Open Forum Infectious Diseases

MAJOR ARTICLE

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

Priya Bhagwat,[1] Ighovwerha Ofotokun,[2] Grace A. McComsey,[3] Todd T. Brown,[4] Carlee Moser,[5] Catherine A. Sugar,[1] and Judith S. Currier[1]

[1]University of California, Los Angeles, Los Angeles, California; [2]Emory University School of Medicine, Department of Medicine, Atlanta, Georgia; [3]Case Western University, Cleveland, Ohio; [4]Johns Hopkins University School of Medicine, Baltimore, Maryland; [5]Harvard T. H. Chan School of Public Health, Boston, Massachusetts

Background. This study investigates the association of clinical and demographic predictors with abdominal fat gain, measured using waist circumference (WC) and self-reported abdominal size.

Methods. We analyzed data from ACTG A5257, a clinical trial that randomized treatment-naïve HIV-infected participants to 1 of 3 antiretroviral regimens: raltegravir (RAL) or the protease inhibitors (PIs) atazanavir/ritonavir (ATV/r) or darunavir/ritonavir (DRV/r), each in combination with tenofovir disoproxil fumarate/emtricitabine. Associations of treatment and baseline/demographic characteristics with 96-week WC change were assessed using repeated-measures models. Ordinal logistic regression was used to examine the associations of predictors with week 96 self-reported abdominal changes.

Results. The study population (n = 1809) was 76.0% male and predominantly black non-Hispanic (41.9%) and white non-Hispanic (34.1%). Mean baseline WC was 90.6 cm, with an average 96-week increase of 3.4 cm. WC increases were higher in the RAL arm compared with DRV/r (P = .0130). Females experienced greater increases in WC on RAL vs ATV/r than males (P = .0065). Similarly, a larger difference in WC change was found for RAL vs DRV/r for black vs nonblack individuals (P = .0043). A separate multivariable model found that in addition to the treatment regimen, higher baseline viral load and lower CD4+ were also associated with WC increases.

Conclusions. With antiretroviral therapy initiation, higher WC increases in the RAL arm compared with PIs were more pronounced in female and black participants, and a more advanced baseline HIV disease state was a strong predictor of larger abdominal increases. Understanding factors predisposing individuals to abdominal fat gain could inform health management after therapy initiation.

Keywords. abdominal fat; central adiposity; lipodystrophy; metabolic complications; waist circumference.

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

Received 9 February 2018; editorial decision 5 August 2018; accepted 11 October 2018.

Correspondence: P. Bhagwat, PhD, Center for HIV Identification, Prevention, and Treatment Services (CHIPTS), University of California, Los Angeles, 10920 Wilshire Blvd., Suite 350, Los Angeles, CA 90024, USA (pbhagwat@ucla.edu).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofy201

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/m^2), CD4+ cell count (cells/mm^3), 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/mm^3 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 change 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/m^2. The baseline HIV disease state included a mean CD4+ level of 308 cells/mm^3 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 ≥100 000 copies/mL, and CD4+ <350 cells/mm^3 (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,

Table 1. Baseline Waist Circumference, Waist Circumference Change Between Week 0 and Week 96, and Self-Reported Abdominal Size Changes at Week 96 Across Demographic and Baseline Characteristics of the A5257 Study Population (n = 1809)

