

Viro-Immunologic Response to Ritonavir-Boosted or Unboosted Atazanavir in a Large Cohort of Multiply Treated Patients: The CARE Study

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ABSTRACT

Currently, comparative data able to define the potency of boosted versus unboosted atazanavir in highly pretreated HIV-infected patients are limited. Specifically, in clinical practice it is very important to establish whether atazanavir-boosting with ritonavir warrants potency and efficacy that overcome the profile of unboosted drug. For this reason, our goal was to evaluate viro-immunologic determinants of response to atazanavir, in unboosted ATV400 or boosted ATV300/r formulation, from baseline to week 48 in highly pretreated HIV-infected patients enrolled in a prospective observational Italian study. Data from 354 patients included in an atazanavir "Early Access Program" (AI424-900) with baseline viremia 500 copies per milliliter or more and with an available virologic follow-up were examined using as-treated analysis. Of these, 200 (56.5%) and 154 (43.5%), respectively, received regimens containing ATV300/r or ATV400. Virologic success (VS) was defined as reaching viremia of less than 500 copies per milliliter during follow-up. Estimated median time to VS was 8 weeks in the ATV300/r group and 13 weeks in the ATV400 group. Proportion of patients achieving VS was higher in the ATV300/r group than in ATV400 group at week 12 (66% versus 47%), as well as at week 48 (86% versus 64%). At multivariate Cox regression, receiving ATV300/r dosing was independently associated with increased probability of achieving VS [adjusted hazard ratio (AHR): 1.57; 95% confidence interval (CI): 1.19–2.06]. Conversely, CDC stage C, higher base-

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line viral load, and more experience with protease inhibitors (PIs) were associated with poorer virologic response. In an unselected population of highly pretreated HIV-infected individuals, receiving atazanavir as part of antiretroviral regimen results in effective virologic response and immunologic recovery. The antiviral efficacy of atazanavir is greater when boosted with low-dose ritonavir.

INTRODUCTION

THE ACHIEVEMENT OF long-term viral suppression and immunological recovery in HIV-1-infected patients starting highly active antiretroviral therapy (HAART) is dependent on many factors, including drug potency, safety, adherence, and plasma concentrations of antiretroviral drugs.¹⁻⁵ Ritonavir (RTV) boosting of protease inhibitors (PIs), results in higher plasma concentration of most of these drugs.⁶ This is due to inhibition of the P450CYP3A4 enzyme system in the intestine and liver and, possibly, to the inhibition of P-glycoprotein efflux.^{7,8} Other benefits of RTV boosting are a reduction in the number of daily doses, fewer restrictions on food intake, and a lower pill burden, which is associated with better adherence. These factors have been found associated with a better treatment outcome, an increased antiviral efficacy and a potentially reduction of resistance.⁹⁻¹¹

However, regimens containing boosted PIs may still be associated with metabolic abnormalities such as elevations of serum lipids, and potential risk for cardiovascular disease.¹²

Atazanavir (ATV), a highly selective PI, seems to overcome some of the above mentioned limitations of many other HIV PIs. This drug has favourable clinical profile, including once-daily administration, and the possible combination of this drug with other antiretroviral agents either boosted or unboosted by RTV.^{13,14}

Several studies, mainly clinical trials, were performed to comparing the efficacy of ATV (unboosted or boosted) to that of other antiretrovirals in drug-naïve patients, patients with multiple virologic failures, and those switching to ATV from other PI-based regimens.^{15-20,22,24}

Despite these studies focused on ATV, until today, comparative data able to define efficacy of boosted versus unboosted ATV are limited.^{21,23,25} Moreover, in clinical practice it is

very important to establish whether the ATV boosting with RTV warrants potency and efficacy that overcome the better safety profile of unboosted drug. For all these reasons, we reputed useful to analyze a fairly robust data set from a national trial network with real-world patients using data outside clinical trials; and so, in the present prospective observational cohort study, we compared probability and determinants of virologic response to ATV400 versus ATV300/r during 48 weeks of follow-up in an extended cohort of highly pretreated HIV-infected patients.

MATERIALS AND METHODS

Study population

This study was an observational prospective study that evaluated clinical performance data from a cohort of 511 highly pretreated HIV-infected patients previously exposed to PIs and treated with ATV through an "Expanded Access Program" (AI424-900). To be considered eligible for the analysis, patients had to have at least another study measurement during follow-up other than baseline values.

