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Measurement of Abdominal Fat Changes and Predictors of Excess Fat Gain in HIV-Infected Individuals Initiating Therapy

Author

Bhagwat, Priya

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Measurement of Abdominal Fat Changes and Predictors of Excess Fat Gain in HIV-Infected Individuals Initiating Therapy

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Epidemiology

by

Priya Bhagwat

2016

ABSTRACT OF THE DISSERTATION

Measurement of Abdominal Fat Changes and Predictors of Excess Fat Gain in HIV-Infected Individuals Initiating Therapy

by

Priya Bhagwat

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2016

Professor Judith Silverstein Currier, Co-Chair

Professor Pamina M. Gorbach, Co-Chair

HIV-infected individuals beginning antiretroviral treatment are faced with several metabolic complications including central fat accumulation and severe weight increases. As the HIV-infected population is at an elevated risk for cardiovascular disease, monitoring abdominal fat changes as well as understanding predictors of fat gain are especially important. This dissertation examines the validity of accessible measures of abdominal fat changes including waist circumference and self-reported changes, as well as risk factors of abdominal fat changes and severe weight gain after therapy initiation.

The first study of this dissertation used data from the AIDS Clinical Trials Group (ACTG) A5260s substudy of the A5257 clinical trial to examine whether changes in abdominal CT-measured visceral adipose tissue (VAT) and total adipose tissue (TAT) and DXA-measured

trunk fat are correlated with changes in waist circumference (WC) and self-reported abdominal changes. Trunk fat, VAT, and TAT changes differed across self-reported abdominal size change categories “No Change/Lost”, “Gained Some/Somewhat Larger”, and “Gained a Lot/Much Larger” ($p<0.0001$ for all), and the group ordering was as expected. WC changes were strongly correlated with CT and DXA changes (trunk fat: $\rho=0.72$, $p<0.0001$; VAT: $\rho=0.52$, $p<0.0001$; TAT: $\rho=0.62$, $p<0.0001$). While WC changes explained a greater proportion of VAT, TAT, and trunk fat variation, self-reported changes remained a significant predictor after controlling for WC ($p<0.05$).

The second study examined the association of patient demographics and baseline predictors with gains in abdominal fat through WC measurements and self-reported changes in the entire A5257 cohort. In addition, effect modification of treatment by sex and race/ethnicity was also examined. Results indicated that the effect of treatment on WC change varied across sex and race, with the treatment difference for Atazanavir/Ritonavir (ATV/r) versus Raltegravir (RAL) being significantly larger for females compared to males, and a larger difference for Darunavir/Ritonavir (DRV/r) versus RAL for black non-Hispanic compared to non-black individuals ($p<0.001$ for each). For these treatment comparisons, the WC increase was much higher in the RAL arm. In addition, for every one log unit (i.e. 10-fold) increase in baseline HIV-1 RNA copies/mL, the WC increased by 1.70 cm (95% CI: 1.07 to 2.33; $p<0.0001$), and for every 100 cell/mm^3 increase in CD4+ levels, the WC decreased by 0.75 cm (95% CI: -0.98 to -0.51; $p<0.0001$), holding all else constant in the final imputed data model. Baseline viral load and CD4+, as well as being female, were associated with higher self-reported abdominal size gains.

The third study investigated potential baseline and demographic predictors of severe weight gain using A5257 study data. Weight gain was defined as a percent weight increase as well as an increase in clinical BMI status over 96 weeks. Results indicated that the odds of a severe percent weight increase are 1.55 times higher for black non-Hispanic compared to white non-Hispanic individuals (95% CI: 1.10 to 2.20; p= 0.0129) in the final imputed model. For black compared to white individuals, the odds of an increase in BMI status were 1.48 times higher (95% CI: 1.06 to 2.07; p=0.0223). In addition, the imputed data analysis showed that for every 1 log (10-fold) increase in HIV-1 RNA, the odds of severe percent weight gain were 2.52 times higher (95% CI: 2.00 to 3.16; p<0.0001). For every 100 cell/mm^3 increase in CD4+ count, the odds of severe weight gain were 0.78 times lower (95% CI: 0.72 to 0.85; p<0.0001). Similar to the other severe weight gain outcome, higher baseline HIV-1 RNA (OR: 1.74 (95% CI: 1.41 to 2.15); p<.0001) and lower CD4+ levels (OR: 0.80 (95% CI: 0.73 to 0.87); p<.0001) were associated with a higher odds of an increase in clinical BMI status at week 96.

In conclusion, this dissertation demonstrates that the simpler, cost-effective waist circumference and self-reported measurements of abdominal changes are correlated with standard CT and DXA measurements, and could be potentially used as monitoring tools for abdominal fat gain in resource-limited and clinical trial settings. Baseline disease severity, including higher viral load and lower CD4+ levels, is associated with both increased abdominal size as well as overall severe weight increases in HIV-infected individuals initiating therapy. In addition, treatment differences in WC increases over 96 weeks may vary by sex and race/ethnicity. Individuals of black non-Hispanic race/ethnicity are also at a higher odds of severe weight increases. Further

research is needed to elucidate why certain race/ethnicities may be more prone to weight and fat increases.

The dissertation of Priya Bhagwat is approved.

Catherine Ann Sugar

Roger Detels

Marjan Javanbakht

Pamina M. Gorbach, Committee Co-Chair

Judith Silverstein Currier, Committee Co-Chair

University of California, Los Angeles

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LIST OF ABBREVIATIONS

Acquired immune deficiency syndrome (AIDS)

AIDS Clinical Trials Group (ACTG)

Antiretroviral (ARV)

Antiretroviral Therapy (ART)

Atazanavir/Ritonavir (ATV/r)

Body mass index (BMI)

Cardiovascular disease (CVD)

Computed tomography (CT)

Confidence interval (CI)

Darunavir/Ritonavir (DRV/r)

Dual x-ray absorptiometry (DXA)

Highly active antiretroviral therapy (HAART)

Human immunodeficiency virus (HIV)

Intention-to-treat (ITT)

Joint United Nations Programme on HIV and AIDS (UNAIDS)

Non-nucleoside reverse transcriptase inhibitor (NNRTI)

Nucleoside reverse transcriptase inhibitor (NRTI)

Odds ratio (OR)

Protease inhibitor (PI)

Raltegravir (RAL)

Subcutaneous adipose tissue (SAT)

Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)

United States (US)

Visceral adipose tissue (VAT)

Waist circumference (WC)

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VITA

EDUCATION

2004-2008 **CORNELL UNIVERSITY**, Ithaca, NY
Bachelor of Science in Human Biology, Health, and Society (HBHS)
Graduated with Honors and Distinction (Top 10% of graduating class)

RESEARCH EXPERIENCE

2009-2013 **HARVARD SCHOOL OF PUBLIC HEALTH**, Boston, MA
Statistical Programmer II, Center for Biostatistics in AIDS Research

2005-2008 **CORNELL UNIVERSITY**, Ithaca, NY
Research Assistant, Division of Nutritional Sciences

TEACHING EXPERIENCE

2015 **UNIVERSITY OF CALIFORNIA, LOS ANGELES**, Los Angeles, CA
Teaching Assistant, Department of Epidemiology

2007-2008 **CORNELL UNIVERSITY**, Ithaca, NY
Teaching Assistant, Department of Molecular Biology and Genetics

ABSTRACTS AND PRESENTATIONS

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FELLOWSHIPS AND AWARDS

2016	**Young Investigator Award**, Conference on Retroviruses and Opportunistic Infections (CROI)
2013-2016	**Fellowship in Epidemiology**, UCLA Fielding School of Public Health
2015	**Graduate Summer Research Mentorship Program Fellowship**, UCLA
2004-2008	**Dean's List**, Cornell University College of Human Ecology
2007	**Cornell Howard Hughes Medical Institute Scholar**, Cornell University
2007	**Summer Research Grant**, Cornell University College of Human Ecology

Chapter 1: Introduction and Background

1.1 Background

With improvements in therapy, infection with human immunodeficiency virus (HIV) has become a chronic disease, with the number of those 50 years or older living with HIV increasing over time. The 2013 UNAIDS estimates indicate that 4.2 million HIV-infected individuals are aged 50 years and older out of the 35 million living with HIV/AIDS.[1,2] In 2011, 1.2 million people were living with HIV in the United States, and those aged 55 and older accounted for 26% of these individuals.[3] The proportion of individuals aged 50 years and older who are living with HIV is on the rise globally. In the United States, for instance, about 17% of individuals living with HIV were aged 50 years and older in 2001. This proportion increased to about 31% in 2008.The increasing older population can be attributed to antiretroviral (ARV) treatments giving enhanced longevity to HIV-infected individuals, as well as the declining rate of HIV infection.[1] This shift in the HIV-infected population has manifested a need for understanding non-communicable disease comorbidities, such as cardiovascular disease (CVD).[1]

Cardiovascular disease is an important cause of morbidity and mortality among HIV-infected individuals.[4] The HIV-HEART study, a multi-center prospective cohort study, found that the prevalence of CVD among HIV-infected individuals is around 10%. In addition, these results show that the risk of CVD increases with age in infected individuals, with those older than 45 having much higher rates of CVD, such as a 4-fold higher rate of coronary artery disease and a 3-fold higher rate of myocardial infarction compared to the younger age group.[5]

