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Efficacy and safety of a switch to unboosted atazanavir in combination with nucleoside analogues in HIV-1-infected patients with virological suppression under antiretroviral therapy

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Background: Limited data are available on the use of unboosted atazanavir in combination with nucleoside reverse transcriptase inhibitors (NRTIs) in treatment-experienced HIV-infected patients.

Methods: We conducted a multicentre, retrospective study among patients with plasma HIV-1 RNA levels <50 copies/mL under antiretroviral therapy who switched to unboosted atazanavir + NRTIs between January 2002 and December 2008. Virological failure during follow-up was defined as a confirmed plasma HIV-1 RNA level >50 copies/mL. Baseline risk factors for virological failure were identified using Cox proportional hazards models.

Results: A total of 886 patients were analysed. At baseline, median age was 44 years, 71.5% were males and median CD4 cell count was 490 cells/mm^3. NRTIs used in combination with atazanavir were tenofovir, abacavir and emtricitabine/lamivudine in 36.9%, 44.1% and 94.4% of patients, respectively. Median follow-up was 21 months. The 3 year probability of virological failure was 20.1%. Only a history of virological failure under NRTIs [hazard ratio (HR) 1.63, $P=0.049$] and under protease inhibitors (HR 2.04, $P=0.006$) were significantly associated with the risk of virological failure. Among the 431 patients without a prior history of virological failure, the 3 year probability of virological failure was 11.3%, and only hepatitis C virus co-infection (HR 2.25, $P=0.026$) and abacavir use (HR 0.43, $P=0.04$) were associated with the risk of virological failure. Safety of the switch was satisfactory, with improvement of the lipid profile.

Conclusions: In patients with virological suppression and no prior history of virological failure, a switch to unboosted atazanavir in combination with NRTIs is associated with a low probability of virological failure and a good safety profile.

Keywords: tenofovir, abacavir, simplification

Introduction

Most HIV-infected patients receiving antiretroviral therapy (ART) today achieve full suppression of viral replication. However, the long-term tolerability and safety of ART can still be improved, and strategies of treatment switches are evaluated in order to simplify treatment or to decrease the occurrence of treatment-related toxicity while maintaining a good

virological efficacy.[1] Most regimens today contain two nucleoside analogue reverse transcriptase inhibitors (NRTIs) and a third agent: a boosted protease inhibitor (PI) or a non-NRTI.[1] There is growing interest, however, in the use of unboosted PIs, mainly to avoid the inconvenience and adverse events associated with the long-term use of ritonavir, such as gastrointestinal symptoms, lipid abnormalities, insulin resistance and drug interactions.[2–5] Among the PIs, atazanavir has been assessed in clinical trials and cohort studies, both with and without ritonavir. In treatment-naive HIV-1-infected patients, the efficacy of unboosted atazanavir (400 mg daily) in combination with lamivudine and stavudine was lower than the use of ritonavir-boosted atazanavir (100/300 mg daily), with 70% and 75% of patients achieving a plasma HIV-1 RNA level <50 copies/mL at 48 weeks, respectively.[6] Also, among patients with virological failure, the emergence of PI and NRTI resistance-associated mutations occurred more frequently in those receiving unboosted atazanavir, leading to the recommendation of using only ritonavir-boosted atazanavir-based regimens in naive patients.[1,6] Two recent trials, however, have compared the efficacy and safety of boosted versus unboosted atazanavir-based regimens in patients with virological suppression under a ritonavir-boosted atazanavir-based therapy.[7,8] In both trials, the switch to unboosted atazanavir was non-inferior to the maintenance of ritonavir-boosted atazanavir, with a similar rate of emergence of resistance, suggesting that unboosted atazanavir-based regimens could be a valuable alternative in patients with virological suppression. Both trials, however, were conducted after a short induction period in treatment-naive patients (26–36 weeks), with the use of abacavir and lamivudine, and have a limited follow-up of only 48 weeks after the switch. Whether these results can be extended to patients with different regimens before the switch, to other NRTI combinations and are sustainable beyond 48 weeks of follow-up is currently unknown. Other randomized or cohort studies have assessed the efficacy and safety of a switch to an unboosted atazanavir-based regimen, but these studies were either relatively small, had a short follow-up or the unboosted atazanavir strategy was not compared with ritonavir-boosted atazanavir.[9–12]

The objective of our study was therefore to assess the long-term efficacy and safety of a switch to unboosted atazanavir in combination with various NRTIs in a large cohort of patients with virological suppression under a variety of ARTs, and to identify baseline risks factors for virological failure.

