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Differential Body Composition Effects of Protease Inhibitors Recommended for Initial Treatment of HIV Infection: A Randomized Clinical Trial

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40-word summary: We found no major differences between atazanavir/ritonavir and darunavir/ritonavir in efficacy, clinically-relevant side effects, or cholesterol fractions. However, atazanavir/ritonavir led to higher triglycerides and total and subcutaneous fat than darunavir/ritonavir and fat gains with atazanavir/ritonavir were associated with insulin resistance.

Abstract

Background: It is unclear whether metabolic or body composition effects may differ between protease inhibitor-based regimens recommended for initial treatment of HIV infection.

Methods: ATADAR is a phase IV, open-label, multicenter randomized clinical trial. Stable antiretroviral-naive HIV-infected adults were randomly assigned to atazanavir/ritonavir 300/100 mg or darunavir/ritonavir 800/100 mg in combination with tenofovir/emtricitabine daily. Pre-defined end-points were treatment or virological failure, drug discontinuation due to adverse effects, and laboratory and body composition changes at 96 weeks.

Results: At 96 weeks, 56 (62%) atazanavir/ritonavir and 62 (71%) darunavir/ritonavir patients remained free of treatment failure (estimated difference 8.2%; 95%CI -0.6 to 21.6); and 71 (79%) atazanavir/ritonavir and 75 (85%) darunavir/ritonavir patients remained free of

virological failure (estimated difference 6.3%; 95%CI -0.5 to 17.6). Seven vs. five patients discontinued atazanavir/ritonavir or darunavir/ritonavir due to adverse effects. Total and HDL cholesterol similarly increased in both arms, but triglycerides increased more in atazanavir/ritonavir arm. At 96 weeks, body fat (estimated difference 2862.2 gr; 95%CI 726.7 to 4997.7; P=0.0090), limb fat (estimated difference 1403.3 gr; 95%CI 388.4 to 2418.2; P=0.0071), and subcutaneous abdominal adipose tissue (estimated difference 28.4 cm²; 95%CI 1.9 to 55.0; P=0.0362) increased more in atazanavir/ritonavir than in darunavir/ritonavir arm. Body fat changes in atazanavir/ritonavir arm were associated with higher insulin resistance.

Conclusions: We found no major differences between atazanavir/ritonavir and darunavir/ritonavir in efficacy, clinically-relevant side effects, or plasma cholesterol fractions. However, atazanavir/ritonavir led to higher triglycerides and total and subcutaneous fat than darunavir/ritonavir and fat gains with atazanavir/ritonavir were associated with insulin resistance.

Trial Registration: clinicaltrials.gov Identifier: NCT01274780

Accepted

Introduction

Both ritonavir-boosted atazanavir (ATV/r) or darunavir (DRV/r) plus tenofovir/emtricitabine (TDF/FTC) are protease inhibitor-based regimens recommended as first-line therapy in major contemporary clinical guidelines (1-3). Each one has demonstrated better overall tolerability than ritonavir-boosted lopinavir (LPV/r) plus TDF/FTC (4, 5).

Short-term low-dose ritonavir 100mg/day has been reported to induce dyslipidemia (6) but not insulin resistance (7). Although ritonavir 100mg/day is equally used in first-line therapy with both protease inhibitors, ritonavir plasma levels have been reported to be higher with ATV than with DRV (8, 9). Antiretroviral-naïve patients starting TDF/FTC-based therapy gained significantly more limb fat with ATV/r than with efavirenz (10, 11) or LPV/r (12) at 96 weeks. Potential body fat effects of DRV/r are not well known. Unlike DRV/r, ATV/r induces hyperbilirubinemia that may cause jaundice in some patients (13) but it could also promote favorable metabolic effects due to its antioxidative properties (14).

A pilot 48-week study with roughly 30 patients per arm compared lipid, biomarkers, and body fat effects of DRV/r vs ATV/r in combination with TDF/FTC in antiretroviral-naïve patients, and concluded that both regimens had a similar metabolic profile (15). ATADAR is a multicenter, randomized, open-label clinical trial comparing between the effects of ATV/r or DRV/r, both with TDF/FTC, on metabolism, body composition, overall tolerability and efficacy in a larger number of antiretroviral-naïve HIV-infected patients followed for 96 weeks. The main study hypothesis was that lipid changes in both regimens would be similar and lower than those reported with LPV/r. In a planned interim analysis at 24 weeks, total cholesterol went up to 7.2 and 11.5 mg/dL, and HDL cholesterol rose to 5.5 and 3.9 mg/dL in ATV/r and DRV/r arms, respectively (16). Longer follow-up was necessary to evaluate whether plasma lipids and other pre-defined parameters of interest might ultimately differ between both regimens. We hereby report the final planned 96-week results of the ATADAR study.