Both HIV infection and antiretroviral therapy have been found to be associated with CVD.[4] HIV infection alone may lead to increased CVD risk through chronic inflammation and

immune activation.[6] The Strategies for Management of Antiretroviral Therapy (SMART) study was a landmark trial that randomized HIV-infected individuals to receive continuous ARV therapy or intermittent ARV therapy. An important finding from the study showed that interrupting ARV therapy was associated with a higher rate of cardiovascular disease.[7] ARV therapy may reduce inflammation and immune activation but the effect appears to be incomplete. Research has shown that those with suppressed HIV on ARV therapy compared to uninfected individuals have higher levels of inflammatory markers, in turn leading to a higher CVD risk.[6,8,9] Thus, despite the benefits of ARV therapy towards reduced CVD risk, continuous inflammation from HIV infection is associated with an overall higher long-term CVD risk. [6] Untangling the impact of ARV therapy and HIV on lipid levels and CVD risk has been challenging. An analysis examining lipid changes in the Multicenter AIDS Cohort Study (MACS) found that there were declines in serum lipids after HIV-infection, and large increases in total cholesterol and LDL-C values after initiation of Highly Active Antiretroviral Therapy (HAART) that were considered a return to health phenomenon. This pivotal research was the only study able to examine lipid levels prior to and post HIV infection.[10]

Different classes of antiretroviral drugs have also been found to have varying levels of association with CVD risk in HIV-infected individuals. For example, previous studies have found an association between use of certain protease inhibitors and increased myocardial infarction as well as CVD risk overall, while non-nucleoside reverse transcriptase inhibitors were not found to be associated with myocardial infarction.[11,12] ARV therapy has been associated with complications such as metabolic abnormalities and lipodystrophy (fat abnormalities). Fat changes during antiretroviral therapy include lipoatrophy (fat loss) and lipohypertrophy (fat

gain). Central fat gain often includes increases in abdominal visceral adipose tissue (VAT), which has been found to be an important risk factor for cardiovascular disease.[13,14]

Visceral adipose tissue is one of the major adipose tissue depots found in the abdominal cavity surrounding the organs. The other major type of depot is subcutaneous adipose tissue (SAT), which has been found to be less active and involved in long-term storage, with increased SAT associated with healthier lipid profiles.[15] It is hypothesized that VAT releases free fatty acids through the portal vein into the liver, and ultimately, part of the fatty acids pass into systemic circulation.[16] VAT has been found to be more metabolically active than SAT, and excess VAT has been found to be associated with metabolic abnormalities.[15,17] Excess VAT accumulation has been found to be associated with non-modifiable risk factors such as sex, age, and race, as well as modifiable risk factors such as behaviors including cigarette smoking, physical inactivity, and low dietary fiber intake.[18]

HIV-infected individuals may have a higher risk of CVD associated with increased VAT compared to uninfected individuals. Previous research has shown that HIV-infected individuals with increased VAT have increased Framingham Risk scores as well as 5-year-all-cause mortality.[19,20] Increased VAT in HIV-infected individuals has also been associated with increased markers of CVD.[21–23] The influence of VAT accumulation on CVD risk in HIV-infected individuals suggests the importance to further investigate the risk factors associated with body fat composition changes, particularly VAT increases.

1.2 Overall Objectives

The purpose of this dissertation is to determine if accessible measures of abdominal changes could be used as valid measures of body fat composition and VAT accumulation. In addition, we would like to examine whether certain patient characteristics and treatments are associated with increases in abdominal fat as well as overall body weight after HIV-infected individuals begin antiretroviral therapy.

The first study will determine whether changes in waist circumference or self-reported changes in abdominal size are correlated with standard measurements of visceral and abdominal fat increases in HIV-infected individuals initiating therapy. This is a retrospective cohort study using data from the ACTG A5260s metabolic substudy of the A5257 clinical trial, which collected additional CT and DXA measurements of abdominal fat. Current valid body fat measurement procedures such as CT and DXA are expensive and not readily available in clinical practice, whereas self-reported fat gain and waist circumference measurements could potentially prove to be more accessible alternatives for clinicians.

The second study will utilize waist circumference and self-reported abdominal changes to evaluate if baseline and demographic characteristics as well as contemporary ARV regimens are associated with abdominal fat changes in the entire A5257 cohort. The full A5257 cohort provides a much larger and more diverse sample size to evaluate these objectives. In addition to understanding risk factors for abdominal fat accumulation, this study will demonstrate the potential use of waist circumference and self-reported abdominal changes for patient monitoring.

The third study will investigate whether treatments and baseline predictors are associated with an increased risk of severe weight gain in the A5257 cohort. Obesity and weight gain represent current metabolic health issues that are becoming increasingly predominant in HIV-

infected individuals. By understanding characteristics associated with severe weight gain, clinicians could determine the likelihood of an HIV-infected patient experiencing extreme weight gain after initiating therapy and then create personalized treatment strategies.

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Chapter 2: Changes in Abdominal Fat Following Antiretroviral Therapy Initiation in HIV-infected Individuals Correlate with Waist Circumference and Self-Reported Changes

2.1 Abstract

Background: We examined whether waist circumference (WC) and self-reported abdominal size changes can estimate visceral adipose tissue (VAT) changes for those initiating antiretroviral therapy (ART).

Methods: Prospectively collected data from ACTG A5257 and its metabolic substudy, A5260s, were used for this analysis. ART-naïve HIV-infected participants were randomized to one of three contemporary ART regimens. Changes in abdominal CT-measured VAT and total adipose tissue (TAT) and DXA-measured trunk fat were tested for association with WC changes (by Pearson correlation) and categories of self-reported abdominal size changes (by ANOVA) between entry and week 96. Linear models compared WC and self-reported changes.

Results: The study population (N=328) was predominantly male (90%) and white non-Hispanic (44%) with a baseline median age of 36 years and BMI of 25 kg/m^2. At week 96, median WC change was +2.8 cm. Of those reporting at week 96, 53% indicated "No Change/Lost", 39% "Gained Some/Somewhat Larger", and 8% "Gained A Lot/Much Larger" as their self-reported changes. Trunk fat, VAT, and TAT changes differed across self-reported groups ($p<0.0001$ for all), and the group ordering was as expected. WC changes were strongly correlated with CT and DXA changes (trunk fat: $\rho=0.72$, $p<0.0001$; VAT: $\rho=0.52$, $p<0.0001$; TAT: $\rho=0.62$, $p<0.0001$). While WC changes explained a greater proportion of VAT, TAT, and trunk fat variation, self-reported changes remained a significant predictor after controlling for WC ($p<0.05$).

Conclusions: WC measurements and self-reported abdominal changes each correlated directly with imaging-derived abdominal fat measures, and can be used as reliable, affordable tools for central adiposity assessment.

2.2 Introduction

Cardiovascular disease (CVD) continues to be an important cause of morbidity and mortality among human immunodeficiency virus (HIV) infected individuals on effective long-term antiretroviral therapy (ART).[4,5,24] Both HIV infection and ART may play a role in the etiology of CVD.[4] Fat changes during therapy include fat loss or lipoatrophy and fat gain or lipohypertrophy. Studies have found that central fat gain continues to frequently occur in the contemporary ART era, and often includes increases in visceral adipose tissue (VAT), which has been found to be an important risk factor for cardiovascular disease.[13,14,25,26]

VAT, the deep adipose tissue depot that surrounds the abdominal organs, has been shown to be metabolically more active than subcutaneous adipose tissue (SAT) and more involved in lipolytic activities and release of pro-inflammatory cytokines.[15] Excess VAT has been associated with insulin resistance, glucose intolerance, dyslipidemia, systemic inflammation, and with elevated CVD risk.[17,27,28] In HIV-infected individuals, increased VAT has been found to be associated with coronary artery calcium (CAC) score, a marker of atherosclerosis.[21,29]

This increase in CVD risk associated with VAT may be higher in HIV-infected individuals compared to uninfected individuals. The Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study found that increased VAT is associated with increased Framingham Risk Scores, and this effect is more pronounced in HIV-infected individuals compared to HIV-negative controls.[19] In addition, increased VAT in HIV-infected individuals is associated with a higher odds of 5-year all-cause mortality.[20] This suggests that VAT accumulation is an important CVD risk factor that should be monitored in HIV-infected individuals.

VAT and other body fat measurements are currently conducted using computed tomography (CT) or dual x-ray absorptiometry (DXA). The CT scan is used to measure visceral and subcutaneous abdominal fat volume, while the DXA scan measures trunk fat mass and cannot distinguish between specific adipose in the region.[30] These techniques, although valid, are expensive and not readily available in clinical practice, making routine monitoring of body fat changes difficult. Self-reported abdominal change perceptions and waist circumference (WC) measurements could potentially prove to be more accessible alternatives for clinicians and for clinical research studies in low resource settings. WC has been found to be strongly associated with visceral and abdominal fat in the general population, and is therefore regarded as a valid measure of regional fat distribution despite its inability to distinguish between VAT and SAT.[30–34] However, the validity of WC changes has not been extensively examined, particularly in the HIV-infected population.

Prior studies have explored whether self-reported fat changes correlate with objective measurements of fat changes. However, such studies are limited, have conflicting results, and have not specifically addressed abdominal fat gain. Several of these studies employed cross-sectional designs, which did not use longitudinal measurements of fat change to predict self-reported lipoatrophy or lipohypertrophy.[35–38] The purpose of this research is to assess whether measured WC and self-reported abdominal changes in patients with HIV prove to be correlated with CT- and DXA-measured changes in central adiposity using prospectively collected clinical trial data, and could therefore be used as valid, cost-effective alternatives to these more labor-intensive and expensive methods of body composition assessment.

