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Treatment simplification to atazanavir/ritonavir + lamivudine versus maintenance of atazanavir/ritonavir + two NRTIs in virologically suppressed HIV-1-infected patients: 48 week results from a randomized trial (ATLAS-M)

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Background: Combination ART (cART)-related toxicities and costs have prompted the need for treatment simplification. The ATLAS-M trial explored 48 week non-inferior efficacy of simplification to atazanavir/ritonavir + lamivudine versus maintaining three-drug atazanavir/ritonavir-based cART in virologically suppressed patients.

Methods: We performed an open-label, multicentre, randomized, non-inferiority study, enrolling HIV-infected adults on atazanavir/ritonavir + two NRTIs, with stable HIV-RNA <50 copies/mL and CD4 + >200 cells/mm^3. Main exclusion criteria were hepatitis B virus coinfection, past virological failure on or resistance to study drugs, recent AIDS and pregnancy. Patients were randomly assigned 1:1 to either switch to 300 mg of atazanavir/100 mg of ritonavir once daily and 300 mg of lamivudine once daily (atazanavir/ritonavir + lamivudine arm) or to continue the previous regimen (atazanavir/ritonavir + two NRTIs arm). The primary study outcome was the maintenance of HIV-RNA <50 copies/mL at week 48 of the ITT-exposed (ITT-e) analysis with switch = failure. The non-inferiority margin was 12%. This study is registered at ClinicalTrials.gov, number NCT01599364.

Results: Between July 2011 and June 2014, 266 patients were randomized (133 to each arm). After 48 weeks, the primary study outcome was met by 119 of 133 patients (89.5%) in the atazanavir/ritonavir + lamivudine arm and 106 of 133 patients (79.7%) in the atazanavir/ritonavir + two NRTIs arm [difference atazanavir/ritonavir + lamivudine versus atazanavir/ritonavir + two NRTIs arm: +9.8% (95% CI + 1.2 to + 18.4)], demonstrating non-inferiority and superior efficacy of the atazanavir/ritonavir + lamivudine arm. Virological failure occurred in two (1.5%) patients in the atazanavir/ritonavir + lamivudine arm and six (4.5%) patients in the atazanavir/ritonavir + two NRTIs arm, without resistance selection. A similar proportion of adverse events occurred in both arms.

Conclusions: Treatment simplification to atazanavir/ritonavir + lamivudine showed non-inferior efficacy (superiority on post-hoc analysis) and a comparable safety profile over continuing atazanavir/ritonavir + two NRTIs in virologically suppressed patients.

Introduction

Combination ART (cART) has markedly improved the prognosis of HIV-infected patients;[1] however, long-term exposure to antiretroviral drugs has been associated with a potential development of drug toxicity. In particular, in recent years NRTI-associated toxicities have become a matter of concern.[2] Several NRTI-sparing regimens have been studied with conflicting results.[3,4] Monotherapies with boosted PIs (PI/r) as simplification strategies have shown interesting results, but their efficacy is not equivalent to standard triple therapy particularly in more advanced patients.[5–7]

Dual cART regimens including a PI/r + lamivudine have been tested in randomized studies in treatment-naive patients[8] or as simplification strategies in virologically suppressed patients.[9–13] Atazanavir/ritonavir + lamivudine showed long-term efficacy and tolerability in the single-arm ATLAS pilot study[11] and demonstrated non-inferior efficacy when compared with atazanavir/ritonavir + two NRTIs in patients previously receiving different three-drug combinations in the randomized SALT trial.[12] The aim of our study was to explore the efficacy and safety of treatment simplification to a dual regimen with atazanavir/ritonavir + lamivudine, as compared with continuing a previously stable, virologically effective regimen with atazanavir/ritonavir + two NRTIs.

Patients and methods

Trial design

ATLAS-M is an open-label, randomized, non-inferiority trial.

Ethics

The protocol was approved by the Ethics Committees of each participating centre (21 hospitals in Italy) and all procedures were performed in accordance with the Declaration of Helsinki. Patients provided written informed consent to study participation before enrolment. The ATLAS-M study was registered with ClinicalTrials.gov, number NCT01599364.

Participants

The study enrolled adult (>18 years old), HIV-1-infected patients on an antiretroviral regimen including atazanavir/ritonavir + two NRTIs for at least 3 months, with HIV-RNA <50 copies/mL, and CD4 >200 cells/μL for at least 6 months. Exclusion criteria were: previous virological failure on or resistance to atazanavir and/or lamivudine; previous exposure to mono/dual therapies; co-administration of proton pump inhibitors or other medications with known drug–drug interactions potentially reducing exposure to atazanavir; hepatitis B virus coinfection; opportunistic infections or other AIDS-related events in the year before screening; pregnancy, lactation or planned pregnancy; major toxicities related to any of the study drugs; grade 4 laboratory abnormalities at screening (excluding blood lipids and bilirubin concentration); and any illness, which could, in the clinician's judgement, jeopardize the patient's compliance. Patients were pre-screened to fulfil inclusion criteria based on medical records, and then underwent a screening visit for confirmation.

Randomization

At baseline, patients were randomized 1:1 to: (i) treatment switch to 300 mg of atazanavir with 100 mg of ritonavir once daily and 300 mg of lamivudine once daily (atazanavir/ritonavir + lamivudine arm); or (ii) to continue 300 mg of atazanavir boosted with 100 mg of ritonavir once daily with the same NRTI backbone (atazanavir/ritonavir + two NRTIs arm). Randomization was web-based, computer-assigned and stratified according to the line of ongoing therapy (first line versus other) and the enrolling centre, using blocks of two or four elements.