The analysis was conducted on all 354 consecutive patients, recruited from 13 Italian clinical centers, with baseline HIV-RNA levels of 500 copies per milliliter or more who had received at least one dose of ATV300/r or ATV400 administered as part of a HAART regimen. The selected patients started the ATV-containing regimen between November 2002 and December 2004. The NRTI basis was chosen by the investigators, based on clinical or virologic criteria. Medical visits were performed at baseline and at weeks 4, 8, 12, 24, 36, 48, and included patient history evaluation, physical examination and blood analysis. Plasma HIV-RNA and CD4 cell count were measured according with standard clinical follow-up. For

patients who discontinued ATV before 48 weeks, data were censored at time of drug interruption.

Efficacy analysis

The primary end point was to determine time to virologic success (VS) according with exposure to different ATV drug dosing. VS was defined as reaching viral load below 500 copies per milliliter during follow-up. Secondary end points included the proportion of patients with plasma HIV-RNA levels less than 500 copies per milliliter and less than 50 copies per milliliter at week 48 (as-treated analysis), the median changes in plasma HIV-RNA levels from baseline through week 48, and the median changes in CD4 cell count from baseline through week 48.

Statistical analyses

The following baseline characteristics were considered in all statistical analyses: gender, age, HIV transmission, Centers for Disease Control (CDC) stage, time from the first detection of HIV infection, CD4 cell count, HIV-RNA levels, antiretrovirals (ARVs) previously used (in terms of single drug exposure, total number of drugs, number of drugs for each class, total numbers of previous regimens), ATV dose, drugs administered with ATV (as single drugs or drug classes) and drugs administered with ATV never used before starting ATV-containing regimen (as single drugs, and as drug classes). Pearson χ^2 , or Fisher's exact test (for categorical variables), and Mann-Whitney test (for continuous variables) were used, when appropriate, to compare ATV300/r and ATV400 groups.

Kaplan-Meier method and Cox proportional hazards model were used to estimate the probability of VS and the predictive value of all main baseline variables when fitted as time-fixed covariates. Wilcoxon test was used to compare the change from baseline to week 48 both in CD4 cell count and HIV-RNA levels within both groups. In all analyses, p values < 0.05 were considered as statistically significant. All statistical analyses were performed by SPSS for Windows (version 11.0.1, SPSS, Chicago, IL).

RESULTS

Patient characteristics

Among the 354 patients eligible for this study, 200 (56.5%) and 154 (43.5%) respectively, were treated with regimens containing ATV300/r or ATV400. Baseline characteristics of 354 patients analyzed are described in Table 1. The study population was predominantly male (65.3%), and had a median age of 41 years; 137 (38.7%) patients were in CDC stage C. The median baseline HIV-RNA level was comparable in patients taking ATV300/r (4.5 log₁₀ copies per milliliter, interquartile range [IQR]: 3.9–5.1) and ATV400 (4.7 log₁₀ copies per milliliter, IQR: 4–5.1) ($p = 0.305$). The two groups differed for median CD4 cell count (ATV300/r group: 253 cells/ μ l; ATV400 group: 230, $p = 0.012$), CDC C stage (ATV300/r group: 34.5%; ATV400 group: 44.1%, $p = 0.050$), median number of ARVs previously used (ATV300/r group: 7; ATV400 group: 9, $p < 0.001$), and drugs previously received (Table 1). Two hundred three patients (57.3%) started the ATV-containing regimen in combination with at least one antiretroviral never used previously (158, 43, and 2 patients with one, 2, and 3 new drugs, respectively). In term of class, 132 patients started a new NRTI, 12 a new PI, 5 a new NNRTI, and 9 the enfuvirtide. The new NRTI more representative was tenofovir (104 patients).

