Antiviral activity and clinical efficacy of atazanavir in HIV-1-infected patients: a review

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SUMMARY

Antiretroviral regimens based on human immunodeficiency virus-1 (HIV-1) protease inhibitors (PIs) are hampered by a number of side effects, mainly diarrhea, dyslipidemia, an increased risk of cardiovascular events and diabetes, and lipoaccumulation in the neck and abdomen. Although challenged by these potential untoward effects, PIs are still the cornerstone of highly active antiretroviral therapy (HAART) because of their potency and high genetic barrier. Atazanavir (ATV) is the first once-daily azapeptide HIV-1 PI and can be boosted by ritonavir. The efficacy of ritonavir-boosted ATV (ATV/r)-containing regimens in patients harboring drug-resistant variants is not statistically different from that of the reference PI lopinavir/ritonavir. In Italy, ATV, either boosted or unboosted, is licensed only for drug-experienced patients. However, in clinical trials ATV/r has proved to be effective in treatment-naïve HIV-1-infected individuals. There is no evidence that ATV/r-based regimens lead to the selection of mutations conferring cross-resistance to other PIs, and this drug combination has now been included among those recommended by the International AIDS Society-USA Panel and the Department of Health and Human Services (DHHS) Panel as initial treatment when a boosted-PI-based regimen is preferred to a NNRTI-based regimen.

KEY WORDS: atazanavir, atazanavir/ritonavir, HIV-1 protease inhibitor, antiretroviral therapy, HIV-1, HIV-1 resistance, once-daily regimen

INTRODUCTION

Human immunodeficiency virus-1 (HIV-1) protease inhibitors (PIs) inhibit the cleavage activity of HIV-1 protease, thus leading to the production of immature viral particles that are inca-

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pable of infecting other susceptible cells. Nine PIs are currently approved by the FDA for the treatment of HIV-1 infection: saquinavir, nelfinavir, indinavir, ritonavir, (fos)amprenavir, lopinavir (in association with a fixed low dose of ritonavir), tipranavir, atazanavir (ATV), and darunavir (TMC114), although ritonavir is no longer used at its full antiviral dose because of its side effects. However, as it is the most potent inhibitor of the CYP3A4 subunit of the P450 cytochromes, and all the other PIs are metabolized through this pathway, low-dose ritonavir can be used to boost their plasma concentrations, which may allow a reduction in the pill burden of the second PI without multiplying side effects. This strategy has also proved to be effective in increasing efficacy and limiting the occurrence of drug resistance, and so the dosing of PIs is now usually recommended in association

with a boosting dose of ritonavir (r) (The Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents, 2006; Hammer *et al.*, 2006).

Antiretroviral regimens based on PIs are still hampered by a number of side effects, mainly diarrhea, dyslipidemia, an increased risk of cardiovascular events and diabetes, and lipoaccumulation in the neck and abdomen. There have been reports linking PIs with impotence, osteopenia and osteoporosis, although the role of PIs in the pathogenesis of these conditions is less clearly established.

Despite the challenge of these potential untoward effects, PIs are still the cornerstone of HAART because of their potency and high genetic barrier (The Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents, 2006; Hammer *et al.*, 2006).

ATAZANAVIR

ATV (Reyataz™), formerly known as BMS-232632, is the first once-daily azapeptide HIV-1 PI that may offer a simpler and safer PI-based HAART as it has been associated with less hyperlipidemia and diarrhea than other drugs in the same class. Like the other PIs, ATV is a substrate of the CYP3A4 subunit of the P450 cytochromes, which means it can be boosted with ritonavir to increase plasma concentration.

Pharmacokinetics

ATV is rapidly absorbed, and peak serum concentration is reached 2.5 hours after dosing. Its bioavailability greatly depends on gastric pH and, in the presence of food, exposure measured as the area-under-the-curve (AUC) can be increased by as much as 70% in comparison with the fasting state. It should therefore be administered with food. Medications that increase gastric pH such as antacids and H2-receptor antagonists should be used with caution as directed in labeling and the use of proton pump inhibitors is contraindicated because of their potent acid reducing effect (Bristol-Myers Squibb Company, 2006; Havlir *et al.*, 2004).

