Changes in Waist Circumference in HIV-Infected Individuals Initiating a Raltegravir or Protease Inhibitor Regimen: Effects of Sex and Race.

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Central fat gain remains a prevalent issue for HIV-infected patients in the contemporary antiretroviral therapy (ART) era [1–7]. Central fat gain often includes increases in visceral adipose tissue (VAT), which is a known risk factor for cardiovascular disease (CVD) [8, 9]. CVD is an important cause of morbidity and mortality in HIV-infected individuals, and infection with HIV has been associated with a higher risk of CVD [10–12]. This increase in risk of CVD associated with VAT may be higher especially in HIV-infected individuals compared with HIV-uninfected individuals [13]. VAT has also been shown to be associated with elevated cardiometabolic risk. In HIV-infected individuals, increased VAT has been found to be associated with increased insulin resistance and to be a predictor of coronary calcification [14–18]. This highlights the importance of further investigating the underlying risk factors and treatments associated with central fat gain, especially VAT increases.

In general, antiretroviral therapy has been associated with weight gain; however, therapy effects on abdominal fat appear to vary by regimen. Atazanavir has been found to be associated with larger increases in abdominal fat compared with other regimens including darunavir, and raltegravir (RAL) may be associated with smaller increases in abdominal fat compared with efavirenz in treatment-naïve individuals initiating therapy [5, 6, 19–23]. A previous analysis of data from A5260s, a substudy of A5257 comparing atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), and RAL, demonstrated that there were significant increases in trunk fat and VAT for all 3 treatments from entry to week 96, but found no differences between the arms in the magnitude of these changes. It also found that higher baseline viral load was associated with larger gains in central fat [24]. A metabolic analysis of the A5257 study, with a larger full cohort sample size, found larger waist
circumference increases in the RAL arm compared with the DRV/r arm over 96 weeks [25]. Although standard measurements of central fat accumulation, such as computed tomography (CT) and dual x-ray absorptiometry (DXA), remain high-cost and labor-intensive, other forms of measurement such as waist circumference (WC) and self-reported abdominal size changes have been shown to be correlated with measurements of abdominal adipose tissue increases. We have previously demonstrated in the A5260s substudy that both WC and self-reported changes in fat are strongly associated with CT- and DXA-measured abdominal fat changes, including VAT changes [26].

WC measurements were obtained in the full A5257 study, giving a much larger sample size than the substudy to examine abdominal fat changes. The objective of this analysis is to examine predictors of abdominal fat change in the A5257 cohort using WC and self-reported abdominal size changes as surrogates for VAT. Specifically, we investigated the association of abdominal increases with demographic and baseline clinical characteristics and also examined the potential modification of treatment effects by sex and race.

METHODS

Study Population
This retrospective cohort analysis was conducted using data from the AIDS Clinical Trials Group (ACTG) A5257 study and was approved by the Institutional Review Board of the University of California, Los Angeles. A5257 was a phase III randomized clinical trial comparing the virologic efficacy and tolerability of 3 non-nucleoside reverse transcriptase inhibitor (NNRTI)—sparing antiretroviral regimens, comprised of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) plus ATV/r, DRV/r, or RAL. The design, eligibility criteria, and results of the A5257 study have been previously reported [25, 27]. In brief, a total of 1814 participants were enrolled into A5257 from May 2009 to June 2013 from 57 sites across the United States. Participants were randomized in a 1:1:1 ratio to each regimen. Eligible subjects included male and female treatment-naïve HIV-infected volunteers (HIV-1 RNA ≥1000 copies/mL) with relatively normal chemistry and complete blood counts, age >18 years, and no evidence of PI or NRTI resistance.

Data Collection

Covariates
Demographic information, including race/ethnicity, age, and sex, was collected at entry, along with body mass index (BMI; kg/m²), CD4+ cell count (cells/mm³), and HIV-1 RNA level (copies/mL). Laboratory assessment of blood samples has been previously described [27, 28]. HIV-1 RNA level was treated as a continuous variable, and log base 10—transformed for the analysis due to skew. Treatment was analyzed as a 3-level categorical variable (ATV/r, DRV/r, RAL). Measures of substance use, current smoking status, income, and health insurance were also collected at baseline. Illicit drug use included use of cocaine, heroin, amphetamines, or other and was coded as never used, used more than 1 month ago, and used within the last month. Drinking status was reported as abstainer, moderate drinker, heavy drinker, and binge drinker. Income was divided into 3 categories: less than $19,999, $20,000–49,999, and $50,000 or higher. Insurance status was coded as “private insurance” and “other,” which included government, out-of-pocket, or another unknown type.

