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Boosted or unboosted atazanavir as a simplification of lopinavir/ritonavir-containing regimens

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SUMMARY

Switches from lopinavir/ritonavir (LPV/r) to either atazanavir/ritonavir (ATV/r) or unboosted ATV (ATV) are increasingly common in clinical practice, but data on outcome comparison between these two simplification strategies are very limited. Methods. Multicenter, observational, retrospective study. Data were collected from five Italian clinics. The objective of the study was to investigate the utcome of LPV/r simplification with ATV/r or ATV and to identify factors predicting virological rebound. Patients who switched from LPV/r to ATV/r or ATV with an HIV-RNA value<50 copies/mL at the time of switch and with at least one follow-up visit were included.
We evaluated 468 patients (74.1% males), followed for a median (Q1-Q3) of 547 (305-788) days: 380 (81%) and 88 (19%) switched to ATV/r and to ATV, respectively. Virological rebound was detected in 78/468 (16.7%, 95% CI: 13.6 -20.3) patients [16/88 (18.2%, 95% CI: 11.4 -27.6) switched to ATV and 62/380 (16.3%, 95% CI: 12.9 -20.4) to ATV/r (p=0.638)]. Virological rebound was more frequent in patients who started LPV/r with HIV-RNA >30000 copies/mL (28% vs 6%, p=0.014).
Replacing lopinavir/r with ATV or ATV/r yielded similar rates of virological rebound. Viral load at the initiation of lopinavir/r may be useful in driving the choice between ATV/r and ATV.

KEY WORDS: Lopinavir, Atazanavir, Ritonavir, Unboosted, Simplification.

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INTRODUCTION

Complete, long-term adherence to combination antiretroviral regimens is necessary to avoid treatment failure and the selection of drug-resistant variants in HIV patients. For this reason, due to the role of dose interval and pill burden as adherence barriers (Stone *et al.,* 2004), simplification regimens with once-daily, low pill burden regimens may favor patient compliance with antiretroviral therapy (Trotta *et al.,* 2002; Trotta *et al.,* 2003).
Among HIV protease inhibitors (PIs), atazanavir (ATV) is the only one licensed for once-daily use and has a more favorable impact on lipid profile compared with lopinavir/ritonavir (LPV/r) (Johnson *et al.,* 2006; Molina *et al.,* 2008). This is particularly important when managing patients with high cardiovascular risk, in view of the association between myocardial infarction and HIV replication, exposure to antiretrovirals (PIs, abacavir, didanosine), and aging of HIV-infected patients (DAD Study Group, 2007; DAD Study Group, 2008).

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Due to its convenience and tolerability, a change from a LPV/r-based regimen to either atazanavir/ritonavir (ATV/r) - or unboosted ATV (ATV) - based regimens is increasingly common in clinical practice despite a lack of clear data indicating which strategy is preferable (ATV/r or ATV) according to the patient's medical history. Replacing LPV/r with ATV- or ATV/r-based regimens in HIV-infected patients with undetectable viremia has been investigated in two randomized studies (Mallolas *et al.,* 2007; Soriano *et al.,* 2008), but neither study managed to define which strategy is preferable. The present study investigated the outcome of LPV/r simplification with boosted or unboosted atazanavir, aiming also to identify factors predicting virological rebound.

MATERIALS AND METHODS

This was a multicenter, observational, retrospective study. Data were collected from the databases of five leading Italian Infectious Diseases Clinics. Demographic and clinical characteristics as well as laboratory parameters including lipidic and glucidic profile were regularly collected at different times of follow-up; HDL-cholesterol, LDL-cholesterol, and the use of lipid-lowering agents were not regularly recorded in the databases.

All patients who switched from a LPV/r- to an ATV/r- or to an ATV-based regimen were included in this analysis if they met both of the following criteria: HIV-RNA <50 copies/mL at the time of medication switch, and at least one follow-up visit after switch to ATV or ATV/r.

Patients were followed until discontinuation of treatment with ATV, a switch from ATV/r to ATV or vice versa, or until data freezing (June 30, 2007 while on ATV), whichever occurred first.

