Protease Inhibitors for Patients With HIV-1 Infection

A Comparative Overview

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INTRODUCTION

Currently, nine protease inhibitors (PIs) are available in the U.S.[1–9] As of October 2010, the FDA had given tentative approval to manufacturers to produce generic versions of atazanavir (Reyataz, ATV, Bristol-Myers Squibb) and lopinavir/ritonavir (Kaletra, LPV/r, Abbott). PIs are often an essential component of highly active antiretroviral (ARV) therapy (HAART) in the fight to control the progression of human immunodeficiency virus type-1 (HIV-1) infection. HAART generally refers to a combination of at least three ARV agents with activity against a particular virus. In combination with other ARV agents, PIs help to achieve the primary goals of HIV treatment, which include suppressing the viral load, reducing morbidity, maximizing survival, improving quality of life, restoring and maintaining immunological function, and preventing further disease transmission.[10]

This article compares commonly used ARV agents in the PI class, with a focus on their efficacy and safety.

INDICATIONS

With the exception of ritonavir (Norvir, RTV, Abbott) and tipranavir (Aptivus, TPV, Boehringer Ingelheim), PIs are indicated for the treatment of HIV-1 infection in combination with at least two other antiretroviral agents as initial therapy in treatment-naive patients.[1–9] Ritonavir is used exclusively in multidrug regimens containing at least three other agents and as a booster for other PIs.[7] TPV should be limited to treatment-experienced patients or patients with infection resistance to other PIs.[9] Several agents in this class are used in an off-label fashion for both occupational and non-occupational postexposure prophylaxis.[11–13]

PHARMACOLOGY

PIs competitively inhibit HIV-1 protease and have activity in both acutely and chronically HIV-infected cells. HIV-1 contains three main genes: *gag, pol,* and *env*. The *gag* and *env* genes code for the nucleocapsid and glycoproteins of the viral membrane; the *pol* gene codes for three essential enzymes (reverse transcriptase, integrase, and protease) as well as other proteins.[14] *Gag* and *pol* genes are translated as long-polypeptide-chain precursors (polyproteins); *pol* is a *gag–pol* fusion protein. *Gag* and *gag–pol* must be cleaved at specific points in order to produce functional proteins.

HIV-1 protease is responsible for the cleavage of the *gag* and *gag–pol* polyproteins into their functional constituent proteins, including the release of the protease itself from the *gag–pol* precursor.[14] This key step in the maturation process of HIV-1 occurs during the final stages of the HIV life cycle as the virion buds from host cells. Regulation of HIV protease activity in the virus-replication cycle is critical for proper assembly and maturation of HIV polyproteins to produce the infectious virus.[15] Thus, inhibition of HIV protease causes the release of immature and noninfectious particles.

PIs used for treating HIV infection are designed to tightly bind HIV protease, but they tend to be bulkier than the natural substrates.[15] Most PIs are prescribed with concomitant low-dose RTV as a boosting agent because of their pharmacokinetic properties. Except for TPV, all PIs are competitive peptidomimetic inhibitors that mimic the natural substrate of the viral protease.[15,16] These compounds contain a hydroxyethylene core that mimics the transition state intermediate formed during protease catalysis.[15,16] TPV is classified as a non-peptidomimetic PI, and it contains a dihydropyrone ring as a central scaffold. This drug is designed to stabilize binding through better interactions at key regions of the protease active site.[15]

PHARMACOKINETICS

The oral bioavailability of PIs is generally considered to be poor or variable (i.e., less than 68%). On average, the time to peak concentration (C_{max}) among agents is 3 hours (range, 1.5–6 hours), with a median half-life of approximately 6 hours. The elimination half-life ranges from 3 to 15 hours.

Except for indinavir (Crixivan, IDV, Merck), all PI agents are extensively protein-bound (i.e., more than 90%). Of all pharmacokinetic parameters, metabolic considerations surrounding PIs can be the most worrisome. This is particularly true for patients who are receiving several therapies (e.g., antifungal agents or antibiotics) for acquired immunodeficiency syndrome (AIDS)–related comorbidities and who are at risk for more than one drug interaction. PIs are inducers and substrates of multiple cytochrome P450 (CYP) isoenzymes, including CYP 3A4, CYP 2D6, CYP 2C9, and p-glycoprotein.

All PIs are eliminated predominantly by the fecal route (i.e., more than 75%) and minimally via urine (i.e., less than 15%). As a result, dose adjustments for renal dysfunction are not usually necessary.[1–9,13,17] PIs are available in a variety of dosage forms (Table 1).