Patients and methods

Patients

This study was an international multicentre, retrospective cohort study enrolling HIV-1-infected patients followed in 10 centres in Europe. All centres were participating in the NEAT network of excellence for the treatment of HIV/AIDS under the European Union 6th Framework Programme.

Patients were enrolled in the study if they had full virological suppression under ART (defined as a plasma HIV-1 RNA level <50 copies/mL at two consecutive measures before the switch) and switched ART to an unboosted atazanavir-based regimen containing one or more NRTIs, from January 2002 to December 2008. In this retrospective study, participants at each centre provided informed consent for the anonymous use of their clinical and biological data for biomedical research at the time their data were entered in the electronic database. This study did not, therefore, need to be approved by a research ethics committee. Data were collected at baseline (time of switch), 1, 3 and 6 months later, and every 6 months thereafter. Baseline data included demographic characteristics [age, sex, CDC stage and co-infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)], duration of HIV infection, CD4 cell count nadir, duration and type of previous ART, prior history of treatment failure, reasons for switching (adverse event, simplification or other reason), and NRTIs used in combination with unboosted atazanavir. The baseline CD4 cell count, plasma HIV-1 RNA levels, fasting total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol and triglycerides, and serum creatinine levels were also recorded at the time of switch and during follow-up. Follow-up data also included the progression of HIV disease (occurrence of an AIDS-defining event or death), severe non-AIDS-defining events and discontinuation of unboosted atazanavir.

Endpoints

The primary endpoint efficacy was virological failure defined by two consecutive plasma HIV-1 RNA levels >50 copies/mL under an unboosted atazanavir-containing regimen, or one plasma HIV-1 RNA level >50 copies/mL under unboosted atazanavir and discontinuation of unboosted atazanavir. The time of virological failure was the time of the first plasma HIV-1 viral load >50 copies/mL. Secondary efficacy endpoints were virological failure defined as a plasma HIV-1 RNA level >400 copies/mL, the emergence of PI- or NRTI-associated resistance in patients with plasma HIV-1 RNA levels >400 copies/mL and the change from baseline in CD4 cell counts.

Safety endpoints were the occurrence of an AIDS-defining event and death, the occurrence of severe non-AIDS events [myocardial infarction (MI) requiring hospitalization or diagnosed by serial Q-wave change on electrocardiogram (silent MI), non-fatal stroke, coronary artery disease requiring surgery, death from cardiovascular disease, renal dialysis, liver cirrhosis, or non-AIDS cancer (excluding basocellular carcinomas)], the occurrence of selected adverse events (diabetes, nephrolithiasis or pregnancy), the time to unboosted atazanavir discontinuation, and the changes from baseline in serum creatinine and fasting lipids (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides).

Statistical analysis

A common electronic database was established for the 10 participating centres. Data were entered at each centre, and transferred to the central database for data monitoring and analysis.

Incidences of virological failure (separately for each threshold of 50 or 400 copies/mL) and of atazanavir discontinuation were analysed in a competing risks framework. For virological failure, atazanavir discontinuation and death were considered as competing events. For atazanavir discontinuation, death was considered as the only competing event. To identify baseline predictors of virological failure (using the 50 copies/mL threshold), univariate and multivariate analyses were performed using Cox proportional cause-specific hazards models. In the multivariate analysis, all factors with a P value of ≤ 0.20 in the univariate analysis were considered and sequentially removed from the model with a P value threshold of 0.05. The proportional hazards assumption was checked by examination of the Schoenfeld residuals, and Grambsch and Therneau's lack-of-fit test.

Changes from baseline in CD4 cell counts, lipid parameters and creatinine levels under unboosted atazanavir were analysed using linear and

non-linear mixed models. The form of fixed effects and the covariance structure of random effects were selected on the basis of Akaike's information criterion, and model goodness-of-fit was assessed by examination of the residuals.

