Simplification to atazanavir/ritonavir monotherapy for HIV-1 treated individuals on virological suppression: 48-week efficacy and safety results

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Objectives: The objective of this study was to assess the 48-week virological efficacy of atazanavir/ritonavir (ATV/r) monotherapy vs. ATV/r along with two nucleoside reverse transcriptase (NRTIs) in HIV-1 treated individuals with HIV-RNA less than 50 copies/ml.

Methods: A multicentre, randomized, open-label, noninferiority trial. HIV-1 treated individuals on ATV/r 300/100 mg along with two NRTIs were randomized to receive ATV/r monotherapy or to maintain their antiretroviral regimen. The primary endpoint was the confirmed viral rebound (CVR: two consecutive HIV-RNA >50 copies/ml) or treatment discontinuation for any reason. Individuals who experienced CVR on ATV/r monotherapy reintroduced NRTIs and discontinued the study if HIV-RNA was more than 50 copies/ml after 12 weeks since reintensification.

Results: One hundred and three patients enrolled. By week 48, 11 patients in ATV/r arm and two in ATV/r along with two NRTIs experienced CVR; four (8%) patients in ATV/r and eight (15%) in ATV/r along with two NRTIs discontinued. At the 48-week primary efficacy analysis (re-intensification = failure), treatment success was 73% in ATV/r arm and 85% in ATV/r along with two NRTIs [difference −12.1%, 95% confidence interval (95% CI) −27.8 to 2.1]. According to the analysis considering re-intensification is equal to success, treatment success was 92% in ATV/r arm and 85% in the ATV/r along with two NRTIs arm (difference 7.5%, 95% CI −4.7 to 19.8). At CVR, no mutation was observed in ATV/r arm and reintensification with NRTIs was effective in all individuals. Overall, Grade 3–4 ($P = 0.003$) and grade 3–4 drug-related ($P = 0.027$) adverse events were less frequent in ATV/r arm. A significant increase in total and low-density lipoprotein (LDL)-cholesterol was observed as well as a significant improvement in high-density lipoprotein (HDL)-cholesterol, fasting glucose, liver fibrosis and alkaline phosphatase was observed in ATV/r monotherapy in comparison with ATV/r along with two NRTIs.

Conclusion: ATV/r monotherapy treatment simplification showed lower virological efficacy in comparison with maintaining triple therapy; NRTIs reintroduction was effective in all the individuals.

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Keywords: atazanavir/ritonavir, HIV, nucleos(t)ide reverse transcriptase inhibitors toxicity, protease inhibitor monotherapy, simplification, virological suppression

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Introduction

Atazanavir/ritonavir (ATV/r) in combination with two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) is a once-a-day, first-line recommended regimen for HIV-1 infection with proven durability, both in clinical trials and clinical practice [1–3] and lack of association with an increased risk of cardio or cerebrovascular disease events [4]. Nevertheless, due to the risk of long-term toxicity, patient's perception, treatment fatigue and costs, an increasing frequency of switches from standard to nonstandard regimens has been observed in clinical practice [5] and prompted the investigation to search for an alternative and affordable antiretroviral regimen in fully suppressed patients. Switching to unboosted atazanavir is an evidence-based approach to effectively address issue related to ritonavir tolerability, dyslipidemia or hyperbilirubinemia [6]. Reductive antiretroviral strategies [7] such as dual therapy with ATV/r and lamivudine has shown encouraging efficacy results in a small nonrandomized study [8] and is still under investigation in a larger randomized study [9].

Ritonavir-boosted protease inhibitor (PI/r) monotherapy with lopinavir/ritonavir or darunavir/ritonavir has been intensively investigated [10–17]. Comprehensively, according to randomized clinical trial results, PI/r monotherapy is less effective than triple-drug antiretroviral therapy (ART) to maintain viral suppression [18]. However, the observed risk difference is small (6–7%) and the increased risk of low-level viraemia with PI/r monotherapy was generally reversible after NRTI reintroduction. Consequently, some European guidelines have positively received the results obtained and consider this strategy as an option for treatment simplification and toxicity issues [19–21].

Few retrospective [22,23] or prospective not randomized, short-term studies with a small sample size [24–26] have evaluated the antiviral efficacy and safety of ATV/r monotherapy in HIV-1 treated, fully suppressed patients. These studies yielded conflicting results with rates of virological failure ranging from 7 to 30%.

The objective of this study was to evaluate the noninferiority of treatment simplification with ATV/r monotherapy in comparison with standard triple-drug regimen, in patients on ATV/r along with two NRTIs fully suppressed and without previous virological failure.

Materials and methods

Monotherapy Once a Day with Atazanavir/r (MODAt) is a multicentre, randomized, open-label, noninferiority trial with a primary endpoint at week 48, performed in Italy.

HIV-1 infected individuals, at least 18 years of age, hepatitis B surface antigen negative, receiving ATV/r along with two NRTIs for at least 48 weeks, with an HIV-1 viral load below 50 copies/ml for at least 24 weeks, no previous virological failure, $CD4^+$ nadir more than 100 cells/μl and no use of the proton-pump inhibitors or H2-receptor antagonists were randomly assigned 1 : 1 to continue the ongoing regimen or to maintain only ATV/r 300/100 mg daily (q.d.). Randomization was stratified by HIV-1 RNA at the start of ART ($\leq$100 000 vs. $>$100 000 copies/ml); the computer-generated list (with equal block sizes) was prepared by the trial statistician and was incorporated within a centralized secure database. Randomization was performed by clinicians of each participating centre by connecting to the interactive Web Interface System (available in the centralized database) at the baseline visit.