Regarding the NRTIs administered in combination with ATV, 239 patients (67.5%) received tenofovir, 214 (60.5%) lamivudine, 127 (35.9%) didanosine, 53 (15%) stavudine, 43 (12.1%) zidovudine, 24 (6.8%) abacavir, 1 (0.3%) zalcitabine. Tenofovir was mostly administered in patients taking ATV300/r than in those taking ATV400 (80.5% versus 50.6%, $p < 0.001$). NRTI combinations more frequently used with ATV were tenofovir plus lamivudine in 138 (39%) patients, and tenofovir plus didanosine in 72 (20.3%) patients. Thirteen (6.5%) patients received another PI in combination with ATV300/r, and 24 (15.6%) with ATV400 ($p = 0.006$). Nine (4.5%) patients received an NNRTI with ATV300/r, and 10 (6.5%) with ATV400 (13 in total with efavirenz, and 6 with nevirapine). Regarding PIs, 21 (5.9%) patients received

TABLE 1. BASELINE PATIENT CHARACTERISTICS

Characteristics	Overall (354 pts)	ATV300/r (200 pts)	ATV400 (154 pts)	p ^a
Men, n (%)	231 (65.3)	132 (66.0)	99 (64.3)	0.737
Age (years), median (IQR)	41 (37.5–46)	41 (38–46)	41 (37–45.5)	0.636
Risk factor, n (%):				
Drug addiction	110 (31.1)	68 (34.0)	42 (27.3)	0.002
Sexual	166 (46.9)	78 (39.0)	88 (57.1)	
Other/unknown	78 (22.0)	54 (27.0)	24 (15.6)	
CDC stage C, n (%)	137 (38.7)	69 (34.5)	68 (44.1)	0.050
Seropositivity (years), median (IQR)	11.3 (7.8–5.7)	11.2 (7.4–16.4)	11.4 (8.2–15.2)	0.834
Coinfection, n (%):				
HBV+	23 (6.5)	15 (7.5)	8 (5.2)	0.400
HCV+	145 (41.0)	94 (47.0)	51 (33.1)	0.015
Viremia (log ₁₀ copies/mL), median (IQR)	4.85 (3.97–5.14)	4.54 (3.91–5.14)	4.67 (4.04–5.16)	0.365
CD4 (cells/ μ L), median (IQR)	239 (121–356)	253 (136–419)	230 (106–309)	0.012
Previous treatment, median (IQR):				
No. of regimens	6 (4–10)	5 (3–8)	8 (6–11)	< 0.001
No. of antiretroviral drugs	8 (6–10)	7 (5–10)	9 (7–11)	< 0.001
No. of PIs used	2 (1–4)	2 (1–3)	3 (2–4)	< 0.001
No. of NRTIs used	5 (4–6)	4 (3–6)	5 (4–6)	0.019
No. of NNRTIs used	1 (1–1)	1 (1–1)	1 (1–2)	0.114
No. of patients with > 2 ARVs in combination with ATV or ATV/r, (%)	57 (16.1)	19 (9.5)	38 (24.7)	< 0.001
No. of patients previously treated with, (%):				
3TC	332 (93.8)	191 (95.5)	141 (91.6)	0.188
AZT	312 (88.1)	177 (88.5)	135 (87.7)	0.939
d4T	273 (77.1)	152 (76.0)	121 (78.6)	0.493
DDI	267 (75.4)	146 (73.0)	121 (78.6)	0.187
TDF	169 (47.7)	96 (48.0)	73 (47.4)	0.957
ABC	163 (46.0)	73 (36.5)	90 (58.4)	< 0.001
DDC	90 (25.4)	44 (22.0)	46 (30.0)	0.085
EFV	192 (54.2)	101 (50.5)	91 (59.0)	0.093
NVP	167 (47.2)	93 (46.5)	74 (48.0)	0.728
LPV	204 (57.6)	103 (51.5)	101 (65.6)	0.006
IDV	196 (55.4)	96 (48.0)	100 (64.9)	0.002
NFV	160 (45.2)	78 (39.0)	82 (53.2)	0.006
SQV	152 (42.9)	75 (37.5)	77 (50.0)	0.016
APV	41 (11.6)	14 (7.0)	27 (17.5)	0.002
T20	16 (4.5)	7 (3.5)	9 (5.8)	0.424

^aIn bold are indicated statistically significant differences in demographic, immunologic, virologic, and therapeutic parameters between patients treated with ATV300/r and ATV400.