All tests were two-sided and P values of ≤ 0.05 were considered as indicating statistical significance. Analyses were performed using R statistical software version 2.6.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Baseline characteristics of 886 patients with virological suppression receiving unboosted atazanavir-based regimens

Characteristics	Median (1st to 3rd quartile) or *n* (%)[a]
Age, years	44 (range 19–79)
Male gender	633 (71.5)
Duration of HIV infection, years	11 (6–17)
CDC classification	
1	149 (19.1)
2	251 (32.0)
3	386 (49.0)
Hepatitis C co-infection	309 (35.5)
Hepatitis B co-infection	51 (6.0)
CD4 cell count nadir (cells/mm^3)	189 (93–278)
Prior ART with a PI	702 (79.2)
PI boosted by ritonavir	677 (76.6)
virological failure under PI	129 (17.8)
Prior ART with NNRTI	557 (63.0)
virological failure under NNRTI	140 (18.8)
Prior ART with NRTI	759 (85.7)
number of NRTIs used	4 (3–6)
virological failure under NRTI	242 (34.1)
No history of virological failure under ART	431 (48.6)
CD4 cell count (/mm^3) at the time of switch	490 (352–688)
Dose of atazanavir: 400 mg daily	865 (97.6)
Reason for switching to unboosted atazanavir	
adverse event	249 (28.3)
simplification	407 (46.3)
other	223 (25.4)
Last line of ART before the switch	
PI + 2 NRTIs	635 (76.1)
NNRTI + 2 NRTIs	106 (12.7)
3 NRTIs	76 (9.1)
other	17 (2.0)
NRTIs associated with atazanavir	
lamivudine/emtricitabine	836 (94.4)
abacavir	391 (44.1)
tenofovir	327 (36.9)
zidovudine	116 (13.1)
didanosine	80 (9.0)
stavudine	13 (1.5)

NNRTI, non-nucleoside reverse transcriptase inhibitor.
[a]Percentages were calculated on available data for each category.

Results

Baseline patient characteristics

We collected data from 886 patients fulfilling the inclusion criteria. Baseline patient characteristics are given in Table 1. Reasons for switching to unboosted atazanavir were mainly simplification (46.3%) and adverse event under prior ART (28.3%). Interestingly, 36.9% patients were receiving tenofovir in combination with unboosted atazanavir. Median follow-up in the study was 21 months (range 1–86 months).

Efficacy endpoints

One hundred and thirty-eight patients experienced virological failure with a threshold of 50 copies/mL during follow-up. The respective 1, 2 and 3 year probabilities of virological failure were 9.7%, 16.1% and 20.1% with a threshold of 50 copies/mL (Figure 1a). Sixty-one patients experienced virological failure with a threshold of 400 copies/mL, and the 1, 2 and 3 year probabilities of virological failure with this threshold were 3.9%, 6.9% and 9.3%, respectively. In univariate analysis, a prior history of virological failure under NRTIs or PI and a PI-containing ART

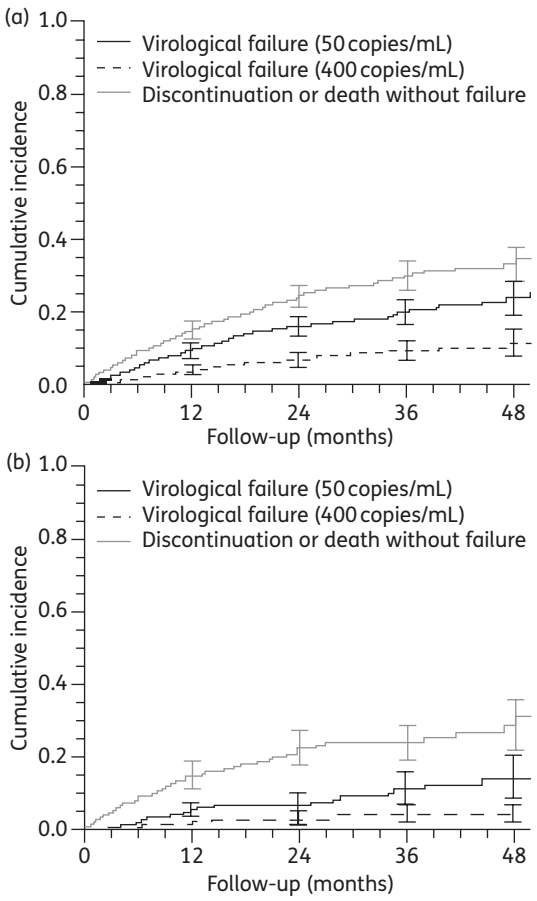

Figure 1. Cumulative incidence of virological failure and discontinuation of unboosted atazanavir (a) during follow-up in 886 patients and (b) during follow-up in 431 patients without a prior history of virological failure.

