

Considerations in Selecting Protease Inhibitor Therapy

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Abstract

Over the past 10 years, highly active antiretroviral therapy that included a protease inhibitor has played a significant role in reducing morbidity and mortality among HIV-infected individuals. The early protease inhibitors were associated, however, with some significant limitations that posed major obstacles to their use – limited potency, difficult side effects, high regimen complexity and potential for cross-resistance. Important advances in the protease inhibitor class, including ritonavir boosting and the approval of two new protease inhibitors with the potential for once daily dosing, have led to simpler, better-tolerated protease-inhibitor therapy with the potential for improved efficacy, less toxicity and a reduced risk of the development of HIV resistance. Protease inhibitor characteristics and patient preferences should be considered in selecting the protease inhibitor that maximizes the opportunity for long-term efficacy and tolerability of highly active antiretroviral therapy. (AIDS Rev 2004;6:218-25)

Key words

Protease inhibitor. Potency. Adherence. Antiretroviral resistance. Lipodystrophy. Lipids. Hepatotoxicity.

Introduction

Protease inhibitors (PI) ushered in the era of highly active antiretroviral therapy (HAART) and have been a mainstay of antiretroviral therapy for almost 10 years. The introduction of these regimens was associated with a significant decline in HIV-related mortality¹ and studies demonstrated their potential to suppress HIV-RNA and support immunologic recovery². The early PI regimens were not easy on patients, however, and their high pill burdens, significant side effects and potential toxicities caused problems with adherence and morbidity and hindered successful treatment.

Fortunately, since their introduction significant progress has been made in improving PI potency, tolerability and toxicity. In that respect, the era of ritonavir (RTV)-boosted PIs is well upon us, with some experts

recommending that, if possible, every PI should be a boosted PI³. The choice of which boosted PI to use depends on many patient characteristics and choices, and requires thought by, and discussion between, the patient and clinician. It is quite clear, however, that like most antiretroviral (ARV) therapy, careful, thoughtful selection is likely to lead to improved patient fit, increased adherence, and improved outcomes.

Under the US Department of Health and Human Services "Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents" (DHHS Guidelines) lopinavir (Lpv)/r is the preferred boosted PI, and the placement of all of the other PIs and boosted PIs as alternative therapies is based on "48-week trial data for virologic potency, patient tolerance, and pill burden of lopinavir/ritonavir" relative to the data supporting the use of the other PIs⁴. Since there are no other trials comparing Lpv/r to a PI other than nelfinavir (NFV) in ARV-naive patients – MaxCMin²⁵ involved a mix of ARV-naive and experienced patients – this conclusion seems somewhat tenuous, especially since cross-study comparisons are rife with problems and potential errors⁶.

The USA International AIDS Society (IAS) Guidelines, which have different selection criteria than the DHHS Guidelines, list four boosted PIs (Lpv/r, saquinavir

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[SQV]/r, indinavir [IDV]/r and atazanavir [ATV]/r) as “recommended”, and two PIs (NFV and ATV) and one boosted PI (fosamprenavir [FPV]/r) as “alternative”³. The IAS Guidelines are less sanguine about Lpv/r than the DHHS Guidelines – “More data are available for lopinavir/ritonavir... than for some other recommended boosted protease inhibitor components... but it is not clear that lopinavir/ritonavir is the preferred boosted protease inhibitor” –, but the other “recommended” boosted PIs are somewhat curious. SQV/r and IDV/r are associated with relatively high pill burdens and/or significant side-effect and tolerance issues. Thus, if there are other boosted-PI options available, these agents are not commonly chosen as first-line PI therapy. On the other hand, while ATV/r is now widely used as a first-line therapy, other than a small, retrospective study⁷, there are no data currently available that support its use in ARV-naïve patients, since all of the major studies involving ATV have used the 400 mg once daily dosing without RTV boosting. This lack of data resulted in ATV/r not even being listed in the DHHS Guidelines as a potential treatment of ARV-naïve patients; however, the authors of the IAS Guidelines note that the potential efficacy and safety of ATV/r are “inferred from other studies of similar drugs”³. Finally, the listing of FOS/r as an “alternative” – behind these other choices – is also questionable given the long-term data that support its efficacy and safety in ARV-naïve patients.