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Table 1 Commercially Available Dosage Forms of Protease Inhibitors

Agent (Brand Name)	Dosage Form	Can Be Crushed	Can Be Dispersed in Liquid
Atazanavir sulfate (ATV, Reyataz)	100-, 150-, 200-, 300-mg capsule	No	No
Darunavir (DRV, Prezista)	75-, 150-, 400-, 600-mg tablet	No	No
Fosamprenavir calcium (FPV, Lexiva); succeeded Amprenavir (Agenerase)	700-mg tablet 50-mg/mL oral suspension	No	N/A: oral suspension available
Indinavir (IDV, Crixivan)	100-, 200-, 400-mg capsule	No	N/A
Lopinavir/ritonavir (LPV/RTV, Kaletra)	100/25-, 200/50-mg tablet 80/20 mg/mL oral solution	No	N/A: oral solution available
Nelfinavir mesylate (NFV, Viracept)	250-, 625-mg tablet 50 mg/g oral powder	Yes	Tablet may be dissolved in small amount of water; oral powder may be mixed with water, milk, formula, soy formula, soy milk, dietary supplements, or dairy foods
Ritonavir (RTV, Norvir)	100-mg capsule 100-mg tablet 80-mg/mL oral solution	No	Oral solution may be mixed with chocolate milk, Ensure, or Advera
Saquinavir mesylate (SQV, Invirase); Fortovase discontinued	200-mg capsule 500-mg tablet	No	No
Tipranavir (TPV, Aptivus)	250-mg capsule 100-mg/mL oral solution	No	N/A: oral solution available

N/A = not applicable.
Data from references 1–9,17.

DRUG–DRUG INTERACTIONS[1–9,17]

All PIs are strong inhibitors of CYP 3A4; thus, coadministration with CYP 3A4 substrates or other CYP 3A4 inhibitors is contraindicated, or a dosage adjustment is warranted. Many of the drug interactions that occur with PI therapy are associated with the PI's effect on CYP enzymes. Medications with interactions rated as severe and likely to warrant alternate therapy include alfuzosin (Uroxatral, Sanofi-aventis), amiodarone (Cordarone, Wyeth), dronedarone (Multaq, Sanofi-aventis), eplerenone (Inspra, Pfizer), ergot derivatives (except cabergoline), everolimus (Afinitor, Novartis; Zortress, Arup), lovastatin (Mevacor, Merck), simvastatin (Zocor, Merck), midazolam (Versed, Roche), triazolam (Halcion, Pfizer), nilotinib (Tasigna, Novartis), nisoldipine (Sular, AstraZeneca), pimozide (Orap, Gate), quinidine, ranolazine (Ranexa, Gilead), rivaroxaban (Xarelto, Bayer/Schering), romidepsin (Istodax, Gloucester), salmeterol (Advair Diskus, GlaxoSmithKline), silodosin (Rapaflo, Watson), tamsulosin (Flomax, Boehringer Ingelheim), and tolvaptan (Samsca, Otsuka America).

In addition to these drug class interactions, several PIs may cause severe interactions that warrant therapy modifications (Table 2). For example, doses of ketoconazole (Nizoral, PriCara) should be limited when used with indinavir (IDV), ritonavir (RTV), or tipranavir (TPV). When orally inhaled corticosteroids are used, beclomethasone (e.g., Beclovent, GlaxoSmithKline), flunisolide (e.g., Nasarel, Ivax), and triamcinolone (e.g., Nasacort, Sanofi-aventis) are preferred, because the other agents in the class have a Category D interaction with PIs.

Among the HMG–CoA reductase inhibitors (statins), fluvastatin (Lescol, Novartis) does not interact with any PIs. Pravastatin (Pravachol, Bristol-Myers Squibb) also lacks interactions with most commonly used PIs, except darunavir (Prezista, DRV, Tibotec). The concomitant use of DRV and pravastatin can raise pravastatin concentrations significantly.[10] Both atorvastatin (Lipitor, Pfizer) and rosuvastatin (Crestor, AstraZeneca) may be used with several PIs, but because of increases in plasma concentrations of the lipid-lowering agent, atorvastatin or rosuvastatin must be initiated at the lowest dose.[1,2,5]

PIs also interact with other ARV classes. Importantly, coadministration of the non-nucleoside reverse transcriptase inhibitor (NNRTI) delavirdine (Rescriptor, DLV, Pfizer) is contraindicated with fosamprenavir (Lexiva, FPV, GlaxoSmithKline/Vertex) because FPV antagonizes DLV metabolism and DLV antagonizes FPV metabolism, leading to a loss of virological response and potential DLV resistance.

Two other NNRTIs, nevirapine (Viramune, NVP, Boehringer Ingelheim/Roxane) and efavirenz (Sustiva, EFV, Bristol-Myers Squibb) interact with most PIs to varying degrees.[12,13]

Although studies are incomplete, the concomitant use of etravirine (Intelence, ETV, Tibotec) the newest NNRTI (approved in 2008) and unboosted PIs is not recommended, nor is the concomitant use of etravirine with ritonavir (RTV)-boosted atazanavir (ATV), FPV, or tipranavir (TPV).[18] Data regarding etravirine with ritonavir-boosted darunavir (DRV/r) or ritonavir-boosted saquinavir (Invirase, SQV, Roche/Genentech) are incomplete. In clinical studies, darunavir/ritonavir (DRV/r) plus ETV was more effective than DRV/r alone, yet the need for ETV dose adjustments with DRV/r has not been established. Plasma levels of etravirine are reduced in the presence of DRV/r.[19]