Outcomes

Waist Circumference Measurements
WC (cm) was measured by trained clinical staff during study visits at entry and week 96. Participants were told to stand erect, relaxed, and to not hold in their stomach during measurement. A midwaist circumference measurement was taken at the level of the upper border of the right ilium. Each measurement was conducted postexhalation with the tape measure parallel to the floor. The WC was required to be measured in triplicate for each participant. The average of the provided readings was used as the final WC value.

Self-Reported Abdominal Change
The A5257 body image questionnaire was adopted from the FRAM study (National Institutes of Health grants R01DK57508, R01HL74814, and R01HL53359) [29] and included self-reported measures on perception of current body weight and assessment of gain or loss of size in specific regions of the body. Our study focuses on self-reported abdominal size changes only. Although the questionnaire was self-administered, participants could request help from the clinical staff for assistance in reading or understanding the items. Questionnaire responses from week 96 were used to examine self-reported belly size changes from baseline, which were scored as “no change/lost,” “gained some/somewhat larger,” and “gained a lot/much larger.”

Data Analysis and Statistical Methods

Increases in Waist Circumference
Linear mixed effects (ie, repeated measures) models were used to examine predictors of WC trajectories between week 0 and week 96. Specifically, we first conducted an intent-to-treat (ITT) analysis, with treatment group, time, and a group-by-time interaction to check for differential waist circumference changes between the 3 regimens. We examined sex and race as potential treatment effect modifiers by adding their higher-order interactions with treatment group and time to the core mixed effects model. Specifically, a significant covariate-by-group-by-time interaction would suggest that the relative effects of the medication regimens on waist circumference differed by sex or race. Significant omnibus tests of the 3-way interactions were followed by post hoc comparisons to delineate the specific pattern of effects.
Then, to examine baseline predictors of WC change, we added sex, race, age, BMI, CD4+, and log HIV-1 RNA counts and their interactions with time to the core mixed effects model. For the purpose of these analyses, CD4+ count was represented as a continuous variable, and presented as per 100 cells/mm³ in regression model output. The mixed effects models assessing baseline predictors and treatment effect modification were adjusted for potential confounding from smoking, drinking, illicit drug use, income status, and health insurance status. In addition to a complete case analysis, multiple imputation analyses were conducted to account for the missing data created from adjusting from multiple covariates. Per-protocol and influence analyses were also conducted for each model.

### Self-Reported Increases in Abdominal Size

Global chi-square goodness-of-fit tests were used to evaluate if treatment was associated with self-reported abdominal size gain category, both overall and by sex and race subgroups. Ordinal logistic regression models examined whether there were treatment differences in the odds of moving to a higher self-reported abdominal size gain category, that is, from “no change/lost” to “gained some/somewhat larger,” and from to “gained some/somewhat larger” to “gained a lot/much larger.”

Ordinal logistic regression models were also used to examine predictors of self-reported abdominal size gain, including treatment, sex, race, age, baseline BMI, and baseline CD4+/HIV-1 RNA, adjusting for smoking, drinking, illicit drug use, income status, and insurance status. Multiple imputation was also conducted to obtain valid parameter estimates in the presence of missing data. Effect modification of the association between treatment and self-reported abdominal size gain was also examined by sex and race.

All analyses were performed using SAS Software, version 9.4, of the SAS System for Windows (SAS Institute Inc., Cary, NC). General statistical considerations can be found in the Supplementary Data.

### RESULTS

#### Participant Disposition, Demographics, and Baseline Characteristics

The analysis population consisted of 1809 HIV-infected adults in A5257 whose age ranged from 18 to 76 years and averaged 37 years; 5 randomized participants were not included in the analysis population [27]. Participants were 76% male, 41.9% black non-Hispanic, 34.1% white non-Hispanic, and 21.6% Hispanic. The average baseline weight was 79 kg, and the average baseline BMI was 26 kg/m². The baseline HIV disease state included a mean CD4+ level of 308 cells/mm³ and HIV-1 RNA level of 4.6 log copies/mL. Participant demographics and baseline values were balanced across the 3 randomized treatment arms [27]. WC and self-reported abdominal gain at week 96 were not available for 13.5% and 13.7% of participants, respectively, but baseline characteristics of the participants with available week 96 data were comparable to those without outcome data.