The DHHS and IAS Guidelines provide some guidance regarding PI selection and should be carefully reviewed by clinicians; however, as discussed in this article, there are some gaps and questionable selections in these guidelines. Accordingly, clinicians and patients should take them to be what they are: guidelines, which do not serve as a substitute for the skill and experience of the clinician, or the important considerations patients may voice regarding ARV selection. The remainder of this article will give brief overviews of the PIs and boosted PIs in four areas that may be important in establishing the right “fit” between patient and PI: overall characteristics (including ease and convenience), potential efficacy, tolerability and toxicity, and resistance.

Overall PI characteristics

The general characteristics of the currently available PIs are shown in table 1. The data do not reflect the pharmacokinetic or other effects of RTV boosting; however, as noted below for those PIs that are significantly

impacted by RTV boosting (all but NFV), in general RTV boosting eliminates any food requirement, increases the serum half-life by increasing the elimination time, and may cause an increase in gastrointestinal-related adverse events.

In addition to these general characteristics, other important characteristics include potential simplicity and the importance of food restrictions and timing. Currently, ATV (ATV/r) is the simplest PI available regarding dosing, requiring only two³ pills per day; however, to improve ATV levels and reduce inter-patient variability it is recommended that it be taken with a meal. Close behind as far as pill burden, and with no meal requirement, is FPV (FPV/r) at four pills per day⁴ given as either four pills once daily or two pills twice daily. Lpv/r is approved for three pills twice daily, but there are some data supporting six pills once daily, and it is recommended that it be taken with a meal. The other PIs, as they are commonly dosed at present, are associated with varying pill burdens and meal restrictions: NFV (five pills twice daily with meal requirement), SQV/r (three pills twice daily, no meal restriction), and IDV/r (three pills twice daily, no meal restriction).

If the patient or clinician is seeking the simplest regimen, which may be important for optimal adherence in all patients⁸, but in particular for those with potential adherence issues, consideration should be given to pill burden, dosing frequency, and meal requirements, before the choice is made. As discussed, some regimens may be simplest in one area, but not another, and the patient should be assessed for which is most important. Furthermore, while simplicity is certainly important, potential efficacy, tolerability and toxicity and potential resistance should also be considered before the regimen is selected, since these also have a major impact on adherence and virologic success.

Potential efficacy of different PIs

As mentioned, the Abbott M98-863 trial is the only study comparing Lpv/r to another PI in ARV-naïve patients⁹. In that trial, which involved 653 patients, subjects were randomized to receive either Lpv/r or NFV along with a backbone in both arms of stavudine (d4T) and lamivudine (3TC). At the end of 60 weeks of therapy, 74 and 61%, respectively, had an HIV-RNA below 400 copies/ml ($p < 0.001$), while 64 and 52%, respectively, had an HIV-RNA below 50 copies/ml ($p = 0.002$). CD4+ cell counts rose by 247 cells/ μ l and 224 cells/ μ l, respectively. There are of course other studies that

Table 1. FDA Approved Protease Inhibitors (partially adapted from MMWR, March 17, 2002)