The primary objective of this study was to evaluate the proportion of virological rebound in virologically suppressed patients switched from a LPV/r to an ATV or an ATV/r-containing regimen. The secondary objectives were to assess if these two strategies led to differences in CD4 changes as well as in lipid and glucose profiles. The primary end-point (outcome of the study) was the proportion of patients with HIV-RNA values of >50 copies/mL (confirmed twice) at data censoring on ATV based regimen. Secondary end-points were absolute and relative changes from baseline in CD4+ cell counts and in the laboratory tests concerning metabolic lipidic profile. HIV-RNA was assessed in each center by means of b-DNA (Versant RNA 3.0, Bayer Puteaux Cedex, France) or Amplicor (Monitor test 1.5, Roche Diagnostics, Manheim, Germany). The detectability ratio was defined as the ratio between the number of detectable (>50 copies/mL) viral loads and the number of viral loads tested prior to the switch to ATV-based regimen.

Statistical analysis

Results were described as median (Q1-Q3) for continuous variables and frequency (%) for categorical variables. The Mann-Whitney rank sum test was used to compare independent distribution values of continuous variables, the Wilcoxon sign rank test was used to assess significant changes from baseline, and the Chi-square or Fisher's exact test were employed to assess significant relationships between categorical variables.

The probability of virological rebound was estimated by the Kaplan-Meier method. The multivariable analysis was performed applying the Cox proportional hazard regression to identify independent predictors of virological rebound. Time zero for the analysis was the date of the switch to ATV; the time to virological rebound was defined as the time to the occurrence of the first confirmed detectable viremia (HIV-RNA values of >50 copies/mL) or the most recent clinical follow-up evaluation while on ATV. The proportional hazards assumption was verified in relation to the covariates included in the model. Hazard ratios were estimated with their corresponding 95% confidence intervals (CI). Two different models were evaluated in relation to the set of the included covariates. The first model considered all covariates with available data for all patients of the five participating centers; the second model included two additional covariates (HIV-RNA at LPV/r start and the detectability ratio), available only in a subgroup of patients. Given the exclusion of a consistent number of observations for this second analysis, the baseline characteristics between the excluded and the included patients were compared. All the statistical tests were two-sided at the 5% level, and performed using SAS Software (SAS Institute), release 9.2.

RESULTS

Four hundred sixty-eight patients (74.1% males) fulfilled the inclusion criteria. Three hundred and eighty (81%) and 88 (19%) were switched to an ATV/r-containing regimen and to an ATV-containing regimen, respectively. The baseline characteristics of the patients included are listed in Table 1. The drugs most frequently used at baseline (in combination with LPV/r) were: lamivudine (64%), tenofovir (42%), didanosine (29%), zidovudine (28%), and stavudine (14%). The

TABLE 1 - *Baseline characteristics of 468 patients with undetectable viral load switched from lopinavir/ritonavir to boosted or unboosted atazanavir.*

		Switched to		
	All N=468	*ATV/r N=380 (81%)*	*ATV N=88 (19%)*	*P-value (ATV/r vs. uATV)*
Age (years) (median (IQR))	44.5 (40.9-49.7)	44.6 (41.0-49.9)	44.3 (40.7-48.5)	0.548
Males [n (%)]	347 (74.1 %)	285 (75.0%)	62 (70.4%)	0.418
Previous AIDS diagnosis (n (%))	140 (29.9%)	112 (29.5%)	28 (31.8%)	0.699
HCVAb+ [n (%)]	111 (38.0%)	82 (36.8%)	29 (42.0%)	0.479
HBsAg+ [n (%)]	20 (7.0%)	16 (7.1%)	4 (6.3%)	0.827
Nadir CD4+ [median (IQR)]	159 (62-246)	156 (57-247)	168 (85-243)	0.664
CD4+/µL [median (IQR)]	433 (302-620)	447 (317-624)	399 (273-561)	0.071
HIV-RNA at LPV/r start (log_{10} copies/mL) <=30000 copies/mL >30000 copies/mL Unknown	4.48 (3.62-5.0) 125 (26.7%) 127 (27.1%) 216 (46.2%)	4.58 (3.85-5.04) 91 (24.0%) 109 (28.7%) 180 (47.4%)	4.1 (3.3-4.8) 34 (38.6%) 18 (20.5%) 36 (40.9%)	0.011 0.017
Duration of LPV/r (days) [median (IQR)]	520 (305-897)	522 (330-905)	514 (238-824)	0.183
Any change in the backbone at switch to ATV [n (%)]	235 (50.2%)	199 (52.4%)	36 (40.9%)	0.059
Change in nucleoside analogues in the regimen at switch to ATV [n (%)]	231 (50.6%)	195 (51.3%)	36 (40.9%)	0.097
Use of tenofovir with ATV [n (%)] Switch to tenofovir	263 (56.2%) 95 (20.3%)	240 (63.2%) 88 (23.2%)	23 (26.1%) 7 (8.0%)	<0.0001
Use of thymidine analogues [n (%)] No TA with LPV/r and ATV No TA with LPV/r but with ATV TA with LPV/r and not with ATV TA with LPV/r and ATV	89 (19.0%) 261 (55.8%) 9 (1.9%) 118 (25.2%) 80 (17.1%)	58 (15.3%) 221 (58.2%) 5 (1.3%) 101 (26.6%) 53 (14.0%)	31 (35.2%) 40 (45.5%) 4 (4.5%) 17 (19.3%) 27 (30.7%)	<0.0001 <0.0001
Total cholesterol (mg/dL) [median (IQR)]	215 (172-248)	213 (173-248)	216 (167-243)	0.832
Triglycerides (mg/dL) [median (IQR)]	213 (139-336)	217 (137-333)	198 (143-338)	0.616
Glucose (mg/dl) [median (IQR)]	91 (82-100)	91 (82-100)	88 (80-99)	0.096