Table 2. Risk factors for virological failure in 886 patients under unboosted atazanavir

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Female gender	1.37 (0.96–1.95)	0.080		
Age ≥45 years	1.00 (0.71–1.40)	>0.99		
CDC classification 2–3	1.45 (0.89–2.37)	0.13		
HCV co-infection	1.30 (0.92–1.84)	0.14		
Nadir CD4 count <200 cells/mm^3	1.36 (0.97–1.92)	0.078		
Peak of HIV viral load >10^5 copies/mL	0.89 (0.63–1.26)	0.5		
Virological failure on PI	2.48 (1.59–3.85)	<0.0001	2.04 (1.22–3.39)	0.006
Virological failure on NRTI	2.14 (1.40–3.28)	0.0005	1.63 (1.00–2.66)	0.049
Virological failure on NNRTI	1.44 (0.91–2.28)	0.12		
CD4 cell count <400 cells/mm^3 at switch	1.11 (0.78–1.57)	0.57		
Switch for simplification	1.23 (0.88–1.72)	0.23		
ART with PI before the switch	1.67 (1.03–2.73)	0.039		
NRTIs associated with atazanavir				
abacavir	0.82 (0.57–1.16)	0.26		
zidovudine	0.85 (0.52–1.39)	0.52		
tenofovir	1.22 (0.87–1.72)	0.25		
didanosine	1.33 (0.83–2.13)	0.24		

Table 3. Risk factors of virological failure in 431 patients without a prior history of virological failure

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Female gender	1.40 (0.68–2.88)	0.36		
Age ≥45 years	0.89 (0.44–1.77)	0.73		
CDC stages 2–3	1.86 (0.64–5.43)	0.25		
HCV co-infection	2.10 (1.03–4.26)	0.041	2.25 (1.10–4.60)	0.026
Nadir CD4 <200 cells/mm^3	1.38 (0.68–2.77)	0.37		
Peak of HIV viral load >10^5 copies/mL	1.11 (0.56–2.23)	0.76		
CD4 cell count <400 cells/mm^3 at switch	0.75 (0.36–1.55)	0.44		
Weight, per 10 kg	0.82 (0.60–1.10)	0.18		
Switch for simplification	0.55 (0.26–1.18)	0.13		
ART with PI before switch	1.57 (0.68–3.64)	0.29		
NRTIs associated with atazanavir				
abacavir	0.49 (0.23–1.06)	0.072	0.43 (0.19–0.96)	0.040
zidovudine	1.54 (0.71–3.30)	0.27		
tenofovir	1.08 (0.52–2.26)	0.84		
didanosine	0.95 (0.33–2.75)	0.92		

before the switch were significantly associated with virological failure (using the 50 copies/mL threshold). In multivariate analysis, only a history of virological failure under NRTIs {hazard ratio (HR) 1.63 [95% confidence interval (CI) 1.00–2.66], $P=0.049$} and under PI [HR 2.04 (95% CI 1.22–3.39), $P=0.006$] were significantly associated with the risk of virological failure (Table 2).

Among the 431 patients without a prior history of virological failure, the respective 1, 2 and 3 year probabilities of virological failure were 5.3%, 7.2% and 11.3% with a threshold of 50 copies/mL (Figure 1b). In the univariate analysis, HCV co-infection was the only factor significantly associated with virological failure. In the multivariate analysis, HCV co-infection [HR 2.25 (95% CI 1.10–4.60), $P=0.026$] and abacavir use [HR 0.43 (95% CI 0.19–0.96), $P=0.040$] were both associated with the risk of virological failure (Table 3). Tenofovir use was not associated with an increased risk of failure [HR 0.70 (95% CI 0.30–1.60), $P=0.39$] when adjusting for HCV co-infection and abacavir use (data not shown).

Among the 61 patients with virological failure using the 400 copies/mL threshold, genotypic resistance tests were performed in only 20 patients at the time of failure. Among these