Methods

Study design

ATADAR was a 96-week phase IV, open-label, multicenter randomized clinical trial performed in 16 Spanish centers. Entry criteria and study design have been detailed elsewhere (15).

Briefly, stable antiretroviral-naïve HIV-infected adults with plasma HIV RNA ≥ 1000 copies/mL were randomly assigned in a 1 : 1 ratio to receive either atazanavir 300 mg or darunavir 800 mg with ritonavir 100 mg plus the fixed-dose combination TDF/FTC as once-daily antiretroviral regimens. After randomization, patients were assessed at least at baseline, 4, 12, and every 12 weeks until 96 weeks. No specific physical or dietary recommendations were given.

Virological failure was defined as confirmed plasma HIV RNA ≥ 50 copies/mL at 24 weeks or later. Genotypic resistance testing was done with the use of ViroSeq HIV genotyping system according to the manufacturer's instructions (Applied Biosystems, Foster City, California, USA). Progression to AIDS was defined according to the 1993 classification of the Centers for Disease Control and Prevention (17).

Study assessments

At each visit, clinical data were collected and blood samples were obtained after at least an 8-hour overnight fast. Analyses including complete blood count, CD4 cell counts; plasma HIV RNA; plasma lipids including total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and triglycerides; creatinine; and total bilirubin were performed at each site using similar pre-established methods throughout the whole follow-up period. Plasma glucose, creatinine, total bilirubin, total and HDL cholesterol and triglycerides were measured using commercial enzymatic kits. LDL cholesterol was calculated by the Friedewald equation, whenever triglycerides were lower than 400 mg/dL (18); otherwise, it was measured directly. Estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease

Epidemiology Collaboration (CKD-EPI) equation using serum creatinine standardized to reference methods (19).

Plasma glucose and insulin were measured at baseline, 24, 48 and 96 weeks by an immunoradiometric method. Insulin resistance was estimated with the homeostatic model assessment (HOMA-IR) (20). Inflammation [high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6)] and oxidation [malondialdehyde (MDA) and Oxidized LDL (LDLox)] markers were centrally measured in -80°C frozen plasma samples collected at baseline and 48 weeks. hsCRP was determined by particle-enhanced immunonephelometry (Dade Behring, Marburg, Germany). IL-6 was measured using a commercially available ELISA assay (Quantikine HS, Human IL-6 Immunoassay, R&D Systems, Minneapolis, MN). MDA was measured by high performance liquid chromatography (21). Oxidized LDL was determined by ELISA using the monoclonal 4E6 antibody (Mercoxia AB, Uppsala, Sweden).

At baseline, 48 and 96 weeks, weight and height were measured and whole body dual-X-absorptiometry (DXA) and abdominal computed tomography (CT) scans were performed to assess body fat, fat-free mass, and bone mineral content, and subcutaneous (SAT), visceral (VAT), and total (TAT) abdominal adipose tissues, respectively. BMI was calculated by dividing weight (in kg) by the square of height (in meters). Ratio of leg fat percentage/BMI was used as a measure of the regional distribution of subcutaneous fat relative to a measure of generalized adiposity (22). DXA and CT imaging were performed locally following previously standardized scanning protocols, for each patient on the same radiographic machine and with identical parameters each time. All scans were centrally read at the end of the study by one radiologist unaware of scanning date and assigned therapy.

Safety was assessed through the reporting of clinical adverse events and laboratory abnormalities. The severity of adverse events was evaluated according to Division of AIDS toxicity table (23).

Statistical analysis

The primary end-point of ATADAR study was the change in total cholesterol at 24 weeks (15).

For the purpose of the final 96-week analysis, pre-defined secondary end-points were: proportion of patients free of treatment failure or virological failure at 96 weeks; proportion of patients with study drug discontinuation due to adverse effects at 96 weeks; changes in lipids, insulin sensitivity (HOMA-IR), total bilirubin, estimated glomerular filtration rate (CKD-EPI), and CD4 cell counts at 48 and 96 weeks; changes in inflammatory and oxidation markers at 48 weeks; and changes in DXA- and CT-derived body composition parameters at 48 and 96 weeks. Further analyses were also planned to assess the relationship between baseline HIV-1 RNA and risk of virological failure, ATV/r-related hyperbilirubinemia and risk of other potential ATV/r-related toxicities, and insulin resistance and body fat changes.