ATV: unboosted atazanavir; ATV/r: boosted atazanavir; LPV/r: lopinavir/ritonavir

drugs used most frequently in combination with ATV were: lamivudine (67%), tenofovir (67%), emtricitabine (29%), didanosine (22%), abacavir (20%) and zidovudine (14%). Thirty patients (6.4%) switched to an ATV-containing regimen not including any NRTIs (8 patients were on ATV/r monotherapy and 5 patients on ATV monotherapy). HIV-RNA at LPV/r start was higher among patients switched to ATV/r (p=0.011) and the concomitant use of tenofovir was more frequent among these patients (ATV/r: 63.2%; ATV: 26.1%, p<0.0001) whereas the concomitant use of thymidine analogues was more frequent among patients switched to ATV (ATV/r: 15.3%; ATV: 35.2%, p<0.0001). The median (IQR) duration of treatment with ATV was 547 (305-788) days, with no differences between the two groups: 555 (322-792) days for patients switched to ATV/r vs 531 (196-755) days for those switched to ATV (p=0.199). During follow-up, 37 (9.7%) patients switched from ATV/r to uATV and 7 (8%) switched from ATV to ATV/r; all patients but 3 switched their initial ATV-containing regimen when they had undetectable viremia.

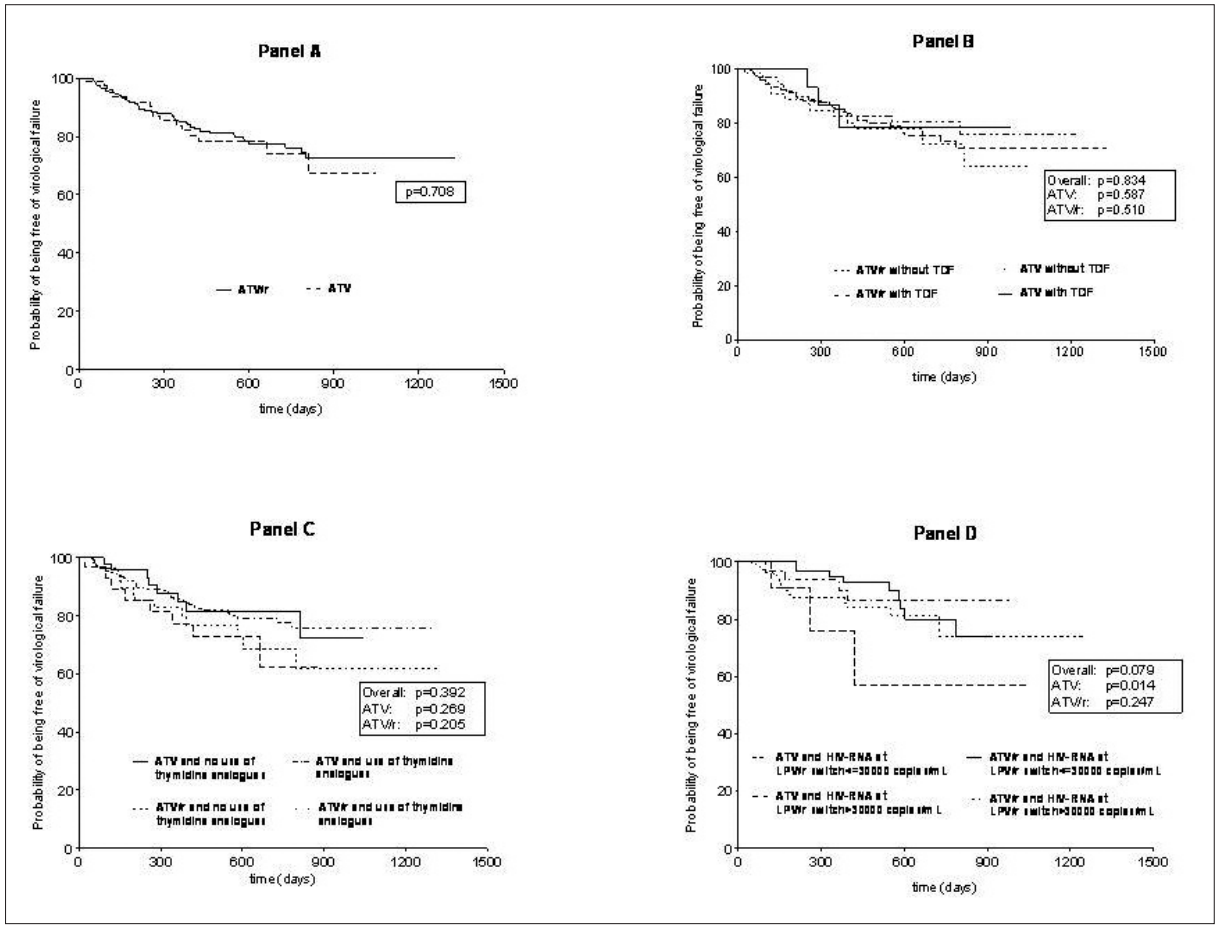

FIGURE 1 - *Panel A - Probability of being free from viral rebound (HIV-RNA >50 copies/mL) according to switch to unboosted (ATV) or boosted atazanavir (ATV/r) (Kaplan-Meier curves). Panel B - Probability of being free from viral rebound (HIV-RNA >50 copies/mL) according to switch to unboosted or boosted atazanavir and use of TDF (Kaplan-Meier curves). Panel C - Probability of being free from viral rebound (HIV-RNA >50 copies/mL) according to switch to unboosted or boosted atazanavir and use of thymidine analogues (Kaplan-Meier curves). Panel D - Probability of being free from viral rebound (HIV-RNA >50 copies/mL) according to switch to unboosted or boosted atazanavir and HIV-RNA at LPV/r start (<=30000 vs >30000 copies/mL) (Kaplan-Meier curves).*

