Treatment simplification to atazanavir/ritonavir plus lamivudine versus maintenance of atazanavir/ritonavir plus two nucleoside reverse transcriptase inhibitors in virologically-suppressed HIV-1-infected patients: 48-weeks results from a randomized trial (ATLAS-M)

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Running title: Atazanavir/r + lamivudine dual therapy

Synopsis

Background: Combination antiretroviral therapy (cART)-related toxicities and costs have prompted the need for treatment simplification. ATLAS-M trial explored 48-week non-inferior efficacy of simplification to atazanavir/ritonavir plus lamivudine versus maintaining three-drugs 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 plus two nucleoside reverse-transcriptase inhibitors (NRTI), with stable HIV-RNA<50 copies/mL, and CD4+>200 cells/mm^3. Main exclusion criteria were: HBV-coinfection, past virological failure on or resistance to study drugs, recent AIDS, and pregnancy. Patients were randomly assigned 1:1 to either switch to atazanavir 300mg/ritonavir100mg once daily and lamivudine 300mg once daily (ATV/rit+3TC arm) or to continue the previous regimen (ATV/rit+2NRTI arm). Primary study outcome was the maintenance of HIV-RNA<50copies/mL at week 48 at the intention-to-treat-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 119/133 patients (89.5%) in the ATV/rit+3TC arm and 106/133 patients (79.7%) in the ATV/rit+2NRTI arm (difference ATV/rit+3TC versus ATV/rit+2NRTI arm: +9.8% [95% CI +1.2 to +18.4]), demonstrating non-inferiority and superior efficacy of the ATV/rit+3TC arm. Virological failure occurred in two (1.5%) patients in the ATV/rit+3TC arm and six (4.5%) in the ATV/rit+2NRTI arm, without resistance selection. A similar proportion of adverse events occurred in both arms.

Conclusions: Treatment simplification to atazanavir/ritonavir plus lamivudine showed non-

inferior efficacy (superiority on post-hoc analysis) and a comparable safety profile over continuing atazanavir/ritonavir+2NRTI in virologically-suppressed patients.

Introduction

Combination antiretroviral therapy (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 nucleoside reverse transcriptase inhibitors (NRTI)-associated toxicities have become a matter of concern.[2] Several NRTI-sparing regimens have been studied with conflicting results.[3,4] Mono-therapies with boosted protease inhibitors (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 plus lamivudine have been tested in randomized studies in treatment naïve patients[8] or as simplification strategies in virologically suppressed patients.[9-13] Atazanavir/ritonavir plus lamivudine showed long-term efficacy and tolerability in the single arm ATLAS pilot study[11] and demonstrated non inferior efficacy when compared to atazanavir/ritonavir plus two NRTI in patient previously receiving different 3-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 plus lamivudine, as compared to continuing a previously stable, virologically effective regimen with atazanavir/ritonavir plus 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 plus two NRTI from at least three months, with HIV-RNA <50 copies/mL, and CD4 >200 cells/µL from at least six 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 (HBV) 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 judgment, jeopardize

the patient's compliance. Patients were pre-screened to fulfil inclusion criteria on the basis of medical records, and then underwent a screening visit for confirmation.

Randomization

At baseline, patients were randomized 1:1 to (i) treatment switch to atazanavir 300 mg with ritonavir 100 mg once daily and lamivudine 300 mg once daily (ATV/rit+3TC arm) or (ii) to continue atazanavir 300 mg boosted with ritonavir 100 mg once daily with the same NRTI backbone (ATV/rit+2NRTI 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 weeks 4, 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 (VAS);[14] patients reporting an adherence below 90% in at least one visit were considered as sub-optimally adherent.

Treatment failure (TF) 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 (VF) was defined as the first of two consecutive HIV-RNA levels >50 copies/mL or a single level above 1,000 copies/mL. Viral blips were

147 defined as a transient HIV-RNA levels above 50 copies/mL preceded and followed by another
148 viral load <50 copies/mL without any treatment change.

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

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

157

158 ***Outcomes***

159 The primary efficacy endpoint was the proportion of patients without treatment failure at
160 week 48. Analysis of the primary efficacy endpoint was performed with both the intention-
161 to-treat-exposed (ITT-e) and the per protocol population. Moreover, a 48 week FDA-
162 snapshot analysis of treatment efficacy on the ITT-e and PP population was carried out.

