUC 392%[99, d]	No effect	—	NA
Amprenavir	No effect[20, e]	NA	NA	NA	NA	—

NA = not available.
[a]Indinavir 400 mg every 12 hours with ritonavir 400 mg every 12 hours likely results in similar serum levels to standard dosing.
[b]Indinavir 1000 mg every 12 hours coadministered with nelfinavir 750 mg every 12 hours results in serum AUC levels similar to standard dosing, nelfinavir trough levels may be lower.
[c]No difference in actual plasma exposures when ritonavir is coadministered with the same dosage of either Invirase or Fortovase. The recommended dosage is 400–600 mg twice/day for both agents with ritonavir.
[d]Suggested dosage is Fortovase 800 mg 3 times/day with nelfinavir 750 mg 3 times/day.
[e]Comparable with historical controls.

Dual-PI Regimens

The pharmacokinetic interactions outlined above have been used as a basis for double-protease inhibitor combination regimens. Dual-PI therapy was investigated with goals of increasing the potency of single PIs, developing synergy between PIs, and avoiding PI toxicities by giving lower dosages than prescribed for single-PI therapy. Efficacy data for many studies investigating dual-PI combinations ritonavir-saquinavir,[43, 99, 103–109] nelfinavir-saquinavir-sgc,[97, 98, 110–112] indinavir-nelfinavir,[113] ritonavir-nelfinavir,[114] and indinavir-ritonavir[115] are outlined below. At present, most clinicians do not consider these to be initial regimens in antiviral-naïve patients and reserve them as second-line therapy when and if the first single-PI regimen fails.

Ritonavir-Saquinavir

Ritonavir and saquinavir, the initial dual PI, was investigated in several trials. In one study, 136 PI-naïve patients (CD4 count 360 cells/mm^3) had reductions in viral load of 2.7–3.0 log copies/ml after 12 weeks of treatment.[99] In a subsequent trial, 141 PI-naïve patients (mean baseline CD4 count 277 cells/mm^3, viral load 4.60 log copies/ml) were treated with one of four ritonavir-saquinavir-hgc regimens: 400-400 mg twice/day; 600-400 mg twice/day; 400-400 mg 3 times/day; and 600-600 mg twice/day.[43] After 60 weeks, 79 (90%) of 88 patients had an undetectable viral load (< 200 copies/ml) with a mean decrease in viral load of 2.3 log copies/ml. The mean increase in CD4 count at 60 weeks was 174 cells/mm^3 There were no significant differences in efficacy among treatments. Because of reduced toxicity, the 400-400 mg twice/day regimen was preferred.

Ritonavir-saquinavir-hgc 400-400 mg twice/day was administered alone or with stavudine 40 mg twice/day in 208 PI- and stavudine-naïve patients (mean baseline CD4 count 270 cells/mm^3, viral load 4.3 log copies/ml).[103] After 48 weeks of treatment, 79% in the two-drug group and 83% in the three-drug group had undetectable viral loads (< 400 copies/ml). The mean increase in CD4 count was 130 cells/mm^3 in both groups.

Eighteen PI-naïve patients with advanced disease (mean baseline CD4 count 12 cells/mm^3, viral load 5.25 log copies/ml) received ritonavir-saquinavir-hgc 600-600 mg twice/day.[104] After 13 weeks, only 22% had an undetectable viral load (< 100 copies/ml); however, the median decrease was 2.04 log copies/ml and the median increase in CD4 count was 19 cells/mm^3. Another study investigated 58 HIV-infected patients (median CD4 count 140 cells/mm^3, viral load 4.8 log copies/ml; 64% antiretroviral naive) who were treated with ritonavir-saquinavir-hgc 600-600 mg twice/day.[105] Eighty-nine percent were given an NRTI; 38% of these patients were taking a new NRTI to which they had never been exposed. After 28 weeks the median decrease in viral load was 2.1 log copies/ml and the median increase in CD4 count was 120 cells/mm^3. Viral load was undetectable in 50% of patients (< 500 copies/ml). Sixty-seven percent of PI-naïve and 27% of PI-experienced patients achieved an undetectable viral load between 21 and 28 weeks.

