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Efficacy and safety of treatment simplification to atazanavir/ritonavir + lamivudine in HIV-infected patients with virological suppression: 144 week follow-up of the AtLaS pilot study

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Objectives: AtLaS was a single-arm pilot study that demonstrated promising efficacy and safety of treatment simplification to a dual regimen with atazanavir/ritonavir+lamivudine in virologically suppressed HIV-positive patients. Here, we report data from the 144 week follow-up.

Methods: At baseline, patients treated with a three-drug atazanavir/ritonavir-based regimen were switched to 300/100 mg of atazanavir/ritonavir plus 300 mg of lamivudine once daily. Major clinical events, laboratory parameters, neurocognitive performance, bone composition and body fat distribution were monitored. Treatment failure was defined as a discontinuation/switch of the regimen or virological failure (HIV-RNA >50 copies/mL in two consecutive determinations or a single level above 1000 copies/mL).

Results: After 144 weeks, 9/40 (22.5%) treatment failures occurred, including two virological failures (Weeks 48 and 53, without resistance). A significant increase in the CD4 count was observed at Week 96 (+124 cells/mm^3; $P=0.002$) and Week 144 (+94 cells/mm^3; $P=0.008$). After 144 weeks, a significant increase in total cholesterol (+25 mg/dL; $P=0.001$), HDL cholesterol (+6 mg/dL; $P=0.024$) and LDL cholesterol (+12 mg/dL; $P=0.008$) was observed, without any change in triglyceride levels, total cholesterol/HDL ratio or LDL/HDL ratio. A significant increase in the estimated glomerular filtration rate (+25 mL/min/1.73 m^2; $P<0.001$) and lumbar spine *T*-score and *Z*-score (+0.2, $P=0.011$; and +0.35, $P=0.001$, respectively) and a decrease in trunk fat (−1.898 g; $P=0.005$) were also observed. Neurocognitive function did not decline over time. Concerning safety, 10 moderate to severe adverse events were recorded in eight patients; overall seven cases of renal colic (possibly treatment related) were observed, leading to a discontinuation of treatment in two patients.

Conclusions: Data from the 144 week follow-up suggested good long-term efficacy of the simplification strategy that was investigated, with rare virological failure and a potential for improvement of the CD4 count, renal function and bone mineral density. This strategy warrants further investigation in a randomized trial.

Keywords: dual therapy, combined antiretroviral therapy, antiviral

Introduction

In recent years, simplification strategies to mono/dual therapies have been investigated to improve the adherence to and long-term tolerability of combined ART (cART) while maintaining virological efficacy.[1–4] Although the results of ritonavir-boosted PI (PI/ritonavir) monotherapy given over a long period have already been reported,[1,2] long-term data for dual strategies are still lacking.

Recently, a 48 week pilot study showed promising efficacy and safety for treatment simplification to atazanavir/ritonavir plus lamivudine.[5] Here, we report data from the 144 week follow-up.

Methods

The study design of the open-label, single-arm AtLaS pilot study (registered as www.clinicaltrials.gov number NCT00885482) has been previously reported.[5] The protocol was approved by the local Ethics Committee and all patients signed an informed consent form before participating in the study.

Briefly, we enrolled 40 HIV-infected adults who had been treated with two NRTIs+atazanavir/ritonavir for at least 6 months, with HIV-RNA <50 copies/mL from ≥3 months, with a CD4 count >200 cells/mm^3 from ≥6 months and without hepatitis B virus (HBV) coinfection, pregnancy, history of virological failure or exposure to mono/dual therapies.

At baseline, patients were switched to 300/100 mg of atazanavir/ritonavir plus 300 mg of lamivudine once daily. Study visits were scheduled at Weeks 4, 12, 24, 36 and 48; follow-up has now been extended to 144 weeks, with visits approximately every 12 weeks to monitor viroimmunological and chemical parameters. Bone mineral density (BMD), biomarkers of bone metabolism [25(OH) vitamin D, parathyroid hormone (PTH) and osteocalcin] and body fat distribution were evaluated at baseline and Weeks 48 and 144.