The combination of SQV/r and ETV results in lower plasma levels of SQV and ETV,[19] although the clinical significance of these reductions has not been established. By contrast, ETV and boosted lopinavir (LPV/r [Kaletra]) can be coadministered without dose adjustments.[18]

PIs also have variable effects on newer classes of ARV agents. For example, dosage adjustments are not necessary when PIs are administered to patients receiving enfuvirtide injection (Fuzeon, Roche/Trimeris), an HIV-1 fusion inhibitor, because enfuvirtide does not inhibit or induce CYP 450 enzymes.[20] Similarly, raltegravir (Isentress, Merck), an HIV integrase strand transfer inhibitor, has minimal effects on the pharmacokinetics of other agents and does not inhibit or induce CYP 450 enzymes. Other medications, including PIs, can have an insignificant effect on raltegravir levels by inhibiting uridine 5′-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase, or UGT).

Boosted or unboosted ATV therapy strongly inhibits *UGT1A1*; therefore, ATV can raise raltegravir concentrations. Although a reduction of plasma raltegravir levels was observed with tipranavir/ritonavir (TPV/r), similar safety and efficacy in phase 3 studies were achieved when raltegravir was combined with TPV/r, in contrast to other regimens. No dosage adjustments are necessary when raltegravir is given with boosted or unboosted ATV or TPV.[21]

Alternatively, dosing of maraviroc (Selzentry, Pfizer), a chemokine co-receptor type 5 (CCR5) antagonist, is highly dependent on the presence or absence of CYP 3A4 inhibitors in a given patient's HAART regimen. Maraviroc is a substrate of CYP 3A4 and p-glycoprotein; thus, coadministration with PIs (except TPV/r) warrants a dose reduction from 300 mg twice daily to 150 mg twice daily.[22] Additional recommendations for dosage adjustments are included in Table 3.

Genetic Polymorphisms

All PIs are metabolized by the CYP 3A4 isoenzyme family to some degree. Furthermore, some PI agents serve as inhibitors of this enzyme; for this reason, PI disposition is difficult to predict in persons who have genetic polymorphisms of CYP 3A4 genes.[17,23] In addition, PIs are substrates of p-glycoprotein and act as inhibitors of UGT, an enzyme involved in the glucuronidation of many drugs.

Of particular importance, atazanavir (ATV) and indinavir (IDV) inhibit bilirubin conjugation by inhibiting *UGT1A1* and, therefore, can cause unconjugated hyperbilirubinemia, especially in patients who have a *UGT1A1* polymorphism that causes lower levels of *UGT1A1* expression.[23] Polymorphisms

Table 2 Category D or X Drug Interactions

Atazanavir (Reyataz)	Buprenorphine Etravirine Indinavir Irinotecan Nevirapine Rifampin
Darunavir (Prezista)	Lopinavir Phenobarbital Phenytoin Topotecan Voriconazole
Fosamprenavir (Lexiva)	Delavirdine Etravirine
Indinavir (Crixivan)	Alprazolam Atazanavir
Lopinavir/ritonavir (Kaletra)	Darunavir Disulfiram (oral solution contains 42% alcohol) Flecainide Pitavastatin Tamoxifen Thioridazine Topotecan Voriconazole
Nelfinavir (Viracept)	Proton pump inhibitors Topotecan
Ritonavir (Norvir)	Disulfiram (oral solution contains 42% alcohol) Etravirine Flecainide Fluticasone Pitavastatin Propafenone Tamoxifen Thioridazine Topotecan Voriconazole (when used with high-dose ritonavir; when used with low-dose ritonavir, benefits should outweigh any risks)
Saquinavir (Invirase)	Darunavir Topotecan
Tipranavir (Aptivus)	Etravirine Flecainide Propafenone Tamoxifen Thioridazine

Table 3 Selected Drug Interactions With Protease Inhibitors (PIs): Dosage and Administration

Medication	Recommended Adjustment
Almotriptan (Axert)	Limit initial dose to 6.25 mg and maximum to 12.5 mg/24 hours.
Atomoxetine (Strattera)	Initiate at 0.5 mg/kg per day in patients weighing up to 70 kg and at 40 mg/day in patients weighing more than 70 kg when used with lopinavir, ritonavir, and tipranavir.
Didanosine (Videx)	Administer atazanavir two hours before or one hour after didanosine. Administer indinavir at least one hour apart from didanosine on an empty stomach. Administer didanosine one hour before or two hours after lopinavir/ritonavir oral solution. Administer tipranavir at least two hours apart from didanosine.
Efavirenz (Sustiva)	Give lopinavir/ritonavir as 500-mg/125-mg tablets or a 533-mg/133-mg solution twice daily. Once-daily dosing should not be used.
Fesoterodine (Toviaz)	Avoid doses greater than 4 mg.
Maraviroc (Selzentry)	Decrease dose to 150 mg twice daily *except* when used with darunavir and tipranavir.
Saxagliptin (Onglyza)	Limit dose to 2.5 mg/day.
Sildenafil (Viagra)	Limit to a maximum of 25 mg per 48 hours. Avoid PIs if sildenafil is used for pulmonary arterial hypertension.
Tadalafil (Cialis)	Limit to a maximum of 2.5 mg/day or 10 mg per 72 hours. Avoid PIs if tadalafil is used for pulmonary arterial hypertension.
Vardenafil (Levitra)	Limit to a maximum of 2.5 mg per 72 hours.

of apolipoproteins *(APO)*, cholesteryl ester transfer proteins *(CETP)*, and resultant adverse serum lipid effects have been studied extensively in patients who have received PIs.[13] Furthermore, polymorphisms in the *MDR1* gene are associated with increased ATV levels.[23] Table 4 outlines the currently known polymorphisms associated with PIs.