At the end of follow-up, virological rebound was detected in 78/468 (16.7%, 95% CI: 13.6 -20.3) patients: 16/88 (18.2%, 95% CI: 11.4 -27.6) were switched from LVP/r to an ATV-containing regimen and 62/380 (16.3%, 95% CI: 12.9 -20.4) were switched from LPV/r to an ATV/r-containing regimen (p=0.638). The probability of being free from virological rebound was not statistically different between the two groups (p=0.708, Figure 1, Panel A).

The univariable analysis both on frequencies of virological rebound or on the probabilities of being free of virological rebound was evaluated according to the use of tenofovir, the use of thymidine analogues and in relation to the viral load data at LPV/r initiation.

For tenofovir, the frequency of virological rebound was similar between patients using this drug or not (No use of TDF: 33/205=16.1%; Use of TDF: 45/263=17.1%, p=0.804). Virological rebound occurrence was similarly frequent both in patients who switched from LVP/r to an ATV-containing regimen (No use of TDF: 13/65 (20.0%); Use of TDF: 3/23 (13.0%), p=0.546) and in those who switched to an ATV/r-containing regimen (No use of TDF: 20/140 (14.3%); Use of TDF: 42/240 (17.5%), p=0.473). Even when considering separately patients using tenofovir or not, no differences in the proportions of virological rebound were detected between patients who switched to ATV and those who switched to ATV/r (No use of TDF: ATV=20% vs ATV/r=14.3%, p=0.313; Use of TDF: ATV=13% vs ATV/r=17.5%, p=0.775). The probability of being free from virological rebound according to the use of tenofovir in combination with atazanavir was not statistically different (p=0.814) as shown in Figure 1, (Panel B). The probability was similar also when considering the type of ATV-regimen:no differences were detected among the four groups (p=0.834) or within the ATV group (p=0.587) or within the ATV/r group (p=0.510). In addition, when considering separately patients using tenofovir or not, the probability of being free from virological rebound did not differ between patients who switched to an ATV- rather than an ATV/r-containing regimen (No use of TDF: p=0.401; Use of TDF: p=0.707).

