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

Esteban Martinez,1 Ana Gonzalez-Cordon,1 Elena Ferrer,2 Pere Domingo,3 Eugenia Negredo,4 Felix Gutierrez,5 Joaquin Portilla,6 Adrià Curran,1 Daniel Podzamczer,2 Esteban Ribera,7 Javier Murillas,8 Jose I. Bernardino,9 Ignacio Santos,10 Jose A. Carton,11 Joaquim Peraire,12 Judit Pich,1 Ramon Deulofeu,1 Ignacio Perez,1 and Jose M. Gatell1; on behalf of the ATADAR Study Groupa

1Hospital Clínic-IDIBAPS, Universitat de Barcelona, 2Hospital Universitari de Bellvitge, Universitat de Barcelona, L’Hospital de Llobregat, 3Hospital de Sant Pau, Universitat Autònoma de Barcelona, Barcelona, 4Lluita Contra la SIDA Foundation, Hospital Garmans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, 5Hospital Universitario de Elche, Universidad Miguel Hernández, 6Hospital Universitario de Alicante, Universidad de Alicante, 7Hospital Universitari Vall d’Hebron, Universitat Autònoma de Barcelona, 8Hospital Son Espases, Palma de Mallorca, 9Hospital Universitario La Paz, Universidad Autònoma de Madrid, and 10Hospital Universitario de La Princesa, Universidad Autònoma de Madrid, 11Hospital Universitario Central de Asturias, Universidad de Oviedo, and 12Hospital Universitari Joan XXIII, Universitat Rovira i Virgili, Tarragona, Spain

Background. It is unclear whether metabolic or body composition effects differ between protease inhibitor-based regimens recommended for initial treatment of human immunodeficiency virus (HIV) infection.

Methods. ATADAR is a phase 4, 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. Predefined endpoints 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% confidence interval [CI], −6.6 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, −5.0 to 17.6). Seven patients discontinued atazanavir/ritonavir and 5 discontinued darunavir/ritonavir due to adverse effects. Total and high-density lipoprotein cholesterol similarly increased in both arms, but there was a greater increase in triglycerides in the atazanavir/ritonavir arm. At 96 weeks, body fat (estimated difference 2862.2 gr; 95% CI, 726.7 to 4997.7; P = .0090), limb fat (estimated difference 1403.3 gr; 95% CI, 388.4 to 2418.2; P = .0071), and subcutaneous abdominal adipose tissue (estimated difference 28.4 cm2; 95% CI, 1.9 to 55.0; P = .0362) increased more in the atazanavir/ritonavir arm than in darunavir/ritonavir arm. Body fat changes in the 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 more total and subcutaneous fat than darunavir/ritonavir. Also, fat gains with atazanavir/ritonavir were associated with insulin resistance.

Clinical Trials Registration. NCT01274780.

Keywords. HIV protease inhibitors; antiretroviral therapy; plasma lipids; body composition.
Both ritonavir-boosted atazanavir (ATV/r) plus tenofovir/emtricitabine (TDF/FTC) and ritonavir-boosted darunavir (DRV/r) plus TDF/FTC are protease inhibitor–based regimens recommended as first-line therapy for human immunodeficiency virus (HIV)-infected patients based on major contemporary clinical guidelines [1–3]. Each regimen has demonstrated better overall tolerability than ritonavir-boosted lopinavir (LPV/r) plus TDF/FTC [4, 5].

Short-term low-dose ritonavir (100 mg/day) has been reported to induce dyslipidemia [6] but not insulin resistance [7]. Although 100 mg/day of ritonavir is 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-naive patients who started 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, which 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 approximately 30 patients per arm was conducted to compare lipid, biomarkers, and body fat effects of DRV/r vs ATV/r in combination with TDF/FTC in antiretroviral-naive patients. It was concluded that both regimens had a similar metabolic profile [15]. ATADAR is a multicenter, randomized, open-label clinical trial comparing the effects of ATV/r with TDF/FTC or DRV/r with TDF/FTC on metabolism, body composition, overall tolerability, and efficacy in a larger number of antiretroviral-naive HIV-infected patients followed for 96 weeks. The main study hypothesis was that lipid changes in both regimens would be similar and would be lower than those reported with LPV/r. In a planned interim analysis at 24 weeks, total cholesterol increased to 7.2 and 11.5 mg/dL and high-density lipoprotein (HDL) cholesterol increased to 5.5 and 3.9 mg/dL in the ATV/r and DRV/r arms, respectively [16]. Longer follow-up was necessary to determine whether plasma lipids and other predefined parameters of interest might ultimately differ between both regimens. Here, we report the final planned 96-week results of the ATADAR study.