CLINICAL EFFICACY

Retrospective, Multiagent Comparative Study[24]

Mendoza et al. retrospectively evaluated patients receiving PI salvage therapy utilizing boosted saquinavir (SQV/r) 1,000 mg/100 mg twice daily, boosted indinavir (IDV/r) 800 mg/100 mg twice daily, boosted lopinavir (LPV/r) 400 mg/100 mg twice daily, boosted amprenavir (Agenerase, APV/r, GlaxoSmithKline) 600 mg/100 mg twice daily, boosted atazanavir (ATV/r) 300 mg/100 mg daily, or boosted tipranavir (TPV/r) 500 mg/200 mg twice daily. Viral load and CD4 responses along with genotype data were assessed. The results of 389 patients were evaluated. Efficacy was determined by virological response, defined as HIV–RNA reductions of more than 1 $\log_{10}$ and/or levels below 50 copies/mL. Ritonavir (RTV)-boosted ATV, TPV, and SQV demonstrated the best virological activity, but ATV/r showed the poorest results, based on intention-to-treat (ITT) and on-treatment analysis.

Atazanavir (Reyataz)[25–31]

In a study by Santoro et al., atazanavir (ATV) had good antiviral efficacy in treatment-experienced patients. Similarly, Elion et al. also found that ATV had good efficacy in ARV-naive patients. ATV can be given unboosted with successful results;[25] however, several studies have demonstrated the superiority of ATV when boosted with ritonavir (RTV) to unboosted ATV.[26,27]

Several studies have compared RTV-boosted lopinavir (LPV/r) with ATV/r; all studies demonstrated a non-inferiority between LPV/r and ATV/r.[27–29] Other studies comparing nelfinavir (Viracept, NFV, Agouron) with ATV/r have all demonstrated non-inferiority between ATV/r and NFV at doses of 400 to 600 mg daily and at 750 to 1,250 mg twice daily, respectively, in ARV-naive patients.

Swindells et al. demonstrated that simplifying treatment to ATV/r 300 mg/day from two nucleoside reverse transcriptase inhibitors (NRTIs) plus one PI was sufficient to keep HIV–RNA levels below 200 copies/mL through 24 weeks.[30] For initial HIV treatment, Squires et al. found that a HAART regimen of ATV 400 mg daily plus zidovudine (Retrovir, ZDV [azidothymidine, AZT], GlaxoSmithKline) 300 mg twice daily, plus lamivudine (Epivir, 3TC, GlaxoSmithKline) 150 mg twice daily, was equally efficacious as efavirenz (EFV) 600 mg daily plus AZT 300 mg twice daily plus 3TC 150 mg twice daily.[31]

Comment. ATV can cause elevations in indirect bilirubin that are usually asymptomatic. There are strict guidelines on the use of acid-reducing agents in patients taking ATV because of their ability to decrease ATV levels. Two dosing options are available for ATV, and both are given once daily; however, RTV boosting is required in treatment-experienced individuals.[1] As explained later (see page 342), ATV is thought to have a less negative effect on lipids than most other PIs.

Darunavir (Prezista)[32–37]

Boosted darunavir (DRV/r) has been found to have greater efficacy than comparative PIs, even when the virus is considered to be fully susceptible to these PIs.[32] Treatment-experi-

Table 4 Polymorphisms Associated With Protease Inhibitors (PIs)

Drug	Gene/Allele/Polymorphism	Reported Effect
Atazanavir (Reyataz), indinavir (Crixivan)	*UGT1A1*28*	Unconjugated hyperbilirubinemia, jaundice
Atazanavir	*MDR1*	Unconjugated hyperbilirubinemia, jaundice
Indinavir (Crixivan)	*CYP3A5*	Accelerated oral clearance
All PIs	*APOA5*	Hyperlipidemia
All PIs	*APOC3*	Hyperlipidemia
All PIs	*APOE*	Hyperlipidemia
All PIs	*ABCA1, CETP*	Hyperlipidemia

enced HIV patients have responded to DRV/r-based ARV regimens,[33] and DRV/r has led to significant reductions in viral loads compared with similar PIs in these patients.[29] DRV/r has shown non-inferiority to lopinavir/ritonavir (LPV/r)[35,36] and has resulted in lower overall virological failure rates and limited cross-resistance to other PIs when compared with LPV/r.[37] Treatment-experienced patients with no baseline DRV resistance-associated mutations achieved similar viral load reductions with DRV/r 800 mg/100 mg once daily and with DRV/r 600 mg/100 mg twice daily.[36]