Procedures

Follow-up study visits were planned at week 4, week 12 and every 12 weeks until week 96. At each visit, physical examination and routine laboratory tests (HIV-RNA, CD4 count, blood chemistry, urinalysis and pregnancy test in women of reproductive age) were performed. Adherence was assessed by a previously published self-report questionnaire measuring adherence on a 0–100 visual analogue scale;[14] patients reporting an adherence <90% in at least one visit were considered as sub-optimally adherent.

Treatment failure was defined by any of the following: virological failure, any treatment modification or discontinuation, loss to follow-up, consent withdrawal, progression to AIDS, or death for any cause. Virological failure was defined as the first of two consecutive HIV-RNA levels >50 copies/mL or a single level >1000 copies/mL. Viral blips were defined as transient HIV-RNA levels >50 copies/mL preceded and followed by another viral load <50 copies/mL without any treatment change.

In case of treatment failure or virological failure, patients discontinued the study. Genotypic resistance testing was performed on plasma samples at the time of virological failure and interpreted according to the HIVDB version 7.0 algorithms.[15] Atazanavir plasma levels were also measured in these patients using a validated technique.[16]

Adverse events (AEs) were defined as any new event of any grade occurring after baseline and were classified as drug related or not on the basis of the investigator's judgement and scored according to the DAIDS grading scale.[17] In addition, grade 3 or 4 laboratory toxicities were recorded as total events and as new events occurring after baseline.

Outcomes

The primary efficacy endpoint was the proportion of patients without treatment failure at week 48. Analysis of the primary efficacy endpoint was performed with both the ITT-exposed (ITT-e) population and the PP population. Moreover, a 48 week FDA snapshot analysis of treatment efficacy on the ITT-e and PP populations was carried out.

Secondary endpoints included the development of virological failure and drug resistance, the occurrence of clinical and laboratory AEs, and the changes of CD4 cell count, blood lipid levels, renal function and self-reported adherence from baseline to week 48.

Statistical analysis

This study was designed as a non-inferiority trial to verify if the proportion of patients without treatment failure in the atazanavir/ritonavir + lamivudine arm was not inferior to that in the atazanavir/ritonavir + two NRTIs arm. The non-inferiority margin was set at −12%. Assuming a proportion of success at 48 weeks in the atazanavir/ritonavir + two NRTIs arm of 90%, an α value of 5% and a power of 80%, we calculated a required sample size of 120 patients per arm. Considering a 10% margin for patients lost to follow-up, the sample size was set at 133 patients per arm.

All patients randomized at baseline, who received at least one dose of the study drugs, were included in the ITT-e population. The PP population included all subjects from the ITT-e population except those with major protocol violations.

Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Continuous variables were compared using the Student *t*-test or Mann–Whitney *U*-test as appropriate. All statistical tests were two-tailed and only $P < 0.05$ was considered significant. All analyses were performed using the SPSS version 18.0 software package (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics

Between July 2011 and June 2014, a total of 275 patients were screened for study participation and 266 patients were randomized, 133 subjects to each study arm (see Figure 1). Baseline patient demographic, clinical, virological and immunological characteristics were similar between arms (see Table 1).

Treatment failures and virological failures

At 48 weeks, at the ITT-e analysis patients free of treatment failure were 119 of 133 (89.5%; 95% CI 84.3–94.7) in the atazanavir/ritonavir + lamivudine arm and 106 of 133 (79.7%; 95% CI 72.9–86.5) in the atazanavir/ritonavir + two NRTIs arm (difference atazanavir/ritonavir + lamivudine minus atazanavir/ritonavir + two NRTIs +9.8%, 95% CI +1.2 to +18.4, $P = 0.027$) (see Figure 2).

Similar results were observed at the PP analysis: 118 of 131 (90.1%, 95% CI 85.0–95.2) patients in the atazanavir/ritonavir + lamivudine arm as compared with 103 of 129 (79.8%, 95% CI 72.9–86.7) patients in the atazanavir/ritonavir + two NRTIs arm were free of treatment failure (difference between arms +10.3%, 95% CI +1.7 to +18.9, $P = 0.021$).

These results fulfil the pre-defined non-inferiority criteria and indicates superior efficacy of switching to atazanavir/ritonavir + lamivudine over continuing atazanavir/ritonavir + two NRTIs.

At 48 weeks, the snapshot analysis also showed non-inferiority of switching to atazanavir/ritonavir + lamivudine. In the ITT-e population, 115 of 133 patients in the atazanavir/ritonavir + lamivudine arm (86.5%; 95% CI 80.7–92.3) versus 106 of 133 in the atazanavir/ritonavir + two NRTIs arm (79.7%; 95% CI 72.9–86.5) were free of treatment failure (difference between arms +6.8%, 95% CI −2.2 to +15.8, $P = 0.141$). In the PP population, treatment success was achieved in 114 of 131 patients in the atazanavir/ritonavir + lamivudine arm (87.0%; 95% CI 81.2–92.8) versus 103 of 129 in the atazanavir/ritonavir + two NRTIs arm (79.8%; 95% CI 72.9–86.7) (difference between arms +7.2%, 95% CI −1.8 to +16.2, $P = 0.119$) (see Figure 2).