2.3 Methods

2.3.1 Study Population

This retrospective cohort study was conducted using data from the AIDS Clinical Trials Group (ACTG) A5257 clinical trial and A5260s substudy, and was approved by the UCLA Institutional Review Board (IRB). A5257 was a phase III randomized clinical trial comparing the virologic efficacy and tolerability of three non-nucleoside reverse transcriptase inhibitors (NNRTI) sparing antiretroviral regimens comprised of Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC) plus Atazanavir/Ritonavir (ATV/r), Darunavir/Ritonavir (DRV/r), or Raltegravir (RAL). The A5260s substudy was designed to evaluate the effects of HIV disease and ART on cardiovascular and metabolic outcomes. The design and results of the main study and substudy have been previously reported.[39–44]

In order to be eligible for the A5260s substudy, participants had to be enrolled in A5257. Participants were excluded if they had diabetes mellitus, known CVD, untreated hypothyroidism/hyperthyroidism, or were using statins or other hypolipemic agents. Participants also could not have intention to start pharmacological or surgical intervention for weight loss. Randomization, stratification, and treatment assignments were given as per the A5257 protocol. Participants enrolled between June 2009 and April 2011 at 26 ACTG sites in the United States. The duration of the A5260s substudy was 144 weeks. The substudy required participants to have comprehensive metabolic tests and body composition measurements.

2.3.2 Data Collection

Demographic and Anthropometric Data

The demographic information, including race/ethnicity, age, and sex, collected at baseline as part of the parent study, was used for these analyses. Baseline BMI (in kg/m^2) was categorized according to the CDC definitions: underweight as a BMI below 18.5 kg/m^2, normal weight between 18.5 kg/m^2 - 24.9 kg/m^2, overweight between 25.0 kg/m^2 - 29.9 kg/m^2, and obese at 30 kg/m^2 and over.[45]

Self-Reported Abdominal Change

The A5257 body image questionnaire was adopted from the FRAM study (NIH Grants: R01DK57508, R01HL74814, and R01HL53359)[46], and included self-reported measures on perception of current body weight, and assessment about gain or loss of size in specific regions of the body. This analysis focused on self-reported belly size changes only. While the questionnaire was self-administered, participants could request help from the clinical staff for assistance in reading or understanding the questions. The 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".

Waist Circumference Measurements

WC (in cm) was measured during study visits by trained clinical staff at week 0 and week 96. Participants were told to stand erect, relaxed, and to not hold in their stomach during measurement. A mid-waist circumference measurement was taken at the level of the upper border of the right ilium. Each measurement was conducted post exhalation 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.

DXA Trunk Fat Measurements

Whole body DXA measurements were conducted in the A5260s substudy at entry and at week 96. DXA measurements of regional body fat content were performed in an anteroposterior view using either a Lunar or Hologic scanner at the local site. The DXA scan was used to measure regional trunk fat mass (in kg). All scans for each participant were performed on the same machine model throughout the study. DXA scans were centrally read at the Body Composition Analysis Center at Tufts University (Boston, MA, USA) by staff blinded to treatment assignment and clinical characteristics.

CT Abdominal Fat Measurements

Non-contrast single slice abdominal CT scans at the L4-L5 level were also conducted at baseline and at week 96. The CT scan was used to measure VAT and TAT by taking cross-sectional images of the abdominal area (in cm^2). All scans for this study were performed on an approved scanner, using the same software version and same type of instrument. CT scans were centrally read at the LA Biomed CT Reading Center (Torrance, CA, USA) by staff blinded to treatment assignment and clinical characteristics.

In absence of a week 96 visit, self-report responses or waist circumference, DXA or CT measurements closest to this time within an 8 week window before and after week 96 were used.

2.3.3 Data Analysis and Statistical Methods

ANOVA was used to determine whether the self-reported perception of body image at week 96 was associated with absolute measurements of body fat change, by examining whether group means of CT- and DXA-measured fat change were not equal across the self-reported categories. Specifically, self-reported change was used as a categorical predictor variable and

trunk fat, VAT, and TAT changes between week 0 and week 96 were used as continuous outcome variables. Pairwise contrasts were used to analyze differences in measured fat between specific self-reported categories, using the Tukey-Kramer method to adjust for multiple comparisons. Stratified analyses were also performed to look at the association in subgroups defined by sex, race, baseline BMI, and age.

Pearson coefficients were used to examine the strength of the correlation between the absolute changes in WC and CT- and DXA-measured fat between baseline and week 96. Changes in WC, trunk fat, VAT, and TAT between week 0 and week 96 were continuous variables used in this analysis. Correlations between WC and trunk fat, VAT, and TAT changes were also examined for sex, race, baseline BMI, and age subgroups.

Separate models with WC and self-reported abdominal changes as single predictors were compared to joint models that included both variables together in order to examine the relative importance of WC and self-reported changes in explaining the variation in trunk fat, VAT, and TAT changes between week 0 and week 96. The Tukey-Kramer multiple comparisons adjustment method was used for pairwise contrasts between self-reported categories. All analyses were performed using SAS Software, Version 9.4 of the SAS System for Windows (© SAS Institute Inc., Cary, NC).

2.4 Results

2.4.1 Study Participants

Of the 334 participants initially enrolled in A5260s, 3 did not meet the study eligibility criteria and 3 were lost to follow-up immediately following enrollment. Details about participant disposition can be found in McComsey et al. (2016).[44]

Our resulting analysis population consists of the 328 HIV-infected adults in A5260s whose age ranged from 19 to 72 years and averaged 37 years (Table 2.1). Participants were 89.6% male (N=294) and 10.4% female (N=34). The diverse substudy population consisted of 43.9% white (N=144), 32.0% black (N=105), and 19.8% Hispanic (N=65) participants. The average baseline weight was 79 kg, with the majority of participants having a normal BMI (N=166, 50.6%) or overweight BMI (N=103, 31.4%) and fewer individuals being obese (N=53, 16.2%) or underweight (N=6, 1.8%) at baseline. The underweight and normal BMI categories were combined for the purposes of the subgroup analyses.

Those who did not have week 96 follow-up measurements for each abdominal fat type, self-report, or waist circumference (10-13%) showed baseline and demographic characteristics that were generally representative of the overall substudy population of 328 individuals.

2.4.2 Self-Reported Abdominal Size Changes

The overall and sex specific average trunk fat, VAT, and TAT measured changes from week 0 to week 96 across self-reported categories can be found in Table 2.2. As participants reported gaining more abdominal size, the measured changes also increased accordingly. This trend was consistent for males, however, it was not significant for trunk fat and TAT in the small female group (Figure 2.1).

ANOVA models revealed that measured average changes in trunk fat, VAT, and TAT were not the same across self-reported groups in the overall substudy population (Overall $p<0.0001$). For trunk fat, when compared to the reference "No Change/Lost" group, the "Gained A Lot/Much Larger" group had greater mean gains in fat (differential mean change of 4.1 kg, 95% CI: 2.8 to 5.5) than the "Gained Some/Somewhat Larger" group (differential mean change

of 1.9 kg, 95% CI: 1.1 to 2.6). A similar pattern was observed for VAT (48.3 cm^2, 95% CI: 32.3 to 64.4 vs. 17.0 cm^2, 95% CI: 8.4 to 25.6) and for TAT (117.3 cm^2, 95% CI: 75.9 to 158.8 vs. 59.3 cm^2, 95% CI: 37.1 to 81.5) (Table 2.3). Pairwise contrasts between each of the self-reported abdominal change categories revealed a significant difference between each of the groups after adjustment for multiple comparisons ($p<0.05$) (Table 2.4).

Subgroup results for males showed similar trends to the overall cohort results for differential mean changes of trunk fat, VAT, and TAT relative to the reference category "No Change/Lost". Analyses for females were not sufficiently powered to draw conclusions about differences in self-reported categories. A sensitivity analysis was conducted for the females by pooling the two self-reported size gain categories together. While those that reported gaining size actually gained more abdominal fat than those reporting "No Change/Lost" for trunk fat, VAT, and TAT, the results indicated that the two groups were not statistically different.

Stratified analyses for trunk fat, VAT, and TAT also failed to show trends in the obese BMI, Hispanic, and age 51-76 subgroups, which similarly had lower sample sizes. From the sensitivity analyses grouping the two self-report gain categories together, the Hispanic and age 18-30 subgroups additionally showed a significant difference between self-reported groups for each of the measured fat types.

2.4.3 Waist Circumference

The median change in WC between entry and week 96 was 2.83 cm (N=287; Q1 25%: -1.50 cm; Q3 75%: 6.47 cm). Pearson correlation tests showed strong correlations between changes in WC and changes in trunk fat, VAT, and TAT (trunk fat: $\rho=0.72$, $p<0.0001$; VAT: $\rho=0.52$, $p<0.0001$; TAT: $\rho=0.62$, $p<0.0001$) (Table 2.5). Correlations of similar size between

WC and each type of abdominal fat change were also observed in all subgroups, except for VAT and TAT in females and VAT in the obese. Figure 2.1 shows changes in WC plotted against trunk fat, VAT, and TAT changes for males and females. The regression results (Table 2.6) indicate that a change of 1 cm in WC corresponds to a 0.32 kg trunk fat change (95% CI: 0.28 to 0.35), 2.68 cm^2 VAT change (95% CI: 2.15 to 3.22), and 8.43 cm^2 TAT change (95% CI: 7.15 to 9.71).

2.4.4 Self-Reported Abdominal Size and Waist Circumference Joint Models

Individual predictor models of self-reported size change and WC change separately were compared to joint models including both measurements with each of the abdominal fat measures as outcome variables (Table 2.6). The individual predictor models show that self-reported abdominal change and WC change were each associated with the measured abdominal fat changes separately ($p<0.0001$). The R^2 values for each of the joint models were modest (trunk fat: $R^2=0.54$; VAT: $R^2=0.30$; TAT: $R^2=0.40$). When included together in the model, both WC ($p<0.0001$) and self-report ($p<0.05$) continued to remain significant predictors of trunk fat, VAT, and TAT changes, even though the R^2 value did not change dramatically from the WC-only model. When examining the differential mean changes of trunk fat, VAT, and TAT compared to the reference group "No Change/Lost", the coefficient for the "Gained A Lot/Much Larger" group was significant ($p<0.05$), while the coefficient for "Gained Some/Somewhat Larger" was no longer significant (Table 2.6). When adjusting for multiple comparisons in the joint model, the pairwise contrast between the "Gained A Lot/Much Larger" group and the "No Change/Lost group" remained statistically significant ($p<0.05$) for the trunk fat, VAT, and TAT models.