ATV is 86% protein bound (Le Tiec *et al.*, 2005), and the trough plasma levels when ATV 300 mg is given in combination with ritonavir 100 mg in HIV-1-infected patients average 709 ng/mL (30- 60 times the protein binding-adjusted EC_{50}) (Agarwala *et al.*, 2003).

ATV is metabolized by the liver CYP3A4 subunit of the P450 cytochromes, which leads to the production of three metabolites (BMS-421419, BMS-551160, and the unidentified keto metabolite M41). None of these metabolites inhibits the P450 cytochrome system or has anti-HIV-1 activity. The plasma half-life of ATV is 6-7 hours for patients taking 400 mg q.d. (unboosted) with a light meal (Agarwala *et al.*, 2003). When ATV is given with a boosting dose of ritonavir, its half-life increases to approximately 11 hours, and the C_{min} and AUC are respectively 5- and 3-fold higher than when it is administrated at the dose of 400 mg q.d. (Bristol-Myers Squibb Company, 2003).

These results have recently been confirmed in a large cohort of 381 patients, 76 treated with ATV-based and 305 with ATV/r-based regimens: a 5.7-fold increase (p <0.0001) in ATV C_{min} was observed with ATV/r. Importantly, the ATV/r regimens were also associated with lower inter-individual C_{min} variability (CV = 77% vs. 119%), and an ATV C_{min} of more than the target concentration of 150 ng/mL was reached by 94% of the patients treated with ATV/r vs. 38% of those who received an unboosted regimen (p <0.0001) (Lukiana *et al.*, 2006). Similar results were observed in 12 patients enrolled in a controlled trial of 200 HIV-1-infected subjects (Agarwala *et al.*, 2006).

The primary route of elimination is biliary, with 79% of the drug being recovered in the feces, meaning that dose adjustment for renal insufficiency is unlikely to be required. In comparison with healthy subjects, a 42% increase in the AUC has been observed in patients with hepatic impairment (Bristol-Myers Squibb Company, 2003), and so a dose reduction to 300 mg q.d. without boosting should be considered in the case of patients with moderate hepatic insufficiency (Child-Pugh class B), and ATV should be avoided in patients in Child-Pugh class C (Bristol-Myers Squibb Company, 2006; Havlir *et al.*, 2004; Busti *et al.*, 2004).

In subjects with hepatic impairment ATV/r has not been studied and therefore is not recommended.

In vitro activity and susceptibility

ATV is one of the most potent drugs in its class, having a 50% effective concentration (EC_{50}) of 3-5 nM and an EC_{90} of 9-15 nM against a variety of HIV-1 isolates in different cell types. The addition of 40% human serum or 1 mg of α_1-acid glycoprotein/mL increases the EC_{50} of ATV by only 2.7-3.6 times (Robinson *et al.*, 2000). Importantly, the spectrum of activity of ATV may extend to non-B subtypes and some HIV-2 isolates (Gong *et al.*, 2006).

In vitro passages of the HIV-1 RF strain in the presence of ATV have shown that the drug selects resistant variants more slowly than nelfinavir or ritonavir. Genotype and phenotype analyses of three different HIV-1 strains (RF, BRU and NL4-3) after multiple passages in the presence of ATV indicate that an 88S substitution in viral protease appeared first during the selection process in two of them, whereas an 84V change appeared to be an important substitution in the evolution to resistance in the third strain, and the signature ATV mutation 50L was only identified in the BRU strain (Gong *et al.*, 2000).