	Waist Circumference				Self-Reported Abdominal Change		
	Baseline WC, cm		WC Change, cm		No Change/Lost	Gained Some/Somewhat Larger	Gained a Lot/ Much Larger
Characteristics	No.	Mean (SD)	No.	Mean (SD)	No. (%)	No. (%)	No. (%)
Overall	1800	90.6 (14.9)	1555	3.4 (8.1)	876 (56.1)	549 (35.2)	137 (8.8)
Treatment							
ATV/r	602	91.2 (15.2)	512	3.3 (8.0)	282 (54.7)	192 (37.2)	42 (8.1)
RAL	598	90.7 (14.3)	526	4.0 (8.3)	299 (56.4)	177 (33.4)	54 (10.2)
DRV/r	600	89.9 (15.2)	517	2.8 (8.0)	295 (57.2)	180 (34.9)	41 (8.0)
Sex							
Male	1366	89.1 (13.5)	1191	3.2 (7.2)	689 (57.6)	425 (35.5)	82 (6.9)
Female	434	95.3 (17.9)	364	4.1 (4.1)	187 (51.1)	124 (33.9)	55 (15.0)
Race/ethnicity							
White non-Hispanic	610	92.3 (13.3)	537	2.6 (7.4)	293 (54.2)	215 (39.7)	33 (6.1)
Black non-Hispanic	754	90.4 (16.9)	641	4.0 (9.0)	362 (56.0)	207 (32.0)	78 (12.1)
Hispanic	389	88.9 (12.9)	333	3.7 (7.3)	191 (57.7)	116 (35.1)	24 (7.3)
Other	43	85.0 (12.1)	41	1.0 (5.5)	28 (70.0)	10 (25.0)	2 (5.0)
Age, y							
18–30	563	85.4 (12.9)	468	3.0 (7.6)	293 (62.6)	152 (32.5)	23 (4.9)
31–50	1010	92.6 (15.4)	886	3.4 (8.4)	476 (53.2)	325 (36.4)	93 (10.4)
51–76	227	94.6 (13.9)	201	4.1 (7.9)	107 (53.5)	72 (36.0)	21 (10.5)
Baseline BMI, kg/m^2							
Underweight: <18.5	61	71.6 (6.6)	54	5.0 (7.7)	35 (66.0)	13 (24.5)	5 (9.4)
Normal: 18.5–24.9	846	81.9 (8.5)	737	3.7 (7.7)	447 (60.7)	251 (34.1)	39 (5.3)
Overweight: 25–29.9	549	93.0 (7.0)	472	2.5 (7.5)	248 (52.1)	174 (36.6)	54 (11.3)
Obese: ≥30.0	344	111.7 (13.9)	292	3.7 (9.7)	146 (49.3)	111 (37.5)	39 (13.2)
HIV-1 RNA level, copies/mL							
<100 000	1248	91.5 (15.7)	1074	2.1 (7.5)	646 (59.7)	350 (32.4)	86 (8.0)
≥100 000	552	88.6 (12.8)	481	6.3 (8.6)	230 (47.9)	199 (41.5)	51 (10.6)
CD4+ level, cells/mm^3							
≥350	740	92.2 (15.5)	639	1.6 (7.3)	394 (61.2)	205 (31.8)	45 (7.0)
<350	1060	89.5 (14.4)	916	4.6 (8.3)	482 (52.5)	344 (37.5)	92 (10.0)

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

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,

Table 2. Intention-to-Treat Analysis of Treatment Arm Differences in Waist Circumference Mean Changes From Baseline for the Overall Treatment Model and the Model Examining Effect Measure Modification of Treatment by Sex and Race/Ethnicity in the ACTG A5257 Study Population (n = 1809)

	Model 1: Overall		Model 2: Effect Measure Modification							
			Females vs Males: Differential Mean Change, cm				Black Non-Hispanic vs Other Race/Ethnicity: Differential Mean Change, cm			
Treatment Comparison	Differential Mean Change (95% CI), cm	*P* Value	Females	Males	Difference (95% CI)	*P* Value	Black Non-Hispanic	Other	Difference (95% CI)	*P* Value
DRV/r - RAL	–1.24 (–2.22 to –0.26)	.0130	–1.53	0.47	–2.01 (–4.32 to 0.31)	.0901	–2.45	0.47	–2.92 (–4.92 to –0.91)	.0043
ATV/r - RAL	–0.69 (–1.67 to 0.29)	.1656	–2.95	0.34	–3.28 (–5.65 to 0.92)	.0065	–0.10	0.34	–0.44 (–2.48 to 1.60)	.6720
DRV/r - ATV/r	–0.55 (–1.53 to 0.44)	.2755	1.41	0.14	1.28 (–1.11 to 3.66)	.2933	–2.34	0.14	–2.48 (–4.52 to –0.43)	.0176