Comment. DRV was originally promoted as an option for treating HIV infection that was resistant to other PIs. Although DRV is still associated with this role, it is also now a preferred initial regimen owing to its tolerability and efficacy. In both treatment-naive individuals and treatment-experienced patients with no DRV-associated resistance mutations, DRV can be taken once daily with RTV. Patients with at least one DRV-associated mutation must take DRV twice daily. DRV contains a sulfonamide moiety, but the incidence and severity of rash have been similar among patients with a sulfonamide allergy and in those with no previous sulfonamide allergy.[2]

Fosamprenavir (Lexiva)[38–43]

Hicks et al. demonstrated that ARV-naive patients maintained significantly improved viral loads and lower triglyceride levels with boosted fosamprenavir (FPV/r) 1,400 mg/100 mg daily than when they received FPV/r 1,400 mg/200 mg daily with abacavir (Ziagen, ABC, GlaxoSmithKline)/lamivudine (3TC) 600 mg daily and lamivudine 300 mg daily. At week 96, the percentages of patients with HIV–RNA levels below 400 copies/mL were 78% with FPV/r 100 mg and 53% with FPV/r 200 mg ($P = 0.026$).[38]

In a study by Smith et al., once-daily regimens of FPV/r 1,400 mg/100 mg and atazanavir/ritonavir (ATV/r) 300 mg/100 mg, in combination with 300 mg of tenofovir (Viread, TDF, Gilead) plus 200 mg of emtricitabine (Emtriva, ETC, Gilead), produced similar virological and immunological results.[39] (Gilead's Truvada comprises tenofovir plus emtricitabine.)

In another trial, Gathe et al. found FPV/r 1,400 mg/200 mg daily to be equally efficacious as nelfinavir (NFV) 1,250 mg twice daily when combined with ABC twice daily and 3TC twice daily.[40]

Molina et al. observed that twice-daily treatment with FPV/r 700 mg/100 mg, FPV/r 1,400 mg/100 mg, or FPV/LPV/RTV 1,400 mg/533 mg/133 mg produced similar virological results when combined with two NRTIs in patients who had not responded to multiple PI-based regimens.[41]

Eron et al. documented similar virological and immunological efficacy in patients receiving FPV/r 700 mg/100 mg twice daily and LPV/r 400 mg/100 mg twice daily when combined with ABC 600 mg/day plus 3TC 300 mg/day.[42]

In the Landman study, RTV-boosted dual-PI regimens were insufficient to rapidly suppress plasma HIV–RNA levels below 50 copies/mL in ARV-naive patients with a high viral load at baseline. The regimen consisted of FPV 700 mg twice daily plus ATV 300 mg daily plus RTV 100 mg twice daily or saquinavir (SQV) 1,500 mg daily plus ATV/r 300 mg/100 mg.[43]

Comment. FPV is a prodrug of amprenavir (Agenerase, APV), which was previously marketed in capsule form but came with a high pill burden. The introduction of FPV subsequently allowed for a decrease in pill burden. There are several dosing options for FPV, including once-daily and twice-daily regimens for patients new to treatment. For treatment-experienced patients, FPV should be used twice daily only along with low-dose RTV. FPV contains a sulfonamide moiety; however, its clinical effects are not clear, because the incidence of rash in patients with and without a pre-existing sulfa allergy is comparable.[3]

Indinavir (Crixivan)[44–49]

Using lower doses of indinavir with ritonavir (IDV/r) and efavirenz (EFV) may prove to be a strong and durable ARV option in patients who do not respond to NRTIs while maintaining a lower toxicity profile than conventional IDV-containing regimens.[44] Dragsted et al. showed comparable ARV effects between saquinavir/ritonavir (SQV/r) and IDV/r. At week 48, infection remained virologically suppressed in more patients receiving SQV/r than IDV/r, probably as a result of the better toxicity profile of SQV/r.[45]

Hirsh et al. demonstrated that patients benefited from the combination of IDV plus GlaxoSmithKline's Combivir—zidovudine (AZT) plus lamivudine (3TC)—compared with regimens containing IDV and AZT plus 3TC.[46] The combination of EFV/AZT/3TC has resulted in more effective reduction of HIV–RNA copies/mL than EFV/IDV or IDV/AZT/3TC regimens.[47]

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According to Staszewski et al., the combination of ABC, 3TC, and AZT (Trizivir, GlaxoSmithKline) brought about reductions in HIV–RNA copies/mL equal to those in regimens containing IDV/3TC/AZT.[48] Despite this benefit, triple-NRTI regimens are considered inappropriate and are inferior to most multiclass regimens. A four-drug regimen containing EFV plus IDV resulted in a superior virological reduction compared with a regimen containing NFV plus IDV.[49]

Comment. Patients must be counseled to drink liquids and stay adequately hydrated because of the increased risk of nephrolithiasis with the use of IDV. It is recommended that IDV be boosted with RTV, but if given at unboosted doses, IDV should be taken one hour before or two hours after a meal to increase absorption.[4] As with all other boosted regimens, IDV and RTV should be taken with food.