To evaluate the cross-resistance profile of ATV, a panel of 551 clinical isolates showing a wide range of PI-resistance patterns were assayed for their susceptibility to ATV and six other PIs (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir). In general, a reduction in ATV susceptibility required several amino acid changes and was relatively moderate, and susceptibility was retained among the isolates resistant to one or two of the six other PIs. There was a clear trend toward a loss of susceptibility to ATV as the isolates showed increasing levels of cross-resistance to multiple PIs. ATV seemed to have a distinct resistance profile in relation to each of the other six PIs. There was a strong correlation between the presence of amino acid changes at specific residues (10I/V/F, 20R/M/I, 24I, 33I/F/V, 36I/L/V, 46I/L, 48V, 54V/L, 63P, 71V/T/I, 73C/S/T/A, 82A/F/S/T, 84V, and 90M) and decreased susceptibility to ATV. Although no single substitution or combination of substitutions was predictive of ATV resistance (change >3.0-fold), the presence of at least five of these substitutions correlated strongly with the loss of ATV susceptibility (Colonno *et al.*, 2003).

Antiviral activity in PI-resistant patients

Unboosted ATV showed limited antiviral activity in drug-experienced patients: virological response was associated with the number of PI mutations, while both the C_{trough} and the genotypic inhibitory quotient (GIQ, i.e. the ratio between the drug concentration and the degree

TABLE 1 - *HIV-1 mutations associated with a reduced virologic response to ATV/r.*

Authors	*Naeger et al., 2006*	*Vora et al., 2006*	*Pellegrin et al., 2006*	*Bertoli et al., 2006*
No. of patients	110	62	71	159
Definition of virologic response	<400 copies/mL HIV-1-RNA at week 48, TLOVR (ITT)	>1 log10 reduction from baseline in HIV-1-RNA at week 12	<50 copies/mL HIV-1-RNA at week 12	<50 copies/mL HIV-1-RNA between weeks 12 and 24
Mutations associated with a reduced virologic response	Any mutation at codons 30, 32, 36, 46, 47, 48, 50, 54, 71, 73, 77, 82, 84, 88, and 90*	10F/I/V, 16E, 33I/F/V, 46I/L, 60E, 84V, 85V, and 90M	10I/F/R/V, 20I/M/R, 24I, 46I/L, 54L/M/T/V, 63P, 71I/L/V/T, 73A/C/F/T, 77I, 90M and the polymorphism substitution 58E	10C/I/V, 32I, 34Q, 46I/L, 53L, 54A/M/V, 82A/F/S/T, 84V,
Proposed genotype breakpoint for response	≤4	≤1	≤4	No breakpoint proposed

* These mutations were chosen for analysis a priori, and not on the basis of a preliminary statistical analysis; ** PI mutations at codons 15, 69 and 72 were associated with a better virologic outcome

of viral resistance expressed as the number of drug resistance mutations) were not predictive of the virological outcome (Gianotti *et al.*, 2005). The mutational pattern affecting the virologic response to ATV/r is still debated. Table 1 summaries the main results of attempts to develop a clinically relevant genotypic resistance score for ATV/r in PI-experienced patients. They show that some PI mutations (e.g. 46I/L and 84V) were consistently associated with a reduced response to ATV/r in all of the studies, but the correlation between virologic outcome and the other mutations is less clear-cut: it is likely that they have different weights in determining virologic outcome, and that plasma ATV concentrations and the activity of the backbone antiretrovirals play a considerable role in virologic responses to regimens containing ATV/r. More studies using shared endpoints and larger datasets are therefore necessary to define a uniform resistance score for ATV/r. At present, it does not seem possible to state that any one of the studied algorithms is better than another.

In 71 antiretroviral-experienced, ATV-naive patients in virological failure, and subsequently treated with an ATV/r-containing regimen, the GIQ was associated with virologic outcome (p=0.04), whereas ATV concentrations alone were not (Pellegrin *et al.*, 2006).

Resistance emerging in naïve patients failing on ATV

Clinical isolates obtained from PI-naive patients designated as experiencing virologic failure while receiving ATV-containing regimens have been found to contain a unique isoleucine-to-leucine substitution at amino acid residue 50 (50L) of HIV-1 protease. Residue 50 is located in the flap region of HIV-1 protease and plays a key role in enzymatic function and PI binding. The signature ATV 50L substitution observed in all of the isolates showing phenotypic resistance to ATV emerged in a variety of different backgrounds, and was most frequently accompanied by 71V, 45R, and/or 73S; however, these isolates did not appear to accumulate additional amino acid changes very rapidly.