All randomized patients, except for those who violated entry criteria and those who never started study medication, were included in the analysis. In the treatment failure analysis, failure was considered in all patients who had progression to AIDS, died, had virological failure, discontinued study medication, withdrew consent or were lost to follow-up. In the virological failure analysis, failure was defined by progression to AIDS, death, or virological failure during treatment, whereas patients who withdrew consent, were lost, or switched or stopped study medication were censored. Switches in the background regimen were not considered treatment failures as long as plasma HIV-1 RNA remained less than 50 copies/mL. Changes from baseline in total cholesterol and other laboratory parameters were analyzed by repeated measures ANCOVA adjusted for clustering within center. ATADAR fulfilled CONSORT 2010 Statement criteria (24).

Statistical analysis was performed with the use of Stata 9.2 (StataCorp, College Station, TX, USA). Chi-squared or Fisher's exact tests were used to compare proportions between treatment arms. Student's t- or Mann-Whitney U-tests were used for comparisons of continuous

variables between arms. Ninety-five percent confidence intervals for treatment differences were also calculated. Correlations between continuous variables were explored using Pearson's correlation tests. Linear regression was used to adjust for baseline variables. All comparisons were made with use of a two-sided alpha level of 0.05.

Results

Baseline characteristics

Two hundred and fourteen patients were assessed for eligibility, 180 underwent randomization and 178 (ATV/r, n=90; DRV/r, n=88) received at least one dose of study drugs and were included in the analysis (**Figure 1**). Baseline characteristics are shown in **Table 1**. No participant received lipid-lowering therapy at baseline.

Efficacy

Fifty-six (62%) ATV/r and 62 (70%) DRV/r patients remained free of treatment failure (estimated difference 8.2%; 95% CI -0.6 to 21.6; P=0.25), and seventy-one (79%) ATV/r and 75 (85%) DRV/r patients remained free of virological failure (estimated difference 6.3%; 95% CI -0.5 to 17.6; P=0.27) at 96 weeks. One patient died (lung cancer) and another one developed a new CDC-C event (non-Hodgkin lymphoma) in ATV/r arm, while there were no deaths or CDC-C events in DRV/r arm. Patients who developed virological failure had mean (SD) higher baseline plasma HIV RNA than those who did not [5.3 (0.5) vs 4.7 (0.7) in ATV/r arm, P=0.0005; 5.3 (1.0) vs 4.7 (0.7) in DRV/r arm, P=0.013]. At 96 weeks, mean (SD) CD4 cells per mm³ increased in both arms [+284 (219) ATV/r vs +298 (182) DRV/r] (P=0.64).

Viral resistance testing

HIV-1 RNA could be amplified in 6 of 17 patients experiencing virological failure in the ATV/r arm, and 4 had mutations detected: patient 1, V245M; patient 2, E35D, K43KN, D60E, I93L; patient 3: A71V, E35D, M36I, I62V, I93L; patient 4: V241V. HIV-1 RNA could be amplified in 5 of 13 patients experiencing virological failure in the DRV/r arm, and 4 had mutations detected: patient 1, I15V; patient 2, E35D, L63P; patient 3: E35D, L63P; patient 4: I13V, M36IM, I62IV, L63HQ. None of these mutations was associated with virological resistance.

Overall Safety

There were more patients in ATV/r than in DRV/r arm experiencing at least one related adverse event [n=52 (57%) vs 37 (41%), P=0.038], at least one serious adverse event [n=24 (26%) vs 7 (8%), P=0.002], and at least one grade 3-4 adverse event [n=40 (44%) vs 12 (14%), P<0.0001]. However, the number of patients with at least one adverse event leading to discontinuation [n=7 (7.8%) vs 5 (5.7%), P=0.25] was similar. Hyperbilirubinemia was computed in 15 (63%) out of 24 patients with at least one serious adverse event, 27 (68%) out of 40 patients with at least one grade 3-4 adverse event, and in 4 (57%) out of 7 patients with at least at one adverse event leading to discontinuation in the ATV/r arm. There was no association between plasma bilirubin elevation and non-bilirubin adverse events in patients allocated to ATV/r.

Lipids and Framingham score assessments

Lipid changes at 48 and 96 weeks are shown in **Table 2**. No patient received lipid-lowering therapy during the study. At 48 and 96 weeks, total and HDL cholesterol increased significantly and total-to-HDL cholesterol ratio tended to decrease in each arm, without significant differences between arms. Increases in triglycerides were higher in ATV/r than in DRV/r arm at 48 (estimated difference 22.4 mg/dL; 95% CI 0.2 to 44.6; P=0.048) and 96 (estimated difference 21.5 mg/dL; 95% CI -0.7 to 43.8; P=0.058) weeks. There were no differences

between arms in mean (SD) changes to Framingham score at 48 [-0.04 (1.5) vs. 0.05 (2.1), P=0.76] and 96 [0.07 (2.0) vs. 0.46 (2.2), P=0.25] weeks.