The protocol was approved by the ethics committee of each participating site and all the enrolled patients provided written informed consent. Study protocols were undertaken in accordance with the Declaration of Helsinki. The MODAt study is registered with ClinicalTrials.gov, number NCT01511809.

Efficacy and safety assessments

Patients were evaluated at screening, baseline and at weeks 4, 8, 12, 16, every 8 weeks until week 48 and then every 12 weeks until week 96 or discontinuation; at each visit, patients underwent a clinical assessment and routine laboratory tests.

Liver fibrosis was evaluated by means of the aspartate aminotransferase (AST)/platelet ratio index (APRI) [27] and by the fibrosis 4 score (FIB-4) index [28]. Estimated glomerular filtration rate (e-GFR) was calculated by the Cockcroft–Gault equation [29].

At baseline, 48, 96 weeks or at discontinuation, patients underwent dual-energy X-ray absorptiometry scan and neurocognitive evaluation.

Patients' adherence to study-drug regimen was assessed by a validated self-report questionnaire including a 1-month recall [30,31]. The self-reported scores were indicated on a visual analogue scale of 0 (worst level) to 100 (best level); patients with an adherence percentage of 100% (no missed doses in the previous month) were considered as adherent.

Treatment-emergent adverse event was defined as any adverse event that occurred after the initiation of the study treatment; treatment-emergent adverse events were assessed as drug-related or not and scored by each site investigators according to the DAIDS grading scale [32].

The primary endpoint was the proportion of patients with treatment success by week 48. Treatment failure was

defined as having one of the following events: confirmed viral rebound (CVR) or treatment discontinuation for any cause. CVR was established when two consecutive viral load values more than 50 copies/ml occurred within 2 weeks during follow-up (for the analysis, the first value was considered).

In case of CVR, patients treated with ATV/r monotherapy had to be reintensified with their previous two NRTIs and, if not suppressed (HIV-RNA <50 copies/ml) after 12 weeks, discontinued from the study; patients treated with ATV/r along with two NRTIs had to be discontinued from the study.

Secondary endpoints included changes in $CD4^+$ cell count, occurrence of adverse events, adherence, emergence of resistance mutations, changes in laboratory parameters measuring lipid and glucidic profile, bone marrow, liver and renal function, changes in bone mineral density and neurocognitive performance.

Genotype and ATV plasma concentration were performed at the time of CVR. Atazanavir resistance mutations (10I/F/V/C, 46I/L, 50L, 54A/L/M/T/V, 82A/F/I/T, 84V, 88S, 90M) were identified from the International AIDS Society-USA resistance testing panel [33].

Statistical analysis

Assessment of noninferiority of ATV/r compared with ATV/r along with two NRTIs was done with a two-sided 95% confidence interval (95% CI) of the difference in percentage of patients with treatment success (monotherapy − triple therapy): a lower limit of the 95% CI of the difference between the two proportions below the prespecified margin of noninferiority of −10% would establish inferiority. A sample size of 342 patients (171 per treatment arm) provides 80% power (one-sided, alpha 0.05) to establish noninferiority of atazanavir monotherapy as compared with atazanavir triple therapy with an overall treatment success rate of 85% at week 48.

Two prespecified interim analyses were planned on the first 100 patients with 24 and 48 weeks of follow-up to monitor that the proportion of treatment failure would not exceed the expected threshold (15%) specified in the sample size calculation; an independent Data and Safety Monitoring Board (DSMB) reviewed the efficacy and safety results. On the basis of the efficacy data review, in June 2013, DSMB recommended to stop further patients' enrolment and to follow-up the enrolled patients until 96 weeks, after having signed an updated informed consent.

All randomized patients who received at least 1 day of study treatment were included in the intent-to-treat (ITT) population.

The ITT population was used for the primary efficacy analysis at week 48: patients treated with ATV/r who reintensified due to CVR were considered as failure (ITT with re-intensification = failure) as well as discontinuations for any reason or loss to follow-up.

Secondary efficacy analyses on the primary endpoint at week 48 were also performed on the ITT population considering that reintensification equals success (ITT with reintensification = success, if patient with CVR achieved virological suppression (HIV-RNA <50 copies/ml) within 12 weeks since NRTI reintroduction). The analyses on the primary endpoint were also stratified according to the level of viral load prior ART initiation (HIV-RNA ≤100 000 vs. >100 000 copies/ml).

The analyses on the secondary safety endpoints were performed on the ITT population, using the reintensification equal to failure approach. All data were summarized with median (interquartile range, IQR) or proportions, as appropriate. Chi-square or Fisher exact's test and the Wilcoxon rank sum test were used to compare discrete and continuous variables, respectively. Significant 48-week changes from baseline were evaluated by the Wilcoxon signed rank test.

A Cox proportional hazard model was applied to investigate factors associated with the risk of treatment failure by week 48 among patients treated with ATV/r monotherapy; the model included the following baseline covariates (supposed to be potentially associated with the risk of treatment failure): age, sex, HIV risk factor, viral load at ART initiation, hepatitis C coinfection, duration of ATV/r treatment, duration of undetectable viral load, nadir and baseline $CD4^+$ cell count. A second multivariate Cox proportional hazard model including adherence as an additional covariate was also calculated.

The analyses were performed using SAS Software, release 9.2 (SAS Institute, Cary, North Carolina, USA).