Pts, Patients; ATV300/r, Atazanavir 300 mg (ritonavir-boosted); ATV400, ATV 400 mg (unboosted); IQR, interquartile range; PIs, protease inhibitors; NRTIs, nucleoside reverse transcriptase-inhibitors; NNRTIs, non-NRTIs; 3TC, lamivudine; AZT, zidovudine; d4T, stavudine; DDI, didanosine; TDF, tenofovir; ABC, abacavir; DDC, zalcitabine; EFV, efavirenz; NVP, nevirapine; LPV, lopinavir; IDV, indinavir; NFV, nelfinavir; SQV, saquinavir; APV, amprenavir; T20, enfuvirtide.

saquinavir (8 in combination with ATV300/r, 13 with ATV400, $p = 0.079$), 11 (3.1%) amprenavir (1 in combination with ATV300/r, 10 with ATV400, $p = 0.001$), 5 (1.4%) lopinavir (4 in combination with ATV300/r, 1 with ATV400, $p = 0.286$). One patient received ATV300/r in combination with another PI (lopinavir/RTV) and one NNRTI (nevirapine). Finally, 16 (4.5%) patients received enfuvirtide (7 in combination with ATV300/r, 9 with ATV400, $p = 0.293$).

Time to VS and predictors analysis

The probability of achieving VS estimated by Kaplan-Meier method significantly differed between ATV dose groups (Fig. 1); in particular, the 12-week probability of VS was higher in the ATV300/r group (66% versus 47%) and remained so at week 48 (86% versus 64%). The estimated median time to VS was 8 weeks for ATV300/r group and 13 weeks for ATV400 group ($p < 0.001$ at the log rank test) (Fig. 1).

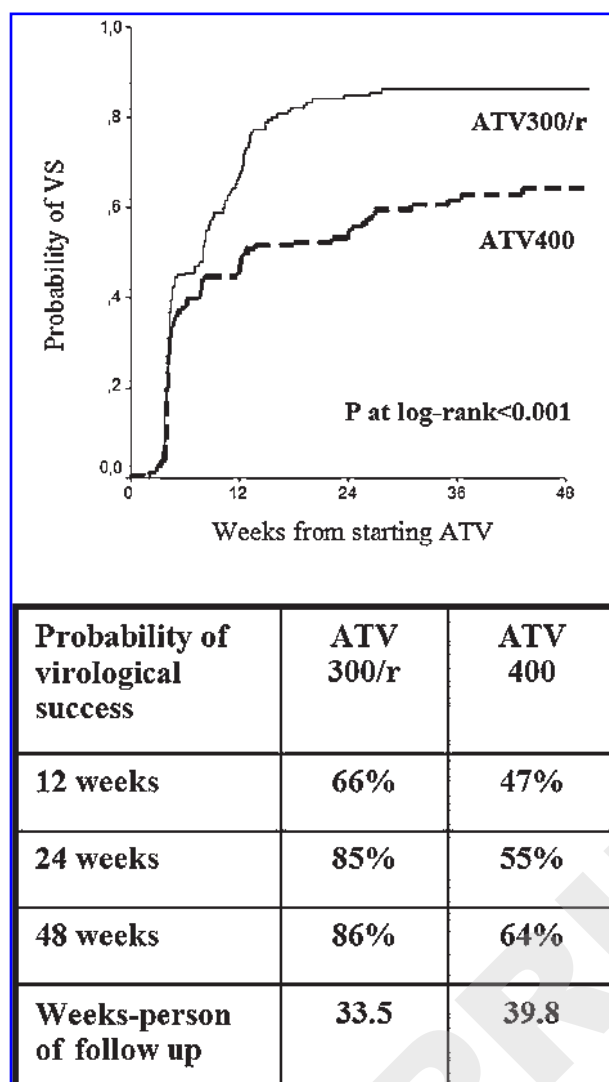


FIG. 1. Kaplan-Meier estimates of probability of virologic success (HIV-RNA < 500 copies per milliliter) according to atazanavir dose. ATV300/r: Atazanavir 300 mg (ritonavir-boosted); ATV400: ATV 400 mg (unboosted). VS, virologic success.

By univariate Cox regression, female gender, higher baseline CD4 cell count, lower baseline HIV-RNA levels, not CDC stage C, lower number of ARVs previously used (lower number of PIs and NNRTIs), and ATV300/r dose, resulted all significantly associated with better virologic response.