Detailed causes of treatment failure are reported in Table 2. Virological failure occurred in two (1.5%) patients in the atazanavir/ritonavir + lamivudine arm (including one at baseline, before treatment switch) and six (4.5%) patients in the triple therapy arm (difference between arms −3%; 95% CI −7.1 to +1.1, $P = 0.282$); all subjects with virological failure were treated with atazanavir/ritonavir + tenofovir/emtricitabine before baseline. At virological failure, plasma samples from seven patients (two patients in the atazanavir/ritonavir + lamivudine arm and five in the atazanavir/ritonavir + two NRTIs arm) were available for genotypic resistance testing and quantification of atazanavir levels. No relevant resistance mutations were detected in the protease gene or in the reverse transcriptase gene. Undetectable atazanavir levels (<0.05 mg/L) were found in one of two (50%) and three of five (60%) plasma samples obtained at the time of virological failure in the atazanavir/ritonavir + lamivudine and atazanavir/ritonavir + two NRTIs arm, respectively. In the remaining patients, the atazanavir concentration was above the suggested mid-dosing interval or trough concentration efficacy cut-off.[18,19] Viral blips not leading to virological failure or treatment discontinuation were observed in 10 (7.5%) patients in the atazanavir/ritonavir + lamivudine arm and 16 (12.0%) in the comparator arm ($P = 0.302$). Treatment failure due to AEs (both potentially treatment related and not treatment related) did not differ between the two arms (see Table 2).

As withdrawal of consent was particularly represented in the triple therapy arm and this could have been influenced by the open-label design of the study, thus influencing the results, we performed an efficacy sensitivity analysis in the ITT-e population excluding patients with treatment failure due to withdrawal of consent. In this analysis, patients free of treatment failure were 115 of 127 (90.6%; 95% CI 85.5–95.7) in the atazanavir/ritonavir + lamivudine arm and 104 of 124 (83.9%; 95% CI 77.4–90.4) in the atazanavir/ritonavir + two NRTIs arm (difference atazanavir/ritonavir + lamivudine minus atazanavir/ritonavir + two NRTIs +6.7%, 95% CI −1.5 to +14.9, $P = 0.113$), confirming non-inferiority of dual therapy.

Clinical and laboratory AEs

Overall, 68 and 90 clinical AEs of any grade occurred in the atazanavir/ritonavir + lamivudine and comparator arms, respectively. The majority of clinical AEs were mild to moderate. There were seven grade 3–4 clinical AEs (three in the atazanavir/ritonavir + lamivudine arm and four in the atazanavir/ritonavir + two NRTIs arm), none of which was considered treatment related. Overall, five renal colics occurred: three in the atazanavir/ritonavir + two NRTIs arm and two in the atazanavir/ritonavir + lamivudine arm. Four patients demonstrated osteopenia/osteoporosis in the atazanavir/ritonavir + two NRTIs arm (all considered related to treatment with tenofovir, leading to regimen discontinuation in two patients), while no bone events were observed in the dual therapy arm. No significant differences were observed between study arms in the proportion of patients with at least one clinical AE. Details about clinical AEs are summarized in Table 3.

The proportion of patients with grade 3–4 laboratory toxicities is shown in Table 4. Most grade 3–4 laboratory toxicities were transient and none led to treatment discontinuation. Incident grade 3–4 hyperbilirubinaemia was more frequent in the dual therapy arm [44 of 99 (44.4%) versus 28 of 99 (28.3%) in the triple therapy arm, $P = 0.027$]. Other laboratory toxicities were equally distributed between the two arms.

Evolution of CD4 cell count, lipid levels and renal function

The evolution of CD4 cell count, estimated glomerular filtration rate (eGFR) and blood lipids is illustrated in Figure 3(a–c).

At 48 weeks, the changes from baseline CD4 cells were not significantly different between atazanavir/ritonavir + lamivudine and comparator arms.

The evolution of eGFR was more favourable in the atazanavir/ritonavir + lamivudine arm as compared with the control arm: at week 48, the mean change from baseline eGFR (using CKD-EPI) was +2 mL/min/1.73 m^2 (95% CI −1 to 6) in the atazanavir/ritonavir + lamivudine arm versus −5 mL/min/1.73 m^2 (95% CI −8 to −2) in the comparator arm ($P < 0.001$). This benefit was confirmed in the subgroup of evaluable patients using tenofovir at baseline (92 and 90 in atazanavir/ritonavir + lamivudine and comparator arms, respectively): +3 mL/min/1.73 m^2 (95% CI −1 to 6) in the