Table 4. Changes in lipid parameters during follow-up

	Triglycerides median (1st to 3rd quartile)	Total cholesterol mean (SD)	HDL mean (SD)	LDL mean (SD)
Baseline				
observed ($n=886$)	1.47 (1.00; 2.30)	1.98 (0.52)	0.46 (0.16)	1.15 (0.44)
6 months				
observed ($n=294$)	1.15 (0.82; 1.72)	1.79 (0.45)	0.47 (0.15)	1.09 (0.35)
model-based variation from baseline (95% CI)	−30% (−26%; −33%)	−0.19 (−0.24; −0.16)	0.01 (−0.01; 0.0.3)	−0.03 (−0.08; 0.02)
model-based test for variation from baseline	$P<0.0001$	$P<0.0001$	$P=0.24$	$P=0.24$
12 months				
observed ($n=272$)	1.19 (0.78; 1.79)	1.82 (0.43)	0.46 (0.13)	1.12 (0.42)
model-based variation from baseline (95% CI)	−21% (−18%; −24%)	−0.12 (−0.15; −0.10)	−0.01 (−0.02; 0.03)	−0.02 (−0.05; 0.01)
model-based test for variation from 6 months	$P<0.0001$	$P=0.0001$	$P=0.067$	$P=0.78$
24 months				
observed ($n=170$)	1.18 (0.84; 1.73)	1.82 (0.44)	0.46 (0.14)	1.13 (0.37)
model-based variation from baseline (95% CI)	−19% (−16%; −23%)	−0.11 (−0.14; −0.08)	0.00 (−0.01; 0.01)	−0.03 (−0.06; 0.01)
model-based test for variation from 12 months	$P=0.087$	$P=0.35$	$P=0.12$	$P=0.70$

All values are in g/L. Observed values only present the measurements performed within the time frame defined in the protocol. Model-based analyses account for all measurements available, regardless of the date at which they were performed. Given their skewed distribution, triglycerides were log-transformed for analysis. Results are thus expressed as relative variation (in %), whereas results for other parameters are given as absolute variation.

20 genotypes, 7 (35%) yielded NRTIs resistance-associated mutations (6 with thymidine analogue mutations and M184V, and 1 with K65R) and 2 (10%) had mutations associated with atazanavir resistance [1 with I50L and 1 with four PI major mutations (L10I, L33V, I84V and L90M)]. For the 13 patients with available genotypes before starting unboosted atazanavir, we observed the emergence of resistance mutations to NRTIs in 2 patients (M184V and K219E) and to atazanavir in 1 patient (I50L).

There was a small but significant increase in the CD4 cell count of 53 cells/mm^3 (95% CI 40–66 cells/mm^3) from baseline to 2 years ($P<10^{-4}$).

Safety endpoints

During follow-up, 17 patients (0.5%) died (only 5 were still on unboosted atazanavir) and 15 (1.7%) developed an AIDS-defining event [oesophageal candidiasis (2), HIV-related encephalopathy (2), chronic herpes simplex virus infection (2), tuberculosis (2), recurrent bacterial pneumonia (2), cytomegalovirus retinitis (1), disseminated herpes zoster (2), Kaposi's sarcoma (1), *Pneumocystis jiroveci* pneumonia (1) and wasting syndrome (1)].

Eleven patients developed a severe non-AIDS event: 3 patients developed MI or coronary artery diseases (0.34%) and 9 (1%) developed non-AIDS-related cancers. Also, during follow-up, 20 (2.2%) patients developed diabetes, 14 (1.5%) liver cirrhosis and 7 (0.8%) nephrolithiasis.

During follow-up, 272 (30.7%) patients discontinued unboosted atazanavir. Reasons for atazanavir discontinuation were virological failure (35 patients), adverse event (97 patients) and other unknown reasons (140 patients).

Among the 97 patients who discontinued atazanavir for adverse events, 46 presented hyperbilirubinaemia, 12 diarrhoea, 1 nephrolithiasis, 3 pregnancy and 35 other reasons.

Total cholesterol decreased in 79% of the patients during follow-up, with a significant mean change at 12 months of −0.12 g/L ($P=0.0001$). Triglyceride levels also significantly decreased at 12 months, with an average diminution from baseline of 21% ($P<0.0001$). However, no significant change in LDL cholesterol or HDL cholesterol occurred during follow-up (Table 4).

A modest but significant increase in plasma creatinine levels occurred during follow-up both in patients on abacavir (+2 μmol/L at 24 months) and those on tenofovir (+5.4 μmol/L at 24 months). There was, however, a greater increase under tenofovir as compared with abacavir ($P=0.005$).