Multivariable Cox proportional hazard model was constructed fitting all time-fixed baseline covariates significantly associated to VS in univariate analysis. Factors independently associated to VS were ATV-dose, CDC stage, baseline viral load, and number of PIs previously used (Table 2).

In particular, patients taking an ATV300/r-containing regimen had an increased risk to achieve VS [adjusted hazard risk (AHR): 1.57; 95% CI: 1.19–2.06] compared to those receiving ATV400. By contrast, CDC C stage, higher baseline viral load, and more experience with PIs were associated with poorer virologic response (Table 2).

Furthermore, a stratified analysis according with the variables independently associated to VS in “time-to-event” analysis (CDC stage C, baseline viral load, and number of PIs previously used before starting ATV) was performed. Regarding the CDC stage, patients in CDC A/B stage were compared to those in stage C (Fig. 2A); regarding the baseline viral load, 3 groups of patients with HIV-RNA levels: 500–10,000, 10,000–100,000, and more than 100,000 copies per milliliter were compared (Fig. 2B); regarding the number of PIs previously used, patients previously treated with 0–1, 2–3, and more than 3 PIs were also compared (Fig. 2C).

TABLE 2. FACTORS RELATED TO VIROLOGIC SUCCESS IN PATIENTS TAKING ATV-CONTAINING REGIMEN ON MULTIVARIATE ANALYSIS (COX MODEL)

	AHR	95% Confidence interval	P
ATV300/r vs. ATV400	1.57	1.19–2.06	0.001
Patients in CDC stage C	0.67	0.51–0.90	0.007
CD4 cell count (50 cells/ μ L) at baseline	1.02	0.98–1.05	0.308
HIV-RNA levels at baseline	0.68	0.56–0.77	<0.001
No. of NRTIs previously used	1.06	0.96–1.17	0.269
No. of PIs previously used	0.83	0.76–0.92	<0.001
No. of NNRTI previously used	0.94	0.76–1.17	0.269

Boldface indicates the factors results were significantly associated ($P < 0.001$) with virological success.

ATV: atazanavir; ATV300/r: ATV300 mg (ritonavir-boosted); ATV400: ATV 400 mg (unboosted); AHR: adjusted hazard ratio; NRTIs: nucleoside reverse transcriptase-inhibitors; PIs: protease inhibitors; NNRTIs: Non-NRTIs.