Treatment failure was defined as any of the following: virological failure, discontinuation of any study drug, reintroduction of standard three-drug regimens, loss to follow-up and progression to AIDS or death.

Virological failure was defined as the first of two consecutive HIV-RNA levels >50 copies/mL or a single level above 1000 copies/mL.

Descriptive statistics were used to evaluate the main study outcomes and adverse events (AEs). Longitudinal differences from baseline were assessed at Weeks 48 and 144 using the Student's *t*-test for paired samples for continuous parameters and McNemar's test for categorical variables. A two-tailed *P* value <0.05 was considered statistically significant.

Results

Population characteristics

Detailed characteristics of the study population have previously been published.[5] Of the 40 patients enrolled, 57.5% were male with a median age of 45 years. At baseline, patients had been on their last cART regimen for a median of 2.6 years; they had had undetectable HIV-RNA for a median of 21 months, a median CD4 count of 598 cells/mm^3 and a median nadir CD4 count of 108 cells/mm^3; almost all (97.5%) had discontinued tenofovir from the NRTI backbone (details in Table S1, available as Supplementary data at *JAC* Online).

Treatment and virological failure

There were 4/40 (10%) treatment failures during the first 48 weeks; between Weeks 49 and 144, five additional treatment failures were observed. Thus, the overall 144 week treatment failure rate was 22.5% (details in Table 1). Overall, only two cases of protocol-defined virological failure occurred (at Weeks 48 and 53) without evidence of resistance. In both patients, virological suppression was re-established while they remained on the dual antiretroviral regimen. One patient discontinued treatment at Week 112 due to frequent HIV-RNA blips without a selection of resistance mutations; stable HIV-RNA resuppression was obtained after the reintroduction of tenofovir/emtricitabine. Two patients discontinued treatment because of recurrent episodes of renal colic at Weeks 50 and 59.

Clinical and laboratory AEs

Twenty-five clinical AEs were reported from follow-up in Weeks 49–144 (Table S2). Most of them were mild to moderate. Two Grade 4 AEs (thyroid and anal cancer) occurred but were not considered to be treatment related.

A high incidence of urolithiasis was observed. Four patients had renal colic during the first 48 weeks, as already described;[5] from Week 49 to Week 144, a new episode was observed in a fifth patient, while two patients had recurring urolithiasis and discontinued atazanavir treatment without any further renal colic.

A non-traumatic vertebral fracture was reported in a 75-year-old man with a history of osteoporosis even though his BMD had remained stable during the study period.

No treatment-limiting or Grade 4 laboratory toxicities occurred (Table S3). Overall, 45% (18/40) of patients experienced a Grade 3 elevation of total bilirubin level (ranging between 3 and 5.5 mg/dL), but none of them discontinued the regimen for this reason. Grade 3 elevations in total cholesterol and LDL cholesterol were observed but were mostly transient.

Evolution of CD4 cell count, fasting lipids, bilirubin and renal function

A significant increase in the CD4 cell count was observed from baseline at Weeks 96 and 144 (mean change +124 cells/mm^3, $P=0.002$; and +94 cells/mm^3, $P=0.008$, respectively). A consensual rise in the CD4/CD8 ratio was reported at Week 144 (mean change +0.06; $P=0.008$). At Weeks 96 and 144, increases were recorded for total cholesterol (mean change +19 mg/dL, $P=0.002$; and +25 mg/dL, $P=0.001$, respectively), HDL cholesterol (mean change +4 mg/dL, $P=0.002$; and +6 mg/dL, $P=0.024$, respectively) and LDL cholesterol (mean change +15 mg/dL, $P=0.001$; and +12 mg/dL, $P=0.008$, respectively). However, triglycerides, total cholesterol/HDL and LDL/HDL ratios showed no significant alterations.