Results

Between October 2010 and June 2012, 109 patients were screened (Fig. 1). Six patients were not included (one nephrolitiasis, one withdrew consent, four failed to meet eligibility criteria) and 103 patients were randomized: 51 patients were assigned to receive ATV/r monotherapy and 52 patients to maintain the ATV/r along with two NRTIs therapy.

Baseline characteristics were well balanced between the two treatment groups (Table 1). At the inclusion in the study, patients were receiving the following NRTIs: tenofovir/emtricitabine (87%), abacavir/lamivudine (8%), other NRTIs (5%).

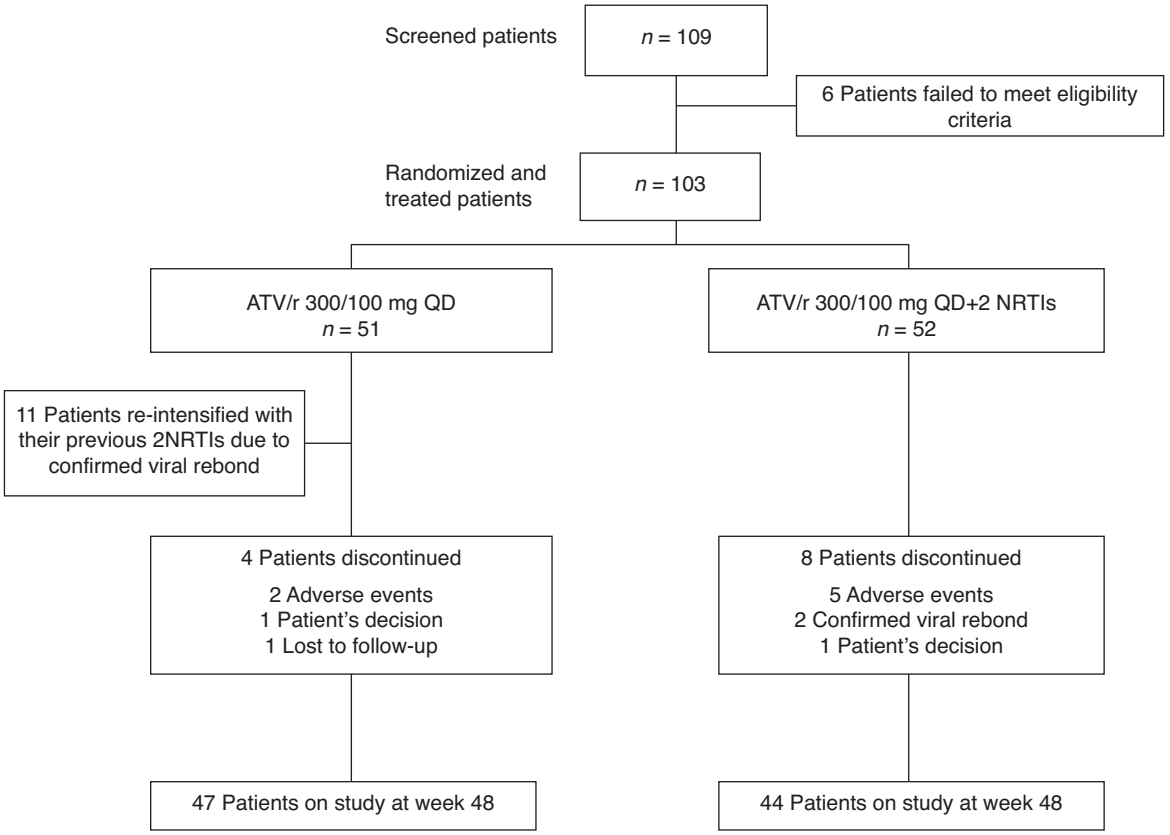

Fig. 1. The MODAt trial: 48-week patients disposition. ATV/r, atazanavir/ritonavir; NRTIs, nucleoside reverse transcriptase inhibitors; QD, quaque die.

Efficacy

At the primary efficacy analysis, the proportion of treatment success was 73% with ATV/r and 85% with ATV/r along with two NRTIs (Fig. 2a). The difference between the two groups was −12.1% with a 95% CI (−27.8 to 3.6), therefore excluding noninferiority. When considering reintensification equal success, noninferiority of ATV/r monotherapy was verified (Fig. 2a).

Among individuals with a viral load prior ART initiation of 100 000 copies/ml or less, the proportion of response to therapy was 75% with ATV/r monotherapy and 81% with triple therapy according to the ITT reintensification equal to failure analysis: the difference between the two groups was smaller (6.1%) but with a larger 95% CI (−26.5 to 14.3), excluding noninferiority that was, instead, confirmed when considering the reintensification is equal to success analysis (Fig. 2b).

Among individuals with a viral load prior ART initiation more than 100 000 copies/ml, both the ITT reintensification equal to failure analysis and the ITT reintensification equal to success excluded noninferiority (Fig. 2c).

Among individuals with hepatitis C virus (HCV) coinfection, the proportion of treatment success at week 48 was 45% (five out of 11 patients) in the ATV/r monotherapy arm vs. 90% (nine out of 10 patients) in the ATV/r along with two NRTIs arm ($P = 0.064$). Among individuals without HCV coinfection, similar proportions of treatment success at week 48 were observed in the two arms [ATV/r arm (80%) and the ATV/r along with two NRTIs arm (83%), $P = 0.779$]. Within the ATV/r monotherapy arm, patients without compared with those with HCV coinfection showed a higher proportion of treatment success (80 vs. 45%, $P = 0.050$).