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

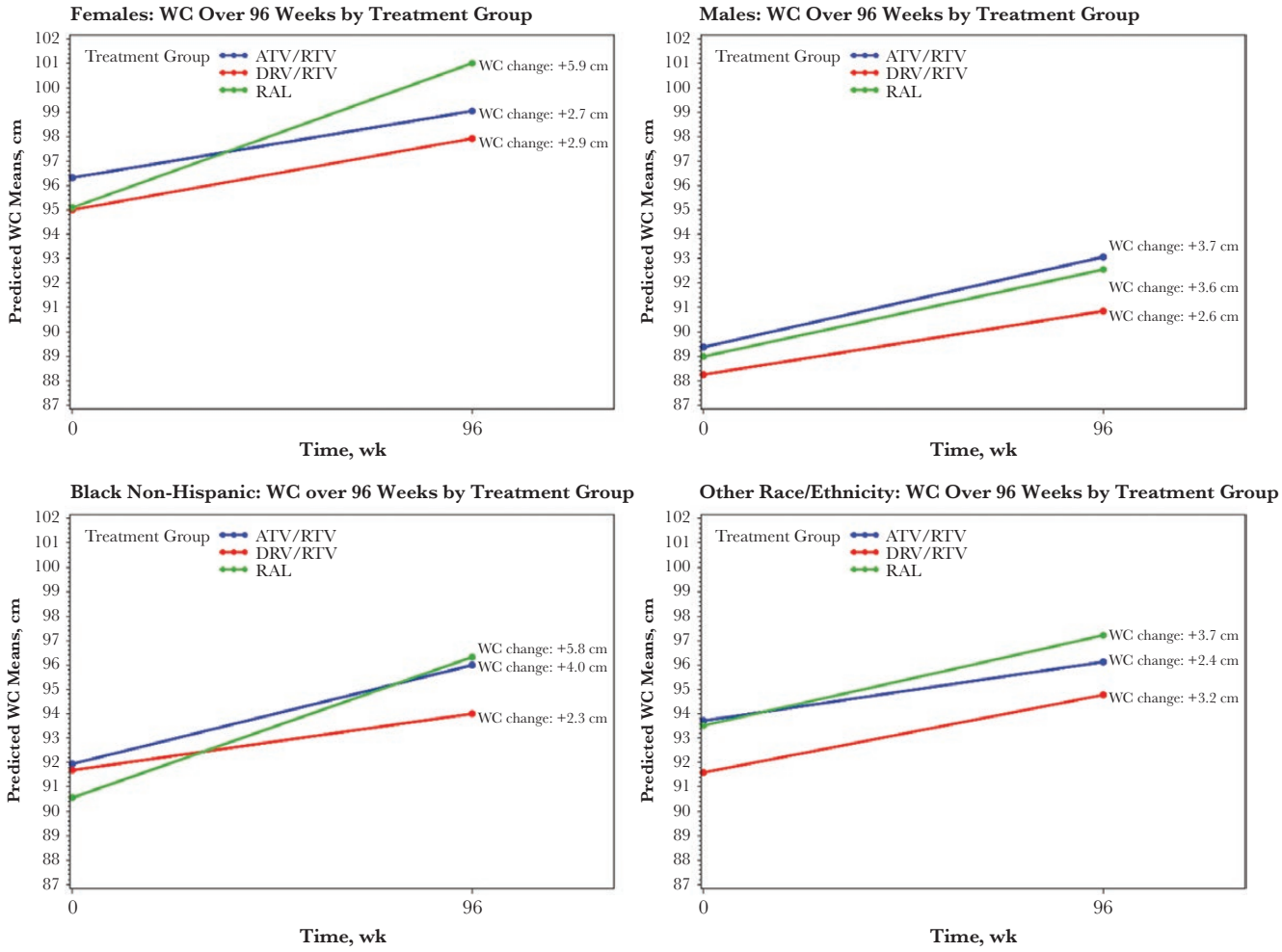

Figure 1. Changes in waist circumference from baseline to week 96 by treatment group across sex and race subgroups in the ACTG A5257 study population (n = 1809). [a]Waist circumference values for males and females are averaged over race, and values for black and others are averaged over sex. Abbreviations: ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; RAL, raltegravir; WC, waist circumference.