Lopinavir/Ritonavir (Kaletra)[50–60]

Several head-to-head comparisons of lopinavir (LPV) and other PIs have been conducted. Dragsted et al. prospectively demonstrated the superior efficacy of LPV/r over boosted saquinavir (SQV/r) in the MaxCmin2 trial.[50] This superiority was demonstrated based on an ITT analysis, but there was no difference when the per-protocol analysis was performed.[24]

De Luca et al. documented the non-inferiority of LPV/r compared with efavirenz (EFV) in double-NRTI regimens, although LPV resulted in increased adverse drug reactions.[51] Domingo et al. confirmed similar findings with a larger cohort study.[52]

In a study by Pulido et al., the long-term efficacy of LPV/r monotherapy was equivalent with that of triple therapy (LPV/r plus two NRTIs); however, larger studies are needed to confirm the findings.[53] In a more recent study, Pulido et al. observed the non-inferiority of LPV/r to triple regimens containing two NRTIs and LPV/r, although episodes of viral rebound occurred more often in the monotherapy group.[54] These findings were contradicted by Delfraissy et al., who found that LPV/r monotherapy was inferior to triple-agent LPV regimens containing lamivudine/zidovudine (AZT/3TC, Combivir) in a larger population.[55]

Other studies investigated the efficacy of various dosing regimens. The Gathe and Eron studies demonstrated the non-inferiority of once-daily dosing of LPV/r compared with twice-daily dosing.[56,57] Molina et al. confirmed these findings in a longer-term non-inferiority study that evaluated once-daily and twice-daily dosing regimens.[58]

Comparing the efficacy of LPV with nelfinavir (NFV), Walmsley et al. demonstrated the superiority of LPV in initial regimens containing 3TC and stavudine (Zerit, d4T, Bristol-Myers Squibb).[59] Murphy et al. noted the long-term efficacy of various regimens of LPV/r in treatment-naive patients.[60]

Comment. LPV is the only PI that is co-formulated with RTV, making it unnecessary to take the medications separately or to purchase two separate PIs. LPV/r was recommended as a preferred option in treatment-naive individuals until the last updated treatment guidelines in December 2009, in which LPV/r was changed to an alternative option as initial therapy.[10]

Nelfinavir (Viracept)[61]

There was no significant difference in the duration of successful therapy between a four-drug regimen and three-drug regimens in which five out of six treatment groups received nelfinavir (NFV).[61]

Comment. NFV should be taken with a meal to decrease its pharmacokinetic variability. Depending on the kilocalorie content of the food, the drug's area-under-the-curve (AUC) concentration can be increased two-fold to five-fold from the fasting state. Ritonavir is not used to boost concentrations of NFV.[6]

Ritonavir (Norvir)[62]

Bierman et al. conducted a systematic review of the available literature up to 2009 that assessed the efficacy of ritonavir (RTV)-boosted PI monotherapy. Twenty-two PI monotherapy studies were identified in peer-reviewed journals or presented at conferences. Using an ITT analysis, the investigators found that 67.9% of patients had undetectable HIV–RNA levels at the end of the follow-up period after RTV-boosted monotherapy (n = 582). In multiple randomized controlled trials, it was confirmed that HAART was superior to RTV-boosted PI monotherapy. The authors concluded that RTV-boosted PI monotherapy was inferior to HAART in overall efficacy, but the results suggested the possibility of simplifying treatment from HAART to RTV-boosted monotherapy in HAART patients with prolonged viral suppression.[62]

Comment. As a result of both poor tolerability and long-term adverse effects, RTV is not currently used at the full dose; it is only used at doses of 100 to 200 mg at a time to boost concentrations of other PIs.

Saquinavir (Invirase)[63–65]

Ananworanich et al. found that saquinavir (SQV), when given with two NRTIs, was an effective first-line HAART regimen in treatment-naive patients.[63] Marin-Niebla et al. reconfirmed this finding in their evaluation of the efficacy of low-dose SQV/r in treatment-naive patients and in those with limited PI exposure.[64] Walmsley et al. demonstrated the non-inferiority of SQV/r, compared with lopinavir (LPV/r) and observed more favorable effects on triglyceride levels with SQV/r than with LPV.[65]

Comment. Although SQV was not originally prescribed with ritonavir (RTV), current HIV treatment guidelines and the prescribing information for SQV require that it be given only with RTV to increase bioavailability and improve outcomes.[8,10]

Recent labeling changes state that SQV/r is contraindicated in patients with heart conduction abnormalities such as congenital or acquired QT prolongation or patients with atrioventricular (AV) block or at high risk of AV block. Electrocardiographic monitoring is recommended if SQV/r therapy is initiated in patients who are at risk for these conditions (i.e., patients with congestive heart failure, underlying structural heart disease, ischemic heart disease, underlying conduction abnormalities).[8]

Tipranavir (Aptivus)[66–69]