Generic name/ Trade Name/ Abbreviation	Food effect	Serum half-life (h)	Elimination	Storage	Common adverse events*
Amprenavir Agenerase APV	High-fat meal decreases blood concentration curve 21%; can be taken with or without food, but high-fat meal should be avoided	7.1-10.6	Cytochrome P450 (3A4 inhibitor; less than ritonavir; similar to indinavir or nelfinavir)	Room temperature	Gastrointestinal intolerance, nausea, vomiting, diarrhea; rash; oral paresthesias; transaminase elevation
Atazanavir Reyataz ATV	Levels increase with meal: -35% w/357 kcal (8.2 g fat, 10.6 g protein) -70% with 721 kcal (37.3 g fat, 29.4 protein)	7	Primarily eliminated by CYP3A	Room temperature	Increased bilirubin levels
Indinavir Crixivan IDV	Levels decrease 77% when taken with a meal; take 1 h before or 2 h after meals; may take with skim milk or low-fat meal Ritonavir-boosting eliminates meal restriction	1.5-2	P450 (3A4 inhibitor; less than ritonavir)	Room temperature	Nephrolithiasis; gastrointestinal intolerance and nausea; increased indirect bilirubinemia (inconsequential); transaminase elevation; headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia; hemolytic anemia
Lopinavir/ritonavir Kaletra LPV/r	Moderate fat meal increases blood concentration curve of capsules and solution by 48 and 80%, respectively; take with food	5-6	Cytochrome P450 (3A4 inhibitor)	Refrigerated capsules are stable until date on label expires; if stored at room temperature, stable for 2 months	Gastrointestinal intolerance, nausea, vomiting, diarrhea; asthenia; elevated transaminase enzymes
Nelfinavir Viracept NFV	Levels increase 2-3-fold; take with meal or snack	3.5-5	Cytochrome P450 (3A4 inhibitor; less than ritonavir)	Room temperature	Diarrhea; transaminase elevation
Ritonavir Norvir RTV	Levels increase 15%; take with food, which helps with tolerability possible; this might improve tolerability	3-5	Cytochrome P450 (3A4 > 2D6; potent 3A4 inhibitor)	Refrigerate capsules; capsules can be left at room temperature for < 30 days; oral solution should not be refrigerated	Gastrointestinal intolerance, nausea, vomiting, diarrhea; paresthesias (circumoral and extremities); hepatitis; pancreatitis; asthenia; taste perversion; elevated creatine phosphokinase and uric acid
Saquinavir, HGC Invirase INV	No food effect when taken with ritonavir	1-2	Cytochrome P450 (3A4 inhibitor; less than ritonavir)	Room temperature	Gastrointestinal intolerance, nausea, and diarrhea; headache; elevated transaminase
Saquinavir, SGC Fortovase FTV	Levels increase 6-fold; take with large meal	1-2	Cytochrome P450 (3A4 inhibitor; less than ritonavir)	Refrigerate or store at room temperature (< 3 months)	Gastrointestinal intolerance, nausea, diarrhea, abdominal pain, and dyspepsia; headache; elevated transaminase

*All PIs are associated with fat redistribution, hyperglycemia, a possible risk of increased bleeding episodes among patients with hemophilia and, except for atazanavir, some degree of lipid abnormalities.

indicate that Lpv/r is an effective and tolerable boosted PI; however, these studies are generally single-arm and non-comparative in nature¹⁰.

In the Bristol-Myers-Squibb (BMS) A1424-034 (034) trial, ATV (400 mg once daily) was compared to efavirenz (EFV), with a background of co-formulated zidovudine (ZDV) and 3TC. ATV performed as well as EFV; however, the outcomes were rather dismal with only 32 and 37%, respectively, achieving an HIV-RNA < 50 copies/ml at 48 weeks¹¹. Despite the explanations posited to explain these results, including the trial design and analysis (e.g. switch of any ARV or rebound equals failure), the use of a more sensitive assay to measure viral load (i.e. Roche Amplicor version 1.5), and sample handling (i.e. use of PPT vs. EDTA tubes for collection of plasma), some experts continue to take issue with the potency of ATV. In addition to the poor outcomes in the BMS-034 trial, in earlier studies the virologic outcomes achieved with ATV were in most respects similar to those of NFV¹²; and in a trial that was recently reported (BMS-043), ATV underperformed Lpv/r in PI-experienced patients¹³.

It is unfortunate that only limited data exist regarding the use of RTV-boosted ATV in ARV-naive patients, because this boosting appears to improve the pharmacokinetics and potency of ATV. While unboosted ATV significantly underperformed Lpv/r in the treatment of PI-experienced patients¹³, in a recent trial, at 96 weeks of therapy, RTV-boosted ATV appeared to be as effective as Lpv/r in three class-experienced patients, without significantly altering its lipid effects or tolerability and with only a slight increase in its primary toxicities (i.e. hyperbilirubinemia, jaundice, and icterus). However, the data are still not very encouraging for either regimen. Using an intent-to-treat, treatment response without prior failure analysis, only 30 and 33% of patients, respectively, achieved an HIV-RNA < 50 copies/ml at the end of 48 weeks of therapy¹⁴.