The viruses containing a 50L substitution were growth impaired, and showed ATV-specific resistance, with increased susceptibility (≤0.4 of the reference strain) to amprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir. Comparison of the viruses bearing 50L with those bearing 50V revealed specific resistance to ATV and amprenavir respectively, with no evidence of cross-resistance (Colonno *et al.*, 2004).

Resistance emerging in naïve patients failing on ATV/r

Virologic failure on ATV/r in treatment-naïve subjects was characterized in the AI424-089 study. Virologic failure at week 48 occurred in 3/95 individuals randomized to ATV/r and 10/105 randomized to unboosted ATV, and paired genotypes and phenotypes were available in two and eight patients respectively. No new PI-related mutations were detected in the former group, whereas the ATV-specific 50L mutation (often associated with the 71V mutation) was selected in three of the patients in the latter group. Thymidine analogue mutations (TAMs) were not selected in any of the patients, and the 184V mutation was detected in more patients failing on unboosted ATV (7 vs. 1) (McGrath *et al.*, 2006).

These results are consistent with a very high genetic barrier of boosted PIs (i.e. no new PI-related mutation selected at failure of the initial regimen) and the notion that boosted PIs protect against the selection of the 184V mutation in treatment-naïve patients when lamivudine is part of the initial regimen (Kempf *et al.*, 2004; MacManus *et al.*, 2004; Eron *et al.*, 2006).

CLINICAL EFFICACY

Atazanavir in naïve subjects

Three studies compared unboosted atazanavir 400 mg QD to either nelfinavir (BMS-007 and BMS-008 trials) or efavirenz (BMS-034 trial) in treatment-naïve patients. The BMS-007 trial (Sanne *et al.*, 2003) was a phase-2 dose-finding trial on 420 patients, which compared different doses of unboosted atazanavir to nelfinavir, each in combination with stavudine and didanosine, showing similar virological and immunological efficacy over 48 weeks.

In the BMS-008 trial (Murphy *et al.*, 2003) 467 patients were randomized to receive either atazanavir 400 mg or 600 mg or nelfinavir 1250 mg BID, with an NRTI backbone of stavudine and
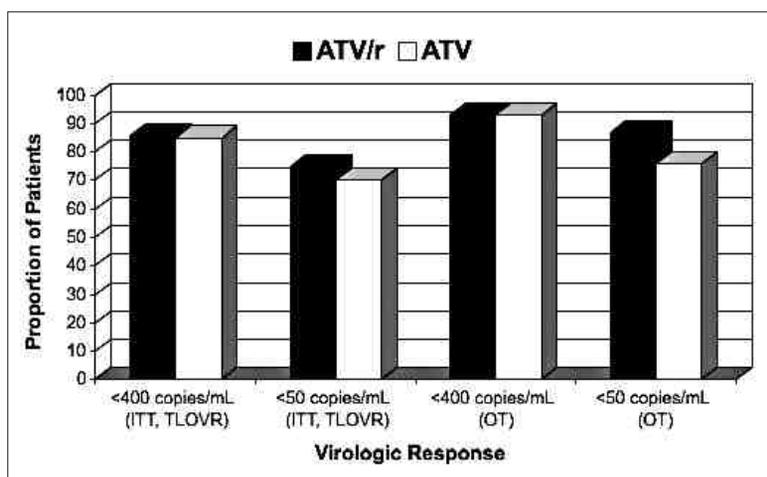
FIGURE 1 - Proportion of treatment-naïve HIV-1-infected patients with less than 400 and 50 copies/mL HIV-1-RNA 48 weeks after starting ATV/r (■) or ATV (□) in combination with lamivudine and stavudine. Number of patients by ITT analysis: ATV/r = 95, ATV = 105; number of patients by OT analysis: ATV/r = 84, ATV = 94.

lamivudine. After 48 weeks, the proportion of patients with viral load below 400 and 50 copies per milliliter was not statistically different between the three arms. Similar results were seen when atazanavir was compared head-to-head with efavirenz in a double-blind trial involving 810 patients (Squires *et al*., 2004): after 48 weeks, the two arms, both with a backbone of zidovudine and lamivudine, achieved nearly the same proportion of patients with viral load <400 copies/mL or <50 copies/mL. The unexpected low proportion of patients with viral load <50 copies/mL in boths arms (32% in atazanavir group and 37% in efavirenz group) has probably been due to technical problems of tubes where samples for ultrasensitive HIV-1 RNA determination were collected. The performance of unboosted atazanavir in this trial was similar to what was considered the standard of care for naïve patients, i.e. efavirenz.