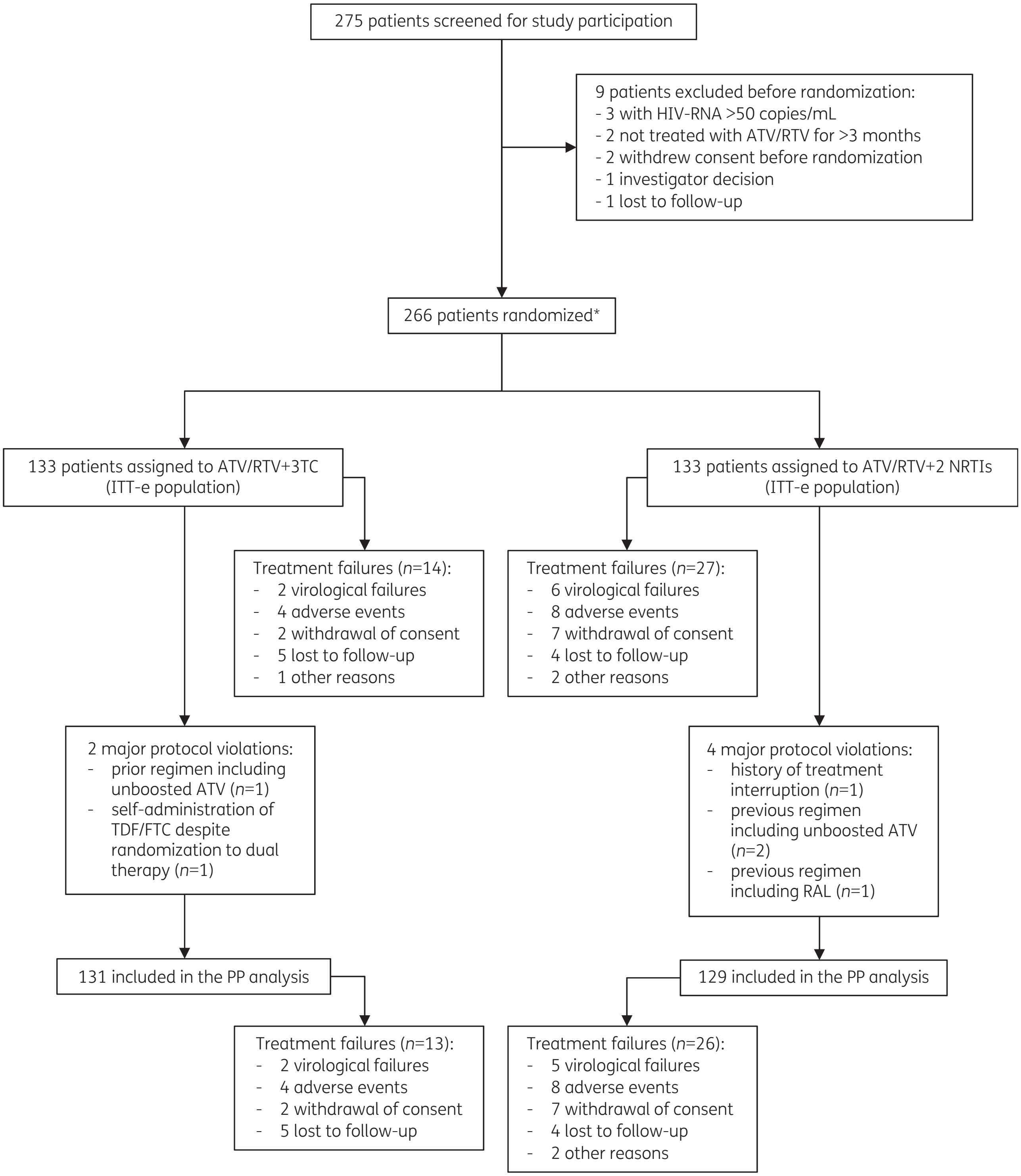

Figure 1. Flow chart showing patient allocation throughout the study and main study outcomes. ATV, atazanavir; RTV, ritonavir; 3TC, lamivudine; TDF, tenofovir; FTC, emtricitabine; RAL, raltegravir. *All randomized patients received at least one dose of study drugs and were thus included in the safety analysis exploring clinical and laboratory AEs.

atazanavir/ritonavir + lamivudine arm versus -5 mL/min/1.73 m^2 (95% CI -9 to -2) in the comparator arm ($P < 0.001$).

Total cholesterol, HDL cholesterol and LDL cholesterol showed a significant increase in the atazanavir/ritonavir + lamivudine arm as compared with the control arm (see Figure 3b). No significant differences in the changes of triglycerides and total cholesterol/HDL cholesterol and HDL cholesterol/LDL cholesterol ratios were observed between the two arms.

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Table 1. Baseline patient characteristics

	Total population, $N = 266$	Atazanavir/ritonavir + lamivudine, $N = 133$	Atazanavir/ritonavir + 2 NRTIs, $N = 133$
Age (years), median (IQR)	44 (36–50)	44 (36–49)	44 (36–51)
Male, *n* (%)	212 (79.7)	112 (84.2)	100 (75.2)
Risk factor, *n* (%)			
heterosexual	108 (40.6)	48 (36.1)	60 (45.1)
homosexual/bisexual	116 (43.6)	64 (48.1)	52 (39.1)
IVDU	20 (7.5)	9 (6.8)	11 (8.3)
other/unknown	22 (8.3)	12 (9.0)	10 (7.5)
Hepatitis C virus coinfection, *n* (%)	28 (10.5)	14 (10.5)	14 (10.5)
Previous AIDS events, *n* (%)	34 (12.8)	18 (13.5)	16 (12.0)
Years from HIV diagnosis, median (IQR)	4.5 (2.2–9.5)	4.2 (2.2–9.0)	5.2 (2.6–10.3)
Years from first cART initiation, median (IQR)	2.7 (1.6–5.5)	2.8 (1.7–5.1)	2.7 (1.6–6.4)
ART line, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)
Months from last regimen initiation, median (IQR)	29.1 (17.1–53.0)	28.7 (17.9–52.9)	29.2 (16.2–54.6)
NRTI backbone, *n* (%)			
tenofovir + emtricitabine/lamivudine	217 (81.6)	105[a] (78.9)	112[a] (84.2)
abacavir + lamivudine	43 (16.2)	25 (18.8)	18 (13.5)
other	6 (2.3)	3[b] (2.3)	3[c] (2.3)
Nadir CD4 count (cells/μL), median (IQR)	265 (132–357)	274 (118–357)	257 (144–357)
Current CD4 count (cells/μL), median (IQR)	617 (481–781)	622 (472–779)	616 (486–783)
Months from last HIV-1 RNA >50 copies/mL, median (IQR)	22.0 (12.6–45.0)	23.5 (12.6–46.5)	20.8 (12.3–44.8)

[a]One patient in each arm treated with tenofovir + lamivudine, all the others with tenofovir + emtricitabine.
[b]Two zidovudine + lamivudine, one didanosine + lamivudine.
[c]One zidovudine + lamivudine, one tenofovir + abacavir, one no NRTI backbone (treated with atazanavir/ritonavir + raltegravir, major protocol deviation).