#### Waist Circumference: Effect Measure Modification of Treatment by Sex and Race/Ethnicity

Descriptive statistics of the study population can be found in Table 1. The mean baseline WC was 90.6 cm, with a mean increase of 3.4 cm over 96 weeks (Table 1). Across baseline and demographic characteristics, all subgroups experienced an increase in WC, with the largest increases appearing in the RAL treatment group and the following subgroups: female, black Non-Hispanic, older, normal and obese BMI, HIV-1 RNA ≥100000 copies/mL, and CD4+ <350 cells/mm³ (Table 1).

Overall, the mean WC change differed by treatment group in the ITT analysis (omnibus F-test \( P = .0448 \)). The mean WC change was lower for DRV/r compared with RAL (differential mean change, –1.24 cm; 95% confidence interval [CI], –2.22 to –0.26; \( P = .0130 \)) (Table 2), and likewise non–statistically significantly lower for DRV/r compared with ATV/r (differential mean change, –0.55 cm; 95% CI, –1.53 to 0.44; \( P = .2755 \)) and lower for ATV/r compared with RAL (differential mean change, –0.69 cm; 95% CI, –1.67 to 0.29; \( P = .1656 \)) (Table 2).

When examining treatment effect modification of WC change, each 3-way interaction term of sex-by-time-by-treatment and race/ethnicity-by-time-by-treatment was statistically significant (F-test \( P < .05 \)), warranting further assessment of the specific treatment differences. Results indicated that the treatment difference for change in WC for ATV/r vs RAL was larger for females than for males (differential mean change, –3.28 cm; 95% CI, –5.65 to 0.92; \( P = .0065 \)). A larger difference in WC change for DRV/r vs RAL was found for black individuals compared with all other races/ethnicities (differential mean change, –2.92 cm; 95% CI, –4.92 to –0.91; \( P = .0043 \)) (Table 2, Figure 1). In addition, black individuals experienced a smaller increase in WC for DRV/r compared with ATV/r (differential mean change, –2.48 cm; 95% CI, –4.52 to –0.43; \( P = .0176 \)) (Table 2).

Varying estimates of WC change over 96 weeks by treatment were observed when examining different combinations of sex and race in the model. For example, the average WC change for a black female on RAL was 6.9 cm. However, for a black male on RAL, the average 96-week WC gain was 4.6 cm. For a black female on DRV/r, the average WC gain was 2.5 cm. For a black male on DRV/r, the average WC gain was only 2.2 cm.

When influential outliers were removed from the data set, the treatment differences in WC change between females and males and black individuals remained directionally consistent but were slightly attenuated. Estimates in the per-protocol analysis were slightly stronger than the original ITT analysis.

#### Waist Circumference: Demographic and Clinical Predictors of WC Change

Subsequent analyses modeled treatment, baseline, and demographic predictors of WC change adjusted for confounding,
as shown in Table 3. From the final imputed data model, both lower baseline CD4+ and higher log HIV-1 RNA levels appeared to be strong predictors of greater WC increases after adjusting for several variables including BMI. For every 1 log unit (ie, 10-fold) increase in baseline HIV-1 RNA copies/mL, the WC change over 96 weeks increased by 1.85 cm (95% CI,...
Abdominal Changes After ART Initiation • OFID • 5

ofid, 5

<1.22 to 2.49; P < .0001), and for every 100 cell/mm³ higher in baseline CD4+ levels, the WC change over 96 weeks decreased by 0.75 cm (95% CI, –0.98 to –0.51; P < .0001). Sex, race/ethnicity, baseline age, and baseline BMI were not found to be associated with WC changes over 96 weeks. Baseline HIV-1 RNA and CD4+ results from influence and per-protocol analyses were consistent in magnitude and direction with these results.

Self-Reported Abdominal Size: Effect Measure Modification of Treatment by Sex and Race/Ethnicity

The overall and subgroup-specific distribution of self-reported abdominal change outcomes can be found in Table 1. Overall, 56.1% of participants reported “no change/lost” in abdominal size at week 96, 35.2% reported “gained some/somewhat larger,” and 8.8% reported “gained a lot/much larger.”

For the ITT analysis, chi-square tests showed no differences in self-reported abdominal size changes between treatment groups overall and by sex and race subgroups. Although not statistically significant, the treatment comparison between DRV/r and RAL was directionally consistent with the WC results, indicating that the odds of “gained a lot/much larger” vs the combined “gained some/somewhat larger” and “no change/lost” categories were 0.94 times lower (95% CI, 0.74–1.19; P = .5949) in the DRV/r arm. Per-protocol analyses’ results were consistent with the ITT analyses.