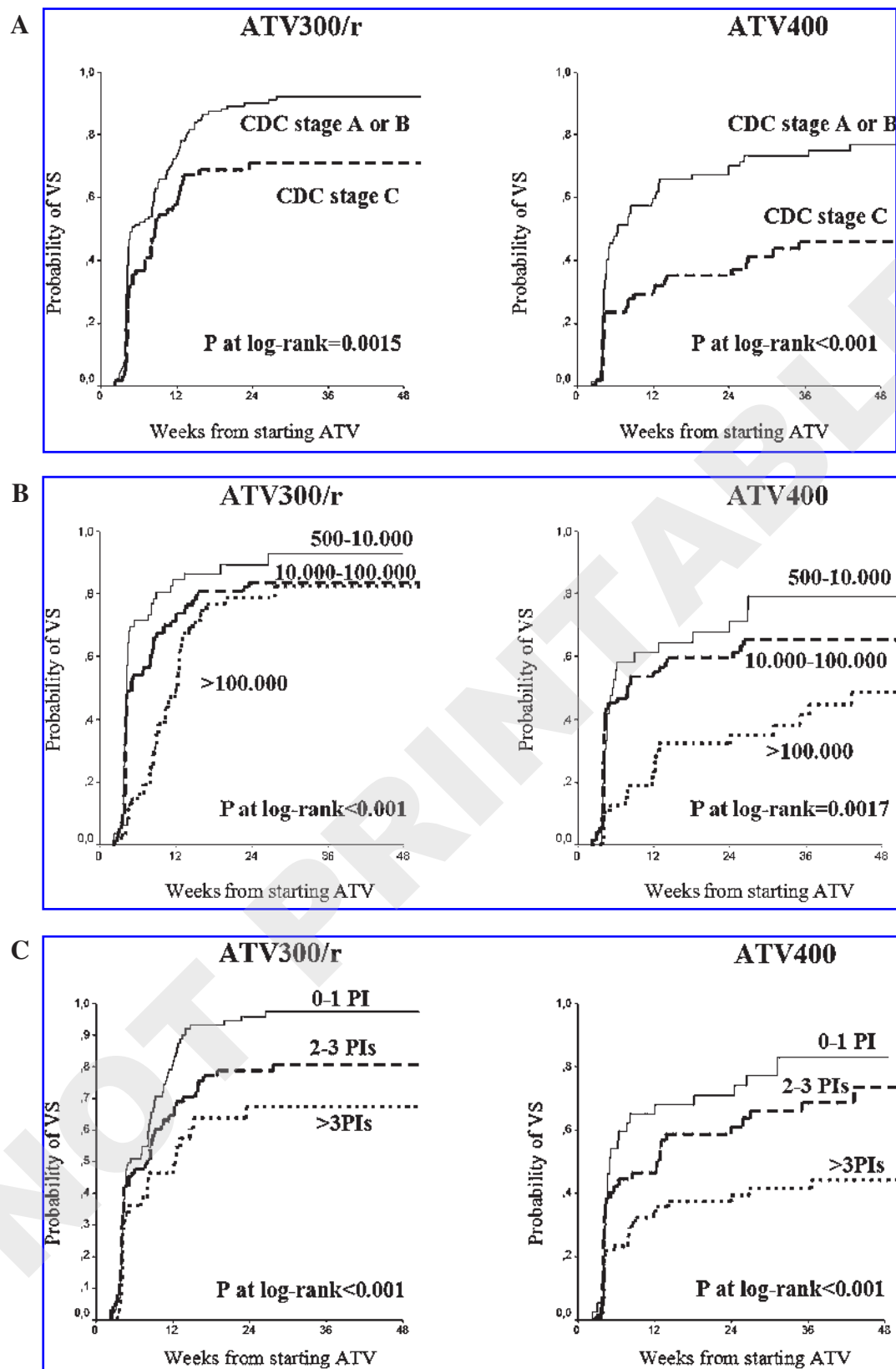


FIG. 2. Kaplan-Meier estimates of probability of virologic success according to (A) CDC stage, (B) baseline HIV-RNA values (copies/mL), (C) number of PIs in previous history of antiretroviral therapy in patients taking different ATV doses. ATV: Atazanavir; ATV300/r: ATV 300mg (ritonavir-boosted); ATV400: ATV 400mg (unboosted). CDC, Centers for Diseases Control; VS, virologic success; PI, protease inhibitor.

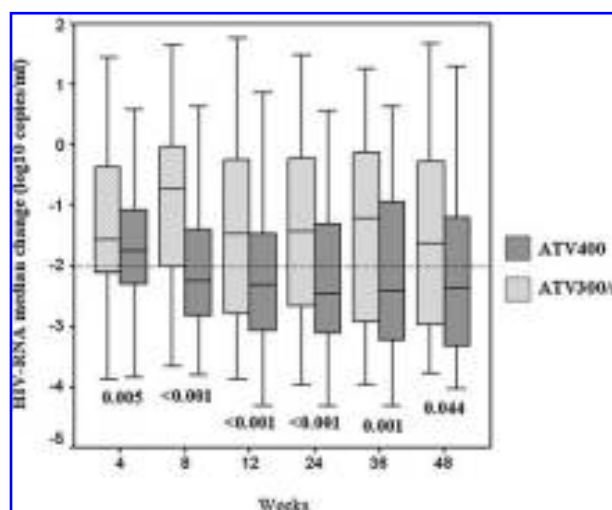


FIG. 3. HIV-RNA median changes from baseline through week 48. ATV300/r: Atazanavir 300 mg (ritonavir-boosted); ATV400: ATV 400 mg (unboosted).