In the ATV/r along with two NRTIs arm, eight patients had treatment failure during the first 48 weeks and discontinued the study (two CVRs, five adverse events, one patient's decision). In the ATV/r arm, 14 patients had treatment failure during the first 48 weeks: 10 patients had CVR and were successfully reintensified; four patients discontinued the study (one nephrolitiasis, one patient's decision, one lost to follow-up, one had CVR at week 16, successfully reintensified and then discontinued at week 32 due to nephrolithiasis).

Main characteristics of patients with CVR are reported in Table 2. None of the patients in the ATV/r arm had resistance mutations at the time of CVR. All patients in the ATV/r arm achieved HIV-1 RNA less than 50 copies/ml within 12 weeks after reintensification with their previous two NRTIs, while the two patients with CVR in the

Table 1. The MODAt study: baseline characteristics of the 103 HIV-1 enrolled patients.

	ATV/r monotherapy ($N=51$)	ATV/r triple therapy ($N=52$)	P
Age (years)	41.4 (35.4–47.7)	41.7 (36.6–49.8)	0.654[a]
Men	42 (82%)	45 (86%)	0.597[b]
Race			0.842[b]
White	46 (90%)	45 (87%)	
Black	2 (4%)	3 (6%)	
Hispanic	3 (6%)	4 (8%)	
BMI (kg/m^2)	24.0 (22.1–25.2)	23.3 (21.6–26.3)	0.942[a]
Years of HIV infection	6 (3–7)	5 (2–9)	0.844[a]
HIV risk factor			0.412[b]
IDU	2 (4%)	4 (8%)	
MSM	29 (57%)	34 (65%)	
Heterosexual	13 (26%)	12 (23%)	
Other/unknown	2 (4%)	2 (4%)	
CDC C stage	0	1 (2%)	0.286[b]
CD4$^+$ cell count nadir (cells/μl)	274 (221–355)	278 (183–364)	0.892[a]
HCV coinfection	11 (22%)	10 (19%)	0.811[b]
First-line therapy	36 (71%)	37 (71%)	0.999[b]
ART duration (months)	25 (16–47)	25 (18–54)	0.672[a]
Months on ATV/r and two NRTIs	22 (15–33)	20 (17–36)	0.393[a]
TDF/FTC backbone	46 (90%)	44 (85%)	0.555[b]
HIV-1 RNA <50 copies/ml (months)	20 (10–49)	18 (12–49)	0.797[a]
HIV-1 RNA at ART start ($\log_{10}$ copies/ml)	4.90 (4.49–5.26)	4.67 (3.99–5.07)	0.087[a]
CD4$^+$ cell count (cells/μl)	599 (457–774)	570 (417–735)	0.571[a]
Fasting glucose (mg/dl)	84 (79–93)	82 (76–90)	0.057[a]
Total cholesterol (mg/dl)	180 (167–217)	191 (161–220)	0.516[a]
LDL-cholesterol (mg/dl)	116 (97–133)	122 (102–145)	0.181[a]
HDL-cholesterol (mg/dl)	43 (37–51)	46 (38–52)	0.690[a]
Triglycerides (mg/dl)	116 (93–172)	123 (92–174)	0.890[a]
ALT (UI/l)	27 (21–39)	27 (17–41)	0.354[a]
AST (UI/l)	21 (17–29)	21 (16–26)	0.511[a]
APRI	0.24 (0.16–0.33)	0.23 (0.17–0.32)	0.798[a]
Creatinine (mg/dl)	0.87 (0.78–1.00)	0.87 (0.77–0.98)	0.729[a]
eGFR[c] (ml/min per 1.73 m^2)	104 (94–128)	111 (97–137)	0.400[a]
ALP (U/ml)	93 (76–115)	99 (85–123)	0.324[a]
Total bilirubin (mg/dl)	1.94 (1.53–3.02)	2.4 (1.59–3.44)	0.472[a]

Results as median (IQR) or frequency (%). ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase/platelet ratio index; ART, antiretroviral treatment; AST, aspartate aminotransferase; ATV/r, atazanavir/ritonavir; FTC, emtricitabine; NRTIs, nucleoside reverse transcriptase; TDF, tenofovir.
[a]By Wilcoxon rank-sum test.
[b]By chi-square or Fisher exact test, as appropriate.
[c]Estimated by Cockroft–Gault equation.

ATV/r along with two NRTIs arm were switched to a rescue regimen. One patient in the ATV/r along with two NRTIs arm developed RTIs resistance mutations.

Viral blips were observed in both treatment arms [nine and four patients on ATV/r and ATV/r along with two NRTIs, respectively, in the range of 50–100 copies/ml ($P=0.149$)]; in the ATV/r monotherapy arm, seven of eight (88%) patients with viral blips presented with HIV-1 RNA more than 100 000 copies/ml at ART initiation.

At multivariate analysis, among patients treated with ATV/r monotherapy, hepatitis C coinfection [hazard ratio$_{(\text{yes vs. no})}$ 7.64, 95% CI 1.44–40.47, $P=0.017$] was the only significant predictor of treatment failure by week 48. Similar results were obtained when including adherence as an additional covariate.

Immunological efficacy

At week 48, we observed an increase in CD4$^+$ cell counts since baseline in both ATV/r monotherapy arm [week 48: 643 (473–773) cells/μl; 48-week change: 50 (−21/+131) cells/μl; $P=0.025$] and in the ATV/r along with two NRTIs arm [week 48: 577 (496–740) cells/μl; 48-week change: 33 (−34/+136) cells/μl; $P=0.056$] without any significant difference in CD4$^+$ cell count change between arms ($P=0.900$).