2.5 Discussion

Findings from this longitudinal study indicate that both WC and self-reported abdominal size changes appear to be correlated with standard measurements of abdominal fat change, including visceral adipose tissue accumulation. Both WC and self-reported abdominal changes were correlated with CT and DXA measurements and explained a moderate proportion of the variation in these objective measurements. Previous studies have shown a range of results concerning the validity of self-reported fat changes. A cross-sectional study of HIV-infected individuals in the thymidine nucleoside reverse transcriptase inhibitor era found a significant correlation between DXA measurements of limb fat and lipoatrophy scores independently reported by both physicians and participants.[35] In addition, it has been found that in HIV-infected women, triceps and thigh skinfold thicknesses as well as DXA measured lower limb fat were predictive of self-reported lipoatrophy, and that waist-to-hip ratio and DXA trunk fat/percentage limb fat were predictive of self-reported lipohypertrophy.[36] Another cross-sectional study of HIV-infected individuals found that self-assessment of both central fat adiposity and peripheral lipoatrophy did not agree with clinical assessment.[37] By using longitudinal measurements over 96 weeks after ART initiation, our study specifically addressed whether self-reported abdominal size changes relative to treatment initiation correlated with centrally read and standardized imaging of central fat using CT and DXA scans. Results from a previous longitudinal study suggested that self-reported lipoatrophy of extremities is not related to DXA measurements in HIV-infected individuals initiating treatment. However, this study did not specifically examine increases in abdominal visceral adipose tissue.[38] It is important to note that these research studies were also conducted in different HIV patient populations, which may have contributed to variation of results.

In our study, subgroup analyses revealed that the usefulness of self-reported abdominal changes may vary by sex, age, and BMI subgroup. The limited female enrollment in the A5260s study resulted in insufficient power to detect differences across self-reported categories. For the female subgroup, our results cannot confirm that self-reported abdominal change is directionally consistent with measured trunk fat and TAT increases. Previous research has shown that women tend to misreport weight more than men, indicating that self-reported size gains may not be an ideal measurement for this demographic.[47,48] Further research is needed to validate this form of measurement in the female population. It has also been found that being older or overweight/obese was also associated with misreporting.[47] Our study also had smaller sample sizes resulting in lower power for the obese and older age subgroups.

Results from this study show that WC measurements are correlated with abdominal fat changes, specifically CT-measured VAT, both overall and by sex, race, age, and BMI subgroups. Previous analyses have shown that CT-measured VAT has been highly associated with WC in cross-sectional settings.[32–34] A recent cross-sectional study of HIV-infected men reported a substantial correlation (ρ=0.613) between WC and CT-measured VAT, and found a limited proportion of variation in VAT explained by WC (R^2=0.35). While the authors of this study concluded that WC was not a reliable predictor of VAT, it is clear that WC does appear to be indicative of VAT levels and may be useful for tracking changes in body composition.[49] In contrast to these studies, our research addressed changes in both WC and abdominal fat over time and showed that WC increases are also a good indicator of changes in abdominal fat.

WC has been shown to be highly associated with cardiometabolic risk.[27,50] Although WC is not a widely utilized clinical measure, its usefulness in practice as a predictor of cardiometabolic risk has been recognized.[51] Showing that changes in WC reflect adipose

accumulation, including VAT increases, further supports its usefulness as a monitoring tool for HIV-infected individuals, who are more prone to abdominal lipohypertrophy.

We show that both WC and self-reported abdominal changes can be utilized to monitor abdominal fat gain in HIV-infected individuals. Between WC and self-reported changes, WC accounts for most of the variability in predicting abdominal fat changes, however, self-reported abdominal size changes may give additional information about those with extreme changes in abdominal fat after treatment initiation, as seen in the joint models with WC.

One limitation of this study is that the results do not indicate whether WC is more strongly correlated with CT-measured VAT or TAT, or DXA-measured trunk fat. Other limitations include the small sample size for the female and extreme BMI subgroups, which reduced the power for those analyses. In addition, our results may not be generalizable to the broader HIV-infected population due to the restrictive inclusion and exclusion criteria of the randomized controlled trial. An important strength of our study is that it was conducted using prospectively collected clinical trial data that specifically addressed the association between WC and self-reported abdominal size changes with changes in standard measures of abdominal fat over 96 weeks. To our knowledge, such proxy measurements for changes in abdominal fat have not been widely examined.

2.6 Conclusion

HIV-associated abdominal lipohypertrophy remains a highly prevalent medical issue for HIV patients on antiretroviral therapy.[52–55] Monitoring visceral adipose accumulation is especially important for HIV-infected patients, who are at a higher risk of metabolic abnormalities and cardiovascular disease. WC and self-reported abdominal size changes are

more accessible and affordable forms of body fat assessment that can be adopted by clinicians as valid measures of fat gain for HIV-infected patients undergoing ART. These measures will be especially valuable in resource-limited settings that do not have access to extensive tests, as well as clinical trial settings for ease of monitoring fat changes in larger study populations.

2.7 Tables and Figures

Table 2.1. Demographic and baseline information about A5260s substudy population (N=328).

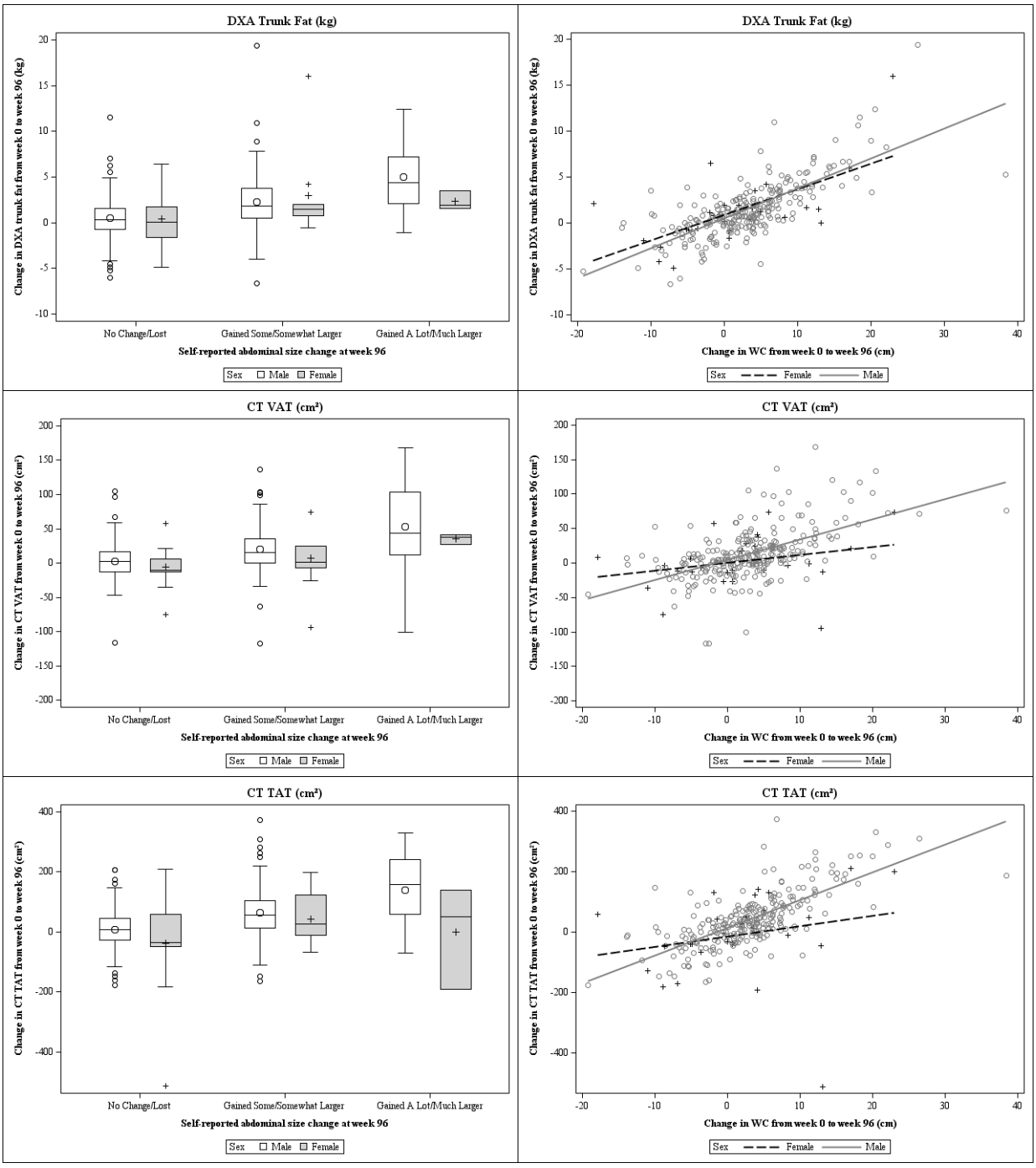
Demographics	**A5260s** *(N = 328)*
Sex [N (%)]	
Male	294 (89.6%)
Female	34 (10.4%)
Race [N (%)]	
White non-Hispanic	144 (43.9%)
Black non-Hispanic	105 (32.0%)
Hispanic	65 (19.8%)
Other	13 (4.0%)
Unknown	1 (0.3%)
Baseline BMI (kg/m^2) [N (%)]	
<18.5	6 (1.8%)
18.5-24.9	166 (50.6%)
25-29.9	103 (31.4%)
≥30.0	53 (16.2%)
Weight (kg) [Mean (SD, range)]	79.0 (16.6, 46.1-138.3)
Height (cm) [Mean (SD, range]	175.4 (8.9, 142.2-196.0)
Age (years) [Mean (SD, range)]	37 (11, 19-72)

Table 2.2. Overall and sex-specific means of trunk fat, VAT, and TAT across self-report abdominal size change categories in A5260s study population (N=328).