At week 48, for ATV300/r the estimated proportion of patients achieving VS was lower in those in CDC stage C (71% versus 92.1%; Fig. 2A), in those with a baseline viral load greater than 100,000 copies per milliliter (82% versus 83% and 93% in 10,000–100,000 and 500–10,000, respectively) (Fig. 2B), and in those previously treated with a number of PIs ($\geq 81\%$ –82% in 2–3 and more than 3 versus 97% in 0–1, respectively, Fig. 2C). Similar differences among groups were observed for patients treated with ATV400. In particular, for ATV400 the estimated 48-week probability of VS was 46% in patients in CDC stage C (versus 77% in CDC stage A/B; Fig. 2A), 49% in those with a baseline viral load greater than 100,000 copies per milliliter (versus 65% or 79% with 10,000–100,000 and 500–10,000, respectively, Fig. 2B), and 44% in those previously treated with a number of PIs more than 3 (versus 73% or 83% with 2–3 and 0–1 PIs, respectively, Fig. 2C).

Virologic response at different time points

The proportion of patients with HIV-RNA levels less than 500 copies per milliliter at 48 week, was 68.6% and 51.1% for patients receiving ATV300/r and ATV400, respectively ($p = 0.043$), while the proportion of those achieving HIV-RNA levels 50 copies per milliliter or less was 52.9% (ATV300/r) and 35.6% (ATV400) ($p = 0.044$).

The change in HIV-RNA levels from baseline was sustained through week 48; in particular, the median HIV-RNA levels decreased from 4.54 (IQR: 3.91; 5.14) to 1.70 (IQR: 1.69; 3.38) \log_{10} copies per milliliter for ATV300/r group and from 4.67 (IQR: 4.04; 5.16) to 2.62 (IQR: 1.69; 4.22), for ATV400 group. The median reductions of plasma HIV-RNA from baseline to week 48 were -2.35 (IQR: -1.14 ; -3.34) and -1.64 (IQR: -0.25 ; -2.97) \log_{10} copies per milliliter for ATV300/r group and for ATV400 group, respectively ($p < 0.001$ for both groups, by Wilcoxon test; Fig. 3). Significant differences were observed between ATV300/r and ATV400 groups at each time point of follow-up (Mann-Whitney test) (Fig. 3).

Immunologic response

Both regimens were associated with significant median CD4 cell count increase from baseline to week 48 (median count change: $+83$ [IQR: 14; 201] cells/ mm^3 for ATV300/r, and $+41$ [IQR: -19 ; 195] cells/ mm^3 for ATV400 group; $p < 0.001$, by Wilcoxon test).

DISCUSSION

ATV is a valuable option as PI in combination with other antiretroviral drugs for the management of HIV-infected adults, in particular where metabolic complications are a concern.

Currently, the antiretroviral guidelines suggest RTV-boosted ATV as recommended PI in adult treatment-naïve patients; RTV-unboosted ATV should be avoided according to the British HIV Association (BHIVA) Guidelines for 2006, while it is an alternative PI according to the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents.^{25,26}

Most of the information previously available on ATV efficacy is filtered from industry-sponsored trials and focused on the comparison of ATV (unboosted or boosted) versus other antiretrovirals.^{15–20,22,24} A study comparing unboosted ATV to the NNRTI efavirenz, each administered as part of a three-drug antiretroviral regimen in combination with fixed-dose zidovudine plus lamivudine in treatment naïve

patients, found no significant difference in efficacy between the two regimens.¹⁵ In the two prospective clinical trials (AI424-007 and AI424-008), virologic activity of unboosted ATV was comparable to unboosted nelfinavir through 48 weeks.^{16,17} In BMS AI424-044, extended use of ATV in drug-naïve patients resulted in sustained virologic suppression over a median treatment time of approximately 108 weeks, and in continued increases in CD4 cell count.¹⁸ The SWAN Study (BMS 097) demonstrated that switching from unboosted or boosted PI-containing regimens to ATV-containing regimens maintained virologic suppression with improvement in plasma lipids through 48 weeks.¹⁹

In the ACTG 5201 study, the sustained virologic success after 24 weeks of simplification to RTV boosted ATV alone supported the idea that this drug formulation is a good attractive as maintenance of therapy because of its reduced pill burden, once daily dosing, safety, and unique resistance profile.²⁰