When compared with baseline, an improvement in glomerular filtration rate, estimated by the Modification of Diet in Renal Disease equation, was reported after 96 and 144 weeks (mean change +17 mL/min/1.73 m^2, $P<0.001$; and +25 mL/min/1.73 m^2, $P<0.001$). No significant change from baseline values was observed for liver enzymes, amylase, total and unconjugated bilirubin after 144 weeks.

Evolution of BMD, bone metabolism markers and body fat distribution

At Week 144, a DXA scan and bone metabolism markers were evaluated in 26 (65%) patients (Table 2).

Lumbar spine *T*-score and *Z*-score BMD values showed a significant improvement from baseline (+0.20, $P=0.011$; and +0.35, $P=0.001$, respectively), but no significant percentage changes in BMD or changes in *T*-score and *Z*-score were observed for other areas of the body that were scanned.

A significant decrease in PTH (mean change −12.31 pg/mL; $P=0.003$), osteocalcin (mean change −12.70 ng/mL; $P<0.001$) and 25(OH) vitamin D (mean change −6.87 ng/mL; $P=0.001$) was reported at Week 144. For most patients (23/26, 88.5%), the dates of the baseline and the 144 week follow-up occurred in the same period of the year (i.e. in a sunny period, from May to October); thus, 25(OH) vitamin D levels were not affected by seasonal changes. Vitamin D supplementation was not routinely administered during the study. In fact, only one patient who had severe osteoporosis complicated by a bone fracture received a long course of calcium and vitamin D supplementation.

Exploring body composition, we observed a significant reduction in trunk fat (−1898 g; $P=0.005$) at Week 144 without any changes in total and limb fat, as well as a consequent improvement in the limb/trunk fat ratio (+0.10; $P=0.005$). Moreover, there was a significant increase in both total and limb lean mass (+3032 g and +2840 g; $P<0.001$) and a slight decrease in lean trunk mass (−772 g; $P=0.009$).

Table 1. Reasons for treatment discontinuation

ID	Withdrawal visit	Reason	Last VL (copies/mL)	Last CD4 (cells/mm^3)	TDM (ng/mL)	GRT after study end	VL after withdrawal (copies/mL)	Comments
1	week 4	pregnancy	<37	586	316 (C_{12})	NA	<37	reinduction with FTC/TDF+ATV/r, with optimal virological control and tolerability
2	week 21	brain haemorrhage	<37	747	330 (C_{12})	NA	NA	not considered treatment related
3	week 36	patient withdrawn (confirmed inadequate TDM)	<37	762	<5 (C_{24})	NA	<37	subsequent VL <37 copies/mL without treatment change
4	week 48	virological failure	4947	482	<5 (C_{12})	no DRMs	<37	subsequent VL <37 copies/mL without treatment change
5	week 50	recurrent renal colic	<37	874	NA	NA	<37	therapeutic change with FTC+DRV/r, with optimal virological control; no further episodes of renal colic
6	week 53	virological failure	112	455	NA	no GRT performed	<37	subsequent VL <37 copies/mL without treatment change; after 1 year, occurrence of high VL (2978 copies/mL) on a single occasion; GTR did not show DRMs; subsequent optimal virological control without treatment change; always referred good adherence to ART
7	week 55	lost to follow-up	<37	647	NA	NA	NA	
8	week 59	recurrent renal colic	<37	567	NA	NA	<37	therapeutic change with TDF/FTC+RAL, with optimal virological control; no further episodes of renal colic
9	week 112	non-consecutive blips in VL	<37	1314	NA	no DRMs	<37	reinduction with FTC/TDF+ATV/r, with optimal virological control and tolerability

VL, viral load; TDM, therapeutic drug monitoring of plasma levels of atazanavir; GRT, genotypic resistance test; C_{12}, mid-dosing interval concentration (12±2 h after drug intake); NA, not applicable; FTC, emtricitabine; TDF, tenofovir; ATV/r, atazanavir/ritonavir; C_{24}, trough concentration (24±2 h after drug intake); DRM, drug resistance mutation; DRV/r, darunavir/ritonavir; RAL, raltegravir.