Several studies provide positive data on the efficacy of tipranavir (TPV). Performing a subanalysis of the RESIST

trials (Randomized Evaluation of Strategic Intervention in Multidrug Resistant Patients with Tipranavir), Walmsley et al. demonstrated the superiority of TPV over lopinavir (LPV).[66] In their analysis of these trials, Hicks et al. noted the similar superiority of TPV over other PIs.[67] In the Markowitz study, sustainable responses were documented with TPV in treatment-experienced patients.[68] The Gathe study compared dosing regimens of TPV in order to determine safety and efficacy.[69]

Comment. In practice, TPV/r is usually reserved for treatment-experienced patients with HIV infection that is resistant to other PIs. In addition to a warning of hepatotoxicity, the prescribing information for TPV carries a boxed warning concerning intracranial hemorrhage. TPV also contains a sulfonamide moiety, but the cross-sensitivity between the drug and sulfonamide medications is not known.[9]

SAFETY AND ADVERSE EVENTS

Common adverse events (AEs) with the protease inhibitors (PIs) include fever, diarrhea, nausea, vomiting, abdominal pain, rash, fatigue, and headache;[1–9] however, AEs vary among agents. In addition to these common effects, several metabolic changes may occur.

In a recent analysis of combined rates and reasons for switching to ARV because of intolerance or toxicity, PIs were identified as being as responsible as NNRTIs for necessitating therapy changes.[70] Regimens were changed for 14% of 3,333 patients treated in the Chelsea and Westminster HIV cohort receiving HAART, with most switches occurring after six months of initial therapy. Toxicity was the reason for the switches in 61% of these patients. Further, the observed toxicity switch rate per 1,000 patient-years between PI-based regimens and NNRTI-based regimens did not differ statistically or clinically. The switch rate for patients receiving PIs was 26.4% (95% confidence interval [CI], 18.3–37). The switch rate for patients receiving NNRTIs was 22.2% (95% CI, 13.6–34.4).

Within the PI class, no statistical or clinically significant differences were noted with respect to the observed toxicity switch rate; CIs associated with this rate for all agents overlapped:[70]

- fosamprenavir, 89.5%; 95% CI, 10.8–323.5
- saquinavir, 81.2%; 95% CI, 37.1–154
- lopinavir, 46.9%; 95% CI, 22.5–86.2
- atazanavir, 27%; 95% CI, 11.7–53.2

Notable metabolic changes associated with PIs are discussed in further detail next.

Lipid Abnormalities

Metabolic laboratory abnormalities, including total cholesterol and triglyceride elevations, are most commonly associated with lopinavir/ritonavir (LPV/r), saquinavir/ritonavir (SQV/r), tipranavir/ritonavir (TPV/r), and fosamprenavir/ritonavir (FPV/r).[1–9] Darunavir (DRV) has been associated with improved lipid effects when compared with LPV/r.

In an efficacy and safety trial comparing DRV/r 800 mg/100 mg once daily with LPV/r 400 mg/100 mg twice daily or 800 mg/200 mg once daily, total cholesterol elevations at 192 weeks were less common in DRV/r patients than in those receiving LPV/r (13% vs. 23%, respectively; $P < 0.01$). In addition, grade 2 to 4 elevations of serum triglycerides were also less frequent in subjects receiving DRV/r than in those receiving LPV/r (3% vs. 11%, respectively; $P < 0.0001$).[35]

Several investigations involving ritonavir-boosted atazanavir (ATV/r) therapy failed to demonstrate clinically significant lipid effects as seen with other ARV agents, including PIs.[29,71,72] At this time, therefore, ATV appears to have the least atherogenic profile of the available PIs.[73]

Testing for triglyceride and total cholesterol levels should be performed before PI therapy is prescribed. These values should be reviewed periodically after therapy is initiated.[3] Lipid abnormalities should be managed appropriately, keeping in mind any potential drug–drug interactions that might be present between lipid-lowering therapies (i.e., statins) and the PI being prescribed.

Pancreatitis

Marked elevation in serum triglycerides is a risk factor for the development of pancreatitis. Thus, patients receiving HAART regimens containing a PI known to increase serum triglyceride levels should be evaluated on a regular basis. Clinical signs and symptoms of pancreatitis include nausea, vomiting, and abdominal pain in conjunction with abnormal laboratory values such as increased serum lipase or amylase levels above three times the upper limit of normal (ULN). Patients with signs or symptoms that are congruent with pancreatitis should be evaluated immediately. Therapy should be discontinued upon a diagnosis of pancreatitis because fatalities resulting from PI-induced pancreatitis have been documented.[5,7]

Hepatotoxicity

Most PI agents have demonstrated relative equivalence with respect to causing hepatic injury, particularly when boosted with ritonavir (RTV). Eron et al. substituted raltegravir (Isentress) 400 mg twice daily for lopinavir (LPV/r) 400 mg/100 mg twice daily in HIV-infected patients receiving PI-based HAART in order to reduce lipid abnormalities and other adverse drug reactions (ADRs) associated with PIs. The proportion of patients experiencing grade 3 and 4 AEs did not differ significantly between groups in terms of all markers of hepatic injury, including total bilirubin and serum transaminases (ALT and AST).[74]