Adherence measures

Self-reported adherence was provided by 247 (92.9%) patients [125 (94.0%) in the atazanavir/ritonavir + lamivudine arm and 122 (91.7%) in the control arm]. During the study, the two treatment arms did not significantly differ for adherence levels at any study visit [mean change versus baseline at 48 weeks: +2% (95% CI −3 to +6) in the atazanavir/ritonavir + lamivudine arm versus −2% (95% CI −4 to +1) in the comparator arm, $P = 0.165$]. Suboptimal adherence was not significantly different in patients experiencing virological failure as compared with those not [71.4% (5 of 7) versus 53.5% (130 of 243), $P = 0.457$].

Discussion

In the ATLAS-M trial, simplification to a dual therapy with atazanavir/ritonavir and lamivudine met non-inferiority over continuation of triple therapy at all analyses. Moreover, a statistically superior efficacy of dual therapy was shown at the primary endpoint analysis, although this analysis was not determined a priori. This superiority resulted from the combination of several factors: a lower rate of virological failure, a lower discontinuation rate for treatment-related toxicity and the less frequent withdrawal of consent in patients randomized to atazanavir/ritonavir + lamivudine. All three reasons may be interpreted as signs of an overall better tolerability of this regimen over the comparator. In agreement with this, a lower number of clinical AEs and a significant improvement of renal function were observed in the atazanavir/ritonavir + lamivudine arm versus the comparator arm. These results are in line with the good efficacy and tolerability observed with atazanavir/ritonavir + lamivudine as switch therapy in the ATLAS single-arm, pilot study, which extended its observation up to 144 weeks.[9,11] In a previous randomized controlled study (the SALT trial) with a similar sample size as the present one, atazanavir/ritonavir + lamivudine showed non-inferior efficacy at 48 weeks as compared with atazanavir/ritonavir + two NRTIs in patients switching from different standard three-drug cART regimens.[12] The very similar efficacy results of the SALT and ATLAS-M trials confirm the robustness of this strategy in different contexts. Superiority of atazanavir/ritonavir + lamivudine was not shown in the SALT study, although the direction of the difference was similar to ATLAS-M, possibly because of the different design of SALT, which enrolled patients on any cART type and allowed switching of the NRTI type at baseline in those with tolerability issues. ATLAS-M did not specifically screen patients with NRTI-related toxicities, but >80% of patients randomized to continuing their ongoing regimen were on tenofovir disoproxil fumarate. Therefore, patients in the comparator arm of ATLAS-M were exposed to a higher risk of NRTI toxicity compared with those in SALT, which could at least in part explain the different results.

Virological failure was rare and no resistance was detected in cases that could be genotyped, confirming that the Met184Val resistance mutation to lamivudine, the drug with the lowest genetic barrier in this regimen, emerges very rarely with this regimen.[9,11,12]

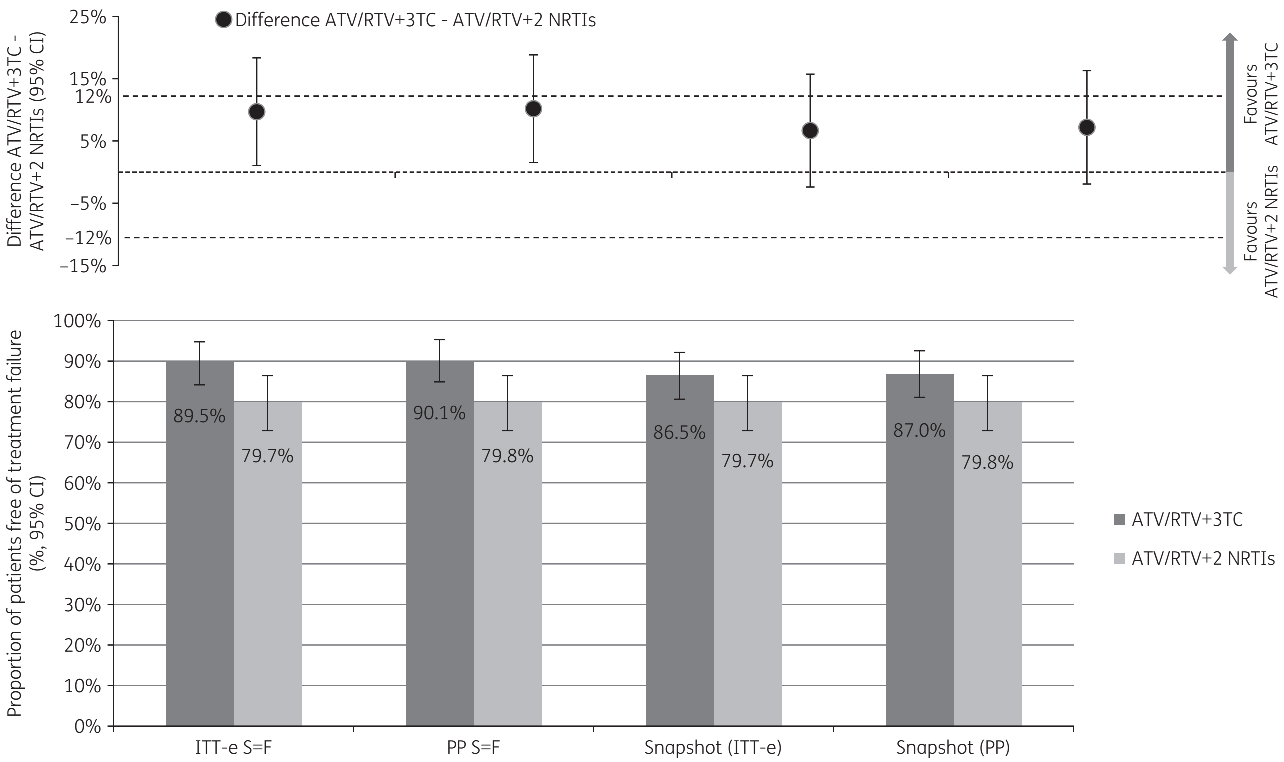

Figure 2. Lower part: proportion of patients without treatment failure at week 48 in the two study arms in the main analysis and the FDA snapshot analysis both in the ITT-e and PP populations. Upper part: main analysis shows superiority of the atazanavir/ritonavir + lamivudine arm over the atazanavir/ritonavir + two NRTIs arm in both the ITT-e population and the PP population. FDA snapshot analysis shows non-inferiority of atazanavir/ritonavir + lamivudine in both the ITT-e and PP populations. Circles represent means and whiskers represent 95% CIs. ATV, atazanavir; RTV, ritonavir; 3TC, lamivudine; S = F, switch = failure.