However, until today comparative data able to define the efficacy of boosted versus unboosted ATV are limited.^{21,23,25} A recent study (AI424-089) comparing antiviral efficacy and safety of ARV regimens containing ATV with or without RTV through 48 weeks in ART-naïve patients, found that ATV, independently from RTV boosting, has a high rate of virological response in treatment-naïve patients. Indeed, the higher rate of failures (in an intention-to-treat analysis) due to hyperbilirubinemia among patients taking RTV-boosted ATV counterbalanced its greater crude antiviral efficacy; this calls for further studies looking at comparative use of RTV boosted versus unboosted ATV.²¹

In our observational study we evaluated the antiviral efficacy, in terms of virologic and immunologic benefits (during 48 weeks of follow-up), of ATV, both unboosted (ATV400) and RTV boosted (ATV300/r), administered as a part of HAART regimen to highly pretreated patients in an expanded access program. From the analysis resulted that ATV-containing regimens provided a sustained suppression of plasma HIV-RNA levels and an immunologic recovery in PI-multiexperienced patients, both using ATV300/r and ATV400. However, the virologic response was significantly better in pa-

tients treated with ATV300/r than in those receiving ATV400. Reductions in plasma HIV-RNA from baseline to week 48 resulted significantly greater in patients treated with boosted ATV than in those treated with unboosted ATV (median reduction: -2.35 versus -1.64 \log_{10} copies per milliliter). BMS AI424-045 and AI424-043 studies on drug-experienced patients for whom multiple HAART regimens failed, revealed mean reductions from baseline in HIV-RNA at 48 weeks of -1.93 / -1.59 \log_{10} copies per milliliter after ATV administration, with or without pharmacologic boosting.^{22,23}

In particular, unboosted ATV resulted in a significantly lower reduction in HIV-RNA than lopinavir/RTV, while BMS AI424-045 found that RTV boosted ATV had comparable virologic efficacy of lopinavir/RTV, each administered with one NRTI and tenofovir, at week 48; this efficacy was durable and not associated with any unexpected or late-emerging adverse events until 96 weeks for both arms.²²⁻²⁴

The greater efficacy of ATV300/r in our observational model confirmed the importance of using RTV boosted ATV to achieve maximum benefit in terms of virologic response in patients who had experienced ARV failure. In fact, multivariate analysis adjusting for all potential confounders showed that different ATV dosing significantly influences the probability of reaching a virologic success, also when this covariate was fitted together with other main predictors as CDC stage, baseline plasma viral load, and previous PI experience.

Multivariate analysis also showed that no interaction with other ARVs in ATV-containing regimens resulted to influence VS (data not shown). Regarding drugs recently approved from the Food and Drug Administration (FDA), such as T20 and TDF, the number of patients receiving T20 in combination with ATV in this study was too small to better assess the clinical implications. The TDF coadministration was present mainly with ATV300/r (80.5% versus 50.3%); however, the presence of TDF did not influence the VS both in ATV300/r and in ATV400. A previous study showed that there were no significant differences in the virologic response in patients taking ATV unboosted with or without TDF.²⁷ It must be considered that at the time the study was performed in-

formation about the use of ATV and/or TDF in combination with other antiretrovirals was not available.

The major limitation of this analysis comes from the characteristics of the study, observational, performed on two groups of highly pre-treated patients enrolled in an expanded access program with different baseline characteristics due to different therapeutic history, CD4 cell count and so CDC stage. It is well known that information on comparative effects of different drugs in observational studies could be more biased than those obtained from randomized allocation of treatment. In our analysis the two drug dosing groups indeed significantly differed for some baseline variables: participants receiving unboosted ATV400 were more advanced, had more prolonged ARV exposure, and were more frequently treated with salvage multidrug regimens. However, all this confounders were controlled in multivariate model, suggesting the independent effect of ATV-boosting over virologic efficacy.

In conclusion, the data obtained in this study show a good antiviral efficacy of ATV-containing regimens, and confirm that ATV, particularly if RTV boosted, is an effective option for antiretroviral therapy in HIV-infected, drug-experienced patients. Further studies are required to better define which, between RTV boosted and unboosted-ATV, better preserves future PI treatment options in ART-experienced patients in term of resistance development. Preliminary results suggest that pattern of mutations conferring resistance to ATV are not the same in boosted versus unboosted regimens; similarly, the resistance profile seems to differ depending on the use of RTV-boosting.²⁸ Studies aimed toward this direction are then required to refine the specific patterns of mutations associated with failure or success of ATV-containing regimens.

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