METHODS

Study Design

ATADAR was a 96-week, phase 4, open-label, multicenter, randomized clinical trial performed in 16 Spanish medical centers. Entry criteria and study design have been detailed elsewhere [15]. Briefly, stable antiretroviral-naive HIV-infected adults with plasma HIV RNA ≥1000 copies/mL were randomly assigned in a 1:1 ratio to receive either atazanavir 300 mg with ritonavir 100 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 ViroSeq HIV genotyping system according to the manufacturer’s instructions (Applied Biosystems, Foster City, California). 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 of complete blood count and CD4 cell counts; plasma HIV RNA; plasma lipids including total, low-density lipoprotein (LDL), and HDL cholesterol and triglycerides; creatinine; and total bilirubin were performed at each site using similar pre-established methods throughout the follow-up period. Plasma glucose, creatinine, total bilirubin, total and HDL cholesterol, and triglycerides were measured using commercial enzymatic kits. LDL cholesterol was calculated using the Friedewald equation whenever triglycerides were <400 mg/dL [18]; otherwise, it was measured directly. Estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease epidemiology collaboration (CKD-EPI) equation with serum creatinine standardized to reference methods [19].

Plasma glucose and insulin were measured at baseline and 24, 48, and 96 weeks using an immunoradiometric method. Insulin resistance was estimated with the homeostatic model assessment of insulin resistance (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 enzyme-linked immunosorbent assay (ELISA) assay (Quantikine HS, human IL-6 immunoassay, R&D Systems, Minneapolis, Minnesota). MDA was measured by high-performance liquid chromatography [21]. LDLox was determined by ELISA using the monoclonal 4E6 antibody (Mercodia AB, Uppsala, Sweden).

At baseline and 48 and 96 weeks, weight and height were measured and whole body dual-X absorptiometry (DXA) scans were performed to assess body fat, fat-free mass, and bone mineral content; abdominal computed tomography (CT) scans were performed to assess subcutaneous (SAT), visceral (VAT), and total (TAT) abdominal adipose tissues. Body mass index (BMI) was calculated by dividing weight (in kilograms) by the square of height (in meters). The ratio of leg
fat percentage-to-BMI was used as a measure of the regional distribution of subcutaneous fat relative to a measure of generalised 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 1 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 the Division of AIDS toxicity table [23].

**Statistical Analysis**

The primary endpoint of the ATADAR study was the change in total cholesterol at 24 weeks [15]. For the purpose of the final 96-week analysis, the predefined secondary endpoints included the following: 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, eGFR (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 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 to follow-up, 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 at <50 copies/mL. Changes from baseline in total cholesterol and other laboratory parameters were analyzed by repeated measures analysis of covariance adjusted for clustering within each center. ATADAR fulfilled CONSORT 2010 Statement criteria [24].

Statistical analysis was performed with Stata 9.2 (StataCorp, College Station, Texas). χ² or Fisher exact tests were used to compare proportions between treatment arms. The Student t
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 1 dose of study drugs and were included in the analysis (Figure 1). Baseline characteristics are listed 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, −6 to 21.6; P = .25), and 71 (79%) ATV/r and 75 (85%) DRV/r patients remained free of virological failure (estimated difference 6.3%; 95% CI, −5.0 to 17.6; P = .27) at 96 weeks. One patient died (lung cancer) and another developed a new CDC-C event (non-Hodgkin lymphoma) in the ATV/r arm, while there were no deaths or CDC-C events in the DRV/r arm. Patients who developed virological failure had mean (standard deviation [SD]) higher baseline plasma HIV RNA than those who did not (5.3 [0.5] vs 4.7 [0.7] in the ATV/r arm, P = .0005; 5.3 [1.0] vs 4.7 [0.7] in the DRV/r arm, P = .013). At 96 weeks, mean (SD) CD4 cells per cubic millimeter increased in both arms (+284 [219] ATV/r vs +298 [182] DRV/r; P = .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; and 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; and patient 4: I13V, M36I, I62V, L63HQ. None of these mutations were associated with virological resistance.