<1.22 to 2.49; $P < .0001$), and for every 100 cell/mm^3 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/

Table 3. Intention-to-Treat Analysis of Waist Circumference Mean Changes From Baseline Across Complete Case Analysis and Change Score Imputed Data Model in the ACTG A5257 Study Population (n = 1809)

	Complete Case Analysis		Imputed Data	
Covariate	Differential Mean Change (95% CI)	*P* Value	Differential Mean Change (95% CI)	*P* Value
Treatment				
RAL	—	—	—	—
ATV/r	–0.34 (–1.39 to 0.71)	.5210	–0.75 (–1.69 to 0.20)	.1208
DRV/r	–0.70 (–1.75 to 0.36)	.1951	–1.23 (–2.18 to –0.28)	.0108
Sex				
Males	—	—	—	—
Females	0.62 (–0.51 to 1.74)	.2833	0.87 (–0.14 to 1.89)	.0927
Race/ethnicity				
White non-Hispanic	—	—	—	—
Black non-Hispanic	1.05 (–0.03 to 2.12)	.0565	0.70 (–0.29 to 1.70)	.1655
Hispanic	–0.10 (–1.40 to 1.20)	.8772	–0.22 (–1.39 to 0.94)	.7060
Other	–1.18 (–3.83 to 1.46)	.3804	–1.96 (–4.46 to 0.54)	.1237
Age, y	0.0084 (–0.032 to 0.049)	.6854	0.019 (–0.018 to 0.055)	.3198
Baseline BMI, kg/m^2	0.026 (–0.053 to 0.10)	.5195	0.016 (–0.055 to 0.087)	.6548
Baseline HIV-1 RNA, $\log_{10}$ copies/mL	1.83 (1.13 to 2.54)	<.0001	1.85 (1.22 to 2.49)	<.0001
Baseline CD4+, 100 cells/mm^3	–0.65 (–0.91 to –0.39)	<.0001	–0.75 (–0.98 to –0.51)	<.0001

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

[a]Models adjusted for baseline smoking status, baseline illicit drug use status, baseline drinking status, baseline income status, and baseline insurance status.

[b]"Complete case analysis" model is a repeated-measures model including all participants with nonmissing data

[c]"Imputed data" model includes estimates summarized over 10 iterations of imputed values.

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)

	Complete Case Analysis		Imputed Data	
Covariate	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Treatment				
RAL	—	—	—	—
ATV/r	0.95 (0.72 to 1.26)	.7362	1.05 (0.82 to 1.34)	.6961
DRV/r	0.92 (0.70 to 1.21)	.5470	0.97 (0.76 to 1.24)	.8249
Sex				
Males	—	—	—	—
Females	1.34 (1.00 to 1.80)	.0496	1.36 (1.05 to 1.76)	.0211
Race/ethnicity				
White non-Hispanic	—	—	—	—
Black non-Hispanic	0.99 (0.75 to 1.32)	.9566	0.95 (0.74 to 1.23)	.7034
Hispanic	0.83 (0.59 to 1.17)	.2786	0.74 (0.55 to 1.01)	.0546
Other	0.67 (0.32 to 1.42)	.3013	0.59 (0.29 to 1.19)	.1391
Age, y	1.01 (0.997 to 1.02)	.1746	1.01 (0.999 to 1.02)	.0778
Baseline BMI, kg/m^2	1.03 (1.01 to 1.05)	.0037	1.04 (1.02 to 1.06)	<.0001
Baseline HIV-1 RNA, $\log_{10}$ copies/mL	1.30 (1.08 to 1.57)	.0058	1.35 (1.14 to 1.59)	.0004
Baseline CD4+, 100 cells/mm^3	0.88 (0.82 to 0.95)	.0005	0.88 (0.83 to 0.94)	.0001

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

[a]Models adjusted for baseline smoking status, baseline illicit drug use status, baseline drinking status, baseline income status, and baseline insurance status.