	No Change/ Lost		Gained Some/ Somewhat Larger		Gained A Lot/ Much Larger	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Overall						
Trunk fat (kg)	152	0.5 (2.5)	110	2.3 (3.4)	20	4.6 (3.5)
VAT (cm^2)	148	1.7 (28.5)	112	18.7 (37.0)	21	50.1 (58.8)
TAT (cm^2)	148	3.1 (85.2)	112	62.4 (88.1)	21	120.5 (129.2)
Males						
Trunk fat (kg)	134	0.5 (2.4)	101	2.3 (3.2)	17	5.0 (3.7)
VAT (cm^2)	131	2.7 (28.5)	103	19.8 (35.6)	18	52.5 (63.4)
TAT (cm^2)	131	8.4 (69.7)	103	64.0 (88.3)	18	140.6 (114.7)
Females						
Trunk fat (kg)	18	0.4 (3.2)	9	3.0 (5.0)	3	2.3 (1.0)
VAT (cm^2)	17	-5.8 (27.6)	9	6.7 (51.3)	3	35.3 (6.9)
TAT (cm^2)	17	-37.5 (159.0)	9	43.7 (89.1)	3	-0.5 (171.7)

VAT = Visceral Adipost Tissue; TAT = Total Adipose Tissue

Figure 2.1. Sex-specific change in trunk fat, VAT, and TAT between week 0 and week 96 across self-reported abdominal size change categories and WC changes in A5260s study population (N=328).



VAT = Visceral Adipose Tissue; TAT = Total Adipose Tissue

Table 2.3. Differential mean changes in trunk fat, VAT, and TAT between week 0 and week 96 for the "Gained Some/Somewhat Larger" and "Gained A Lot/Much Larger" self-reported categories relative to the "No change/Lost" category in A5260s study population (N=328).

		Trunk Fat (kg)			VAT (cm^2)			TAT (cm^2)	
		Gained Some/ Somewhat Larger	Gained A Lot/ Much Larger		Gained Some/ Somewhat Larger	Gained A Lot/ Much Larger		Gained Some/ Somewhat Larger	Gained A Lot/ Much Larger
Subgroup	**N**	**Differential Mean Change (95% CI)**	**Differential Mean Change (95% CI)**	**N**	**Differential Mean Change (95% CI)**	**Differential Mean Change (95% CI)**	**N**	**Differential Mean Change (95% CI)**	**Differential Mean Change (95% CI)**
Overall	282	1.9 (1.1, 2.6)	4.1 (2.8, 5.5)	281	17.0 (8.4, 25.6)	48.3 (32.3, 64.4)	281	59.3 (37.1, 81.5)	117.3 (75.9, 158.8)
Sex									
Male	252	1.8 (1.1, 2.5)	4.5 (3.1, 6.0)	252	17.1 (8.0, 26.1)	49.8 (32.5, 67.1)	252	55.7 (34.6, 76.8)	132.2 (91.9, 172.5)
Female	30	2.6 (-0.6, 5.7)	1.9 (-2.9, 6.7)	29	12.5 (-17.8, 42.8)	41.1 (-4.9, 87.2)	29	81.2 (-39.5, 201.8)	36.9 (-146.4, 220.2)
Baseline BMI (kg/m^2)									
Underweight/Normal: ≤24.9	153	1.5 (0.7, 2.4)	4.7 (2.5, 6.9)	152	21.6 (12.0, 31.2)	46.0 (23.5, 68.5)	152	59.8 (33.1, 86.5)	149.5 (87.0, 212.0)
Overweight: 25-29.9	85	1.6 (0.4, 2.7)	5.9 (3.7, 8.2)	84	11.3 (-4.8, 27.4)	74.1 (43.5, 104.7)	84	53.2 (17.9, 88.5)	177.8 (110.6, 245.1)
Obese: ≥30.0	44	3.8 (1.1, 6.6)	3.1 (-0.3, 6.6)	45	12.8 (-19.9, 45.5)	34.5 (-7.00, 75.9)	45	75.6 (-8.0, 159.1)	70.1 (-35.9, 176.1)
Race/Ethnicity									
White Non-Hispanic	129	2.5 (1.4, 3.6)	5.7 (3.4, 7.9)	127	14.4 (1.3, 27.5)	58.6 (31.8, 85.4)	127	73.3 (38.6, 108.0)	157.2 (86.1, 228.2)
Black Non-Hispanic	85	0.9 (-0.3, 2.2)	3.3 (0.9, 5.7)	85	16.1 (1.0, 31.1)	59.0 (32.3, 85.7)	85	46.0 (6.2, 85.7)	144.1 (73.7, 214.4)
Hispanic	55	2.5 (0.9, 4.2)	2.6 (-0.3, 5.5)	56	32.1 (9.7, 54.5)	22.8 (-17.2, 62.8)	56	65.6 (23.3, 107.9)	71.4 (-4.2, 147.0)
Other	12	2.5 (-0.04, 5.0)	5.7 (2.3, 9.0)	12	8.5 (-12.2, 29.2)	28.0 (0.6, 55.4)	12	65.8 (-58.9, 190.6)	7.2 (-157.8, 172.3)
Age (years)									
18-30	81	2.2 (0.5, 3.9)	2.1 (-2.4, 6.6)	83	13.6 (0.6, 26.7)	15.7 (-14.3, 45.7)	83	65.4 (25.2, 105.7)	86.4 (-6.4, 179.2)
31-50	170	2.0 (1.2, 2.8)	4.8 (3.4, 6.2)	168	20.7 (9.4, 32.0)	47.6 (27.6, 67.6)	168	66.5 (38.8, 94.3)	145.1 (96.0, 194.1)
51-76	31	0.3 (-1.8, 2.4)	3.4 (-0.1, 6.8)	30	6.5 (-29.2, 42.2)	93.1 (35.7, 150.4)	30	-0.3 (-91.1, 90.5)	23.6 (-122.3, 169.4)

VAT = Visceral Adipose Tissue; TAT = Total Adipose Tissue

Table 2.4. Differential mean changes in trunk fat, VAT, and TAT between self-reported abdominal size change categories adjusted for multiple comparisons in A5260s study population (N=328)..

	Trunk Fat (kg)		VAT (cm^2)		TAT (cm^2)	
	Differential Mean Change (Simultaneous 95% CI)	**P-value**	**Differential Mean Change (Simultaneous 95% CI)**	**P-value**	**Differential Mean Change (Simultaneous 95% CI)**	**P-value**
Gained A Lot/Much larger vs. Gained Some/Somewhat larger	2.28 (0.60 - 3.96)	0.0044	31.32 (11.71 - 50.93)	0.0006	58.04 (7.48 - 108.60)	0.0198
Gained A Lot/Much larger vs. No Change/Lost weight	4.13 (2.49 - 5.78)	<.0001	48.32 (29.09 - 67.6)	<.0001	117.34 (67.76 - 166.92)	<.0001
Gained Some/Somewhat larger vs. No Change/Lost weight	1.9 (0.99 - 2.72)	<.0001	17.00 (6.67 - 27.33)	0.0004	59.30 (32.67 - 85.93)	<.0001

VAT = Visceral Adipose Tissue; TAT = Total Adipose Tissue

Table 2.5. Overall and subgroup-specific Pearson correlations between WC and trunk fat, VAT, and TAT changes between week 0 and week 96 in A5260s study population (N=328)..

	Trunk Fat (kg)			VAT (cm^2)			TAT (cm^2)		
Subgroup	**N**	**ρ**	**p-value**	**N**	**ρ**	**p-value**	**N**	**ρ**	**p-value**
Overall	276	0.72	<.0001	274	0.52	<.0001	274	0.62	<.0001
Sex									
Male	246	0.74	<.0001	246	0.55	<.0001	246	0.71	<.0001
Female	30	0.64	0.0001	28	0.27	0.162	28	0.21	0.282
Baseline BMI (kg/m^2)									
Underweight/Normal: ≤24.9	149	0.69	<.0001	148	0.61	<.0001	148	0.68	<.0001
Overweight: 25-29.9	82	0.83	<.0001	80	0.62	<.0001	80	0.82	<.0001
Obese: ≥30.0	45	0.70	<.0001	46	0.26	0.082	46	0.34	0.021
Race/Ethnicity									
White Non-Hispanic	125	0.73	<.0001	123	0.58	<.0001	123	0.60	<.0001
Black Non-Hispanic	83	0.61	<.0001	83	0.32	0.003	83	0.53	<.0001
Hispanic	55	0.86	<.0001	55	0.64	<.0001	55	0.86	<.0001
Other	12	0.86	0.0004	12	0.45	0.146	12	0.55	0.067
Age (years)									
18-30	79	0.81	<.0001	81	0.46	<.0001	81	0.69	<.0001
31-50	166	0.69	<.0001	163	0.55	<.0001	163	0.59	<.0001
51-76	31	0.67	<.0001	30	0.51	0.004	30	0.60	0.0004

VAT = Visceral Adipose Tissue; TAT = Total Adipose Tissue; WC = Waist Circumference

Table 2.6. Individual predictor and joint models for change in trunk fat, VAT, and TAT between week 0 and week 96 in A5260s study population (N=328)..