Chemistry parameters other than plasma lipids and biomarkers

Table 3 shows changes in insulin resistance (HOMA-IR), eGFR, and bilirubinemia at 48 and 96 weeks, and changes in hsCRP, IL-6, MDA, and LDLox at 48 weeks. HOMA-IR showed a trend towards a higher increase in ATV/r relative to DRV/r arm at 96 weeks (estimated difference 0.7; 95% CI -0.1 to 1.5; P=0.093). Each arm showed significant eGFR decreases at 48 and 96 weeks, but there were no significant differences between arms. As expected, bilirubin significantly increased in ATV/r arm at 48 and 96 weeks, and differences between arms were highly significant. There were no significant differences between arms in hsCRP, IL-6, MDA, and LDLox changes at 48 weeks.

Supplementary Table 1 shows correlations between changes in plasma lipids and changes in bilirubin in each arm at 48 and 96 weeks. In ATV/r arm, changes in bilirubin at 96 weeks were significantly associated with changes in total or HDL cholesterol at 96 weeks. **Supplementary**

Table 2 shows correlations between changes in biomarkers and changes in lipids or bilirubin in each arm at 48 weeks. Changes in LDLox were significantly associated with changes in total cholesterol in both arms.

Body composition

Changes in body composition are shown in **Table 4**. Body fat increased more in ATV/r arm than in DRV/r arm at 48 (estimated difference 1432 gr; 95% CI -67 to 2932; P=0.061) and 96 (estimated difference 2862 gr; 95% CI 727 to 4998; P=0.009) weeks. There were no significant differences in BMI, body fat-free mass or bone mineral content changes between arms at 48 and 96 weeks. Both limb and trunk fat increased in ATV/r arm (but not in DRV/r arm) at 48 and 96 weeks. Limb fat (but not trunk fat) change was significantly higher in ATV/r arm than in

DRV/r arm at 96 weeks (estimated difference 1403 gr; 95% CI 388 to 2418; P=0.007). SAT increased significantly more in ATV/r arm than in DRV/r arm at 96 weeks (estimated difference 28.4 cm²; 95% CI 1.9 to 55.0; P=0.037). Mean (SD) ratio of leg fat percentage/BMI at 96 weeks was 0.91 (0.36) in ATV/r arm and 1.05 (0.42) in DRV/r arm (P between arms= 0.048). Although VAT and TAT significantly increased in both arms at 48 and 96 weeks, differences between arms were not significant. We were unable to detect any influence of gender, age, fat mass, BMI, CD4 cell count or HIV-1 RNA at baseline on subcutaneous or total fat gain.

There were no correlations between changes in limb fat and changes in bilirubin in each arm at 48 and 96 weeks (**Supplementary Table 3**). **Figure 2** shows correlations between changes in HOMA-IR and changes in BMI and body fat parameters derived from DXA and CT scans at 96 weeks. There were significant correlations between changes in HOMA-IR and changes in BMI, body fat, and SAT in ATV/r arm. These correlations remained significant after adjustment by baseline variables including gender, age, fat mass, BMI, CD4 cell count and HIV-1 RNA. There were no correlations between HOMA-IR changes and changes in BMI and body fat parameters in DRV/r arm.

Discussion

In general, major outcomes were similar in both study arms and there was little to differentiate ATV/r vs DRV/r for use in first-line HIV treatment in terms of differences in efficacy or clinically-relevant side effects. The proportions of patients remaining free of treatment failure at 96 weeks in ATADAR (62%, ATV/r; 71%, DRV/r) were roughly similar to those ones reported according to FDA snapshot in the recently published ACTG 5257 trial (63%, ATV/r; 73%, DRV/r) (25). As expected (26), there was no evidence for primary resistance mutations to protease inhibitors in patients developing virological failure. A substantial proportion of adverse events in ATV/r arm were related to hyperbilirubinemia although they

played a minor clinical relevance because there was no association between plasma bilirubin elevation and non-bilirubin adverse events in patients allocated to ATV/r, and because the number of adverse events leading to discontinuation was similarly low in both arms. While the proportion of patients who discontinued DRV/r in ATADAR (6%) was similar to that in ACTG 5257 (5%), the proportion of patients who discontinued ATV/r in ATADAR (8%) was half that seen in ACTG 5257 (16%) (25). Rates of ATV/r discontinuation due adverse events in other major randomized clinical trials (4, 27, 28) were closer to those in ATADAR than to those in ACTG 5257. Atazanavir-related hyperbilirubinemia is a cosmetic effect, reversible upon drug discontinuation (29), but persistently high bilirubinemia or development of jaundice may make some patients or doctors consider ATV/r discontinuation.