Overall Safety

There were more patients in the ATV/r than in the DRV/r arm who experienced at least 1 related adverse event (n = 52 [57%] vs 37 [41%]; P = .038), at least 1 serious adverse event (n = 24 [26%] vs 7 [8%]; P = .002), and at least 1 grade 3–4 adverse event (n = 40 [44%] vs 12 [14%]; P < .0001). However, the number of patients with at least 1 adverse event that led to discontinuation (n = 7 [7.8%] vs 5 [5.7%]; P = .25) was similar. Hyperbilirubinemia was computed in 15 (63%) of 24 patients with at least 1 serious adverse event, 27 (68%) of 40 patients with at least 1 grade 3–4 adverse event, and 4 (57%) of 7 patients with
at least 1 adverse event that led to discontinuation in the ATV/r arm. There was no association between plasma bilirubin elevation and nonbilirubin 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 the total-to-HDL cholesterol ratio tended to decrease in each arm, without significant differences between arms. Increases in triglycerides were higher in the ATV/r arm than in the DRV/r arm at 48 weeks (estimated difference 22.4 mg/dL; 95% CI, .2 to 44.6; \( P = .048 \)) and 96 weeks (estimated difference 21.5 mg/dL; 95% CI, −7 to 43.8; \( P = .058 \)). There were no differences between arms in mean (SD) changes in the Framingham score at 48 weeks (−.04 [1.5] vs. .05 [2.1]; \( P = .76 \)) and 96 weeks (0.07 [2.0] vs. 0.46 [2.2]; \( P = .25 \)).

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 toward a higher increase in the ATV/r arm relative to the DRV/r arm at 96 weeks (estimated difference 0.7; 95% CI, −1 to 1.5; \( P = .093 \)). Both arms showed significant eGFR decreases at 48 and 96 weeks, but there were no significant differences between arms. As expected, bilirubin significantly increased in the ATV/r arm at 48 and 96 weeks, and differences between arms were very 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. 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 the ATV/r arm than in the DRV/r arm at

### Table 2. Lipid Changes at 48 and 96 Weeks

<table>
<thead>
<tr>
<th>Lipid Change</th>
<th>48 Weeks</th>
<th>96 Weeks</th>
<th>48 Weeks</th>
<th>96 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>ATV/r (n = 78)</td>
<td>DRV/r (n = 80)</td>
<td>( P = 9441 )</td>
<td>ATV/r (n = 72)</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>+9.64 (34.05)</td>
<td>+11.37 (28.17)</td>
<td>+11.31 (35.96)</td>
<td>+14.63 (29.18)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>−2.88 (25.36)</td>
<td>+4.89 (26.95)</td>
<td>0.0913</td>
<td>+1.86 (29.44)</td>
</tr>
<tr>
<td>Total-to-HDL cholesterol ratio</td>
<td>+5.20 (10.42)</td>
<td>+4.67 (7.40)</td>
<td>0.539</td>
<td>+4.90 (10.91)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>+41.04 (81.97)</td>
<td>+17.13 (63.46)</td>
<td>0.048</td>
<td>+38.89 (71.74)</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation).

Abbreviations: ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; HDL, high-density lipoprotein cholesterol.

### Table 3. Changes in Chemistry Parameters Other Than Plasma Lipids at 48 and 96 Weeks, and Changes in Biomarkers at 48 Weeks