Neurocognitive performance

At Week 144, 19/40 (47.5%) patients completed the neurocognitive examination (Table S4). At baseline, 4/19 patients (21%) showed a profile of Asymptomatic Neurocognitive Impairment;[6] at Week 144, this proportion remained identical ($P=1.000$). Overall, no significant differences from baseline were observed in neurocognitive performance on any test, except for an improvement in Stroop test errors (mean change −1.39; $P=0.033$). The total number of pathological performances did not differ from baseline (mean change −0.16; $P=0.591$).

Discussion

After the 144 week follow-up, the AtLaS pilot study showed an overall treatment failure rate of 22.5%, with a low incidence of virological failure. Indeed, only two virological failures (5%) occurred during the follow-up, probably due to transient suboptimal adherence. In both patients, virological suppression was regained without a change in treatment and no resistance mutations were selected. Furthermore, immunological recovery from baseline, which was not found during the first 48 weeks, was reported at Weeks 96 and 144. This reconstitution of the immune system was expressed not only by an increase in CD4 cell count but also by a rise in the CD4/CD8 ratio, which is considered to be a stronger predictor of immune dysfunction/activation and thereby of morbidity and mortality.[7] This finding is difficult to interpret because of the small population studied and the lack of a comparator arm. One explanation could be that the constant and sustained virological suppression, which was also maintained after treatment simplification to a dual regimen, could have led to progressive immunological recovery. However, these data must be confirmed in larger randomized trials.

Trials investigating simplification to PI/ritonavir monotherapy have produced conflicting results in terms of long-term efficacy. At Week 144, the MONET trial did not confirm a non-inferior efficacy of

Table 2. Changes in bone composition, bone metabolism biomarkers and body fat distribution after 144 weeks

	Baseline values	Changes after 144 weeks	Percentage change in BMD after 144 weeks	*P*
Weight, kg	74 (15)	+0.9 (3.8)	—	0.218
BMI (kg/m^2)	25 (4)	+2.6 (11.4)	—	0.242
Bone composition				
total BMD (g/cm^2)	1.03 (0.09)	−0.05 (0.04)	−0.69% (4.26)	0.607
total *Z*-score	−0.60 (0.92)	+0.10 (0.57)	—	0.429
total *T*-score	−1.07 (1.03)	−1.79 (7.97)	—	0.317
femoral neck BMD (g/cm^2)	0.79 (0.14)	0.00 (0.80)	+0.39% (10.14)	0.948
femoral neck *Z*-score	−0.32 (1.02)	+0.02 (0.50)	—	0.816
femoral neck *T*-score	−0.87 (1.04)	−0.09 (0.48)	—	0.333
total hip BMD (g/cm^2)	0.92 (0.14)	−0.02 (0.06)	−2.24% (6.48)	0.076
total hip *Z*-score	−0.16 (0.96)	−0.07 (0.47)	—	0.433
total hip *T*-score	−0.48 (0.98)	−0.17 (0.47)	—	0.073
L2–L4 column BMD (g/cm^2)	0.99 (0.17)	+0.01 (0.06)	+1.13% (5.63)	0.289
L2–L4 column *Z*-score	−0.59 (1.53)	+0.35 (0.47)	—	**0.001**
L2–L4 column *T*-score	−0.99 (1.56)	+0.20 (0.36)	—	**0.011**
Bone metabolism biomarkers				
25(OH) vitamin D (ng/mL)	27.20 (8.25)	−6.87 (8.92)	—	**0.001**
PTH (pg/mL)	53.71 (17.31)	−12.31 (18.27)	—	**0.003**
osteocalcin (ng/mL)	34.07 (13.05)	−12.70 (12.96)	—	**<0.001**
Body fat distribution				
total fat mass (g)	21488 (8014)	−1739 (4653)	—	0.094
limb fat mass (g)	8451 (3114)	−83 (2182)	—	0.857
trunk fat mass (g)	12001 (5409)	−1898 (2890)	—	**0.005**
limb/trunk fat mass ratio	1.10 (0.30)	+0.10 (0.16)	—	**0.005**
total lean mass (g)	51804 (11356)	+3032 (2092)		**<0.001**
limb lean mass (g)	21094 (5291)	+2840 (2099)		**<0.001**
trunk lean mass (g)	27138 (5842)	−772 (1260)		**0.009**