Several small studies examined the effectiveness of this combination and new NRTIs as salvage therapy in 21 patients who failed

initial therapy with either indinavir or nelfinavir (defined by a detectable viral load after 16 weeks of therapy).[106] After 33 weeks, 71% of patients failing indinavir had viral loads of fewer than 400 copies/ml. Viral loads at the time of the switch were 4.13 and 4.25 log copies/ml among responders and nonresponders, respectively.

Twenty-one patients failing initial combination therapy with ritonavir, nelfinavir, or indinavir were changed to ritonavir-saquinavir-hgc 400-400 mg twice/day plus nevirapine 200 mg twice/day with or without NRTIs.[107] Viral load ranged from 3.55–5.90 log copies/ml. Ninety percent of patients achieved viral load suppression to fewer than 500 copies/ml for 6 months after the change in therapy.

Thirteen patients receiving regimens containing indinavir or ritonavir were changed to ritonavir-saquinavir-hgc plus nevirapine or delavirdine plus a new NRTI when they failed therapy.[108] The mean viral load at switch was 31,000 copies. After 6 months, 85% of patients taking the salvage regimen had viral loads below 400 copies/ml. Nine of 11 had viral loads below 25 copies/ml.

The combination was much less effective as salvage therapy in another study. Sixty-seven patients failing indinavir-containing regimens were treated with ritonavir-saquinavir with or without one or two NRTIs.[109] Only 8/54 and 2/34 patients had undetectable viral loads (< 500 copies/ml) at 1–2 and 5–6 months, respectively. This poor response may have been secondary to low CD4 counts (27 cells/mm^3) and high viral load (5.1 log copies/ml) at study entry. These studies suggest that ritonavir-saquinavir in combination with or without NRTIs may be an effective salvage regimen particularly when given early after virologic failure of a PI-containing regimen.

Nelfinavir-Saquinavir

In one of three studies assessing this combination, 157 PI-naïve patients (CD4 count 301 cells/mm^3, viral load 4.8 log copies/ml) received one of four regimens: saquinavir-sgc 1200 mg 3 times/day with two NRTIs; nelfinavir 750 mg 3 times/day with two NRTIs; saquinavir-sgc 800 mg 3 times/day plus nelfinavir 750 mg 3 times/day and two NRTIs; and saquinavir-sgc 800 mg 3 times/day plus nelfinavir 750 mg 3 times/day without NRTIs.[97] After 32 weeks of treatment, 70%, 55%, 83%, and 69% of patients, respectively, had viral loads below 400 copies/ml. Mean reductions in viral load at 32 weeks were 2.48, 2.23, 2.46, and 2.39 log copies/ml, respectively. Median increases in CD4 count at 32 weeks were 92, 73, 134, and 161 cells/mm^3, respectively.

Nelfinavir 750 mg 3 times/day plus saquinavir-sgc 800 mg 3 times/day was studied in 14 patients with a median baseline CD4 count of 327 cells/mm^3 and viral load of 4.60 log copies/ml.[98] After 11 months of treatment 90% (9/10) of patients had an undetectable viral load (< 500 copies/ml) with a median decrease of 2.25 log copies/ml, and median increase in CD4 count of 172 cells/mm^3.

A large study is currently under way involving 825 PI-naïve patients treated with saquinavir-sgc 1200 mg 3 times/day plus one new NRTI; saquinavir-sgc 1600 mg 3 times/day plus one new NRTI; or saquinavir-sgc 1200 mg twice/day plus nelfinavir 1250 mg twice/day and one new NRTI.[110] Eight-week results for the first 120 patients show that 62%, 65%, and 51% of patients, respectively, had viral loads below 400 copies/ml. Mean decreases in viral loads were 2.2, 2.2, and 1.9 log copies/ml, respectively. Mean increases in CD4 counts were 114, 89, and 117 cells/mm^3, respectively. Routine administration of this dual-PI combination in PI-naïve patients awaits the results of this and other studies.