Unlike ATV, FPV has been studied with and without RTV boosting in ARV-naive and experienced patients, and while the data for unboosted FPV are respectable, due to the resistance advantage discussed in the resistance section below, FPV is likely to be used predominately once or twice daily with RTV boosting. Studies supporting use of FPV in ARV-naive patients include the NEAT¹⁵ and SOLO¹⁶ studies. In NEAT, using an intent-to-treat, missing or rebound equals failure analysis (ITT, M/R = F), unboosted FPV (1400 mg twice daily) outperformed NFV, with 55 vs. 41%, respectively, achieving an HIV-RNA below 50 copies/ml at 48 weeks. Further analysis of these data indicate that the most remarkable differences in FPV and NFV per-

formance occurred where potency matters most, i.e. in patients with higher baseline viral loads and lower baseline CD4 counts¹⁷. In SOLO, again using an ITT, M/R = F analysis, FPV/r (1400 mg FPV + 200 mg RTV once daily) was compared to NFV, and at the end of 48 weeks 56 and 52%, respectively, achieved an HIV-RNA below 50 copies/ml, with FPV/r again outperforming most notably in the patients with higher baseline viral loads and lower baseline CD4 counts¹⁸. Finally, recent updates regarding NEAT and SOLO indicated that the results with FPV and FPV/r regimens in these trials were durable in the patients who remained on therapy^{19,20}. At 96 weeks, in the FPV arm of NEAT and the FPV/r arm of SOLO, 85 and 86%, respectively, maintained an HIV-RNA below 50 copies/ml and CD4+ cell count increases of 255 cells/ μ l and 263 cells/ μ l, respectively. Based upon these data, FPV and FPV/r appear to be effective PI and boosted PI choices in ARV-naive patients that have some potential advantages over other boosted PIs (pill burden, flexibility of dosing including once daily administration). Important resistance data and information regarding the effectiveness of FPV/r in ARV-experienced patients are discussed below.

While this discussion has focused on the three PIs most commonly used (Lpv/r, ATV and FPV), there are also studies that indicate that SQV/r and IDV/r are relatively potent regimens^{5,21}. However, interpretation of these studies is difficult due to the diverse patient populations involved, which included individuals that were PI-naive, PI-experienced with virologic failure, and PI-experienced with PI intolerance. Further, as mentioned previously, there are obstacles to the use of these regimens, including pill burden and/or side-effect and tolerability issues.

The studies indicate that many PI regimens achieve satisfactory levels of success in ARV-naive patients. Since cross-study comparison is of very limited reliability⁶, it is difficult to say which PI would outperform in a head-to-head comparison of the available PIs. Thus, while potential efficacy should be one consideration in choosing a PI regimen, it is difficult to establish any PI as the clear choice based upon the currently available studies, and other factors, such as simplicity and tolerability to the individual patient, may be more important in predicting long-term success.

Resistance issues

While the superior virologic success rate of Lpv/r compared with that of NFV is the most important aspect of the M98-863 trial discussed above, most clini-

cians are concerned not only with the likelihood of success, but also with the consequences of failure, i.e. resistance that develops with a failing regimen. For the first time, the M98-863 trial demonstrated a significant difference in resistance development between a boosted PI (Lpv/r) and an unboosted PI (NFV)²². This difference has now been confirmed in other studies, and is an important reason for choosing a boosted PI.

In the M98-863 trial, an HIV genotype was obtained in patients with a viral load of greater than 400 copies/ml from week 24 through the end of the study. A patient was considered to have virus resistant to NFV if D30N or L90M was present or if M46I/L was present with a confirmed reduction in susceptibility; resistant to Lpv/r if any primary or active site mutation was present; resistant to d4T if thymidine associated mutations (TAMs) (including M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N) were present; and resistant to 3TC if M184V/I/T was present.

Between week 24 and the end of the study, baseline and post-rebound genotypes were available for 96 of 327 NFV-treated patients and for 51 of 326 Lpv/r-treated patients. The cumulative buildup of resistance through 108 weeks of the study is shown in table 2.