Table 2. Causes of treatment failure

	Atazanavir/ ritonavir + lamivudine, $N = 133$, *n* (%)	Atazanavir/ ritonavir + 2 NRTIs, $N = 133$, *n* (%)	*P*
Any cause	14 (10.5)	27 (20.3)	**0.042**
Virological failure	2 (1.5)	6 (4.5)	0.282
AEs (potentially treatment related)[a]	2 (1.5)	5 (3.8)	0.447
AEs (not treatment related)[b]	2 (1.5)	3 (2.3)	1.000
Withdrawal of consent	2 (1.5)	7 (5.3)	0.172
Loss to follow-up	5 (3.8)	4 (3.0)	1.000
Other	1 (0.8)	2 (1.5)	0.624

[a]Atazanavir/ritonavir + lamivudine arm: skin rash (week 4) and renal colic (week 26). Atazanavir/ritonavir + 2 NRTIs arm: creatinine increase (weeks 3 and 7), osteopenia (week 16), renal colic (week 24) and drug nephropathy (week 43).
[b]Atazanavir/ritonavir + lamivudine arm: death (week 10, sudden death, probably cardiac), thyroid carcinoma (week 24). Atazanavir/ritonavir + 2 NRTIs arm: spinal disc herniation (week 3), pneumonia (week 12) and abdominal cancer (week 48).

Self-reported adherence measures did not change significantly over time in both study arms, but in most cases of virological failure, plasma atazanavir levels were undetectable, suggesting a relevant role of insufficient adherence in these cases.

Table 3. Proportion of patients with clinical AEs of any grade

	Atazanavir/ ritonavir + lamivudine, $N = 133$, *n* (%)	Atazanavir/ ritonavir + 2 NRTIs, $N = 133$, *n* (%)	*P*
CNS	3 (2.3)	4 (3.0)	1.000
Gastrointestinal	6 (4.5)	9 (6.8)	0.595
Skin and soft tissues	4 (3.0)	0	0.122
Urinary tract	5 (3.8)	8 (6.0)	0.571
Respiratory tract	8 (6.0)	6 (4.5)	0.784
Infections	12 (9.0)	13 (9.8)	0.834
Neoplasm	3 (2.3)	1 (0.8)	0.622
Bone	0	4 (3.0)	0.122
Other	12 (9.0)	20 (15.0)	0.187
Patients with at least one AE	33 (24.8)	40 (30.1)	0.410

Grade 3–4 clinical AEs: three in the atazanavir/ritonavir + lamivudine arm (sudden death probably cardiac, thyroid carcinoma, atrial fibrillation) and four in the atazanavir/ritonavir + two NRTIs arm (abdominal cancer, pneumonia, radiculitis, traumatic tibia fracture and finger amputation); all were not considered treatment related.

Renal function, as measured by the change of the eGFR from baseline at 48 weeks, showed a significantly better performance with atazanavir/ritonavir + lamivudine as compared with atazanavir/ritonavir + two NRTIs. The difference was slightly more

Table 4. Proportion of patients with grade 3–4 laboratory toxicities

	Total grade 3–4 toxicities			New[a] grade 3–4 toxicities		
	atazanavir/ritonavir + lamivudine, *n*/*N* (%)	atazanavir/ritonavir + 2 NRTIs, *n*/*N* (%)	*P*	atazanavir/ritonavir + lamivudine, *n*/*N* (%)	atazanavir/ritonavir + 2 NRTIs, *n*/*N* (%)	*P*
Total cholesterol	7/133 (5.3)	3/133 (2.3)	0.334	6/126 (4.8)	1/126 (0.8)	0.120
LDL cholesterol	17/133 (12.8)	8/133 (6.0)	0.093	10/111 (9.0)	5/115 (4.3)	0.188
Triglycerides	8/133 (6.0)	2/133 (1.5)	0.103	8/126 (6.3)	2/128 (1.6)	0.059
Total bilirubin	71/133 (53.4)	58/133 (43.6)	0.141	44/99 (44.4)	28/99 (28.3)	0.027
ALT	0/133 (0)	1/133 (0.8)	1.000	0/133 (0)	0/133 (0)	Nc
At least one laboratory toxicity	92/133 (69.2)	87/133 (65.4)	0.601	64/133 (48.1)	49/133 (36.8)	0.082

Nc, not computable.
[a]Incident toxicity, not present at baseline.