Self-Reported Abdominal Size: Demographic and Clinical Predictors of Abdominal Changes

A model including all the baseline and demographic predictors of interest was also examined. Results indicated that sex, baseline BMI, baseline HIV-1 RNA, and baseline CD4+ count were each associated with self-reported abdominal size changes (Table 4). From the imputed data model, we see that the odds of “gained a lot/much larger” vs the combined lower categories were 1.36 times greater for females compared with males, while all other variables in the model held constant (95% CI, 1.05 to 1.76; P = .0211). For every 1 log unit (ie, 10-fold) higher in HIV-1 RNA copies/mL, the odds of "gained a lot/
much larger” compared with the other self-reported categories were 1.35 times greater (95% CI, 1.14 to 1.59; \( P = .0004 \)). In addition, the odds of highest self-reported gain compared with the combined middle and lower categories were 0.88 times lower for every 100 cells/mm\(^3\) more in baseline CD4+ (95% CI, 0.83 to 0.94; \( P = .0001 \)). We also found that a higher baseline

### Table 4. Intention-to-Treat Analysis Examining Odds of Reporting a Higher Category of Self-Reported Abdominal Size Change Across Complete Case Analysis and Imputed Data Models in the ACTG A5257 Study Population (n = 1809)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Complete Case Analysis</th>
<th>Imputed Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Differential Mean Change (95% CI)</td>
<td>( P ) Value</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV/r</td>
<td>–0.34 (–1.39 to 0.71)</td>
<td>.5210</td>
</tr>
<tr>
<td>DRV/r</td>
<td>–0.70 (–1.75 to 0.36)</td>
<td>.1951</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>0.62 (–0.51 to 1.74)</td>
<td>.2833</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
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<tr>
<td>White non-Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black non-Hispanic</td>
<td>1.05 (–0.03 to 2.12)</td>
<td>.0565</td>
</tr>
<tr>
<td>Hispanic</td>
<td>–0.10 (–1.40 to 1.20)</td>
<td>.8772</td>
</tr>
<tr>
<td>Other</td>
<td>–1.18 (–3.83 to 1.46)</td>
<td>.3904</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.0084 (0.032 to 0.049)</td>
<td>.6854</td>
</tr>
<tr>
<td>Baseline BMI, kg/m(^2)</td>
<td>0.026 (–0.053 to 0.10)</td>
<td>.5195</td>
</tr>
<tr>
<td>Baseline HIV-1 RNA, log(_{10}) copies/mL</td>
<td>1.83 (1.13 to 2.54)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Baseline CD4+, 100 cells/mm(^3)</td>
<td>–0.65 (–0.91 to –0.39)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Abbreviations: ATV/r, atazanavir/ritonavir; CI, confidence interval; DRV/r, darunavir/ritonavir; PIs, protease inhibitors atazanavir/ritonavir and darunavir/ritonavir; RAL, raltegravir.

*Models adjusted for baseline smoking status, baseline illicit drug use status, baseline drinking status, baseline income status, and baseline insurance status.

**“Complete case analysis” model includes estimates summarized over 10 iterations of imputed values.
BMI was associated with increased odds of reporting a higher self-reported gain category (odds ratio, 1.04; 95% CI, 1.02 to 1.06; \( P < .0001 \)).

Associations between each of the covariates and self-reported abdominal changes were consistent in both the per-protocol and ITT analyses, with odds ratios of similar magnitude and direction.

**DISCUSSION**

Results from this study indicated that ART initiation was associated with increases in WC. These increases were more pronounced with the RAL-based regimen relative to DRV/r, and the strength depended on sex and race/ethnicity. In addition, baseline HIV disease state was strongly associated with abdominal changes over 96 weeks through both self-report and WC outcomes.

Although this study did not confirm sex and race/ethnicity as individual predictors of abdominal fat changes, it found that the treatment effects on WC appear to differ by sex and race/ethnicity. Previous research has shown an association between sex and changes in body composition, including women showing greater increases in central fat [30–34]. Our study results did find that women experienced greater WC increases compared with males on RAL compared with ATV/r. Our results from analyses with self-reported abdominal size changes found that females had a higher odds of reporting gains compared with males. Although this may be due to differences in self-reporting between males and females, it has been previously shown that females tend to under-report weight [35, 36].