	Trunk Fat (kg)							
	Individual Predictor Models				Joint Model			
	N	R^2	Prob > F	Differential Mean Change (95% CI)	N	R^2	Prob > F	Differential Mean Change (95% CI)
Waist Circumference	276	0.53	<.0001	0.32 (0.28, 0.35)	273	0.54	<.0001	0.30 (0.26, 0.34)
Self-Reported Abdominal Size Change	282	0.15	<.0001		--	--	0.0114	
No Change/Lost				ref				ref
Gained Some/ Somewhat Larger				1.85 (1.13. 2.58)				0.42 (-0.16, 1.00)
Gained A Lot/Much Larger				4.13 (2.76, 5.51)				1.62 (0.54, 2.69)

	VAT (cm^2)							
	Individual Predictor Models				Joint Model			
	N	R^2	Prob > F	Differential Mean Change (95% CI)	N	R^2	Prob > F	Differential Mean Change (95% CI)
Waist Circumference	274	0.27	<.0001	2.68 (2.15, 3.22)	272	0.30	<.0001	2.35 (1.78, 2.92)
Self-Reported Abdominal Size Change	281	0.13	<.0001		--	--	0.0014	
No Change/Lost				ref				ref
Gained Some/ Somewhat Larger				17.00 (8.37, 25.63)				5.15 (-3.27, 13.56)
Gained A Lot/Much Larger				48.32 (32.26, 64.39)				28.57 (13.21, 43.92)

	TAT (cm^2)							
	Individual Predictor Models				Joint Model			
	N	R^2	Prob > F	Differential Mean Change (95% CI)	N	R^2	Prob > F	Differential Mean Change (95% CI)
Waist Circumference	274	0.38	<.0001	8.43 (7.15, 9.71)	272	0.40	<.0001	7.55 (6.17, 8.93)
Self-Reported Abdominal Size Change	281	0.15	<.0001		--	--	0.0068	
No Change/Lost				ref				ref
Gained Some/ Somewhat Larger				59.30 (37.05, 81.55)				22.96 (2.61, 43.31)
Gained A Lot/Much Larger				117.34 (75.92, 158.76)				54.08 (16.96, 91.21)

VAT = Visceral Adipose Tissue; TAT = Total Adipose Tissue; WC = Waist Circumference

Chapter 3: Role of Treatment Effect Modification and Baseline Predictors on Abdominal Changes In ACTG A5257 HIV-infected Individuals Initiating Therapy

3.1 Abstract

Introduction: Visceral adipose tissue (VAT) accumulation after antiretroviral therapy (ART) initiation remains a prevalent issue for HIV-infected individuals. This study focuses on understanding potential treatment as well as baseline and demographic predictors of abdominal fat gain measured using the more accessible waist circumference (WC) and self-reported abdominal size change.

Methods: A retrospective study was conducted using data from the ACTG A5257 study, where treatment-naïve HIV-infected participants were randomized to one of three antiretroviral regimens including the protease inhibitors atazanavir/ritonavir (ATV/r) or darunavir/ritonavir (DRV/r), or the integrase inhibitor raltegravir (RAL) each in combination with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). Baseline and week 96 follow-up data on WC and self-reported belly size change at week 96 were collected during the study. Associations of treatment and baseline/demographic characteristics with WC change over 96 weeks were assessed using repeated measures models and linear regression. Ordinal logistic regression modeling was used to examine the associations of treatment/baseline characteristics with week 96 self-reported abdominal changes. Imputed data models were used to address missing data.

Results: The study population (N=1,809) included 76% male and 24% female participants who were predominantly black non-Hispanic (41.9%) and white non-Hispanic (34.1%). Participants averaged 37 years age at study entry and had an average baseline BMI of 26 kg/m^2. The mean baseline WC was 90.6 cm with an average WC increase of 3.4 cm over 96 weeks. Self-reported

changes in belly size at week 96 were reported as 56.1% “No Change/Lost”, 35.2% “Gained Some/Somewhat Larger”, and 8.8% “Gained A Lot/Much Larger”. Results indicated that the effect of treatment on WC change varied across sex and race, with the treatment difference in WC change for ATV/r versus RAL being significantly larger for females compared to males, and a larger difference in WC change for DRV/r versus RAL for black compared to non-black individuals ($p<0.001$ for each). For these treatment comparisons, the WC increase was much higher in the RAL arm. In addition, it was found that higher baseline viral load and lower CD4+ were both significantly associated with increases in WC ($p<0.0001$ for each). When examining risk factors for self-reported abdominal changes, baseline viral load and CD4+, as well as being female, were consistently associated with higher self-reported gains of abdominal size.

Conclusion: Our analyses show that that treatment differences in WC increases may be modified by sex and race, and that a more advanced baseline disease state is associated with both WC increases and higher levels of self-reported abdominal change. Treatment, viral load, and CD4+ appear to be strong predictors of abdominal fat gain, and both WC and self-reported changes could potentially be used for monitoring patient heath.

3.2 Introduction

HIV-associated abdominal lipohypertrophy remains a prevalent issue for human immunodeficiency virus (HIV) infected patients in the contemporary antiretroviral therapy (ART) era.[25,52–57] Central fat gain often includes increases in visceral adipose tissue (VAT), which has been found to be an important risk factor for cardiovascular disease (CVD).[13,14] VAT has also been shown to be associated with elevated cardiometabolic risk, and in HIV-infected individuals, increased VAT has been found to be associated with increased insulin resistance as well as a predictor of coronary artery calcium (CAC) score, a marker of atherosclerosis.[21,23,27–29]

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.[4,5,24] This increase in risk of CVD associated with VAT may be higher especially in HIV-infected individuals compared to uninfected individuals.[19] This highlights the importance of further investigating the underlying risk factors and treatments associated with central fat gain, especially VAT increases.

For current ARV treatments in treatment-naïve individuals, it appears that atazanavir may be associated with larger increases in abdominal fat when compared to other regimens, darunavir may be superior to atazanavir and associated with lower increases in abdominal fat, and raltegravir (RAL) may be associated with smaller increases in abdominal fat when compared to efavirenz in treatment-naïve individuals initiating therapy. [25,56,58–62] An analysis of the data from A5260s, a substudy of A5257 comparing Atazanavir/Ritonavir (ATV/r), Darunavir/Ritonavir (DRV/r), and Raltegravir (RAL), showed that there were significant increases in trunk fat and VAT for all three treatment regimens from week 0 to week 96, but found no differences between changes in trunk fat and visceral fat accumulation between RAL and the PI arms. It also found that higher baseline viral load was associated with larger gains in central fat.[44] In addition, a

metabolic analysis of the A5257 study indicated that there were larger waist circumference increases in the RAL arm compared to the DRV/r arm over 96 weeks.[40]

While 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 proven to be correlated with measurements of abdominal adipose tissue increases. We previously reported in Chapter 2 that in the A5260s substudy, both WC and self-report show strong associations with CT- and DXA- measured abdominal fat changes.

The objective of this study is to examine predictors of abdominal fat in the entire A5257 study cohort using WC and self-reported abdominal size changes. In addition, we further investigate the possible treatment differences to determine if the treatment effect is modified by certain demographic factors including age and race.

3.3 Methods

3.3.1 Study Population

This retrospective cohort study was conducted using data from the AIDS Clinical Trials Group (ACTG) A5257 clinical trial 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 three 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 and results of the A5257 study have been previously reported.[39,40]

A total of 1,814 subjects were enrolled into the A5257 study from May 2009 to June 2013, when the study was completed. This domestic study was conducted in 57 sites across the United States. Subjects were randomized in a 1:1:1 ratio to each regimen. In order to be eligible for the clinical trial, subjects were required to be treatment-naïve (≤10 days of ART at any time prior to entry), HIV-1 infected males and females, at least 18 years of age, candidates for the study treatments, and have no evidence of PI or NRTI resistance. Individuals also had to have a screening HIV-1 RNA ≥ 1,000 copies/mL within 90 days prior to study entry, as well as other lab tests such as absolute neutrophil count, hemoglobin, platelet count, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, and CrCl. Women of reproductive potential could not be included if pregnant and had to agree to use of contraception during study treatment. Subjects were excluded if they were breastfeeding, used specific medications, or had decompensated cirrhosis, serious illness, imprisonment, or known allergy to drugs.

3.3.2 Data Collection

Exposures

Demographic information, including race/ethnicity, age, and sex, was collected at baseline. Other measurements including BMI (in kg/m^2), CD4+ ($cells/mm^3$), and HIV-1 RNA count (copies/mL) were also collected at study baseline. Blood samples were drawn at study entry and sent to core study laboratories for processing. HIV-1 RNA levels were measured using the Abbott RealTime HIV-1 assay at Johns Hopkins University. Flow cytometry was used to phenotype CD4+ T-cells. Laboratory assessment of blood samples has been previously described.[39,42] For the purposes of these analyses, CD4+ count was represented as a continuous

variable, with 100 cells/mm^3 as units for better understandability of model coefficients and output. HIV-1 RNA was also a continuous variable that was log base 10 transformed into log HIV-1 RNA count, measured in log copies/mL. Treatment was coded according to the three randomization arms: ATV/r, DRV/r, and RAL.

Outcomes

Self-Reported Abdominal Change

The A5257 body image questionnaire was adopted from the FRAM study (NIH Grants: R01DK57508, R01HL74814, and R01HL53359)[46], and included self-reported measures on perception of current body weight and assessment about gain or loss of size in specific regions of the body. This study focused on self-reported belly size changes only. While the questionnaire was self-administered, participants could request help from the clinical staff for assistance in reading or understanding the questions. 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".

Waist Circumference Measurements

WC (in cm) was measured during study visits by trained clinical staff at week 0 and week 96. Participants were told to stand erect, relaxed, and to not hold in their stomach during measurement. A mid-waist circumference measurement was taken at the level of the upper border of the right ilium. Each measurement was conducted post exhalation 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.

In absence of a week 96 visit, self-report responses or waist circumference closest to this time within an 8 week window before and after week 96 were used.