<table>
<thead>
<tr>
<th>Laboratory Parameter Change</th>
<th>48 Weeks</th>
<th>96 Weeks</th>
<th>48 Weeks</th>
<th>96 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homeostatic model assessment of insulin resistance</td>
<td>+0.34 (4.96)</td>
<td>+0.73 (9.21)</td>
<td>0.5711</td>
<td>+0.88 (2.68)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (mL/min/1.73 m²)</td>
<td>−10.01 (20.37)</td>
<td>−6.18 (12.29)</td>
<td>1.544</td>
<td>−8.63 (22.29)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>+1.60 (2.62)</td>
<td>−0.05 (0.25)</td>
<td>&lt;.0001</td>
<td>+1.50 (2.47)</td>
</tr>
<tr>
<td>High-sensitivity C reactive protein (mg/dL)</td>
<td>−0.04 (0.51)</td>
<td>−0.22 (0.76)</td>
<td>0.1174</td>
<td>NA</td>
</tr>
<tr>
<td>Interleukin 6 (pg/mL)</td>
<td>+14.43 (104.04)</td>
<td>+4.30 (25.10)</td>
<td>0.5796</td>
<td>NA</td>
</tr>
<tr>
<td>Malondialdehyde (mmol/L)</td>
<td>−99.19 (963.97)</td>
<td>+20.55 (609.22)</td>
<td>0.4103</td>
<td>NA</td>
</tr>
<tr>
<td>Oxidized low-density lipoprotein (mU/L)</td>
<td>−0.22 (6.34)</td>
<td>−0.03 (7.09)</td>
<td>0.8294</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation).

Abbreviations: ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; NA, not available.
48 weeks (estimated difference 1432 gr; 95% CI, −67 to 2932; \( P = .061 \)) and 96 weeks (estimated difference 2862 gr; 95% CI, 727 to 4998; \( P = .009 \)). 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 the ATV/r arm (but not in the DRV/r arm) at 48 and 96 weeks. Limb fat (but not trunk fat) change was significantly higher in the ATV/r arm than in the DRV/r arm at 96 weeks (estimated difference 1403 gr; 95% CI, 380 to 2418; \( P = .007 \)). SAT increased more significantly in the ATV/r arm than in the DRV/r arm at 96 weeks (estimated difference 2841 cm²; 95% CI, 1.9 to 55.0; \( P = .037 \)). Mean (SD) ratio of leg fat percentage-to-BMI at 96 weeks was 0.91 (0.36) in the ATV/r arm and 1.05 (0.42) in the DRV/r arm (\( P \) between arms = .048). Although VAT and SAT 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 both arms 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 the ATV/r arm. These correlations remained significant after adjustment for 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 the 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 the ATADAR study (62%, ATV/r; 71%, DRV/r) were roughly similar to those reported according to the Food and Drug Administration snapshot in the recently published AIDS Clinical Trials Group (ACTG) 5257 trial (63%, ATV/r; 73%, DRV/r) [25]. As expected [26], there was no evidence of primary resistance mutations to protease inhibitors in patients who developed virological failure. A substantial proportion of adverse events in the ATV/r arm were related to hyperbilirubinemia, although they were of minor clinical relevance because there was no association between plasma bilirubin elevation and nonbilirubin adverse events in patients allocated to ATV/r and because the number of adverse events that led 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 to adverse events in other major randomized clinical trials [4, 27, 28] were closer to those in ATADAR than to those in ACTG 5257. ATV-related hyperbilirubinemia is a cosmetic effect that is reversible upon drug discontinuation [29]; however, 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 the ATV/r and DRV/r arms. However, triglycerides tended to rise more in the ATV/r arm at 96 weeks. This finding was also reproduced in a planned intensive lipid substudy with a subpopulation of ATADAR patients in which the higher increase of triglycerides in the ATV/r arm was consistently associated with increases in small and dense LDL particles and a greater prevalence of LDL intermediate and B phenotypes compared with the DRV/r arm [30]. We also found higher insulin resistance in the ATV/r arm relative to the 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 assigned to DRV/r. 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 suggests differential drug effects because baseline BMI was normal and the 96-week BMI change was not different between arms. In our study, the ratio of leg fat percentage-to-BMI decreased in the ATV/r arm while it increased in the DRV/r arm, with significant differences between arms at 96 weeks. The lower the ratio of leg fat percentage-to-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 than 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 the 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 the ATV/r arm than in the 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 that switched 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. The 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 the ATV/r arm than in the DRV/r arm at 96 weeks, differences between arms were not 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. The 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 for 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 ATZ/r were associated with insulin resistance. Further studies are needed to confirm our observations and to determine their clinical relevance.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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References


APPENDIX

Members of the ATADAR Study Group.

Trial chairs: Esteban Martínez, José M Gatell.

Trial coordinators and monitors: Juan A Arnaiz, Helena Beleta, David García, Judit Pich, Andrea Pejenaute, Nuria Ramos.

Trial statistician: Ignacio Pérez.