We also found that black individuals compared with other races/ethnicities experienced greater WC increases on RAL compared with DRV/r. The limited research in the literature addressing this question shows varying results [34, 37, 38]. In examining treatment modification specifically, a study examined treatment differences between PI-based vs non-PI-based ARV therapies across race/ethnicities and found that black non-Hispanics had the greatest increase in triglyceride levels when on PI treatment, showing that the metabolic effects of treatment may be modified by patient characteristics [39].

For other baseline covariates, older age has been previously reported to be associated with alteration in body composition, including central fat accumulation [31, 32, 37]. Our study was not able to confirm an association between age and abdominal changes. Although we did not find a significant association between baseline BMI and WC increases, we did find that a larger baseline BMI was associated with a higher odds of reporting abdominal gains at week 96. The A5224s substudy of A5202 also found that a larger baseline BMI was associated with significant increases in VAT at week 96 [5].

Regardless of the model or outcome examined, we found that baseline HIV-1 RNA and CD4+ levels were significantly associated with abdominal changes, with higher viral load and lower CD4+ consistently being associated with WC increases and self-reported abdominal size gains. Models were adjusted for BMI to account for a “return to health,” with results remaining consistent. In addition, we conducted a sensitivity analysis examining the baseline CD4 and HIV-1 RNA variables after underweight BMI individuals (<18.5 kg/m²) were excluded from the analysis population. Results indicated that the estimates remained essentially unchanged and just as significant (all results remained \( P < .0001 \)) for both the complete case and imputed models. Several research studies to date have drawn mixed conclusions around the directionality and magnitude of the effects of these risk factors on abdominal changes. Some studies have found no association between baseline viral load and central lipohypertrophy [31, 33]. Other research has found that a lower viral load and higher CD4+ count are associated with increased risk of abdominal adiposity. However, these were cross-sectional studies that did not examine baseline HIV-1 RNA and CD4+ as predictors of abdominal fat increases [40, 41]. One study found that higher CD4+ and lower HIV-1 RNA count were associated with fat accumulation; however, these were measured after ARV initiation at a follow-up visit [38]. Another study found that after initiation of PI therapy, a greater increase in CD4+ from baseline was associated with isolated fat accumulation, which included accumulation of fat in the face or breasts, “buffalo hump,” or increased waist size [42]. A greater increase in CD4+ may be indicative of a lower baseline CD4+ before therapy initiation. Results from the A5260s substudy of A5257 were consistent with our main study results, showing that a higher baseline viral load was associated with increased VAT [24]. McCombey et al. proposed that the association between disease severity at baseline and increased abdominal fat may be due to HIV-infected macrophages that exacerbate inflammation in the adipose tissue and lead to their expansion, similar to the adipose tissue expansion due to macrophages observed with other inflammatory diseases such as Crohn’s disease [24, 43–45]. Our results indicate that advanced disease state before start of therapy is associated with fat gain, which supports the advantages of earlier ART initiation.

One limitation of our study is the incomplete data for several baseline covariates, which we addressed by conducting multiple imputation analysis. Follow-up data for the outcomes of interest were also missing for 11%–14% of study participants, although the baseline characteristics of these individuals did not differ substantially from the rest of the study population. We also could not adjust for potential confounding by diet and exercise as this information was not collected during the A5257 study. Although we were able to statistically compare differences in WC changes between treatment arms and examine these differences across specific subgroups, follow-up analyses would be helpful to understand the clinical significance of such increases in WC. Some strengths of our study were that it utilized prospectively collected clinical trial data to examine predictors of longitudinal abdominal changes over 96 weeks and included a
large sample size to address the questions of interest. Based on previous findings, WC and self-report can be used as surrogate measures of abdominal VAT increases [26]. In this study, we were able to demonstrate the clinical utility of these simple, cost-effective tools for observing abdominal fat changes.

CONCLUSIONS

Although abdominal fat increases continue to occur for HIV-infected individuals on ART, it is important to understand the inherent differences in patient characteristics, especially HIV disease severity, and treatments that may affect such outcomes. Understanding treatment differences for females, males, and race/ethnicity groups, as well as other key baseline predictors, will allow health providers to determine therapeutic approaches better suited to preventing central fat accumulation. As lipohypertrophy continues to be prevalent in low- and middle-income countries [46], waist circumference and self-report may prove to be extremely useful monitoring tools where access to extensive tests is not feasible. Finally, our study highlights reduction in risk of abdominal fat gain as another potential benefit for earlier initiation of ART.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors and do not necessarily reflect the official views of the corresponding author.

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