Covariates

Information about substance use, current smoking status, income, and insurance was collected at baseline. These variables were included in the models as potential confounders for the associations between exposures and outcomes of interest. Smoking status at baseline was reported as being a current smoker or not. Illicit drug use included use of cocaine, heroin, amphetamines or other, and was coded as: never used, more than 1 month ago, and within the last month. Drinking status was reported as abstainer, moderate drinker, heavy drinker, and binge drinker. Income was divided into three earning categories: less than $19,999, $20,000 - $49,999, and $50,000 or higher. Insurance status was coded as "Private Insurance" if individuals had some form of private insurance, and "Other" if individuals had types of insurance other than private insurance, including government, out-of-pocket, or some other unknown type.

3.3.3 Data Analysis and Statistical Methods

Increases in Waist Circumference

Repeated measures linear modeling was used to examine predictors of WC increases between week 0 and week 96. The correlation structure for this analysis was compound symmetry due to the use of only two time points. First, an intention-to-treat (ITT) analyses examining effect measure modification of treatment by sex and race was conducted by including a three-way interaction between treatment, time, and each covariate. A per-protocol analysis restricting the study population to individuals who stayed on their randomized treatment was also conducted for both the overall treatment model as well as effect measure modification model. A sensitivity analysis removing potential influential observations was carried out to determine if certain data points were affecting the study results. Influential observations were removed based

on their MDFFITS and Cook's D values as well as number of additional iterations performed to update parameter estimates after observation removal.

In order to examine baseline predictors of WC increases, treatment, sex, race, age, baseline BMI, baseline CD4+, and baseline HIV-1 RNA were then included in a repeated measures model with time interactions. This model was adjusted for potential confounding from smoking, drinking, illicit drug use, income status, and 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. Fully conditional specification was used to conduct multiple imputation. The first multiple imputation analysis created a singular imputed dataset that could be used in a repeated model with time interactions. Since imputation procedures were unable to summarize over several imputations of repeated measures models, a second multiple imputation analysis was conducted using the WC change score between baseline and week 96 as an outcome of a linear regression model. This analysis included results that summarized over 10 iterations of imputations. Both imputation procedures included all of the covariate and outcome variables in the imputation models. Per-protocol and influence analyses were also conducted on the final imputed data models.

Self-reported Increases in Abdominal Size

Global chi-square goodness-of-fit tests were conducted in order to examine whether self-reported belly size gain is independent of treatment group overall and by sex and race subgroups. Ordinal logistic regression models were used to examine treatment differences in the odds of moving to a higher category of the three level outcome self-reported abdominal size gain, from "No Change/Lost", to "Gained Some/Somewhat Larger", to "Gained A Lot/Much Larger". Interaction models between treatment and sex as well as treatment and race were also reported.

An ordinal logistic regression model including treatment, sex, race, age, baseline BMI, and baseline CD4+/HIV-1 RNA was then examined to determine predictors of self-reported abdominal size gain adjusting for smoking, drinking, illicit drug use, income status, and insurance status. Multiple imputation was also conducted to replace missing values. A per-protocol analysis and influence analysis were also carried out on the final imputed data model. All analyses were performed using SAS Software, Version 9.4 of the SAS System for Windows (© SAS Institute Inc., Cary, NC).

3.4 Results

3.4.1 Participant Disposition

Of the 1,814 individuals who enrolled in the study, five were excluded due to acute illness, presence of a resistance mutation, or previous use of antiretroviral therapies. Details about participant disposition can be found in Lennox et al. (2014).[39]

3.4.2 Subject Demographics and Baseline Characteristics

Our resulting analysis population consists of 1,809 HIV-infected adults in A5257 whose age ranged from 18 to 76 years and averaged 37 years. Participants were 76% male (N=1,374) and 24% female (N=435). The study population consisted of 41.9% black non-Hispanic (N= 757), 34.1% white non-Hispanic (N= 615), and 21.6% Hispanic (N=390) participants. The average baseline weight was 79 kg and average baseline BMI was 26 kg/m^2. The participants' baseline HIV disease state included a mean CD4+ level of 308 $cells/mm^3$ and HIV-1 RNA level of 144,699 copies/mL. Patient demographics and baseline values were balanced between the three randomized treatment arms.[39]

Those who did not have week 96 follow-up measurements for self-report or WC outcomes (WC: N=245; self-report: N=247) showed baseline and demographic characteristics that were generally representative of the study population with follow-up data.

3.4.3 Increases in Waist Circumference

The mean baseline WC was 90.6 cm with an average increase of 3.4 cm over 96 weeks (Table 3.1). Across baseline and demographic characteristics, all subgroups experienced an increase in WC, with the largest increases appearing in the RAL treatment group, as well as the female, Black Non-Hispanic, older, normal BMI, obese BMI, HIV-1 RNA $\geq$ 100,000 copies/mL and CD4+ < 350 cells/mm^3 subgroups (Table 3.1).

The ITT analysis revealed that the protease inhibitors (PIs) combined had a lower average WC increase over 96 weeks compared to RAL (Differential mean change: -0.97cm [95% CI: -1.81 to -0.12]; p=0.0252). Specifically, there was a significant difference in mean WC change from baseline for DRV/r compared to RAL (Differential mean change: -1.24 cm [95% CI: -2.22, -0.26]; p=0.0130) (Table 3.2). The difference in WC change from baseline between treatment groups is also graphically depicted (Figure 3.1).

When examining effect measure modification by sex, the difference in WC increase for PIs versus RAL was significantly larger for females compared to males (Table 3.2, Figure 3.2). For example, the treatment difference for change in WC for ATV/r versus RAL was significantly larger for females than for males (Differential mean change: -3.28 cm [95% CI: -5.65 to 0.92]; p=0.0065). When compared to the white non-Hispanic individuals, black non-Hispanic and Hispanic individuals were not statistically different, with results for black individuals showing more difference and suggesting a need for further investigation. An exploratory analysis revealed a significantly larger difference in WC change from baseline for DRV/r versus RAL for black

individuals compared to all other race/ethnicities (Differential mean change: -2.92 cm [95% CI: -4.92 to -0.91]; p=0.0043) (Table 3.2, Figure 3.2). In addition, black individuals experienced a significantly smaller increase in WC for DRV/r compared to ATV/r (Table 3.2).

For different combinations of sex and race, the model exhibited varying estimates for change in waist circumference over 96 weeks. For example, the average WC for a black female on RAL at week 0 was 93.6 cm and at week 96 was 100.5 cm, resulting in a WC gain of 6.9 cm. However, for a black male on DRV/r, the average WC at week 0 was 88.3 cm and at week 96 was 90.5 cm, resulting in a gain of only 2.2 cm. For a non-black male on DRV/r, the change in WC over 96 weeks was 3.0 cm. These examples demonstrate the potential influence of various sex, race, and treatment combinations on WC changes.

The influence analysis of the ITT model (Table 3.3) indicated that the treatment comparison for ATV/r versus RAL for WC change was no longer significantly different for females compared to males (Differential mean change: -2.30 cm [95% CI: -4.60 to 0.01]; p=0.0506). However, for black individuals compared to others, the treatment comparison for DRV/r versus RAL (Differential mean change: -2.60 cm [95% CI: -4.54 to -0.66]; p=0.0088) and ATV/r versus RAL (Differential mean change: -2.24 cm [95% CI: -4.23 to -0.26]; p=0.0269) remained significantly different between the two race/ethnicities.

When the data were restricted to individuals who remained on their randomized treatment in the per-protocol analyses (N=1,369), it was found that the pairwise treatment comparisons between individual treatments that were significant from the ITT overall treatment and effect measure modification models (Table 3.2) remained significant in the per-protocol model as well (Table 3.4). However, the difference between the PIs combined and RAL become non-significant. For females compared to males, the difference of this treatment comparison also

became non-significant, while becoming significantly different between black individuals and other race/ethnicities.

Subsequent analyses modeled treatment, baseline, and demographic predictors of WC change through a complete case analysis as well as two imputed data analyses as shown in Table 3.5. After data were imputed through both methods, treatment differences reverted back to similar estimates from the original ITT model examining overall treatment differences, with DRV/r showing a smaller increase in WC change over 96 weeks compared to RAL. In addition, both baseline CD4+ as well as log HIV-1 RNA levels appeared to be strong predictors of WC change, with higher HIV-1 RNA levels and lower CD4+ levels being associated with higher increases in WC. In the change score imputed data model, for every one log unit (i.e. 10-fold) increase in baseline HIV-1 RNA copies/mL, the WC change over 96 weeks increased by 1.70 cm (95% CI: 1.07 to 2.33; $p<0.0001$), and for every 100 cell/mm^3 increase in CD4+ levels, the WC change over 96 weeks decreased by 0.75 cm (95% CI: -0.98 to -0.51; $p<0.0001$), holding all else constant. Sex, race/ethnicity, baseline age, and baseline BMI were not found to be significantly associated with WC changes over 96 weeks.

Results from influence (Table 3.6) and per-protocol (Table 3.7) analyses were consistent in magnitude and direction with the results from the original ITT imputed data models. Treatment differences in WC change between DRV/r and RAL, as well as associations between baseline HIV-1 RNA and CD4+ levels appeared to be stronger in the per-protocol models.

3.4.4 Self-reported Increases in Abdominal Size

The overall and subgroup specific distribution of self-reported abdominal change outcomes can be found in Table 3.1. Overall, 56.1% of participants reported “No Change/Lost”

in belly 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 found no differences in self-reported belly size changes between treatment groups overall and by sex and race subgroups. When examining treatment differences in odds of reporting a higher level of self-reported abdominal changes and differences in treatment effect by sex and race, results indicated that treatment was not significantly associated with self-reported changes. While 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” versus the combined “Gained Some/Somewhat Larger” and “No Change/Lost” categories were 0.94 times lower (95% CI: 0.74-1.19; p=0.5949). In addition, it appears from the model with sex and race interactions, that being female may be associated with self-reported abdominal changes. Per-protocol analyses results were consistent with the ITT analyses.