Values are expressed as mean (SD) change.
Bold values represent statistically significant *P* values.

darunavir/ritonavir monotherapy compared with darunavir/ritonavir plus two NRTIs using the time to loss of virological response algorithm (switch=failure).[2] The OK04 study (lopinavir/ritonavir monotherapy versus lopinavir/ritonavir+two NRTIs) reported similar results at 96 weeks.[1] The MODAt trial was prematurely halted due to inferior virological efficacy after 48 weeks of simplification to atazanavir/ritonavir monotherapy over the continuation of a standard atazanavir-based triple therapy.[8] Theoretically, the addition of another agent to PI monotherapy should improve the long-term efficacy, but no head-to-head comparison between PI/ritonavir-based mono and dual therapies is available. Recent studies have compared different types of PI/ritonavir-based dual regimens (NRTI-sparing or lamivudine-based) with standard triple regimens in both treatment-naive and virologically controlled treatment-experienced patients. Although dual therapy showed an optimal safety profile, the findings are controversial in terms of virological efficacy. Indeed, some trials have demonstrated comparable virological efficacy between dual and triple therapies,[4,9–11] but in others dual regimens did not reach non-inferiority when compared with standard regimens in either the whole population[12,13] or the hard-to-treat subgroups (e.g. patients with a low CD4 cell count).[14] For these reasons, PI/ritonavir-based dual strategies should be further investigated.

With regard to safety, a high incidence of urolithiasis was observed in our study, which resulted in treatment discontinuation in two patients. Urolithiasis has already been described in patients receiving atazanavir/ritonavir-based cART.[15,16] In our population, discontinuation of tenofovir could have increased atazanavir levels, thus acting as a trigger for urinary stone formation.[17] However, an individual predisposition and environmental factors such as a low fluid intake and dehydration could also have had an important role. Since a comparator arm was not included in the study, no firm conclusions can be drawn about this AE. Nevertheless, preliminary results from two ongoing randomized trials exploring an atazanavir/ritonavir plus lamivudine simplification regimen have not shown a higher incidence of renal colic for dual versus three-drug therapy.[18,19] Only a few other severe AEs were reported during the follow-up; however, they were not considered to be treatment related and did not require an interruption of treatment. Although hyperbilirubinaemia was the most frequent laboratory-reported AE, no treatment interruptions for jaundice were reported. This finding is consistent with many previous trials reporting low rates of atazanavir discontinuation due to an elevation in bilirubin level.[20,21] It should be emphasized that all the patients in our study were already

being treated with atazanavir; thus, it is possible that simplification from a non-atazanavir-containing regimen could have led to higher rates of discontinuation, especially for toxicity. Since a recent trial showed a better tolerability of darunavir when compared with atazanavir,[22] we can probably assume that dual therapy with darunavir/ritonavir plus lamivudine might be a valuable and competitive simplification strategy. Nevertheless, as the superiority of darunavir in terms of tolerability has not always been proven,[23] this hypothesis needs to be evaluated in further studies.