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

166

167 ***Statistical analysis***

This study was designed as a non-inferiority trial to verify if the proportion of patients without treatment failure in the ATV/rit+3TC arm was not inferior to that in the ATV/rit+2NRTI arm. Non-inferiority margin was set at -12%. Assuming a proportion of success at 48 weeks in the ATV/rit+2NRTI 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 χ2 test or Fisher's exact test, as appropriate. Continuous variables were compared using Student t-test or Mann-Whitney U-test as appropriate. All statistical tests were 2-tailed, and only P values of <0.05 were considered to be 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 patients 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 TF were 119 of 133 (89.5%; 95% CI 84.3 to 94.7) in the ATV/rit+3TC arm and 106 of 133 (79.7%; 95% CI 72.9 to 86.5) in the ATV/rit+2NRTI arm (difference ATV/rit+3TC minus ATV/rit+2NRTI +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 to 95.2) patients in the ATV/rit+3TC arm as compared to 103 of 129 (79.8%, 95% CI 72.9 to 86.7) patients in the ATV/rit+2NRTI arm were free of TF (difference between arms +10.3%, 95% CI +1.7 to +18.9, p=0.021).

These results fulfils the pre-defined non-inferiority criteria and indicates superior efficacy of switching to ATV/rit+3TC over continuing ATV/rit+2NRTI.

At the 48 weeks the snapshot analysis also showed non-inferiority of switching to ATV/rit+3TC. In the ITT-e population, 115 of 133 patients in the ATV/rit+3TC (86.5%; 95% CI 80.7 to 92.3) versus 106 of 133 in the ATV/rit+2NRTI arm (79.7%; 95% CI 72.9 to 86.5) were free of TF (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 ATV/rit+3TC (87.0%; 95% CI 81.2 to 92.8) versus 103 of 129 in the ATV/rit+2NRTI arm (79.8%; 95% CI 72.9 to 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. VF occurred in two (1.5%) patients in the ATV/rit+3TC arm (including one at baseline, before treatment switch) and six (4.5%) patients in the TT arm (difference between arms -3%; 95% CI -7.1 to +1.1, p=0.282); all subjects with VF were treated with atazanavir/ritonavir plus tenofovir/emtricitabine before baseline. At VF, plasma samples from seven patients (two patients in the ATV/rit+3TC arm and five in ATV/rit+2NRTI arm) were available for genotypic resistance testing and quantification of atazanavir levels. No relevant resistance mutations were detected neither in the protease nor 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 VF in the ATV/rit+3TC and ATV/rit+2NRTI arm, respectively; in the remaining patients, atazanavir concentration was above the suggested mid-dosing interval or trough concentration efficacy cut-off.[18,19] Viral blips not leading to VF or treatment discontinuation were observed in ten (7.5%) patients in the ATV/rit+3TC arm and 16 (12.0%) in the comparator arm (p=0.302). TF due to adverse events (both potentially treatment-related and not treatment-related) did not differ between the two arms (see table 2).

Since 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 TF due to withdrawal of consent. In this analysis, patients free of TF were 115 of 127 (90.6%; 95% CI 85.5 to 95.7) in the ATV/rit+3TC arm and 104 of 124 (83.9%; 95% CI 77.4 to 90.4) in the ATV/rit+2NRTI arm (difference ATV/rit+3TC minus ATV/rit+2NRTI +6.7%, 95% CI -1.5 to +14.9, p=0.113), confirming non inferiority of dual therapy.

Clinical and laboratory adverse events

Overall, 68 and 90 clinical AE of any grade occurred in the ATV/rit+3TC and comparator arm, respectively. The majority of clinical AE were mild to moderate. There were seven grade 3-4 clinical AE (three in the ATV/rit+3TC and four in the ATV/rit+2NRTI arm), none of which was considered treatment-related. Overall, five renal colics occurred: three in the ATV/rit+2NRTI and two in the ATV/rit+3TC arm. Four patients demonstrated osteopenia/osteoporosis in ATV/rit+2NRTI arm (all considered related to treatment with tenofovir, leading to regimen discontinuation in 2 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 AE 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 hyperbilirubinemia was more frequent in the DT arm [44 of 99 (44.4%) versus 28 of 99 (28.3%) in TT, p=0.027]. Other laboratory toxicities were equally distributed between the two arms.

Evolution of CD4 cells count, lipid levels and renal function

The evolution of CD4 cells counts, estimated glomerular filtration rate (eGFR), and blood lipids is illustrated in figure 3a-c.

At 48 weeks, the changes from baseline CD4 cells were not significantly different between ATV/rit+3TC and comparator arm.

The evolution of eGFR was more favorable in the ATV/rit+3TC as compared to the control arm: at week 48, mean change from baseline eGFR (using CKD-EPI) was +2 mL/min/1.73m^2 (95% CI -1 to 6) in ATV/rit+3TC versus -5 mL/min/1.73m2 (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 ATV/rit+3TC and comparator arms, respectively): +3 mL/min/1.73m^2 (95% CI -1 to 6) in ATV/rit+3TC versus -5 mL/min/1.73m^2 (95% CI -9 to -2) in the comparator arm ($p<0.001$).