The finding in the M98-863 trial that the development of PI and nucleoside analogue resistance is lower in patients receiving a RTV-boosted PI than in those receiving a non-boosted PI has been confirmed by the comparison of FPV or FPV/r and NFV in the NEAT and SOLO trials^{15,16,23}. In these trials, the emergence of resistance was assessed using genotypic and phenotypic analyses that were performed on all patients with a confirmed viral load greater than 1000 copies/ml between week 12 and the end of the study. In the NEAT study, 249 ARV-naïve patients were treated with either FPV or NFV in combination with abacavir (ABC) and 3TC. In that study, resistance testing failed to show any significant differences between the development of resistance in the FPV and NFV arms regarding the rates of PI (24 vs. 31%, respectively; $p = 1.0$) or nucleoside analogue resistance (62 vs. 77%, respectively; $p = 0.157$). In contrast, in the SOLO study, in which 649 ARV-naïve patients were treated with FPV/r once daily or NFV in combination with ABC and 3TC, a significant difference was found between FPV/r and NFV, respectively, in rates of both PI (0 vs. 50%; $p < 0.001$) and nucleoside (13 vs. 62%; $p < 0.001$) resistance development.

Regarding ATV resistance, studies have demonstrated that in patients failing ATV as their first PI, the signature mutation is I50L. However, these studies also

Table 2. Cumulative resistance through 108 weeks in the M98-863 trial

Resistance	Nelfinavir arm	Lopinavir/ritonavir arm	P value
PI	20%	0%	< 0.001
Lamivudine	29%	7%	< 0.001
PI + lamivudine	20%	0%	< 0.001
TAMs	5%	0%	< 0.001
TAMs + lamivudine	5%	0%	< 0.001

PI: protease inhibitor; TAMs: thymidine-associated mutations.

have shown that other PI mutations may occur on failure (notably A71V) and that there are high rates of nucleoside resistance on failure¹¹. A comparison of the resistance found in virologically failing patients in the BMS-034, SOLO and M98-863 trials is shown in figure 1, and is notable for a decreased rate of PI and nucleoside resistance in the RTV-boosted PI regimens relative to the non-nucleoside reverse transcriptase inhibitor (NNRTI) or unboosted PI regimens.

Based on these resistance data, it could be argued that RTV-boosted PI regimens, with their formidable pharmacokinetic and genetic barriers, which pose significant barriers to the development of resistance, should be used preferentially over unboosted-PI regimens. While the resistance benefit of RTV-boosted PI regimens is not noted in the DHHS Guidelines, other benefits of RTV boosting are: "Low-dose ritonavir can enhance the drug exposure of other PIs, and ritonavir-boosted regimens are being used more often because of convenience in reducing pill burden, improved scheduling, and elimination of food restrictions (in the case of indinavir)"⁴. When these reasons for RTV-boosted PI regimens are taken together with the resistance data, the argument for RTV boosting of PI regimens appears strong and impressive, to say the least. Clearly more studies are needed in this area, and while RTV boosting of PIs may not be possible in some patients because of their refusal of RTV, RTV intolerance, or lipid issues, it appears that the advantages of RTV boosting are such that, if possible, all PIs should be RTV boosted.

An important resistance-related issue which PI to choose in patients who are ARV- and PI-experienced. As mentioned above, recent 96-week data in the BMS-045 trial¹⁴ indicate that, overall, ATV/r performs as well as Lpv/r in patients who are PI experienced. However, if the patient has five or more PI mutations, or three or more primary PI mutations including L90M, chances of

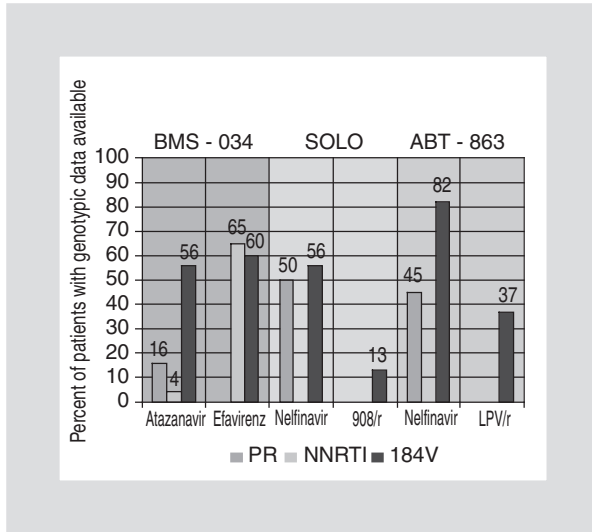


Figure 1. Comparing resistance between BMS-034, SOLO and M98-863.