Confirming the results of the 48 week follow-up, an elevation in total and LDL cholesterol was also observed at the 144 week follow-up. Since these alterations were well balanced by a proportional increase in HDL cholesterol, the total cholesterol/HDL cholesterol and HDL/LDL cholesterol ratios, which are good predictors of coronary disease risk, did not change. These findings could be explained by the discontinuation of tenofovir (which has a recognized lipid-lowering effect)[24] in most patients.

Simplification to atazanavir/ritonavir + lamivudine led to a progressive improvement of renal function and an increase in lumbar column BMD, possibly due to the discontinuation of tenofovir.[25–27] Likewise, the decrease in PTH and 25(OH) vitamin D could be explained by the removal of the tenofovir-induced bone mineral loss or by dysfunction of the proximal renal tubule.[28,29] These findings might be particularly relevant in the ageing HIV-infected population, in whom an accelerated deterioration of renal function and bone mineralization can occur.

An improvement in body mass composition, with a reduction in trunk fat and a gain in total and limb lean mass, emerged from our study. These findings are not consistent with data from previous trials investigating simplification to PI/ritonavir monotherapies in which an increase in limb and/or trunk fat was reported in the monotherapy arm.[30,31] In terms of fat-free mass, an increased lean body mass has already been described in treatment-naive patients starting cART,[32,33] whereas changes in lean mass in treatment-experienced subjects after simplification of their treatment regimen are less clear.[33,34] The observed increase in lean body mass in our population might be related to sustained virological control and immunological recovery, thus reflecting an improvement in health status[34]; however, an influence of tenofovir withdrawal on this change cannot be completely excluded. Indeed, an association between tenofovir use and a decrease in lean mass has already been reported.[35] Given the small size of our population and the lack of a comparator arm, this finding should be further investigated in randomized trials.

Finally, neurocognitive performance was no worse 144 weeks after the simplification of treatment. Although these results should be interpreted with caution, the lack of neurocognitive deterioration in a long-term follow-up might be relevant in light of the concern that atazanavir has low cerebrospinal penetration.[36] Our findings are consistent with the results of other trials that reported no detrimental effects on short- and long-term neurocognitive performance assessed by a test battery after simplification to boosted-PI mono or dual therapy.[37–39] However, a possible viral escape has recently been hypothesized in patients treated with PI/ritonavir monotherapy.[40]

In summary, the 144 week follow-up results of the AtLaS pilot study suggest that simplification therapy using atazanavir/ritonavir plus lamivudine can be safe and effective. The long-term virological suppression with few virological failures and the good safety profile suggest that this regimen might be suitable as a long-term antiretroviral maintenance treatment. The efficacy and safety of this simplification strategy are currently being investigated in two large ongoing multicentre randomized trials in Spain (the SALT trial)[18] and Italy (the ATLAS-M trial).[19] The 48 week results of the former and the 24 week interim analysis results of the latter are very encouraging because they show non-inferior efficacy and similar safety for the atazanavir/ritonavir plus lamivudine dual therapy compared with a standard three-drug regimen.

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M. F. has received speakers' honoraria from Abbott Virology, Merck Sharp & Dohme and Janssen-Cilag. M. C. has been a paid consultant for Merck Sharp & Dohme, Italy and was employed by Bristol-Myers Squibb, Italy from 10 May 2010 to 28 February 2011. R. C. has been an advisor for Gilead and Janssen-Cilag, has received speakers' honoraria from ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme and Janssen-Cilag, and has received research support from 'Fondazione Roma'. A. D. L. has received speaker's honoraria and fees for attending advisory boards from ViiV Healthcare, Gilead, Abbott Virology, Janssen-Tibotec, Siemens Diagnostics and Monogram Biosciences. S. D. G. has received speakers' honoraria and support for travel to meetings from Gilead, Bristol-Myers Squibb, Abbott, Boehringer Ingelheim, Janssen-Cilag and GlaxoSmithKline. All the other authors: none to declare.

Supplementary data

Tables S1 to S4 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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