Boosted atazanavir has risen in the treatment guidelines (Hammer *et al*., 2006; The Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents, 2006) to be listed as one of the preferred options with other boosted PIs, but this is mostly based on clinical experience and general principles, because the amount of actual data is limited.

The only study since presented is the BMS-089 trial (Malan *et al*., 2006) which randomized 200 naïve patients to receive either atazanavir 400 mg or atazanavir 300 mg, boosted with 100 mg of ritonavir, both in combination with lamivudine

and extended release formulation of stavudine. At 48 weeks, by intent-to-treat analysis, 75% and 70% of the patients in the ritonavir-boosted and unboosted arms respectively, had viral load reduced to <50 copies/mL (difference, 5.0; 95% CI -7.0, 17.0). CD4 increases were +189 and +224 cells/mm^3 (difference -21.1; 95% CI -48.9, 6.6) (Figure 1). The numbers are very small, but 10% of the atazanavir group versus 3% of the atazanavir/ ritonavir group experienced virologic failure.

More data on comparison between boosted atazanavir and other boosted PIs are awaited. Of great interest is the ongoing AI424-138 trial which compares boosted atazanavir with boosted lopinavir in naïve patients, both with a backbone of co-formulated tenofovir and emtricitabine. Results of this trial could be crucial to strengthen the evidence that boosted atazanavir is as valid an option as boosted PI for first line regimen, thus accelerating approval in Europe for naïve patients. However, atazanavir/ritonavir option is rated AIII in the last updated version of DHHS guidelines on antiretroviral therapy (The Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents, 2006), and BIII in the guidelines edited by International AIDS Society (IAS) (Hammer *et al*., 2006).

Atazanavir in treatment-experienced subjects
Atazanavir in treatment-experienced patients has been evaluated either unboosted or boosted with low-dose ritonavir.

TABLE 2 - *Summary of randomized clinical trials in naïve and experienced patients, with main efficacy endopoint outcome.*

Study	Regimens	No. of randomized patients	Efficacy end-point at week 48 (ITT)	
BMS-007	ddI-d4T-ATV vs ddI-d4T-NFV	420	% of pts with VL < 400 % of pts with VL < 50	64% vs 56% 36% vs 39%
BMS-008	d4T-3TC-ATV vs d4T-3TC-NFV	467	% of pts with VL < 400 % of pts with VL < 50	64% vs 53% 35% vs 34%
BMS-034	ZDV-3TC-ATV vs ZDV-3TC-EFV	810	% of pts with VL < 400 % of pts with VL < 50	70% vs 64% 32% vs 37%
BMS-089	d4TXR-3TC-ATV vs d4TXR-3TC-ATV/r	200	% of pts with VL < 400 % of pts with VL < 50	85% vs 86% 70% vs 75%
BMS-043	2 NRTIs + ATV vs 2 NRTIs + LPV/r	300	reduction in log HIV-1-RNA	-1.59 vs -2.02
BMS-045	TDF-NRTI-ATV/r vs TDF-NRTI-LPV/r	358	reduction in log HIV-1-RNA (at week 96)	-2.29 vs -2.08

(ddI = didanosine, d4T = stavudine, ATV = atazanavir, NFV = nelfinavir, 3TC = lamivudine, ZDV = zidovudine, d4TXR = extended release stavudine, ATV/r = atazanavir boosted with low-dose ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, LPV/r = lopinavir boosted with low-dose ritonavir, ITT = intent-to-treat, VL = viral load).