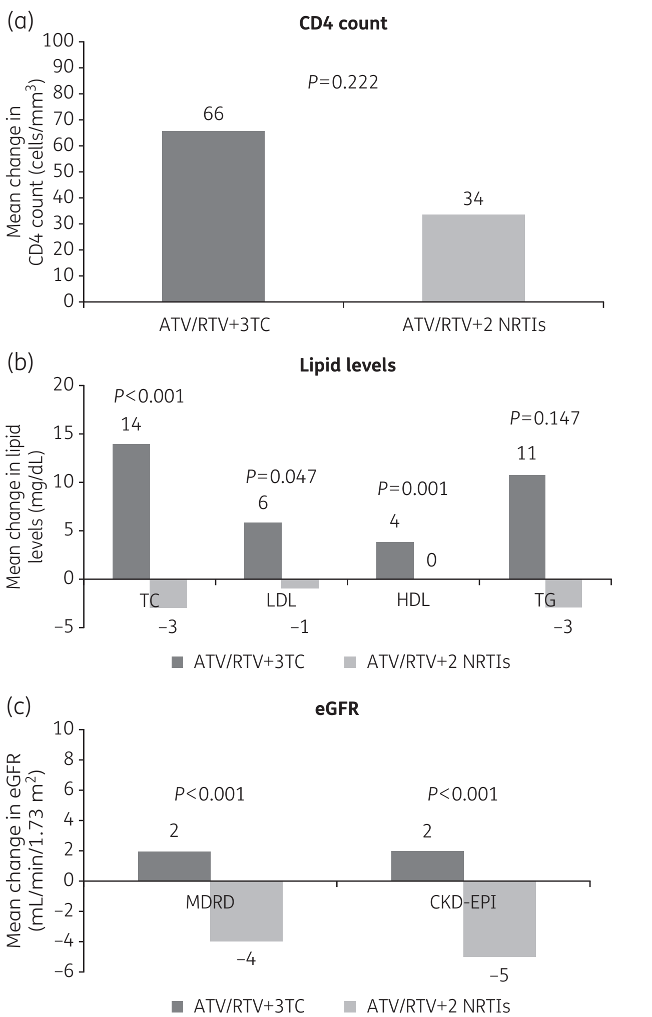

Figure 3. Mean change from baseline values at week 48 in the atazanavir/ritonavir + lamivudine arm and the atazanavir/ritonavir + two NRTIs arm for (a) peripheral blood CD4+ T cell count, (b) blood lipids and (c) eGFR based on the MDRD and the CKD-EPI equations. ATV, atazanavir; RTV, ritonavir; 3TC, lamivudine; TC, total cholesterol; LDL, LDL cholesterol; HDL, HDL cholesterol; TG, triglycerides.

prominent in the subset of patients discontinuing tenofovir. Given the renal toxicity associated with both tenofovir and atazanavir,[20] we suggest that an improvement in eGFR may be particularly notable in patients interrupting tenofovir after using the two drugs combined. Unfortunately, ATLAS-M did not collect markers of tubular proteinuria, which could have allowed analysis of the effect on more specific tenofovir-related renal toxicity parameters.

As in several other studies contemplating the discontinuation of tenofovir disoproxil fumarate,[9,12,21,22] we demonstrated an increase in total cholesterol and LDL cholesterol in the atazanavir/ritonavir + lamivudine arm. This change has been previously described as a statin-like effect of tenofovir disoproxil fumarate.[23] However, due to the concomitant increase in HDL cholesterol, the total cholesterol/HDL cholesterol and the HDL cholesterol/LDL cholesterol ratios remained unchanged. Therefore, the effect of these changes on the cardiovascular risk is probably neutral.

Overall, the results of this study significantly strengthen the evidence of the efficacy of cART strategies based on the combination of a PI/ritonavir with lamivudine. Randomized studies have shown non-inferior efficacy of lopinavir/ritonavir with lamivudine in previously untreated and in virologically suppressed patients.[8,13] However, lopinavir is associated with significant toxicities and comparator arms in these studies do not represent standard ART any more. Darunavir/ritonavir with lamivudine has shown interesting results, but only in small, observational studies.[10,24] Other dual therapies have shown less encouraging results both in naive and in virologically suppressed patients.[3,4,25,26] Therefore, at the moment, simplification to atazanavir/ritonavir with lamivudine shows the most robust data among the two-drug regimens.

In our opinion, the main strength of ATLAS-M lays in its design. Indeed, the study allowed the inclusion of patients who were already on a stable atazanavir/ritonavir-based triple therapy only and prescribed the continuation of the same NRTI in the comparator arm. Therefore, the results in terms of efficacy and safety were less likely to be affected by toxicities related to the changes of other components of the regimen.

The open-label design of the study represents a limitation, as it may have introduced certain biases, including a higher propensity of discontinuation due to toxicity in the triple therapy arm, which may have affected the main outcome. However, we believe that the absence of major toxicity at baseline and the use of an identical pill burden in both study arms should have minimized this effect.

The reduced cost of this dual regimen, thanks to both the discontinuation of an NRTI (tenofovir or abacavir in the majority of patients) and to the availability of generic lamivudine, represents an additional benefit. Moreover, the patent of atazanavir is close to expiration and this could additionally reduce costs of this combination.

In conclusion, the simplification to ritonavir-boosted atazanavir with lamivudine in virologically suppressed patients on ritonavir-boosted atazanavir with two NRTIs is non-inferior and superior in a *post-hoc* analysis as compared with the continuation of the previous triple therapy at 48 weeks. A significant beneficial effect of atazanavir/ritonavir + lamivudine in the evolution of eGFR was also observed, particularly in subjects discontinuing tenofovir disoproxil fumarate. In virologically suppressed patients on ritonavir-boosted atazanavir with two NRTIs who are not coinfected with hepatitis B virus, a switch to dual therapy with boosted atazanavir and lamivudine may be considered.

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Author contributions

S. D. G., R. C. and A. D. L. designed the study, analysed the data and finalized the drafting of the paper. M. F. analysed the data and contributed to literature search and article drafting. All other authors were responsible for data collection and AE reports for the respective enrolling centres. All authors contributed to and approved the final version of the manuscript.

References

1 Palella FJ Jr, Baker RK, Moorman AC *et al.* Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* 2006; **43**: 27–34.

2 Margolis AM, Heverling H, Pham PA *et al*. A review of the toxicity of HIV medications. *J Med Toxicol* 2014; **10**: 26–39.