In general, the risk of hepatotoxicity is increased in patients with hepatic impairment or underlying hepatitis B or C viral infections. Other risk factors for hepatotoxicity (clinical hepatitis or asymptomatic elevated transaminases) include alcoholism, concomitant hepatotoxic drugs (i.e., rifampin), elevated ALT/AST levels at baseline, and underlying liver disease. Appropriate laboratory monitoring of serum transaminases is warranted when therapy is begun and periodically thereafter during PI-based HAART.[1–9,75]

Glycemic Effects

PIs are associated with a five-fold increase in the incidence of hyperglycemia, defined as one random glucose level above 200 mg/dL (incidence rate ratio, 5.0; 95% CI, 1.3–19.4). Approximately 30% of patients with new-onset hyperglycemia require treatment with glucose-lowering agents.[76] PI agents are

associated with adverse glycemic effects and an increased incidence of diabetes mellitus, a result that may require patients to begin taking oral antihyperglycemic agents, insulin, or both, or to adjust their existing diabetes therapy.[1–6] Symptoms of hyperglycemia may persist even after PI therapy is discontinued. Variations among PIs with respect to glycemic and other metabolic effects are most likely mechanistic in nature. Pathways include inhibition of insulin-stimulated glucose disposal by the glucose transporter type-4 (GLUT-4) transporter, sterol regulatory element protein processing, and adipocytokine secretion.[73]

In a study of the inhibition of the GLUT-4 transporter, amprenavir (APV), LPV/r, and RTV demonstrated more potent glucose uptake inhibition than ATV. For these reasons, the mechanistic qualities of each PI agent should be considered before a PI is prescribed; different patient regimens dictate therapeutic decisions.[73]

CONTRAINDICATIONS AND PRECAUTIONS

As a class, PIs have relatively few contraindications to their use, but several precautions should be considered. Most PIs should not be used with inducers or inhibitors of the CYP 3A4 enzyme. Safety, hepatotoxicity, and the effects on lipids and glucose must also be considered in the decision to prescribe PIs. Additional precautions include the potential for nephrolithiasis, rash, lipodystrophy, and cross-resistance between PIs.[1–9] Cardiac conduction abnormalities have been loosely associated with the use of lopinavir, nelfinavir, ritonavir, and saquinavir.[5–8]

COST AND ECONOMIC BURDEN

PIs are an integral component of combination antiretroviral (ARV) treatment for HIV infection. In 2006, the average annual cost of care for patients with the virus was nearly $20,000.[77] This figure included inpatient care, outpatient services, and medications, which make up the largest proportion of the cost incurred. This estimate might be conservative, because the statistics included patients with CD4 counts in all ranges, even patients with higher CD4 values who did not need ARV therapy.[77]

A commonly recommended PI-based regimen, darunavir/ritonavir (DRV/r) plus a nucleoside/nucleotide backbone, costs $26,287 per patient per year for medications alone.[78] Although this therapy seems expensive, PIs as a class have decreased morbidity and mortality rates since their introduction in 1995.[79] The use of ritonavir-boosted PIs in combination ARV therapy is recommended as initial treatment by the current treatment guidelines in addition to regimens based on efavirenz, a NNRTI, or raltegravir, an integrase inhibitor.[10] Although PI-based regimens may be more costly than regimens based on efavirenz and raltegravir, they have proved to be very effective and durable treatment options.

CONCLUSION

Protease inhibitors (PIs) competitively inhibit HIV-1 protease and have activity in both acutely and chronically HIV-infected cells. Multiple studies have demonstrated the efficacy of these drugs in the treatment of HIV-1 infection. Common adverse effects include fever, diarrhea, nausea, vomiting, abdominal pain, rash, fatigue, and headache.

PIs are CYP 3A4 inhibitors, and they affect the metabolism of drugs involved in the CYP 3A4 system. The use of PIs is contraindicated with drugs having extensive CYP 3A4 metabolism. Monitoring of patients who take PIs includes liver function tests, viral burden, CD4 counts, lipid panels, blood glucose assessment, and complete blood count differential.

PIs are available in capsule, tablet, oral suspension, and oral powder formulations.

Based on the efficacy, adverse-event profile, and dosing schedule for the available ARV therapies, the most recent guidelines recommend four possible regimens for initiating therapy in treatment-naive individuals. Two of these regimens are PI-based and include either ritonavir (RTV)-boosted atazanavir (ATV) or RTV-boosted DRV, although lopinavir/ritonavir (LPV/RTV) is still recommended as a first-line option in pregnant women.[10] RTV-boosted PIs are always preferred to unboosted PIs. The prescribing information for darunavir (DRV), tipranavir (TPV), and saquinavir (SQV) specifies that RTV should be given along with each PI.

After a patient has been exposed to HIV therapy, medication choices are determined based on previously and currently used ARV agents as well as the patient's response, resistance profile, and disease state. Because of the many factors involved, the treatment of HIV and selection of ARV regimens is sometimes considered as much an art as a science.

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