The analysis in relation to the use of thymidine analogues showed that the frequency of virological rebound was not significantly different (No use of thymidine analogues: 57/379=15%; Use of thymidine analogues: 21/89=23.6%; p=0.058). The frequency of virological rebound was also similar between patients using thymidine analogues or not, both in patients who switched to an ATV-containing regimen (No use of thymidine analogues: 8/57 (14.0%); Use of thymidine analogues: 8/31 (26.0%), p=0.247) and in those who switched to an ATV/r-containing regimen (No use of thymidine analogues: 49/322 (15.2%); Use of thymidine analogues: 13/58 (22.4%), p=0.179). Even when considering separately patients using thymidine analogues or not, no differences in the proportions of virological rebound were detected between patients who switched to ATV and those who switched to ATV/r (No use of thymidine analogues: ATV= 14% vs ATV/r=15%, p=0.999; Use of thymidine analogues: ATV=26% vs ATV/r=22%, p=0.796). The probability of being free from virological rebound according to the use of thymidine analogues in combination with atazanavir was not statistically different (p=0.087) as shown in Figure 1 (Panel C). The probability was similar also when considering the type of ATV-regimen (overall effect: p=0.392; ATV group: p=0.269; ATV/r group: p=0.205). In addition, when considering separately patients using or not using thymidine analogues, the probability of being free from virological rebound was not different between patients who switched to an ATV- rather than to an ATV/r-containing regimen, (use of thymidine analogues: p=0.810; no use of thymidine analogues: p=0.879).

Then the analysis was restricted to those patients with available viral load data at LPV/r initiation stratified according to the median value (30000 copies/mL =4.4771213 $\log_{10}$). The frequency of virological rebound was not significantly different although it tended to occur more frequently among patients who started LPV/r with HIV-RNA values above or below 30000 copies/ml th HIV-RNA values of >30000 copies/mL (21/127=16.5% vs 11/125=8.8%, p=0.088). In addition, although the difference in virological rebound was not statistically different between patients who switched to ATV or to ATV/r within each virological strata, in patients with HIV-RNA values of >30000 copies/ml at LPV/r start, virological rebound was roughly twofold more frequent in those who switched to ATV than in those who switched to ATV/r (HIV-RNA >30000 copies/ml: ATV=28% vs

ATV/r=15%, p=0.178; HIV-RNA <=30000 copies/ml: ATV=6% vs ATV/r=10%, p=0.726). Among patients switched to an ATV-containing regimen, virological rebound was more frequent in those who started LPV/r with HIV-RNA values of >30000 copies/mL (28% vs 6%, p=0.041) whereas no difference was observed among patients switched to ATV/r (15% vs 10%, p=0.392). The probability of being free from virological rebound, according to strata of viral load at LPV/r initiation and ATV-regimen, is shown in Figure 1 (Panel D): overall no statistical difference was found among the four groups (p=0.079) or among patients switched to an ATV/r-containing regimen (p=0.226). On the contrary, the probability of being free from virological rebound was statistically different between the two HIV-RNA strata (p=0.014) when considering patients switched to an ATV-containing regimen but not among patients switched to an ATV/r-containing regimen (p=0.247). In addition, when considering separately patients above or below 30000 copies/ml, the probability of being free from virological rebound was not different between patients who switched to an ATV- rather than to an ATV/r-containing regimen (HIV-RNA> 30000 copies/ml: p=0.178; HIV-RNA <=30000 copies/ml: p=0.397). At multivariable analysis, after adjustment for age, gender, nadir CD4+ and baseline CD4+, duration of treatment with LPV/r, switch to ATV or ATV/r, change in the nucleoside analogues in the regimen, use of tenofovir, patients using thymidine analogues in the ATV- based regimen were more likely to have virological rebound during follow-up [HR=1.862, 95% CI; 1.036-3.347, p=0.038 (Table 2 - Model 1)]. Notably, switching to ATV rather than to ATV/r did not independently predict virological failure.