Total cholesterol (TC), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL) showed a significant increase in the ATV/rit+3TC as compared to the control arm (see figure 3b). No significant differences in the changes of triglycerides, TC/HDL, and HDL/LDL ratios were observed between the two arms.

Adherence measures

Self-reported adherence was provided by 247 (92.6%) patients (125 [94.0%] in the ATV/rit+3TC 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 ATV/rit+3TC versus -2% [95% CI -4 to +1] in the comparator arm, p=0.165). Suboptimal adherence was not significantly different in patients experiencing VF as compared to those not (71.4% [5 of 7] versus 53.5% [130 of 243], p=0.457).

Discussion

In 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 ATV/rit+3TC. 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 adverse events and a significant improvement of renal function were observed in the ATV/rit+3TC arm versus the comparator. These results are in line with the good efficacy and tolerability observed with ATV/rit+3TC 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, ATV/rit+3TC showed non-inferior efficacy at 48 weeks as compared with ATV/rit+ 2NRTIs in patients switching from different standard three-drug cART regimens.[12] The very similar efficacy results of the SALT and ATLAS-M trial confirm the robustness of this strategy in different contexts. Superiority of ATV/rit+3TC 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 more than 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 as 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]

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.

Renal function, as measured by the change of the eGFR from baseline at 48 weeks, showed a significantly better performance with ATV/rit+3TC as compared to ATV/rit+2NRTIs. The difference was slightly more 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 to analyze 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 of total cholesterol and LDL cholesterol in the ATV/rit+3TC arm. This change has been previously described as a statin-like effect of tenofovir disoproxil fumarate.[23] However, due to the concomitant increase of HDL cholesterol, the total/HDL cholesterol and the HDL/LDL cholesterol ratios remained unchanged. Therefore, the effect of these changes on the cardiovascular risk is probably neutral.

Overall, results of this study significantly strengthen the evidence of the efficacy of cART strategies based on the combination of a PI/rit 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 the state of the art of antiretroviral therapy 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 naïve 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 lies on 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, since 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 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 to the continuation of the previous triple therapy at 48 weeks. A significant beneficial effect of atazanavir/ritonavir plus 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 co-infected with HBV, a switch to dual therapy with boosted atazanavir and lamivudine may be considered.

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SDG, RC and ADL designed the study, analyzed the data and finalized the drafting of the paper. MF analyzed the data and contributed to literature search and article drafting. All other authors were responsible for data collection and adverse events reports for the respective enrolling centres.

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525

526 **Table 1.** Baseline patients characteristics.

	Total population n=266	ATV/rit + 3TC n=133	ATV/rit + 2 NRTIs n=133
Age, years*	44 (36-50)	44 (36-49)	44 (36-51)
Male gender	212 (79.7)	112 (84.2)	100 (75.2)
Risk factor:			
Heterosexual	108 (40.6)	48 (36.1)	60 (45.1)
Homo/bisexual	116 (43.6)	64 (48.1)	52 (39.1)
IDU	20 (7.5)	9 (6.8)	11 (8.3)
Other/unknown	22 (8.3)	12 (9.0)	10 (7.5)
HCV co-infection	28 (10.5)	14 (10.5)	14 (10.5)
Previous AIDS events	34 (12.8)	18 (13.5)	16 (12.0)
Years from HIV diagnosis*	4.5 (2.2-9.5)	4.2 (2.2-9.0)	5.2 (2.6-10.3)
Years from first cART initiation*	2.7 (1.6-5.5)	2.8 (1.7-5.1)	2.7 (1.6-6.4)
Antiretroviral treatment line*	2 (1-3)	2 (1-3)	2 (1-3)
Months from last regimen initiation*	29.1 (17.1-53.0)	28.7 (17.9-52.9)	29.2 (16.2-54.6)
NRTI backbone:			
TDF+FTC/3TC	217 (81.6)	105[a] (78.9)	112[a] (84.2)
ABC+3TC	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*	265 (132-357)	274 (118-357)	257 (144-357)
Current CD4 count, cells/µL*	617 (481-781)	622 (472-779)	616 (486-783)
Months from last HIV-1 RNA >50 copies/mL*	22.0 (12.6-45.0)	23.5 (12.6-46.5)	20.8 (12.3-44.8)

527

528 **Notes:** values are expressed as n (%) except for *median (interquartile range, IQR); [a] one

529 patient in each arm treated with TDF+3TC, all the others with TDF+FTC; [b] two zidovudine +

530 3TC, one didanosine + 3TC; [c] one zidovudine + 3TC, one TDF + ABC, one no NRTI backbone

531 (treated with atazanavir/ritonavir + raltegravir, major protocol deviation).