virologic success may be higher with Lpv/r than ATV/r. On the other hand, while the 48-week data from the CONTEXT trial^{24,25} failed to show non-inferiority of either once or twice daily FPV/r to Lpv/r using the primary endpoint (average area under the curve minus baseline), despite higher rates of baseline PI resistance and ARV experience in the FPV/r twice daily arm, it achieved rates of HIV-RNA suppression to less than 50 copies/ml similar to those achieved with Lpv/r (46 and 50%, respectively). An analysis of the baseline resistance data failed to show that particular mutations were predictive of success with one arm more than the other; however, the presence of M46I/L or L90M reduced the chance of virologic success with either FPV/r or Lpv/r.

Taken together, these two studies indicate that three boosted PIs (Lpv/r, ATV/r and twice daily FPV/r) appear to be relatively similar in achieving an HIV-RNA below 50 copies/ml, and that use of once daily FPV/r should be avoided in PI-experienced patients. Further, the particular resistance profile of the patient should be considered when selecting the boosted PI to use, and

the presence of five or more mutations, or certain specific mutations (e.g. L90M), should affect, as demonstrated by the data cited above, the boosted PI chosen. There are few comparative data available at this time to make decisions regarding other PIs, but clearly a boosted PI is preferred in PI-experienced patients. Finally, two new protease inhibitors, tipranavir and TMC-114, should become available in the next year or so, and data indicate that these may be more effective than Lpv/r, ATV/r or FPV/r in treating patients with significant PI resistance. In patients with few treatment choices and significant PI resistance, clinicians and patients should weigh carefully the risks and benefits of using one of the currently available PIs or waiting until TPV or TMC-114 become available.

Side effects and potential toxicities

The incidence of selected side effects for each PI (with RTV boosting where applicable) is shown in table 3. From this table it is apparent that FPV and ATV, even when RTV-boosted, may offer some side-effect advantages over the other PIs, especially regarding gastrointestinal tolerance issues. It should be noted, however, that some side effects, such as hyperbilirubinemia and associated jaundice, which occur with ATV, do not occur with the other PIs.

Regarding potential toxicities, as a class the PIs are associated with risks of lipodystrophy, hepatotoxicity, lipid disturbances, and increased glucose levels. Recent data indicate, however, that some PIs may be less likely to cause these problems than others.

Up to now, the etiology of lipodystrophy remains unknown. There are numerous studies that have implicated the PIs in this process, and in particular in visceral fat accumulation. It is unclear at this point whether any of the PIs are less likely to cause lipodystrophy. However, studies are ongoing and some preliminary reports regarding Lpv/r, ATV and FPV/r indicate that some differences may exist. In the Abbott Labs M97-720 trial, after five years of therapy with Lpv/r + d4T +

Table 3. Comparison of PI (and B-PI) side effects

	SQV (+RTV)	NFV	APV/r Qd	Lpv/r	FOS (+RTV)	ATV (+RTV)
Vomiting	4.4 (6.2)	2.4	10	2.5	2 (6)	4 (0)
Nausea	17.8 (22.2)	4.6	23	6.7	5 (7)	14 (2)
Headache	8.9 (NR)	1.8	15	2.5	2 (2)	6 (NR)
Fatigue	6.7 (2.5)	3.4	5	4	2 (3)	NR
Diarrea/GI	48.9 (4.9)	20.8	38	21.7	5 (11)	1 (3)
Jaundice	0	0	0	0	0	5 (6)

3TC, 15 of the 68 (15%) patients who remained on therapy had developed lipodystrophy¹⁰. In the BMS-034 trial, after 48 weeks of treatment with ATV or EFV – in combination with ZDV and 3TC – there were no significant changes in average peripheral or visceral fat levels¹¹. Finally, in the SOLO trial, after 48 weeks of treatment with FPV/r or NFV – in combination with ABC and 3TC – there were no differences between the two arms regarding fat wasting or accumulation²⁶ and, when the rollover study (APV-30005) is considered, after 120 weeks of treatment with FPV/r, 5% of patients developed fat wasting and 19% developed fat accumulation. However, the fat accumulation that occurred tended to be modest, with a median increase of 4 kg, which may have been related to a recovery of overall health and resumption of normal weight, and this was stable and did not progress from weeks 48 through 120²⁷.