TABLE 2 - *Multivariable analysis: adjusted hazard ratios for viral rebound estimated by Cox proportional hazard regression model.*

	Model 1 (N=453)			*Model 2 (N=158)*		
Covariate	*HR*	*95% CI (HR)*	*P-value*	*HR*	*95% CI (HR)*	*P-value*
Age (per 1-year increment)	0.976	0.949-1.004	0.096	0.996	0.932-1.064	0.898
Gender (M vs F)	0.989	0.582-1.680	0.967	0.518	0.166-1.612	0.256
Nadir CD4 (per 1-cell/mL increment)	0.999	0.997-1.001	0.346	0.996	0.991-1.000	0.053
Baseline CD4 (per 1-cell increment)	1.001	1.000-1.002	0.221	1.001	0.998-1.003	0.503
HIV-RNA at LPV/r start >30000 vs <=30000 copies/mL	-	-	-	3.615	1.499-8.717	0.004
Detectability ratio (# detectable VLs/ # tested VLs prior to ATV±r) (per 1-unit increment)	-	-	-	12.998	1.299-130.042	0.029
LPV/r duration (per 1-day increment)	1.000	0.999-1.000	0.316	1.00	0.999-1.001	0.976
Switch to unboosted vs boosted ATV	0.859	0.472-1.562	0.618	1.536	0.588-4.012	0.381
Change in nucleoside analogues in the regimen at switch to ATV (Yes vs No)	1.414	0.867-2.306	0.166	1.087	0.451-2.624	0.852
Use of thymidine analogues with ATV (Yes vs No)	1.862	1.036-3.347	0.038	3.462	1.164-10.295	0.026
Use of tenofovir with ATV (Yes vs No)	1.139	0.677-1.914	0.624	1.252	0.454-3.453	0.664

ATV: unboosted atazanavir; ATV/r: boosted atazanavir; LPV/r: lopinavir/ritonavir; VL: viral load.

The increased risk of virological rebound associated with the use of thymidine analogues was confirmed (HR=3.462, 95% CI: 1.164-10.295, p=0.026) even when the analysis was restricted to those patients with available data for HIV-RNA at LPV/r start and for the calculation of the detectability ratio (Table 2 - Model 2). In this model, virological rebound was more likely among patients with HIV-RNA values at LPV/r start above 30000 copies/mL compared to those with HIV-RNA values at LPV/r start ≤30000 copies/mL (HR=3.615, 95% CI: 1.499-8.717, p=0.004) as well as with increasing values of the detectability ratio (HR=12.998 per 1-unit increment, 95% CI: 1.299-130.042, p=0.029). The baseline characteristics of the patients included or excluded in Model 2 were compared, and the results of the comparisons between the two groups are illustrated in Table 3.

Change in CD4+ cell counts from baseline was similar between patients who switched to ATV compared to those who switched to an ATV/r-containing regimen (Absolute change: 50 (-19/+140) vs 40 (-46/+124) cells/mm^3, p=0.222; relative change: 14% (-5/+38) vs 9% (-10/+34), p=0.266).

TABLE 3 - *Baseline characteristics according to inclusion in the two models of multivariable analysis.*

	Patients not included in Multivariable model 2 (N=295)		*Patients included in Multivariable model 2 (N=158)*		*P-value (for patients treated with ATV/r)*	*P-value (for patients treated with ATV)*
	ATV/r (n=257)	*ATV (n=38)*	*ATV/r (n=115)*	*ATV (n=43)*		
Age (years) [median (IQR)]	44 (40 – 50)	44 (40 - 49)	46 (43 – 50)	44 (41 – 49)	0.104	0.646
Males [n (%)]	194 (76%)	25 (66%)	86 (75%)	32 (74%)	0.897	0.468
Previous AIDS diagnosis [n (%)]	79 (31%)	12 (32%)	30 (26%)	13 (30%)	0.390	0.999
HCVAb+ [n (%)]	43 (38%)	11 (48%)	37 (36%)	15 (38%)	0.780	0.440
HBsAg+ [n (%)]	11 (10%)	1 (5%)	5 (5%)	2 (5%)	0.197	0.999
Nadir CD4+ [median (IQR)]	136 (44-222)	191 (84-250)	196 (100-311)	163 (95-248)	<0.0001	0.970
CD4+/µL [median (IQR)]	429 (300-602)	408 (273-509)	473 (346-670)	394 (268-575)	0.028	0.969
Duration of LPV/r (days) [median (IQR)]	515 (324-871)	558 (238-805)	548 (336-952)	456 (238-731)	0.253	0.557
Change in nucleoside analogues in the regimen at switch to ATV [n (%)]	151 (59%)	20 (53%)	40 (35%)	11 (26%)	<0.0001	0.021
Use of tenofovir with ATV [n (%)]	169 (66%)	7 (18%)	68 (59%)	13 (30%)	0.244	0.303
Use of thymidine analogues with ATV [n (%)]	34 (13%)	11 (29%)	20 (17%)	19 (44%)	0.339	0.174
Total cholesterol (mg/dL) [median (IQR)]	205 (168-241)	218 (180-262)	221 (188-258)	218 (167-242)	0.021	0.718
Triglycerides (mg/dL) [median (IQR)]	219 (136-338)	196 (152-305)	214 (146-326)	204 (138-491)	0.890	0.654
Glucose [median (IQR)]	95 (84-100)	89 (82-100)	88 (78-102)	86 (80-98)	0.035	0.531

ATV: unboosted atazanavir; ATV/r: boosted atazanavir; LPV/r: lopinavir/ritonavir.