Adherence

Seventy-nine (76.7%) patients had available data on adherence in at least one visit. Similar proportions of patients reported not having missed at least one dose at baseline: 20 out of 34 (58.8%) and 19 out of 38 (50.0%) were adherent in the ATV/r monotherapy arm and in the ATV/r along with two NRTIs arm, respectively ($P=0.486$). At week 48 or discontinuation, self-reported adherence was 60.0% ($n=21/35$ in the ATV/r monotherapy arm, $P=0.999$ by McNemar test) and 39.5% ($n=15/38$ in the ATV/r along with two NRTIs, $P=0.317$ by McNemar test; monotherapy vs. triple therapy at week 48: $P=0.103$).

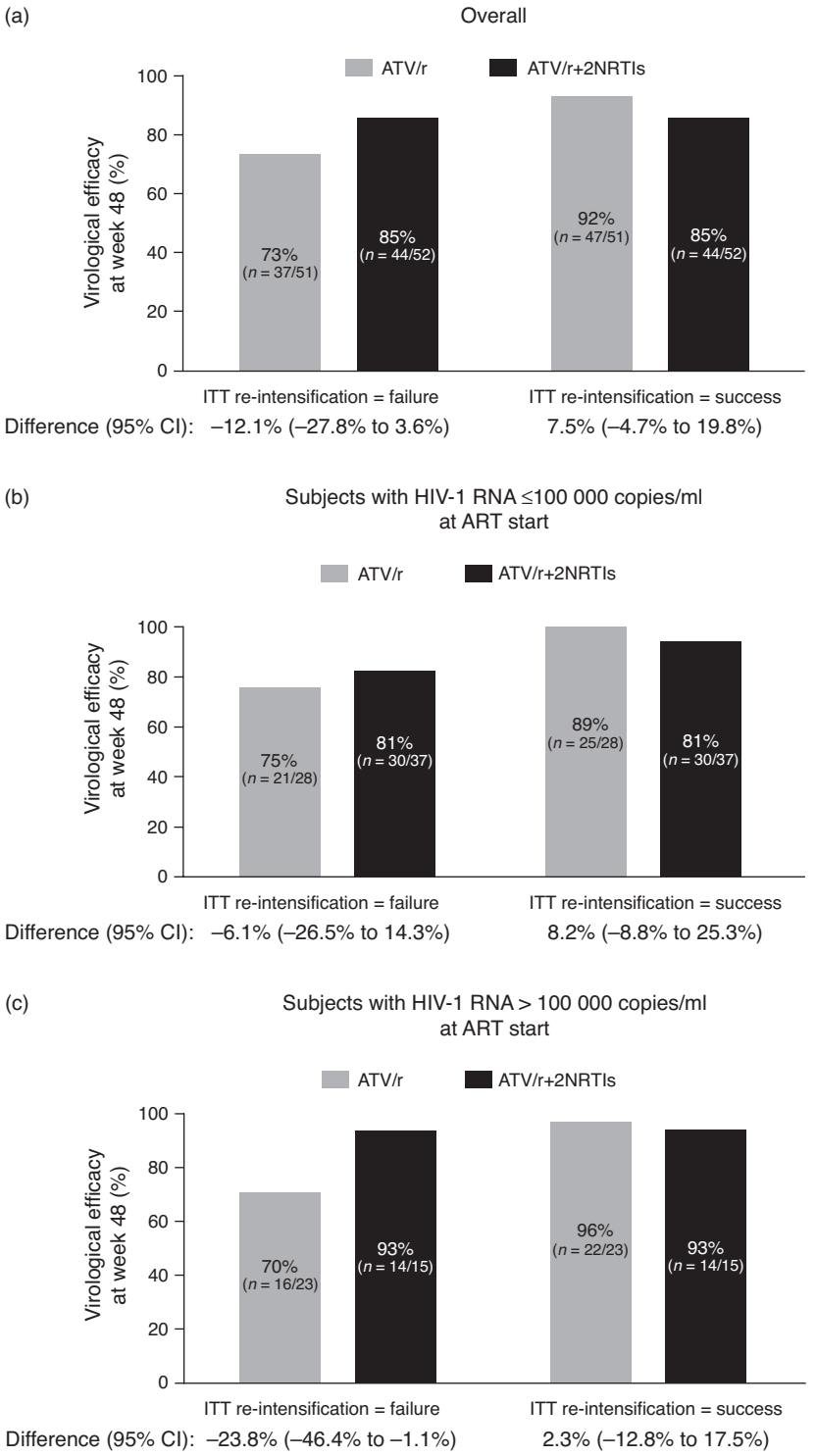

Fig. 2. The MODAt trial: 48-week virological efficacy in all study individuals (a), in patients with HIV-RNA at ART start ≤100 000 copies/ml (b) and in patients with HIV-RNA at ART start >100 000 copies/ml (c). ART, antiretroviral therapy; ATV/r, atazanavir/ritonavir; ITT, intention to treat; NRTIs, nucleoside reverse transcriptase inhibitors.

Adverse events

Grade 3–4 clinical adverse events were less frequent [6 (11.8%) vs. 19 (36.5%)] in patients treated with ATV/r monotherapy than those on ATV/r along with two NRTIs ($P = 0.003$); two serious adverse events (one acute coronary stenosis, one left basal pneumonia), not judged as drug-related and thus not leading to study discontinuation, were observed in the ATV/r monotherapy

Table 2. The MODAt study: main characteristics of patients with confirmed viral rebound.