The combination of nelfinavir-saquinavir was also evaluated as salvage therapy. Twenty-five patients who either failed therapy or were intolerant to PI plus NRTIs were treated with nelfinavir 1250 mg twice/day plus saquinavir-sgc 1000 mg twice/day and two NRTIs.[111] Nineteen patients with mean CD4 counts of 118 cells/mm^3 and viral loads of 4.5 log copies/ml, respectively, finished 24 weeks of treatment. The mean decrease in viral load and increase in CD4 count were 1.6 log copies/ml and 140 cells/ml, respectively. After 24 weeks,viral load was below 500 copies/ml in 45% of patients and below 40 copies/ml in 35%.

Ten patients with a viral load greater than 3.40 log copies/ml after more than 24 weeks of an indinavir-containing combination were salvaged with nelfinavir 1250 mg twice/day plus saquinavir-sgc 1200 mg twice/day plus abacavir 300 mg twice/day and an NRTI, and 10 received nelfinavir-saquinavir-sgc plus abacavir plus nevirapine 200 mg twice/day.[112] Median baseline CD4 count was 290 cells/mm^3 and viral load 4.33 log copies/ml. At 20 weeks median decreases in viral load were 0.59 and 2.67 log copies/ml,

respectively. Only one of seven patients in group 1 achieved a viral load below 50 copies/ml, compared with seven of nine in group 2. The combination of nelfinavir and saquinavir-sgc, particularly in combination with an NRTI or NNRTI, is a salvage therapy option in patients with extensive antiretroviral experience.

Indinavir-Nelfinavir

The pharmacokinetics, safety, and efficacy of indinavir 1000 mg-nelfinavir 750 mg twice/day were studied in 18 PI-naïve patients (median CD4 count 259 cells/mm^3, median viral load 4.70 log copies/ml).[113] After 24 weeks of treatment, viral load was below 400 copies/ml in 61% of patients and below 50 copies/ml in 55%. The median increase in CD4 count over 24 weeks was 133 cells/mm^3. Indinavir trough levels were not significantly different from levels from historic monotherapy trials (205 nM for combination therapy vs 251 nM for monotherapy). Nelfinavir trough levels, however, differed by a factor of 2; combination therapy levels (750 mg twice/day) were 0.7 mg/L and monotherapy levels (750 mg 3 times/day) were 1.5 mg/L. The investigators suggested that a higher nelfinavir dosage be tested, and this combination requires further study before is can be prescribed routinely in clinical practice.

Ritonavir-Nelfinavir

Twenty PI-naïve patients (median baseline CD4 count 325 cells/mm^3, viral load 4.51 log copies/ml) received ritonavir 400 mg twice/day plus nelfinavir 750 or 500 mg twice/day.[114] After 16 weeks, 4/10 patients receiving 500 mg and 6/10 receiving 750 mg had undetectable viral loads (< 400 copies/ml), with a mean decrease of 2.2 and 2.7 log copies/ml, respectively. Mean increases in CD4 counts were 202 and 37 cells/mm^3, respectively.

Indinavir-Ritonavir

Twenty-four patients were treated with indinavir 400 mg twice/day plus ritonavir 400 mg twice/day plus stavudine and lamivudine.[115] Group A consisted of 12 patients treated with ritonavir-saquinavir, stavudine, and lamivudine for more than 6 months who maintained a viral load below 400 copies/ml. Group B were treatment naïve with a mean viral load of 4.82 log copies/ml. At 36 weeks viral loads were below 400 copies/ml in all group A patients. At 12 weeks they were below 400 copies/ml in 10/12 group B patients. The authors suggested that the increase in indinavir levels in the presence of ritonavir allows for twice/day dosing of indinavir and eliminates the requirement that indinavir be taken without food. They also suggested that a lowered maximum concentration for indinavir might decrease the frequency of nephrolithiasis. Further study of this combination is required.

Summary

Clinicians who care for HIV-infected patients now have many options when selecting a PI-containing antiretroviral regimen. A patient's symptoms, the toxicity profile of an individual agent, and the likelihood of a patient adhering to a dosing schedule of 3 times/day must be taken into account. Dual-PI regimens have demonstrated efficacy and their principal indication is as second-line therapy at the present time. Adverse reactions to and metabolic complications with PIs will become more important as experience grows. Thanks to the efficacy of PIs, more attention will be paid to managing complications that occur as a result of their prolonged administration to extend the lives of HIV-infected patients.

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