Change in CD4+ cell counts was also evaluated according to the use of tenofovir, the use of thymidine analogues or the HIV-RNA level at LPV/r start but none of these characteristics showed significant differences (data not shown).
At the end of follow-up no significant differences in lipidic and glucidic changes from baseline were found between the two groups (Total cholesterol: ATV=-31 (-51/-11), ATV/r=-24 (-49/-2), p=0.193; Triglycerides: ATV=-69 (-136/-14), ATV/r=-55 (-143/0), p=0.450; Glucose: ATV=0 (-8/+7), ATV/r=+1(-10/+10), p=0.580). However, when changes with regard to the National Cholesterol Education Programme (NCEP) normality thresholds were analyzed, several differences were found.
Abnormal values of triglycerides were observed at baseline in 260/361 (72%) of patients switched to ATV/r and in 57/81 (70.4%) of those switched to ATV (comparison between the two groups: p=0.786). At the end of follow-up, these proportions decreased to 52.7% (175/332) and 36% (27/75), respectively (comparison between the two groups: p=0.010). A normalization of triglyceride levels at the end of follow-up was observed in 75/231 (32.5%) and in 26/49 (53.1%) of patients with abnormal levels at baseline and switched, respectively, to ATV/r and ATV (p=0.008).
Abnormal values of total cholesterol were observed at baseline and at the end of treatment, respectively, in 211/362 (58.3%) and 135/339 (39.8%) in patients switched to ATV/r, and in 50/82 (61%) and 22/78 (28.2%) in those switched to ATV (comparison between the two groups: at baseline: p=0.710; at the end of follow-up: p=0.069). A normalization of total cholesterol levels at the end of follow-up was observed in 74/189 (39.2%) and in 27/45 (60%) of patients with abnormal levels at baseline who switched to ATV/r and ATV, respectively (p=0.012).
Abnormal values of glucose (≥100 mg/l) were observed at baseline and at the end of treatment, respectively, in 66/360 (18.3%) and 85/346 (24.6%) in patients switched to ATV/r, and in 15/81 (18.5%) and 14/83 (16.9%) in those switched to ATV (comparison between the two groups: at baseline: p=0.999; at the end of follow-up: p=0.149). A normalization of glucose levels at the end of follow-up was observed in 29/66 (43.9%) and in 8/14 (57%) of patients with abnormal levels at baseline who switched to ATV/r and ATV, respectively (p=0.394).

DISCUSSION

Simplification of complex, PI - based regimens with simpler, non-nucleoside reverse transcriptase inhibitor (NNRTI) - based (Barreiro *et al.,* 2000; Dieleman *et al.,* 2002; Bucher *et al.,* 2003; Molina *et al.,* 2005) or a triple nucleoside-based regimens (Clumeck *et al.,* 2001; Katlama *et al.,* 2003) has been advocated as a strategy to improve patient compliance and has been associated with comparable or even improved control of viral replication as compared with continuing the current PI. However, this strategy is not always feasible because of hypersensitivity, contraindications, or resistance to these drugs; in these cases, a switch within the PI class can be pursued, in particular when it can also improve the patients' metabolic profile. In a randomized clinical trial of antiretroviral naïve patients, ATV/r and ATV showed partially different effects on blood lipid levels, with more patients in the ATV/r than in the ATV arm (30% vs 18%) shifting upward by at least one NCEP category in fasting triglycerides. On the contrary, no between-groups differences were observed with regard to cholesterol levels and virological response (Malan *et al.,* 2008). In this retrospective observational analysis of patients switching from a virologically-controlled LPV/r regimen to boosted or unboosted ATV, we found a virological rebound rate of 16.7% after a median of 547 days follow-up, with no differences in virological rebound or in changes in CD4+ cell counts according to the presence of boosting or not. Our findings are consistent with those observed in a large retrospective study not specifically focused on LPV/r switch (Pavie *et al.,* 2011) and those observed in a prospective randomized study focused on switch from ATV/r to ATV in naïve patients (Ghosn *et al.,* 2010). Interestingly, although the use of unboosted atazanavir with TDF has not been tested in clinical trials and is not currently recommended because of the risk of suboptimal ATV pharmacokinetics, we did not find an increased risk of virological failure in patients using this combination. On the contrary, use of timidine analogues was an independent predictor of virological failure, possibly reflecting the impact of NRTI archived mutations in favouring the virological rebound in patients largely pretreated.