Arm	Patient ID	Time to CVR	HIV-1 RNA at ART start (copies/ml)	$CD4^+$ cell count nadir (cells/μl)	HCV coinfection	HCV RNA at CVR (UI/ml)	First HIV-1 RNA (copies/ml)	Second HIV-1 RNA (copies/ml)	Adherence at CVR	ATV $Ctrough_{24}$ (ng/ml)	Mutations at CVR	HIV-1 RNA >12 weeks (copies/ml)
ATV/r	T020	W24	166 700	220	Neg	–	376	515	88%	920	None	<50
	T033	W24	84 000	450	Neg	–	1704	505	95%	943	None	<50
	T046	W24	424	269	Neg	–	121	164	100%	1357	None	<50
	T055	W32	118 660	396	Neg	–	260	211	91%	294	Not amplifiable	<50
	T061	W24	328 920	149	Neg	–	72	146	90%	903	None	<50
	T026	W16	95 354	223	Pos	985 091	150	182	95%	323	None	<50
	T038	W32	138 827	166	Pos	4803	50	279	99%	1979	None	<50
	T050	W8	108 900	264	Pos	406 782	1397	250 000	72%	200	None	<50
	T053	W8	70 450	116	Pos	<12	6695	3897	88%	349	None	<50
	T003	W12	290 600	330	Pos	28 000	57	98	96%	Not available	Not amplifiable	<50
	T002	W32	64 760	286	Pos	1813	93	52	95%	Not available	Not amplifiable	<50
ATV/r and 2 NRTIs	T025	W24	280 900	445	Neg	–	138	9602	89%	269	L10I, V179D	NA
	T065	W48	19 380	253	Neg	–	254	92	93%	836	None	NA

ART, antiretroviral therapy; ATV $Ctrough_{24}$, 24-h atazanavir trough concentration; ATV/r, atazanavir/ritonavir; CVR, confirmed viral rebound; NA, not applicable; NRTIs, nucleoside reverse transcriptase inhibitor.

arm. Two patients developed acute hepatitis: one in ATV/r monotherapy arm due to occurrence of acute HCV infection and one in ATV/r along with two NRTIs due to concomitant use of anabolic hormones.

None of the patients in ATV/r monotherapy arm developed grade 3–4 drug-related clinical adverse events, which were observed in six (11.5%) patients of the ATV/r along with two NRTIs arm (two nephrolithiasis, one cholecystitis due to cholelithiasis, one arthritis and hyperuricemia, two gross haematuria with proteinuria) ($P = 0.027$).

Safety parameters

No significant 48-week change in BMI was observed in both treatment arms [ATV/r monotherapy: 0.2 (−0.3/+0.7) kg/m^2; ATV/r triple therapy: 0 (−0.8/+0.5) kg/m^2; ATV/r vs. ATV/r along with two NRTIs: $P = 0.086$].

Two (3.9%) patients in the ATV/r along with two NRTIs arm had grade 3–4 total cholesterol elevations. There were three (5.9%) patients in the ATV/r monotherapy arm and three (5.8%) patients in the triple-therapy arm with grade 3–4 elevations in low-density lipoprotein (LDL)-cholesterol. One (2%) patient per arm had grade 3–4 triglycerides elevation during follow-up.

A significant 48-week increase in total cholesterol [ATV/r monotherapy: 15 (−13/+36) mg/dl, $P = 0.008$; ATV/r triple therapy: 1 (−15/+11) mg/dl; ATV/r vs. ATV/r along with two NRTIs: $P = 0.012$] and LDL-cholesterol [ATV/r monotherapy: 2 (−15/+16) mg/dl; ATV/r triple therapy: −9 (−25/+6) mg/dl, $P = 0.010$; ATV/r vs. ATV/r along with two NRTIs: $P = 0.025$] was observed in ATV/r monotherapy arm.

A significant improvement of high-density lipoprotein (HDL)-cholesterol was found in patients on ATV/r monotherapy (Fig. 3). No significant 48-week change of triglycerides was observed in both groups [ATV/r monotherapy: −2 (−24/+31) mg/dl; ATV/r along with two NRTIs: −8 (−21/+7) mg/dl; ATV/r vs. ATV/r along with two NRTIs: $P = 0.452$].

No grade 3–4 elevations in fasting glucose levels were found in both arms and a favourable decrease at week 48 was observed in the ATV/r monotherapy arm (Fig. 3).

Grade 3–4 hyperbilirubinemia occurred in 20 (39%) patients in ATV/r and 17 (33%) patients in the ATV/r along with two NRTIs arm ($P = 0.542$). By week 48, no significant changes were detected in both groups for total bilirubin [ATV/r monotherapy: 0.20 (−0.47/+0.83) mg/dl; ATV/r triple therapy: 0 (−0.74/+0.67) mg/dl; ATV/r vs. ATV/r along with two NRTIs: $P = 0.276$] or in indirect bilirubin [ATV/r monotherapy: 0.09 (−0.78/+0.60) mg/dl; ATV/r triple therapy: 0.17