All FDA-approved PIs have been associated with elevations in serum transaminase (e.g. AST, ALT, or GGT) levels that can occur at any time during treatment. While the majority of patients with these elevations are asymptomatic, and the transaminase elevations are mild or resolve spontaneously without PI discontinuation or change, rare patients can have significant, progressive liver damage. Some of the risks for PI-associated hepatotoxicity are well known, while others are not. Some studies have indicated that severe hepatotoxicity (ALT or AST > 5 times the upper limit of normal) is more likely to occur in patients taking relatively high doses of RTV (400 to 600 mg twice daily) as a part of their HAART regimen, but that lower doses of RTV, which are commonly used to boost the other PIs, do not seem to be associated with a significant increase in the risk of hepatotoxicity relative to the other PIs²⁸.

Coinfection with hepatitis C virus (HCV) or hepatitis B virus (HBV) is reported to increase the risk for hepatotoxicity after PI initiation, and in one study, coinfecting patients treated with ATV/r had higher rates of transaminase than those treated with Lpv/r¹⁴. In some patients, this may be related to HAART-induced immune reconstitution rather than liver injury caused by the direct liver toxic effects of the PIs or hepatitis viruses. Other risk factors associated with transaminase elevations in patients receiving PI-based HAART include alcohol abuse, elevated liver enzymes at baseline, and concomitant use of other potentially hepatotoxic medications.

Hyperglycemia and new-onset diabetes mellitus have been reported in patients receiving PI-based HAART. While there are many potential causes of these problems, PI use appears strongly associated with them. While the etiology for PI-induced hyperglycemia has

not been well determined, it might result from relative insulin deficiency, peripheral and hepatic insulin resistance, or an impairment of the liver's ability to extract insulin. In several retrospective studies, hyperglycemia has been reported among 3 to 17% of patients on PI therapy. In these studies, symptoms of hyperglycemia were reported a median of approximately 60 days following the start of PI therapy. Usually, the hyperglycemia resolved when the PI therapy was discontinued, although it is not certain that it is reversible in all patients. There are some preliminary data which indicate that unlike the other PIs (in particular IDV) ATV is not associated with significant changes in insulin resistance or hyperglycemia^{29,30}.

All of the currently FDA-approved PIs, except ATV, are associated with lipid elevations including an increase in total serum cholesterol, low-density lipoprotein (LDL), and fasting triglycerides. The range of lipid changes is large, with some patients developing substantial changes while others develop little or none. In addition, each of the PIs has different lipid effects. High-dose RTV is recognized to be the most likely to cause significant lipid disturbances³¹; Lpv/r is associated with significant lipid increases, especially regarding triglycerides^{10,14}; ATV causes almost no changes in lipids – even when boosted with RTV^{11,12,14,32}; and some PIs, such as FPV, cause an increase in cholesterol that is somewhat balanced by an increase in HDL cholesterol, which results in little or no change of the total cholesterol/HDL ratio³³. It is unclear whether the increase in lipids associated with PI therapy is associated with a higher rate of cardiovascular disease; however, in studies involving other patient groups, prolonged exposure to elevated lipids has been documented to lead to increased risk of coronary artery disease (CAD). The indications for monitoring and intervention regarding hyperlipidemia are the same in HIV-infected patients as in the general population.

It is difficult to choose a particular PI based solely on the risks of side effects or adverse events; however, in some cases, certain PIs may be avoided or selected preferentially based upon risks of side effects or adverse events but, for the most part, selection of the PI most likely to be effective in the patient, followed by careful monitoring and appropriate management of problems, is the most effective strategy.

Conclusion

The selection of a PI involves many PI characteristics that should be discussed by patient and clinician prior

to starting PI-based HAART. Patient characteristics or preferences should guide the clinician in selecting the PI that maximizes the chance of full adherence and effective therapy.

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