[b]Self-reported change in abdominal size outcome ordered from "no change/lost" as the lowest category to "gained a lot/much larger" as the highest category for the ordinal logistic regression models.

[c]"Complete case analysis" model includes all participants with nonmissing data.

[d]"Imputed data" 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/m^2) 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]. McComsey 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, so questions or comments should be addressed to the corresponding author.

Acknowledgements

The authors would like to acknowledge the participants and sites that were part of the ACTG A5257 study. The AIDS Clinical Trials Units that participated can be found in the Supplementary Data.

Financial support. Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (grant numbers UM1 AI068634, UM1 AI068636, and UM1 AI106701). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Preparation of this manuscript was supported by the Postdoctoral HIV Research Training Program for HIV Combination Prevention (T32MH109205).

Potential conflicts of interest. Dr. Currier received research grants to UCLA from Theratechnologies. Dr. McComsey has served as a consultant to Gilead Sciences, ViiV Healthcare, and Merck. Dr. Brown has served as a consultant to Gilead Sciences, Merck, AbbVie, EMD-Serono, and Theratechnologies, and his research is supported in part by National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID) K24AI120834. Dr. Moser served as a consultant for Northwestern University Infectious Diseases, and her research is supported in part by NIH/NIAID UM1 AI068634 and NIH/NHLBI R01 HL095132. Dr. Sugar's research is supported in part by the UCLA Center for AIDS Research (2P30 A1 028697-24-R2). Dr. Bhagwat and Dr. Ofotokun have no conflicts to disclose. 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.