Discussion

In this large retrospective, multicentre study, we confirm and extend previous observations regarding the use of unboosted atazanavir-based regimens in patients with full suppression of HIV-1 replication under ART. Indeed, the 1 year incidence of virological failure using a 50 copies/mL threshold was only 9.7% in our study, which compares favourably with other studies in which the 1 year rate of virological failure ranged from 7% to 13%.[7,9,10] Also, we were able to identify risk factors for virological failure in our study, i.e. a prior history of virological failure under a PI- or NRTI-based regimen (Table 2). Restricting our study only to patients without prior virological failure, a 1 year rate of virological failure of only 5.3% and a 3 year virological failure rate of only 11.3% were observed, which makes this strategy of an unboosted atazanavir-based regimen quite attractive in patients

without prior virological failure. Using a higher threshold of 400 copies/mL for virological failure, we observed a 1 year rate of virological failure of <2% among patients without prior virological failure, comparable to those rates reported in the INDUMA (5%) and ARIES (2%) studies with similar populations.[7,8]

We were also able to identify risk factors for virological failure in patients without prior virological failure (Table 3). HCV co-infection was associated with a 2.25-fold increased HR of failure ($P=0.026$), a finding consistent with previous studies and that might be a proxy for intravenous drug use and non-adherence.[13–15] Indeed, previous studies have reported that atazanavir plasma levels are not affected by HCV infection and liver fibrosis.[15,16] Unfortunately, plasma drug levels were not recorded in our study and the potential benefit of therapeutic drug monitoring could not be assessed. Also, no data on co-medication with antacids (proton pump inhibitors), which may decrease the atazanavir plasma concentration, were collected in this study. Abacavir use in our study was also associated with a significantly lower risk of virological failure (HR 0.43, $P=0.04$), whereas a trend for a higher risk of virological failure was observed with the use of zidovudine (Table 3). Of note, tenofovir was one of the most frequently used NRTIs in this study, although its combination with unboosted atazanavir is not recommended. We do not have a clear explanation for the large tenofovir use observed, but can hypothesize that tenofovir was prescribed preferentially in patients with HBV co-infection, who presented with abacavir hypersensitivity or with a high cardiovascular risk. Interestingly, the use of tenofovir was not associated with virological failure in our study. Indeed, in the multivariate analysis, tenofovir use was associated with a 1.08 (95% CI 0.52–2.26, $P=0.84$) HR for virological failure, and in an adjusted analysis for HCV co-infection and abacavir use, the HR was even lower [HR 0.70 (95% CI 0.30–1.60), $P=0.39$] (data not shown).

These data are of potential clinical relevance, since the use of tenofovir with unboosted atazanavir is not recommended today due to the reduced AUC of atazanavir when combined with tenofovir.[17] Also, in healthy volunteers, the addition of tenofovir to unboosted atazanavir was associated with a significant reduction in the minimum concentration of atazanavir as compared with the use of atazanavir alone, with a ratio of geometric mean points estimate of 0.72 (90% CI 0.63–0.82).[18] Recent studies also suggest that tenofovir co-administration with unboosted atazanavir may not be associated with lower atazanavir plasma exposure in HIV-infected patients and is associated with favourable outcomes.[19,20] Although, in patients without previous virological failure, tenofovir use was not associated with a higher risk of virological failure, abacavir use was associated with a significantly lower risk of virological failure. Therefore, we should be cautious with the combination of tenofovir and unboosted atazanavir, pending the availability of further data ideally obtained in the setting of a prospective randomized.

This large cohort of patients was also an opportunity to assess the long-term safety of unboosted atazanavir-based regimens. As expected in this well-controlled patient population with high baseline CD4 cell counts, few patients had a clinical progression of HIV disease during a median follow-up of 21 months (1.7%) and only five deaths were reported while patients were still receiving atazanavir. Interestingly, only seven patients (0.8%) reported nephrolithiasis during follow-up, a relatively common adverse event in patients receiving long-term boosted atazanavir regimens.[21]

Hyperbilirubinaemia was reported as the reason for atazanavir discontinuation in 5.2% of patients during follow-up, which is a rate much lower than that reported with unboosted atazanavir in previous studies.[6–10] A low rate of cardiovascular events was reported in this study, with only three patients developing an MI or coronary artery disease. This could be related to the beneficial effect of atazanavir on the carotid intima-media thickness and/or the improved lipid profile associated with unboosted atazanavir use.[6–11,22] Indeed, a significant reduction of total cholesterol and triglycerides levels from baseline was also observed up to 12 months in our study, with no significant changes in LDL or HDL cholesterol (Table 4). Finally, a modest but significant increase in plasma creatinine levels from baseline was reported during follow-up in patients under tenofovir (+5.4 μmol/L at 24 months), which is consistent with previous reports on long-term tenofovir toxicity, especially when used in combination with atazanavir.[17,23]

In conclusion, this large retrospective cohort study suggests that a switch to unboosted atazanavir-based regimens in patients with no prior virological failure is associated with a low risk of virological failure and a good safety profile, and warrants further investigation in prospective randomized trials.

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