In our opinion, the most interesting finding is that patients who started the LPV/r-containing regimen with >30000 copies/mL had a higher likelihood of experiencing virological rebound, in particular those who were switched to ATV. Furthermore, the risk of virological failure after simplification increased with higher viral load levels at the start of treatment with LPV/r. Although we did not have a control group, this finding might discourage the switch from LPV/r to ATV, and particularly to ATV, in patients who started LPV/r with >30000 copies HIV-RNA/ml.

In general, we observed an improvement in the lipid profile and, in particular, we found some differences between the two groups: more patients among those switched to ATV reached normal values of triglycerides and cholesterol. The differences between the two groups in lipid and immunological changes were consistent with the results from naïve patients randomized to receive ATV or ATV/r, both with extended-release stavudine and lamivudine, in the clinical trial previously mentioned (Malan *et al.,* 2008).

Other studies investigated the safety of switching from other PI- to ATV-based regimens; none of these studies investigated whether switching from LPV/r to ATV/r or ATV leads to different outcomes. In the ATAZIP Study 248 patients with less than three failures to PI-containing regimens, less than five PI resistance mutations, and undetectable viral load while on a stable LPV/r-containing regimen were randomized 1:1 to change LPV/r to ATV/r or not. Virological failure after 48 weeks of follow-up were 5% in the ATV/r arm and 6% in the LPV/r arm; patients switched to ATV/r showed a significant reduction in total cholesterol and triglycerides at the end of the study (Mallolas *et al.,* 2007). Virological failures were slightly higher (11% in the ATV/r and 13% in the LPV/r arm) in a sub-analysis restricted to patients with a history of virological failure on PIs or with HIV mutations associated with PI resistance (Podzamczer *et al.,* 2007).

Our results are not directly comparable with those from the ATAZIP study. Our virological rebound rates are slightly higher, but this difference might be explained by the difference in study design. Glucose levels did not change after switch in either group in line with previous findings (Guffanti *et al.,* 2007), but in the present study insulin and oral glucose tolerance tests were not performed to assess for changes in insulin sensitivity.

The present study has several limitations. Patients who interrupted ATV without having at least one follow-up visit and CD4 and viral load while still on-drug were excluded from the analysis. Moreover, data on previous virological failures and drug resistance were available for a minority of patients. So it is possible that patients with more virological failures before the start of LPV/r were preferentially switched to ATV/r rather than to ATV. This may represent a confounder by indication that has not been completely controlled in the analysis. In an attempt to correct for this bias, when data were available, we calculated the detectability ratio as an indirect tool to measure previous virological failures, but it did not prove to be predictive of virological rebound in a second multivariable model. The switch to an ATV-containing regimen was associated with a significant reduction in the normalized-for-age cardiovascular risk score (Colafigli *et al.,* 2008). As we could not calculate the cardiovascular risk score for all patients, because some cardiovascular risk factors were not reported in the clinical records of some patients, we were not able to assess if the switch to ATV reduced the cardiovascular risk score more than the switch to ATV/r. Finally, samples for lipid and glucose were drawn without absolute certainty of the fasting state of the patient, and information on changes in concomitant medications (including lipid-lowering agents) were not available for all of the patients; such changes could have affected the results. Nevertheless, the follow-up of our patients was much longer than that of other studies (78 vs. 48 weeks) and we studied patients with a median exposure to LPV/r of 520 days.

In conclusion, our study provides some useful information on switches within the PI class: replacing LPV/r with ATV (boosted or unboosted) yielded a similar rate of virological rebound at one-year follow-up. Viral load at the initiation of LPV/r may be useful in driving the choice between boosted or unboosted ATV. We suggest that in patients virologically suppressed while receiving a combination of drugs including LPV/r, a switch to an ATV regimen could be preferentially offered to patients who started LPV/r with a relatively low viral load: in these conditions switching to an ATV-based regimen does not

seem to favour virological failure as compared to a switch to an ATV/r-based antiretroviral combination, and it is associated with a more frequent normalization of total cholesterol and triglyceride levels.

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