The BMS-043 study (Cohen *et al.*, 2005) was a randomized, open trial to compare unboosted atazanavir to lopinavir/ritonavir in patients with prior PI failure, and included 300 subjects. Patients received a genotype and phenotype before randomization. Tenofovir was not admitted in the backbone regimen, because it is known that it can reduce atazanavir concentration if this is not boosted with ritonavir. The trial was stopped after 24 weeks because of a reduced efficacy of atazanavir with respect to lopinavir/ritonavir in intent-to-treat analysis (proportion of patients with viral load <400 copies/mL: 59% and 77%, respectively, P <0.05; proportion of patients with viral load <50 copies/mL: 38% and 54% respectively, P < 0.05). A post-hoc analysis showed that decrease in HIV-1-RNA was comparable between regimens in patients without NRTI mutations at baseline.

The BMS-045 study (Johnson *et al.*, 2006) actually compared three arms: boosted lopinavir, boosted atazanavir and atazanavir/saquinavir, because atazanavir boosts saquinavir levels. The primary efficacy measure was originally defined as the time-averaged difference (TAD) in the reduction in HIV-1-RNA at week 48 but, as an interim analysis at week 24 indicated that the efficacy of ATV/SQV was inferior to LPV/r, and that of ATV/r was not inferior to LPV/r, an amendment gave the patients the opportunity to change therapy and the study was extended through 96 weeks.

The time-averaged difference (TAD) in reduction in HIV-1-RNA at week 96 demonstrated the non-inferiority of boosted atazanavir with respect to boosted lopinavir, with a mean change from baseline in HIV-1-RNA of -2.29 and -2.08 $\log_{10}$ copies/mL, respectively [TAD (95% confidence interval): 0.14 $\log_{10}$ copies/mL (-0.13, 0.41)]. By intent-to-treat (ITT) analysis (non completer = failure), using the time to loss of virologic response (TLOVR) algorithm as definition of virologic response, the proportion of patients with less than 400 and 50 copies/mL at week 96 in the ATV/r arm was 44% and 33%, respectively. By the same analysis, the proportion of patients with less than 400 and 50 copies/mL at week 96 in the LPV/r arm was 46% and 36%, respectively, with no statistical difference between arms. No between-arms statistically significant difference was also observed in CD4+ T-lymphocyte changes from baseline. Baseline number of PI mutations appeared to influence viral response in both arms.

Other experiences with boosted atazanavir in treatment-experienced populations yielded similar results. Short-term virologic efficacy of a boosted atazanavir-based regimen was seen in 64 patients switched to boosted atazanavir after virologic failure, with a decrease at 3 months of >1 $\log_{10}$ HIV-1-RNA plasma level in 82% of the subjects and a HIV-1-RNA plasma level of <50 copies/mL in 56% of the subjects (Vora *et al.*, 2006). Similar results have been obtained in another cohort of 73 individuals: 73% of subjects achieved >1 $\log_{10}$ reduction in viral load from baseline to week 12, while 49% achieved a viral load below the limit of quantification (Pellegrin *et al.*, 2006).

Despite the good performance of boosted atazanavir-based regimen in short and long-term treatment of experienced patients, its efficacy is limited in more heavily pretreated patients. In the ANRS 107 trial (Piketty *et al.*, 2006), boosted atazanavir was used in a cohort of 53 HIV-1 infected patients who were failing their current HAART. Patients were highly experienced, with multiple previous failures. The median number of PI mutations (primary and secondary) was 8, ranging from 1 to 15. In this background condition, the new treatment with boosted atazanavir, combined with tenofovir and another NRTI, achieved only a median decrease of 0.2 $\log_{10}$ HIV-1-RNA from baseline to week 26.

A similar experience, but with different outcome, has been conducted in Spain (Dronda *et al.*, 2006) where a prospective study of 56 patients who introduced atazanavir/ritonavir as a rescue therapy showed the achievement of undetectability of viral load for nearly half of the patients at month 12. The better outcome could be ascribed to the lower degree of PI resistance (median number of PI mutation at baseline: 5), although comparison between two different prospective studies lacks statistical significance.