We found no significant differences in total, LDL, HDL, and total-to-HDL cholesterol ratio changes at 48 and 96 weeks between ATV/r and DRV/r arms. However, triglycerides tended to rise more in ATV/r arm at 96 weeks. This finding was also reproduced in a planned intensive lipid sub-study with a subpopulation of ATADAR patients in which the higher increase of triglycerides in ATV/r arm was consistently associated with increases in small and dense LDL particles and a greater prevalence of LDL intermediate and B phenotypes as compared with DRV/r arm (30). We also found higher insulin resistance in ATV/r arm relative to DRV/r arm at 96 weeks, a finding consistent with that of increased plasma triglycerides (31). We did not see significant changes in inflammation or oxidation markers at 48 weeks. Changes in bilirubin were not associated with changes in inflammation or oxidation biomarkers.

We found consistent differences between arms in several fat parameters. Patients assigned to ATV/r experienced greater increases in body fat than patients in the DRV/r arm. Although an increase in BMI and body fat following the initiation of effective antiretroviral therapy may reflect the “return-to-health” phenomenon in underweight patients (32), the observed difference in body fat between arms rather suggests differential drug effects because baseline

BMI was normal and 96-week BMI change was not different between arms. In our study, the ratio of leg fat percentage/BMI decreased in ATV/r arm while it increased in DRV/r arm, with significant differences between arms at 96 weeks. The lower the ratio of leg fat percentage/BMI, the more evident the phenotype of lipoatrophy in patients treated with thymidine analogues although values reported in lipoatrophic patients (≤ 0.65) (33) were far lower from those measured in ATADAR participants at 96 weeks (≥ 0.91). Patients assigned to ATV/r experienced greater increases in triglycerides and HOMA-IR at 96 weeks than those assigned to DRV/r, thus supporting a potential association between body fat gain and insulin resistance. We found that changes in BMI, total body fat, and SAT were significantly related to HOMA-IR in ATV/r arm after adjustment for baseline variables. In this context, it was surprising that limb fat and SAT, which reflect the same subcutaneous fat compartment, consistently increased more in ATV/r than in DRV/r arm, while VAT increased similarly in both arms. Subcutaneous fat in the limbs has been traditionally associated with beneficial metabolic effects (34, 35) while VAT has been considered a major culprit in development of insulin resistance. However, recent evidence suggests that an increase in SAT can also have a significant metabolic impact in persons in whom VAT is not necessarily increased (36, 37). Increases in trunk fat, predominantly SAT, have been reported in other studies switching from LPV/r (38) or twice-daily ritonavir-boosted protease inhibitors (39) to ATV/r at 48 and 96 weeks respectively. Moreover, ATV/r was shown to exert multiple effects on cultured adipocytes compared with a relatively neutral impact of DRV/r (40).

Our study had limitations. Sample size was estimated for detecting differences in total cholesterol but not in other parameters. Although increases in triglycerides and insulin resistance tended to be greater in ATV/r than in DRV/r at 96 week, differences between arms were not fully significant and therefore should be interpreted with caution. We found consistent differences in several body fat parameters, but their ultimate clinical meaning is not

completely clear. ATADAR study did not include adipose tissue biopsies and *in vivo* studies of adipose tissue could have been helpful.

In conclusion, no major differences between ATV/r and DRV/r were found in efficacy, clinically-relevant side effects, or plasma cholesterol fractions after 96 weeks. However, ATV/r-based therapy led to higher triglycerides and higher total fat and subcutaneous fat than DRV/r-based therapy and fat gains with atazanavir/ritonavir were associated with insulin resistance. Further studies will be needed to confirm our observations and to determine their clinical relevance.

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Figure 1. Trial profile for the ATADAR study up to week 96.

Figure 2. Pearson correlations between changes in insulin resistance (HOMA-IR) and changes in body mass index or body fat parameters in each arm at 96 weeks.

ATV/r arm (in blue): BMI change (coefficient 0.35, P=0.04), total body fat change (coefficient 0.35; P=0.05), limb fat change (coefficient 0.29; P=0.11), trunk fat change (coefficient 0.34; P=0.05), SAT change (0.67, P=0.0001), VAT change (coefficient 0.21; P=0.28).