3 Raffi F, Babiker AG, Richert L *et al*. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. *Lancet* 2014; **384**: 1942–51.

4 Van Lunzen J, Pozniak A, Gatell JM *et al*. Switch to ritonavir-boosted atazanavir plus raltegravir in virologically suppressed patients with HIV-1 infection: a randomized pilot study. *J Acquir Immune Defic Syndr* 2016; **71**: 538–43.

5 Mathis S, Khanlari B, Pulido F *et al*. Effectiveness of protease inhibitor monotherapy versus combination antiretroviral maintenance therapy: a meta-analysis. *PLoS One* 2011; **6**: e22003.

6 Arribas JR, Girard PM, Paton N *et al*. Efficacy of protease inhibitor monotherapy vs. triple therapy: meta-analysis of data from 2303 patients in 13 randomized trials. *HIV Med* 2016; **17**: 358–67.

7 Paton NI, Stohr W, Arenas-Pinto A *et al*. Protease inhibitor monotherapy for long-term management of HIV infection: a randomised, controlled, open-label, non-inferiority trial. *Lancet HIV* 2015; **2**: e417–26.

8 Cahn P, Andrade-Villanueva J, Arribas JR *et al*. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48 week results of the randomised, open label, non-inferiority GARDEL trial. *Lancet Infect Dis* 2014; **14**: 572–80.

9 Di Giambenedetto S, Fabbiani M, M Colafigli *et al*. Safety and feasibility of treatment simplification to atazanavir/ritonavir + lamivudine in HIV-infected patients on stable treatment with two nucleos(t)ide reverse transcriptase inhibitors + atazanavir/ritonavir with virological suppression (Atazanavir and Lamivudine for treatment Simplification, AtLaS pilot study). *J Antimicrob Chemother* 2013; **68**: 1364–72.

10 Casado JL, Banon S, Rodriguez MA *et al*. Efficacy of dual therapy with lamivudine plus darunavir boosted with ritonavir once daily in HIV-infected patients with nucleoside analogue toxicity. *J Antimicrob Chemother* 2015; **70**: 630.

11 Mondi A, Fabbiani M, Ciccarelli N *et al*. 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. *J Antimicrob Chemother* 2015; **70**: 1843–9.

12 Perez-Molina JA, Rubio R, Rivero A *et al*. Dual treatment with atazanavir-ritonavir plus lamivudine versus triple treatment with atazanavir-ritonavir plus two nucleos(t)ides in virologically stable patients with HIV-1 (SALT): 48 week results from a randomised, open-label, non-inferiority trial. *Lancet Infect Dis* 2015; **15**: 775–84.

13 Arribas JR, Girard PM, Landman R *et al*. Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open-label, non-inferiority trial. *Lancet Infect Dis* 2015; **15**: 785–92.

14 Murri R, Cingolani A, De Luca A *et al*. Asymmetry of the regimen is correlated to self-reported suboptimal adherence: results from AdUCSC, a cohort study on adherence in Italy. *J Acquir Immune Defic Syndr* 2010; **55**: 411–2.

15 Liu TF, Shafer RW. Web resources for HIV type 1 genotypic-resistance test interpretation. *Clin Infect Dis* 2006; **42**: 1608–18.

16 Fabbiani M, Di Giambenedetto S, Bracciale L *et al*. Pharmacokinetic variability of antiretroviral drugs and correlation with virological outcome: 2 years of experience in routine clinical practice. *J Antimicrob Chemother* 2009; **64**: 109–17.

17 US Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. *Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014*. http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf.

18 Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Department of Health and Human Services. Last updated July 14, 2016. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

19 Fabbiani M, Di Giambenedetto S, Ragazzoni E *et al*. Mid-dosing interval concentration of atazanavir and virological outcome in patients treated for HIV-1 infection. *HIV Med* 2010; **11**: 326–33.

20 Mocroft A, Lundgren JD, Ross M *et al*. Cumulative and current exposure to potentially nephrotoxic antiretrovirals and development of chronic kidney disease in HIV-positive individuals with a normal baseline estimated glomerular filtration rate: a prospective international cohort study. *Lancet HIV* 2016; **3**: e23–32.

21 Castagna A, Spagnuolo V, Galli L *et al*. Simplification to atazanavir/ritonavir monotherapy for HIV-1 treated individuals on virological suppression: 48-week efficacy and safety results. *AIDS* 2014; **28**: 2269–79.

22 Mills A, Arribas JR, Andrade-Villanueva J *et al*. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. *Lancet Infect Dis* 2016; **16**: 43–52.

23 Fabbiani M, Bracciale L, Doino M *et al*. Lipid-lowering effect of tenofovir in HIV-infected patients. *J Antimicrob Chemother* 2011; **66**: 682.

24 Fabbiani M, Di Giambenedetto S, Poli A *et al*. Simplification to a dual regimen with darunavir/ritonavir plus lamivudine or emtricitabine in virologically-suppressed HIV-infected patients. *J Infect* 2016; **73**: 619–23.

25 Stellbrink HJ, Le Fevre E, Carr A *et al*. Once-daily maraviroc versus tenofovir/emtricitabine each combined with darunavir/ritonavir for initial HIV-1 treatment. *AIDS* 2016; **30**: 1229–38.

26 Rossetti B, Gagliardini R, Meini J *et al*. Switch to maraviroc (MVC) + darunavir/ritonavir (DRV/r) in virologically suppressed patients with R5-tropic virus is associated with an excess of virological failures: 48 weeks results of the GUSTA study. In: *Abstracts of the Fifteenth European AIDS Conference, Barcelona, Spain*, 2015. Abstract PE7/14. European AIDS Clinical Society.