With this body of evidence it can be concluded that in treatment-experienced patients a salvage therapy based on boosted atazanavir could be a valuable option, except in heavily-pretreated patients with a high burden of PI mutations.

Atazanavir as maintenance therapy

The long-term adverse effects, expense, and difficulty of adherence to antiretroviral regimens have led to studies of simpler maintenance therapies. After promising results coming from pilot studies of maintenance therapy with a single boosted PI (Arribas *et al.*, 2005), atazanavir boosted with low-dose ritonavir was tested in a prospective pilot open-label trial as a simplified maintenance regimen after sustained virologic suppression (Swindells *et al.*, 2006). The primary endpoint of the ACTG 5201 trial was the risk of virologic failure in the first 24 weeks after simplification. Three out of 34 patients had virologic breakthrough at weeks 12, 14 and 20. Genotyping of plasma samples from the 3 patients experiencing virologic failure did not identify drug resistance mutations in protease. Of the three participants experiencing virologic failure, one continued taking atazanavir/ritonavir alone and the plasma HIV-1-RNA resuppressed to below 50 copies/mL by week 20. The other two resumed a triple combination therapy and had a plasma RNA level of below 50 copies/mL at week 32 and 41 respectively. Moreover, a correlation between virologic failure and low level of atazanavir concentration was documented in the three patients. Hence a poor adherence to treatment could have determined the virologic breakthrough. Although preliminary and based on a small number of patients, these data make atazanavir/ritonavir a good candidate for maintenance therapy, and warrant larger randomized clinical trials to fully address this issue.

Another induction-maintenance strategy is currently tested in a still ongoing clinical trial whose preliminary results are awaited soon: the AI424-136 or INDUMA trial compares 48 weeks of boosted versus unboosted atazanavir-based therapy, after an induction phase of 24 weeks with boosted atazanavir-based treatment and the achievement of 2 consecutive viral loads below 50 copies/mL. If the objective of non-inferiority of unboosted atazanavir is achieved, this induction-maintenance strategy could be used in naïve patients to spare PI-related metabolic toxicity without compromising long-term virologic efficacy.

CONCLUDING REMARKS

Eight PIs are currently approved in Italy for the treatment of HIV-1 infection: saquinavir, nelfi-

navir, indinavir, ritonavir, (fos)amprenavir, lopinavir (in association with a fixed dose of ritonavir), tipranavir, and ATV, although ritonavir is no longer used at its full antiviral dose because of its side effects. Current guidelines recommend that either efavirenz or a boosted PI is included in the first-line regimens because of their high efficacy, and different boosted PIs can be effectively used to treat drug-experienced individuals; their relative potency in this setting depends on the degree of baseline HIV-1 resistance.

ATV/r is a relatively simple alternative to other boosted PIs in treatment-naïve and treatment-experienced HIV-1-infected patients, as it has proved to be effective in both. Its pharmacokinetics allows once-daily dosing, and ATV shows a unique resistance profile.

Virological failure on an ATV-based regimen does not appear to be associated with the development of multi-drug resistant variants. In treatment-experienced patients, ATV/r was not inferior to LPV/r when baseline PI mutations were less than five.

No head-to-head comparison with other boosted PIs has been performed. Common untoward effects of boosted PIs are diarrhea and increased serum lipid levels. ATV/r is generally well tolerated; jaundice and scleral icterus are its main side effects, and are more common among subjects treated with ATV/r than in those receiving ATV or LPV/r; however, they seldom lead to treatment discontinuation. In treatment-experienced patients, lipid changes and diarrhea have been observed less frequently with ATV/r-containing regimens than with LPV/r-containing regimens.

Future clinical trials should address other outstanding issues, including the efficacy of ATV/r-containing regimens in comparison with efavirenz and other boosted PIs in treatment-naïve patients, the long-term safety of high indirect bilirubin levels, the incidence of morphological alterations, safety of the regimens during pregnancy, and their efficacy and safety in HIV-1-infected children.

Finally, ongoing studies are investigating whether either maintenance with unboosted ATV after an "induction" phase of ATV/r or ATV/r monotherapy can reduce side effects without jeopardizing virologic response.

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