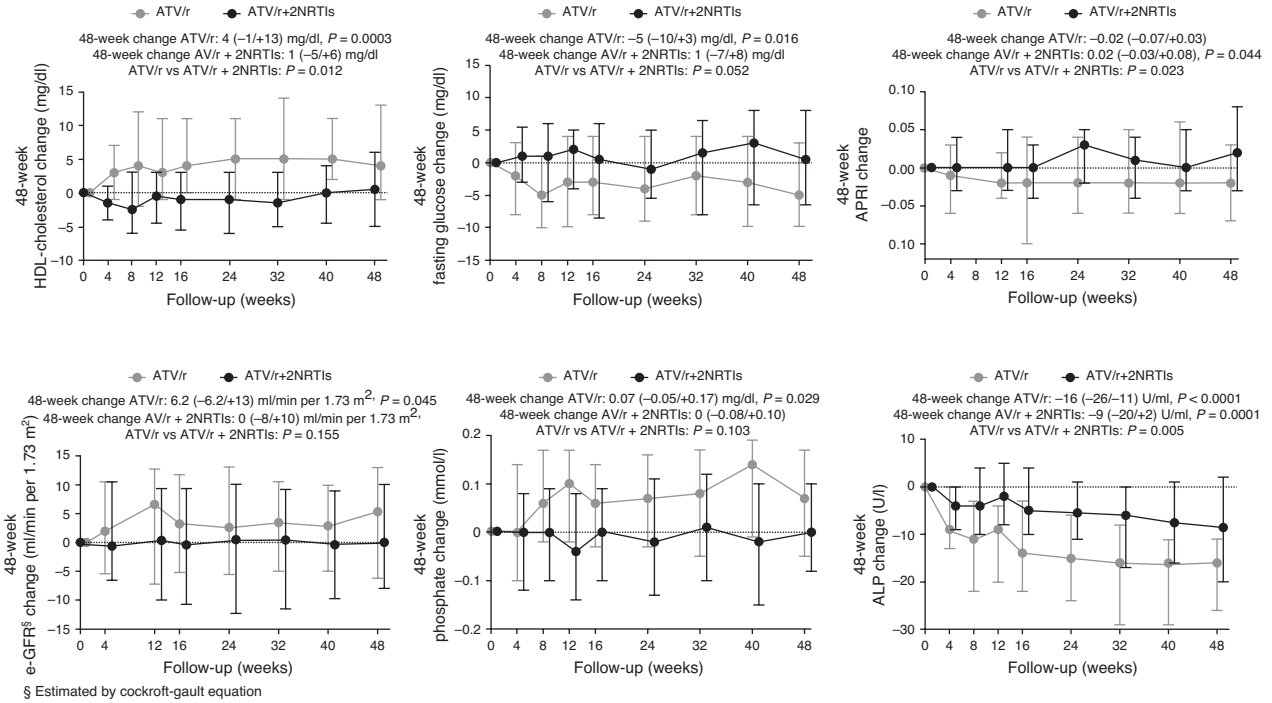

Fig. 3. The MODAt trial: 48-week median (interquartile range) changes from baseline in safety parameters. ALP, alkaline phosphatase; APRI, aspartate aminotransferase/platelet ratio index; ATV/r, atazanavir/ritonavir; e-GFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; NRTIs, nucleoside reverse transcriptase inhibitors.

(−0.45/+0.75) mg/dl; ATV/r vs. ATV/r along with two NRTIs: $P = 0.858$].

No significant ALT changes at week 48 were observed in either arm [ATV/r monotherapy: −3 (−10/+3) UI/l; ATV/r triple therapy: 0 (−3/+7) UI/l; ATV/r vs. ATV/r along with two NRTIs: $P = 0.094$].

We observed a small but significant improvement of liver fibrosis markers in ATV/r monotherapy arm, both considering FIB-4 [48-week change was −0.01 (−0.17/+0.16) in the ATV/r monotherapy arm and 0.06 (−0.06/+0.19) in the ATV/r triple-therapy arm ($P = 0.030$); ATV/r vs. ATV/r along with two NRTIs: $P = 0.071$] and APRI algorithms (Fig. 3).

Trend of creatinine change was similar in the two arms [ATV/r monotherapy: −0.02 (−0.10/+0.06) mg/dl; ATV/r along with two NRTIs: 0 (−0.06/+0.06) mg/dl; ATV/r vs. ATV/r along with two NRTIs: $P = 0.337$], but a significant improvement of estimated glomerular filtration rate (e-GFR) was observed in ATV/r monotherapy arm (Fig. 3).

Individuals treated with ATV/r monotherapy showed a significant 48-week improvement of phosphate and alkaline phosphatase levels (Fig. 3).

Finally, the analysis showed that the benefits seen in the ATV/r monotherapy arm tended to disappear during the reintensification phase for almost all the considered parameters: pre and post reintensification changes were significantly different only for fasting glucose [change before reintensification: −11 (−13/−3) mg/dl; change during reintensification: 0 (0–7) mg/dl; pre vs. post reintensification: $P = 0.004$] and alkaline phosphatase [change before reintensification: −14 (−26/−4) U/l; change during reintensification: 0 (−5/0) U/l; pre vs. postreintensification: $P = 0.039$].

Discussion

The MODAt study is the first randomized trial evaluating treatment simplification with ATV/r monotherapy compared with standard ATV/r triple therapy for treatment in HIV-1 patients who achieved initial virologic suppression.

The primary efficacy analysis showed a 73% rate of treatment success for ATV/r monotherapy, which therefore offered less protection from treatment failure than did ATV/r standard triple therapy. Better results were obtained by other studies considering lopinavir/ritonavir [10–12] or darunavir/ritonavir [13,14] monotherapy, which showed rates of 48-week treatment success ranging from 80 to 94%.

CVR and viral blips in ATV/r monotherapy arm were more frequently observed in individuals with HIV-RNA

more than 100 000 copies/ml at ART initiation. Similar findings have also been reported in darunavir/ritonavir monotherapy studies [34]. Patients with high viral load at ART initiation have a delayed and lower treatment success rate and an increased risk of viral rebound [35]: these findings suggest that in patients with a high viremic set-point, use of a single antiretroviral agent in maintenance therapy, although with a high genetic barrier as protease inhibitors, may be more risky.