References

1. Jaime PC, Florindo AA, Latorre Mdo R, Segurado AA. Central obesity and dietary intake in HIV/AIDS patients. Rev Saude Publica **2006**; 40:634–40.
2. Leclercq P, Goujard C, Duracinsky M, et al. High prevalence and impact on the quality of life of facial lipoatrophy and other abnormalities in fat tissue distribution in HIV-infected patients treated with antiretroviral therapy. AIDS Res Hum Retroviruses **2012**; 29:761–8.
3. Moyle G, Moutschen M, Martínez E, et al. Epidemiology, assessment, and management of excess abdominal fat in persons with HIV infection. AIDS Rev **2010**; 12:3–14.
4. Cabrero E, Griffa L, Burgos A; HIV Body Physical Changes Study Group. Prevalence and impact of body physical changes in HIV patients treated with highly active antiretroviral therapy: results from a study on patient and physician perceptions. AIDS Patient Care STDS **2010**; 24:5–13.
5. McComsey GA, Kitch D, Sax PE, et al. Peripheral and central fat changes in subjects randomized to abacavir-lamivudine or tenofovir-emtricitabine with atazanavir-ritonavir or efavirenz: ACTG Study A5224s. Clin Infect Dis **2011**; 53:185–96.
6. Martinez E, Gonzalez-Cordon A, Ferrer E, et al; ATADAR Study Group. Differential body composition effects of protease inhibitors recommended for initial treatment of HIV infection: a randomized clinical trial. Clin Infect Dis **2015**; 60:811–20.
7. Stanley TL, Grinspoon SK. Body composition and metabolic changes in HIV-infected patients. J Infect Dis **2012**; 205(Suppl 3):S383–90.
8. Domingo P, Estrada V, López-Aldeguer J, et al. Fat redistribution syndromes associated with HIV-1 infection and combination antiretroviral therapy. AIDS Rev **2012**; 14:112–23.
9. Hughes-Austin J, Larsen B, Allison M. Visceral adipose tissue and cardiovascular disease risk. Curr Cardiovasc Risk Rep **2013**; 7:95–101.
10. Cheruvu S, Holloway CJ. Cardiovascular disease in human immunodeficiency virus. Intern Med J **2014**; 44:315–24.
11. Esser S, Gelbrich G, Brockmeyer N, et al. Prevalence of cardiovascular diseases in HIV-infected outpatients: results from a prospective, multicenter cohort study. Clin Res Cardiol **2013**; 102:203–13.
12. Currier JS, Lundgren JD, Carr A, et al; Working Group 2. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. Circulation **2008**; 118:e29–35.
13. Lake JE, Wohl D, Scherzer R, et al. Regional fat deposition and cardiovascular risk in HIV infection: the FRAM study. AIDS Care **2011**; 23:929–38.
14. Katzmarzyk PT, Heymsfield SB, Bouchard C. Clinical utility of visceral adipose tissue for the identification of cardiometabolic risk in white and African American adults. Am J Clin Nutr **2013**; 97:480–6.
15. Fox CS, Massaro JM, Hoffmann U, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation **2007**; 116:39–48.
16. Grunfeld C, Rimland D, Gibert CL, et al. Association of upper trunk and visceral adipose tissue volume with insulin resistance in control and HIV-infected subjects in the FRAM study. J Acquir Immune Defic Syndr **2007**; 46:283–90.
17. Guaraldi G, Stentarelli C, Zona S, et al. Lipodystrophy and anti-retroviral therapy as predictors of sub-clinical atherosclerosis in human immunodeficiency virus infected subjects. Atherosclerosis **2010**; 208:222–7.
18. Guaraldi G, Zona S, Orlando G, et al. Progression of coronary artery calcium in men affected by human immunodeficiency virus infection. Int J Cardiovasc Imaging **2012**; 28:935–41.
19. Jemsek JG, Arathoon E, Arlotti M, et al. Body fat and other metabolic effects of atazanavir and efavirenz, each administered in combination with zidovudine plus lamivudine, in antiretroviral-naive HIV-infected patients. Clin Infect Dis **2006**; 42:273–80.
20. Vrouenraets SM, Wit FW, Fernandez Garcia E, et al; BASIC Study Group. Randomized comparison of metabolic and renal effects of saquinavir/r or atazanavir/r plus tenofovir/emtricitabine in treatment-naïve HIV-1-infected patients. HIV Med **2011**; 12:620–31.
21. Moyle GJ, Hardy H, Farajallah A, et al. Comparison of body composition changes between atazanavir/ritonavir and lopinavir/ritonavir each in combination with tenofovir/emtricitabine in antiretroviral-naïve patients with HIV-1 infection. Clin Drug Investig **2014**; 34:287–96.
22. Lennox JL, Dejesus E, Berger DS, et al; STARTMRK Investigators. Raltegravir versus efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. J Acquir Immune Defic Syndr **2010**; 55:39–48.
23. Rockstroh JK, Lennox JL, Dejesus E, et al; STARTMRK Investigators. Long-term treatment with raltegravir or efavirenz combined with tenofovir/emtricitabine for treatment-naive human immunodeficiency virus-1-infected patients: 156-week results from STARTMRK. Clin Infect Dis **2011**; 53:807–16.
24. McComsey GA, Moser C, Currier J, et al. Body composition changes after initiation of raltegravir or protease inhibitors: ACTG A5260s. Clin Infect Dis **2016**; 62:853–62.