DRV/r arm (in red): BMI change (coefficient 0.08, P=0.65), total body fat change (coefficient 0.08; P=0.63), limb fat change (coefficient 0.07; P=0.68), trunk fat change (coefficient 0.14; P=0.40), SAT change (0.01, P=0.96), VAT change (coefficient 0.08; P=0.66).

DRV/r: darunavir/ritonavir; ATV/r: atazanavir/ritonavir; BMI: body mass index; SAT: subcutaneous abdominal adipose tissue; VAT: visceral adipose tissue

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Contributions

E Martinez and JM Gatell designed the study. I Pérez undertook the statistical analyses. E Martínez, A González-Cordón, E Ferrer, D Podzamczar, P Domingo, E Negro, F Gutiérrez, J Portilla, A Curran, E Ribera, J Murillas, JI Bernardino, I Santos, J Pich, I Pérez, and JM Gatell

were involved in the interpretation of data. E Martinez drafted the manuscript. All authors critically reviewed and subsequently approved the final version.

Conflicts of interests

The following authors have received research funding, consultancy fees, or lecture sponsorships, or served on advisory boards:

E Martinez: Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme, Theratechnologies, Tibotec, and ViiV Healthcare.

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The rest of authors do not declare any conflict of interests.

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Table 1. Baseline characteristics.

	ATV/r (n=90)	DRV/r (n=88)
Age, years	35 (8)	37 (9)
Male gender (n, %)	78 (87%)	78 (89%)
Hepatitis C co-infection (n, %)	8 (9)	6 (7)
Plasma HIV-1 RNA, log copies/mL	4.8 (0.7)	4.8 (0.8)
Plasma HIV-1 RNA $\geq 100,000$ copies/mL (n, %)	32 (35.6)	29 (33)
CD4 cells per mm ³	328 (205)	341 (171)
CD4 >200 cells per mm ³ (n, %)	65 (72.2)	73 (85.9)
CD8 cells per mm ³	1052 (729)	1094 (618)
CD4/CD8 ratio	0.37 (0.25)	0.38 (0.20)
Total cholesterol, mg/dL	158 (33)	158 (31)
LDL cholesterol, mg/dL	97 (28)	98 (29)
HDL cholesterol, mg/dL	39 (11)	39 (12)
Total-to-HDL cholesterol ratio	4.5 (2.0)	4.4 (1.8)
Triglycerides, mg/d	106 (59)	108 (66)
Framingham score	3.8 (3.5)	4.3 (3.9)
HOMA-IR	2.4 (1.7)	2.5 (1.3)
Total bilirubin, mg/dL	0.54 (0.12)	0.58 (0.13)
eGFR (CKD-EPI), mL/min/1.73m ²	110 (24)	106 (18)
hsCRP (mg/dL)	0.3 (0.3)	0.3 (0.3)
IL-6 (pg/mL)	2.9 (2.9)	2.7 (3.3)
MDA (nmol/L)	955.6 (805.3)	791.8 (468.2)
LDLox (mU/L)	17.2 (6.6)	16.4 (6.8)
BMI, kg/m ²	23.0 (3.3)	23.0 (3.1)
Body fat, gr	15837 (8245)	14588 (7250)
Body fat-free mass, gr	51324 (8492)	50829 (7718)

Bone mineral content, gr	2736 (485)	2751 (458)
Limb fat, gr	6239 (3559)	5893 (3623)
Trunk fat, gr	8273 (4624)	7929 (4749)
Ratio of leg fat percentage/BMI	0.95 (0.38)	0.91 (0.42)
SAT, cm²	166.0 (105.2)	153.4 (103.4)
VAT, cm²	70.1 (54.7)	71.8 (54.5)
TAT, cm²	236.1 (135.9)	225.2 (141.3)

Data are expressed as mean (SD) unless otherwise stated.

ATV/r: atazanavir/ritonavir; DRV/r: darunavir/ritonavir; HOMA-IR: homeostatic model assessment; eGFR: estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; hs CRP: high-sensitivity C reactive protein; IL-6: interleukin 6; MDA: malondialdehyde; LDLox: Oxidized LDL; BMI: body mass index; SAT: subcutaneous abdominal adipose tissue; VAT: visceral adipose tissue; TAT: total abdominal adipose tissue

Table 2. Lipid changes at 48 and 96 weeks.