CVR was more frequently observed in patients with HCV coinfection. The effect of HCV coinfection on the risk of treatment failure among individuals treated with ATV/r monotherapy was also confirmed at multivariate analysis. Hepatitis C coinfection was reported as a significant predictor of confirmed HIV-RNA elevations also in the MONET study both in the analysis at 48 weeks and at 144 weeks [14,34]. Other randomized clinical trials on protease inhibitor monotherapy did not evaluate the effect of this covariate [13,36,37]. We think it is unlikely that this result was seen simply by chance as the limited sample size (and the consequent low statistical power) of the monotherapy arm in the MODAt study could have obscured the effect of HCV on virological failure that was observed.

Mechanisms involved in this process are not fully investigated. Our hypothesis is that, apart from eventual patient adherence issues, a negative virus–virus interplay in controlling HIV replication [38,39] might become more evident when a single antiretroviral agent is used.

An adequate selection of candidates for reductive antiretroviral strategy is the key question on the protease inhibitor/r monotherapy field and needs to be rigorously assessed. We did not find any association between virological failure and haemoglobin levels, adherence, atazanavir plasma concentrations or $CD4^+$ cell count nadir. It is possible that in our study, the importance of these variables in predicting the risk of virological failure was attenuated because of the uniformity of patient's characteristics (nadir $CD4^+$ cell count >100 cells/μl, similar type of antiretroviral regimen and similar treatment duration); on the contrary, we cannot exclude that our limited sample size may preclude our ability to assess the effects observed in the lopinavir/ritonavir monotherapy studies [37].

In our study, we did not find an association between the risk of treatment failure and the extent of previous virological suppression, consistently with what shown in larger randomized protease inhibitor/r monotherapy studies with long follow-up [10,11,13,14,34,36,40].

As previously reported [13], we obtained more positive results in patients with low viral load at ART initiation and in patients without HCV infection suggesting that these patients may be more safely selected for ATV/r monotherapy.

At the secondary efficacy analysis (ITT with reintensification equal success), we found no difference between monotherapy and triple therapy thus establishing noninferiority. All of the patients who experienced a loss of virologic suppression while on ATV/r monotherapy had no evidence of resistance mutations and were able to resuppress and maintain suppression after resumption of previously used NRTIs. This observation confirmed what was previously observed in LPV/r or DRV/r monotherapy studies, showing that NRTIs reintroduction was a successful strategy preserving future treatment options [16,41,42].

Although the long-term clinical benefit needs to be evaluated, ATV/r monotherapy was associated with a clear-cut 48-week safety profile: grade 3–4 adverse events occurred less frequently than among patients on three-drug regimen and none of the patients in ATV/r arm developed a grade 3–4 drug-related adverse event, while about 11% of the patients in the control arm did. These events mainly involved renal function indicating a significant contributing role of tenofovir on the occurrence of these adverse events [43].

Concerns have been raised about the possibility of insufficient central nervous system penetration of atazanavir for patients on ATV/r monotherapy [25]; nevertheless, we did not register any neurologic or neuropsychiatric episodes in our trial. A substudy combining neurocognitive tests, magnetic resonance (MR) brain imaging and lumbar puncture is ongoing to specifically address this question.

Consistently with previous reports, a mild increase in bilirubin levels [8,9], total cholesterol and LDL-cholesterol as well as the improvement in e-GFR [13,14], serum phosphate and alkaline phosphatase observed in the ATV/r arm may be most likely related to the removal of tenofovir.

Interestingly, we observed a small but significant improvement in HDL-cholesterol, in fasting glucose and in markers of liver fibrosis suggesting that the removal of the two NRTIs may have a positive effect on the mechanisms favouring the development of glucose impairment and metabolic syndrome [44,45].

We need to recognize that our results mainly apply to patients receiving ATV/r along with two NRTIs for about 2 years and without previous virological failures. In addition, our results were based on the 48-week interim analysis, estimated on the first 103 enrolled patients and not on the expected number of individuals as defined by the sample size calculation. We acknowledge that the reduced number of individuals is a limitation with a clear impact on statistical power; nevertheless, we think that treatment success results were clear with no risk of falsely claiming noninferiority and that a different finding would

be unlikely in a full sample size. In addition, 103 patients were enough to show a benefit with respect to adverse events and trend of safety parameters that would not emerge with unpowered samples.

In conclusion, although it is difficult to draw firm conclusions because these results are based on interim analyses, virologic efficacy of ATV/r monotherapy is inferior in comparison with triple therapy, especially in individuals with high viral load at ART initiation or HCV coinfection. Nevertheless, in ATV/r monotherapy arm, 73% of the patients were able to maintain virological suppression and 92% of the patients are still on study at week 48 with a safety benefit. Therefore, we think that ATV/r monotherapy may be considered, given the efficacy of NRTIs reintensification and the observed safety benefit, as a possible treatment strategy for managing NRTIs toxicity.

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A.C., V.S., A.L. provided scientific input to study design, C.V., E.C., S.N., A.D.M., FM, A.A., A.D.B., S.R. assisted in the enrolment and management of the patients. All the authors evaluated clinical data from the study, reviewed and edited the manuscript. L.G. performed the statistical analyses.

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Conflicts of interest

A.C. has received consultancy payments and speaking fee from Bristol-Myers Squibb, Gilead, ViiV Healthcare, Merck Sharp Dohme, ABBvie, Janssen.

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