25. Ofotokun I, Na LH, Landovitz RJ, et al; AIDS Clinical Trials Group (ACTG) A5257 Team. Comparison of the metabolic effects of ritonavir-boosted darunavir or atazanavir versus raltegravir, and the impact of ritonavir plasma exposure: ACTG 5257. Clin Infect Dis **2015**; 60:1842–51.
26. Bhagwat P, Ofotokun I, McComsey GA, et al. Changes in abdominal fat following antiretroviral therapy initiation in HIV-infected individuals correlate with waist circumference and self-reported changes. Antivir Ther **2017**; 22:577–86.
27. Lennox JL, Landovitz RJ, Ribaudo HJ, et al. A phase III comparative study of the efficacy and tolerability of three non-nucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naïve HIV-1-infected volunteers: a randomized, controlled trial. Ann Intern Med **2014**; 161:461–71.
28. Kelesidis T, Tran TT, Stein JH, et al. Changes in inflammation and immune activation with atazanavir-, raltegravir-, darunavir-based initial antiviral therapy: ACTG 5260s. Clin Infect Dis **2015**; 61:651–60.
29. Tien PC, Benson C, Zolopa AR, et al. The study of fat redistribution and metabolic change in HIV infection (FRAM): methods, design, and sample characteristics. Am J Epidemiol **2006**; 163:860–9.
30. McComsey G, Rightmire A, Wirtz V, et al. Changes in body composition with ritonavir-boosted and unboosted atazanavir treatment in combination with lamivudine and stavudine: a 96-week randomized, controlled study. Clin Infect Dis **2009**; 48:1323–6.
31. Martinez E, Mocroft A, García-Viejo MA, et al. Risk of lipodystrophy in HIV-1-infected patients treated with protease inhibitors: a prospective cohort study. Lancet **2001**; 357:592–8.
32. Joly V, Flandre P, Meiffredy V, et al. Increased risk of lipoatrophy under stavudine in HIV-1-infected patients: results of a substudy from a comparative trial. AIDS **2002**; 16:2447–54.
33. Jacobson DL, Knox T, Spiegelman D, et al. Prevalence of, evolution of, and risk factors for fat atrophy and fat deposition in a cohort of HIV-infected men and women. Clin Infect Dis **2005**; 40:1837–45.
34. Andany N, Raboud JM, Walmsley S, et al. Ethnicity and gender differences in lipodystrophy of HIV-positive individuals taking antiretroviral therapy in Ontario, Canada. HIV Clin Trials **2011**; 12:89–103.
35. Wen M, Kowaleski-Jones L. Sex and ethnic differences in validity of self-reported adult height, weight and body mass index. Ethn Dis **2012**; 22:72–8.
36. Krul AJ, Daanen HA, Choi H. Self-reported and measured weight, height and body mass index (BMI) in Italy, the Netherlands and North America. Eur J Public Health **2011**; 21:414–9.
37. Silverberg MJ, Jacobson LP, French AL, et al. Age and racial/ethnic differences in the prevalence of reported symptoms in human immunodeficiency virus-infected persons on antiretroviral therapy. J Pain Symptom Manage **2009**; 38:197–207.
38. Nguyen A, Calmy A, Schiffer V, et al. Lipodystrophy and weight changes: data from the Swiss HIV Cohort Study, 2000–2006. HIV Med **2008**; 9:142–50.
39. Foulkes AS, Wohl DA, Frank I, et al. Associations among race/ethnicity, ApoC-III genotypes, and lipids in HIV-1-infected individuals on antiretroviral therapy. PLoS Med **2006**; 3:e52.
40. Engelson ES, Kotler DP, Tan Y, et al. Fat distribution in HIV-infected patients reporting truncal enlargement quantified by whole-body magnetic resonance imaging. Am J Clin Nutr **1999**; 69:1162–9.
41. Miller J, Carr A, Emery S, et al. HIV lipodystrophy: prevalence, severity and correlates of risk in Australia. HIV Med **2003**; 4:293–301.
42. Savès M, Raffi F, Capeau J, et al; Antiprotéases Cohorte (APROCO) Study Group. Factors related to lipodystrophy and metabolic alterations in patients with human immunodeficiency virus infection receiving highly active antiretroviral therapy. Clin Infect Dis **2002**; 34:1396–405.
43. Damouche A, Lazure T, Avettand-Fènoël V, et al. Adipose tissue is a neglected viral reservoir and an inflammatory site during chronic HIV and SIV infection. PLoS Pathog **2015**; 11:e1005153.
44. Kredel LI, Siegmund B. Adipose-tissue and intestinal inflammation - visceral obesity and creeping fat. Front Immunol **2014**; 5:462.
45. Drouet M, Dubuquoy L, Desreumaux P, Bertin B. Visceral fat and gut inflammation. Nutrition **2012**; 28:113–7.
46. Finkelstein JL, Gala P, Rochford R, et al. HIV/AIDS and lipodystrophy: implications for clinical management in resource-limited settings. J Int AIDS Soc **2015**; 18:19033.