	48 weeks			96 weeks		
	ATV/r (n=78)	DRV/r (n=80)	P-value	ATV/r (n=72)	DRV/r (n=74)	P-value
Total cholesterol (mg/dL)	+9.64 (34.05)	+11.37 (28.17)	0.9441	+11.31 (35.96)	+14.63 (29.18)	0.7134
LDL cholesterol (mg/dL)	-2.88 (25.36)	+4.89 (26.95)	0.0913	+1.86 (29.44)	+8.22 (25.70)	0.1711
HDL cholesterol (mg/dL)	+5.20 (10.42)	+4.67 (7.40)	0.5339	+4.80 (10.50)	+4.90 (10.91)	0.8211
Total-to-HDL cholesterol ratio	-1.20 (6.59)	-0.02 (1.26)	0.9145	-0.82 (6.60)	-0.29 (1.06)	0.5188
Triglycerides (mg/dL)	+41.04 (81.97)	+17.13 (63.46)	0.0480	+38.89 (71.74)	+15.65 (69.53)	0.0567

Data are mean (SD)

ATV/r: atazanavir/ritonavir; DRV/r: darunavir/ritonavir

Table 3. Changes in insulin resistance (HOMA-IR), estimated glomerular filtration rate (CKD-EPI), and bilirubinemia at 48 and 96 weeks, and changes in high-sensitivity C reactive protein, interleukin 6, malondialdehyde, and Oxidized LDL at 48 weeks.

	48 weeks			96 weeks		
	ATV/r (n=78)	DRV/r (n=80)	P-value	ATV/r (n=72)	DRV/r (n=74)	P-value
HOMA-IR	+0.34 (4.96)	+0.73 (9.21)	0.5711	+0.88 (2.68)	-0.25 (2.94)	0.0928
eGFR (mL/min/1.73m²)	-10.01 (20.37)	-6.18 (12.29)	0.1544	-8.63 (22.29)	-7.27 (13.80)	0.6962
Total bilirubin (mg/dL)	+1.60 (2.62)	-0.05 (0.25)	<0.0001	+1.50 (2.47)	+0.00 (0.28)	<0.0001
hs CRP (mg/dL)	-0.04 (0.51)	-0.22 (0.76)	0.1174	NA	NA	
IL-6 (pg/mL)	+14.43 (104.04)	+4.30 (25.10)	0.5796	NA	NA	
MDA (nmol/L)	-99.19 (963.97)	+20.55 (609.22)	0.4103	NA	NA	
LDLox (mU/L)	-0.22 (6.34)	-0.03 (7.09)	0.8294	NA	NA	

Data are mean (SD)

ATV/r: atazanavir/ritonavir; DRV/r: darunavir/ritonavir

eGFR: estimated glomerular filtration rate; hs CRP: high-sensitivity C reactive protein; IL-6: interleukin 6; MDA: malondialdehyde; LDLox: Oxidized LDL

NA: not available

Table 4. Changes in body composition at 48 and 96 weeks.