532 **Abbreviations:** ATV/rit, atazanavir/ritonavir; 3TC, lamivudine; NRTI, nucleos(t)ide reverse

533 transcriptase inhibitors; HCV, hepatitis C virus; cART, combination Antiretroviral Therapy;

534 TDF, tenofovir; FTC, emtricitabine; ABC, abacavir.

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Table 2: Causes of treatment failure.

	ATV/rit + 3TC N=133	ATV/rit + 2 NRTIs N=133	p
Any cause	14 (10.2)	27 (20.3)	**0.042**
Virological Failure	2 (1.5)	6 (4.5)	0.282
Adverse events (potentially treatment-related)[a]	2 (1.5)	5 (3.8)	0.447
Adverse events (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

Abbreviations: ATV/rit, atazanavir/ritonavir; 3TC, lamivudine; NRTI, nucleos(t)ide reverse transcriptase inhibitors.

Notes:

[a] ATV/rit + 3TC arm: skin rash (week 4) and renal colic (week 26); ATV/rit + 2NRTI arm: creatinine increase (week 3 and week 7), osteopenia (week 16), renal colic (week 24), drug nephropathy (week 43).

[b] ATV/rit + 3TC arm: death (week 10, sudden death, probably cardiac), thyroid carcinoma (week 24); ATV/rit + 2NRTI arm: spinal disc herniation (week 3), pneumonia (week 12), abdominal cancer (week 48).

Table 3: Proportion of patients with any grade clinical adverse events.

	ATV/rit + 3TC n=133	ATV/rit + 2NRTI n=133	P
Central Nervous System	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

Abbreviations: ATV/rit, atazanavir/ritonavir; 3TC, lamivudine; NRTI, nucleos(t)ide reverse transcriptase inhibitors.

Note: Grade 3-4 clinical AE were 3 in the ATV/rit + 3TC arm (sudden death probably cardiac, thyroid carcinoma, atrial fibrillation) and 4 in the ATV/rit + 2NRTI arm (abdominal cancer, pneumonia, radiculitis, traumatic tibia fracture and finger amputation): all were not considered treatment-related.

566

567 **Table 4:** Proportion of patients with grade 3-4 laboratory toxicities.

	Total grade 3-4 toxicities			New* grade 3-4 toxicities		
	ATV/rit + 3TC n (%)	**ATV/rit + 2NRTI n (%)**	**P**	**ATV/rit + 3TC n (%)**	**ATV/rit + 2NRTI 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

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569 **Abbreviations:** Nc, not computable.

570 **Notes:** * incident toxicity, not present at baseline.

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578 **Figure legends**

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580 **Figure 1.** Flow chart showing patient allocation throughout the study and main study
581 outcomes. ATV/rit = atazanavir/ritonavir; 3TC = lamivudine; NRTI = nucleos(t)ide reverse
582 transcriptase inhibitors); TDF/FTC, tenofovir/emtricitabine; RAL, raltegravir; ITT-e = intent-
583 to-treat-exposed; PP = per protocol.

584 Note: * All randomized patients received at least one dose of study drugs and were thus
585 included in the safety analysis exploring clinical and laboratory adverse events.

586

587 **Figure 2.** Lower part: proportion of patients without treatment failure at week 48 in the two
588 study arms in the main analysis and the FDA snapshot analysis both in the ITT-e (intent-to-
589 treat-exposed) and PP (per protocol) populations. Upper part: the main analysis shows
590 superiority of the atazanavir/ritonavir + lamivudine arm (ATV/rit+3TC) over the
591 atazanavir/ritonavir + 2 nucleoside analogues (ATV/rit+2NRTI) arm in both the ITT-e and the
592 PP population. The FDA snapshot analysis shows non-inferiority of ATV/rit+3TC in both the
593 ITT-e and PP population.

594

595 **Figure 3.** Mean change from baseline values at week 48 in the atazanavir/ritonavir +
596 lamivudine arm (ATV/rit+3TC) and the atazanavir/ritonavir + 2 nucleoside analogues
597 (ATV/rit+2NRTI) arm for (a) peripheral blood CD4+ T cell counts, (b) blood lipids and (c)

598 estimated glomerular filtration rate (eGFR) based on the MDRD and the CKD-EPI equations.
599 TC, total cholesterol; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein
600 cholesterol; TG, triglycerides.

601