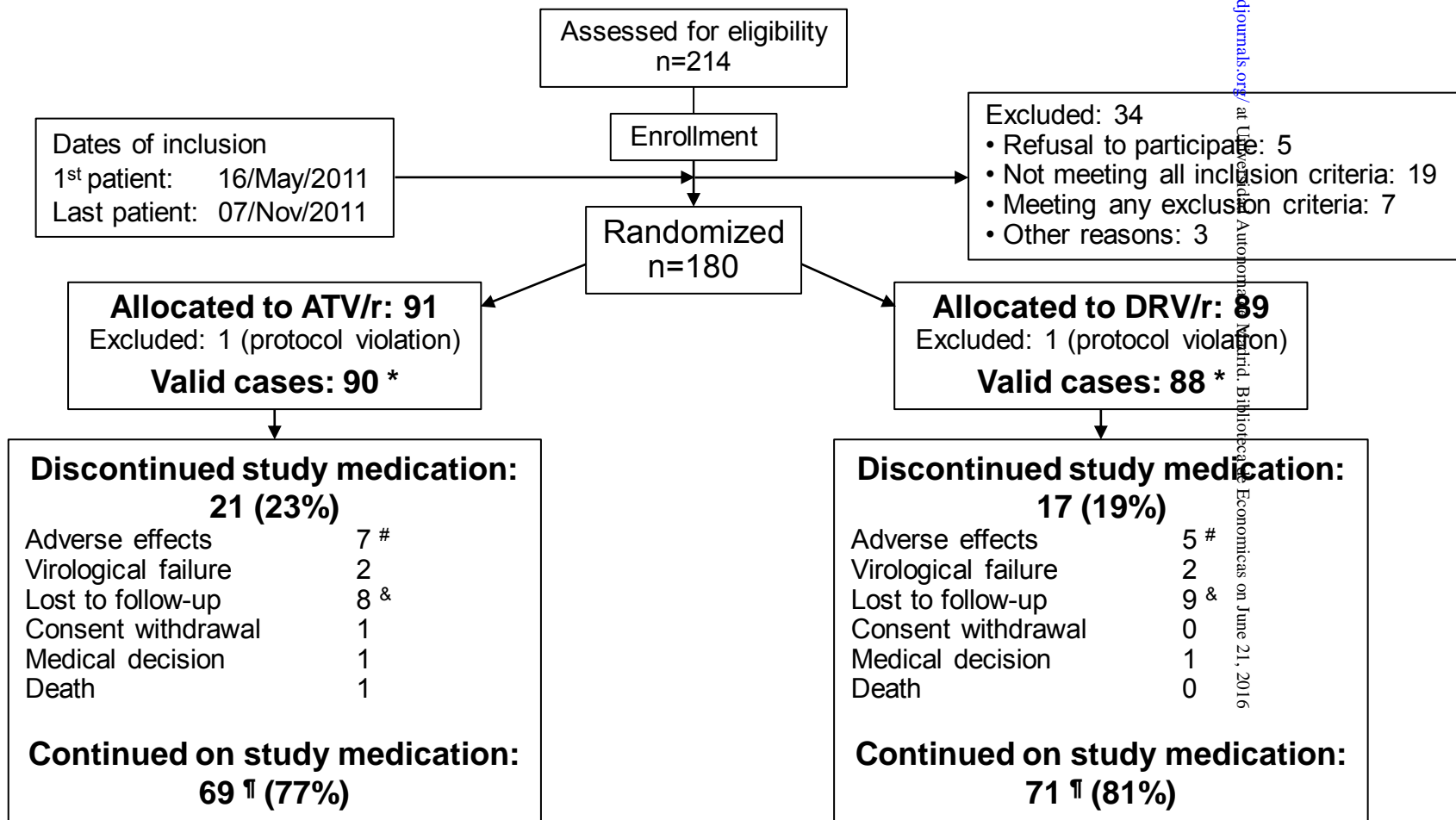
	48 weeks			96 weeks		
	ATV/r (n=88)	DRV/r (n=84)	P-value	ATV/r (n=78)	DRV/r (n=80)	P-value
BMI (kg/m²)	+0.79 (1.76)	+0.30 (2.22)	0.1467	+1.25 (1.84)	+0.67 (2.36)	0.1347
Body fat (gr)	+1726.27 (4715.87)	+416.33 (4483.85)	0.0610	+3373.10 (6763.66)	+1096.38 (5286.11)	0.0090
Body fat-free mass (gr)	+1029.39 (2839.39)	+536.99 (2830.61)	0.2986	+893.52 (4260.24)	+660.80 (2903.28)	0.7076
Bone mineral content (gr)	-198.55 (506.96)	-111.67 (448.72)	0.2854	-79.77 (168.39)	-80.15 (242.93)	0.9900
Limb fat (gr)	+707.22 (2036.37)	-16.99 (3319.34)	0.1161	+1235.04 (2823.91)	-168.29 (2863.19)	0.0071
Trunk fat (gr)	+990.16 (2825.16)	+240.35 (4620.34)	0.1876	+1565.72 (2706.83)	+541.46 (4614.61)	0.1001
SAT (cm²)	+17.76 (73.58)	+7.09 (72.02)	0.2626	+38.81 (74.95)	+14.94 (71.43)	0.0362
VAT (cm²)	+16.46 (45.84)	+14.44 (44.31)	0.7997	+38.53 (66.21)	+30.14 (60.02)	0.4719

TAT (cm²)	+34.22 (92.02)	+21.53 (86.55)	0.3465	+77.34 (106.65)	+45.09 (98.83)	0.0621
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Data are mean (SD)

ATV/r: atazanavir/ritonavir; DRV/r: darunavir/ritonavir

BMI: body mass index; SAT: subcutaneous abdominal adipose tissue; VAT: visceral adipose tissue; TAT: total abdominal adipose tissue



ATV/r: Hyperbilirubinemia (n=4; with jaundice, n=2), rash (n=1), nephrolithiasis (n=1) and suicide attempt (n=1)

DRV/r: Gastrointestinal effects (n=2), and rash (n=2)

* 17 (18.9%) ATV/r and 13 (14.8%) DRV/r patients had confirmed HIV-1 RNA >50 copies/mL

† 12 ATV/r and 9 DRV/r patients had confirmed HIV-1 RNA >50 copies/mL

& 3 patient in AV/r and 2 patients in DRV/r had confirmed HIV-1 RNA >50 copies/mL before discontinuation