A model including all the baseline and demographic predictors of interest was then examined. Complete case analysis and imputed data analysis showed consistent results, indicating that sex, baseline BMI, baseline HIV-1 RNA, and baseline CD4+ count were each associated with self-reported abdominal size changes (Table 3.8). From the imputed data model, we see that the odds of “Gained A Lot/Much Larger” versus the combined lower categories were 1.36 times greater for females compared to males, with all other variables in the model held constant (95% CI: 1.05 to 1.76; p=0.0211). For every 1 log unit (i.e. 10-fold) increase in HIV-1 RNA copies/mL, the odds of “Gained A Lot/Much Larger” compared to the other self-reported categories were 1.35 times greater (95% CI: 1.14 to 1.59; p=0.0004). In addition, the odds of highest self-reported gain compared to the combined middle and lower categories was 0.88 times

lower for every 100 cells/mm^3 increase in baseline CD4+ (95% CI: 0.83 to 0.94; p=0.0001), holding all else constant. It was also found that holding all else constant, a higher baseline BMI was associated with higher odds of reporting a higher self-reported gain category (OR=1.04 [95% CI: 1.02 to 1.06]; p<.0001). Per-protocol analysis of the imputed data model showed associations of sex, baseline BMI, CD4+ levels, and HIV-1 RNA levels with self-reported abdominal changes consistent with the ITT analysis, with odds ratios of similar magnitude and direction (Table 3.9).

3.5 Discussion

Results from this study indicated that the treatment effect on WC gains is modified by sex and race/ethnicity, and that in addition to treatment, baseline disease state is strongly associated with abdominal changes over 96 weeks through both self-report and WC outcomes.

Sex was not found to be significantly associated with WC change after adjusting for other baseline covariates. Previous research has shown an association between sex and lipodystrophy outcomes, including central fat gain. In a study randomizing treatment-naïve individuals to atazanavir or ritonavir-boosted atazanavir in combination with stavudine and lamivudine, women had greater increases in visceral adipose tissue, subcutaneous adipose tissue, total adipose tissue, and trunk fat at week 96, compared with men.[63] Other studies, both longitudinal and cross-sectional, have also found this association between sex and central fat accumulation.[64–67] While our study results are directionally consistent with other research, we could not confirm this association, which could be due to our smaller female sample size, as well as differences in the assessment of central lipohypertrophy. Our results from analyses with self-reported abdominal size changes did show that females had a higher odds of reporting gains compared to males.

While 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.[47,48]

We also could not confirm an association between race/ethnicity and WC or self-reported abdominal changes. There has been limited research in the literature addressing this question. One study found that black women had an increased risk of reporting lipohypertrophy in comparison with white men, while another study reported that Caucasian and Hispanic women compared to African American women on therapy had a higher odds of self-reporting redistribution of fat.[67,68] Another study of individuals initiating therapy found that being black compared to white was associated with fat accumulation.[69]

While 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 across sex and race/ethnicity. This has not been previously examined in detail. One research study examining treatment differences between PI-based ARV therapies versus other ARV therapies across race/ethnicities 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.[70] From our results, it appears that females on RAL experienced a higher increase in WC compared to ATV/r, and that black individuals on RAL experienced a higher increase in WC compared to DRV/r.

For other baseline covariates, older age has been previously reported to be associated with lipodystrophy and central lipohypertrophy.[64,65,68] Our study was not able to confirm an association between age and abdominal changes. While we do not find a significant association between baseline BMI and WC increases, we did find that a higher baseline BMI is associated

with a higher odds of reporting abdominal gains at week 96. The A5224s substudy of A5202 also found that higher baseline BMI was associated with significant increases in VAT at week 96.[25]

Regardless of the model or outcome examined, we found that baseline HIV-1 RNA and CD4+ levels were significantly associated with abdominal changes (both WC and self-reported), with higher viral load and lower CD4+ consistently being associated with WC increases and self-reported abdominal size gains. 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.[64,66] Other research has found that a lower viral 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.[71,72] One study found that higher CD4+ and lower HIV-1 RNA count was found to be associated with fat accumulation, however these were measured after ARV initiation at a follow-up visit.[69] 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.[73] A greater increase in CD4+ may be indicative of a lower baseline CD4+ before therapy initiation. Results from the A5260s substudy of A5227 were consistent with our main study results, showing that a higher viral load was associated with increased VAT.[44] McComsey et al. propose 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.[44,74–76] 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. In addition, the randomized controlled trial on which this study is based had restrictive inclusion/exclusion criteria, which may limit the generalizability of our study results to the HIV-infected population at large. We also could not adjust for potential confounding by diet and exercise as this information was not collected during the A5257 study. 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. In addition, we were able to demonstrate the clinical utility of more simple, cost-effective tools, such as WC and self-report, for observing abdominal fat changes.

3.6 Conclusion

While adverse abdominal fat increases continue to occur for HIV-infected individuals on ARV therapy, it is important to understand the inherent differences in patient characteristics 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. In addition, since lipohypertrophy continues to be a prevalent issue in low- and middle-income countries,[77] the use of waist circumference and self-report as monitoring tools

may prove to be extremely useful for lower-income settings which may not have access to extensive tests.

3.7 Tables and Figures

Table 3.1. 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 A5257 study population (N=1,809).

	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	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N (%)**	**N (%)**	**N (%)**
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 (years)							
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							
< 100,000 copies/mL	1248	91.5 (15.7)	1074	2.1 (7.5)	646 (59.7)	350 (32.4)	86 (8.0)
≥ 100,000 copies/mL	552	88.6 (12.8)	481	6.3 (8.6)	230 (47.9)	199 (41.5)	51 (10.6)
CD4+ Level							
≥ 350 cells/mm^3	740	92.2 (15.5)	639	1.6 (7.3)	394 (61.2)	205 (31.8)	45 (7.0)
< 350 cells/mm^3	1060	89.5 (14.4)	916	4.6 (8.3)	482 (52.5)	344 (37.5)	92 (10.0)

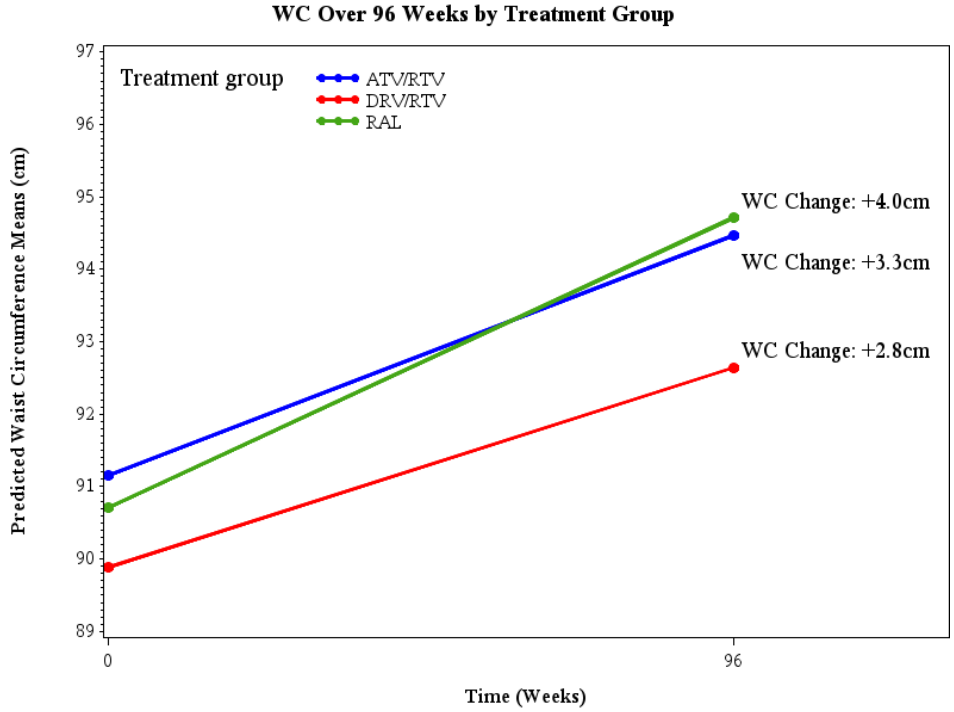
RAL: Raltegravir; ATV/r: Atazanavir/Ritonavir; DRV/r: Darunavir/Ritonavir; PIs: Protease Inhibitors Atazanavir/Ritonavir and Darunavir/Ritonavir

Table 3.2. Intention-to-treat analysis of treatment arm differences in waist circumference mean changes from baseline for overall treatment model and model examining effect measure modification of treatment by sex and race/ethnicity in the ACTG A5257 study population (N=1,809).

	Model 1: Overall		**Model 2: Effect Measure Modifiction**			
			Females versus Males		**Black Non-Hispanic versus Other Race/Ethnicity**	
Treatment Comparison	**Differential Mean Change (cm) (95% CI)**	**p-value**	**Differential Mean Change (cm) (95% CI)**	**p-value**	**Differential Mean Change (cm) (95% CI)**	**p-value**
DRV/r - RAL	-1.24 (-2.22, -0.26)	0.0130	-2.01 (-4.32, 0.31)	0.0901	-2.92(-4.92, -0.91)	0.0043
ATV/r - RAL	-0.69 (-1.67, 0.29)	0.1656	-3.28 (-5.65, 0.92)	0.0065	-0.44 (-2.48, 1.60)	0.6720
DRV/r - ATV/r	-0.55 (-1.53, 0.44)	0.2755	1.28 (-1.11, 3.66)	0.2933	-2.48 (-4.52, -0.43)	0.0176
PIs - RAL	-0.97 (-1.81, -0.12)	0.0252	-2.64 (-4.66, -0.63)	0.0102	-1.68 (-3.42, 0.06)	0.0589

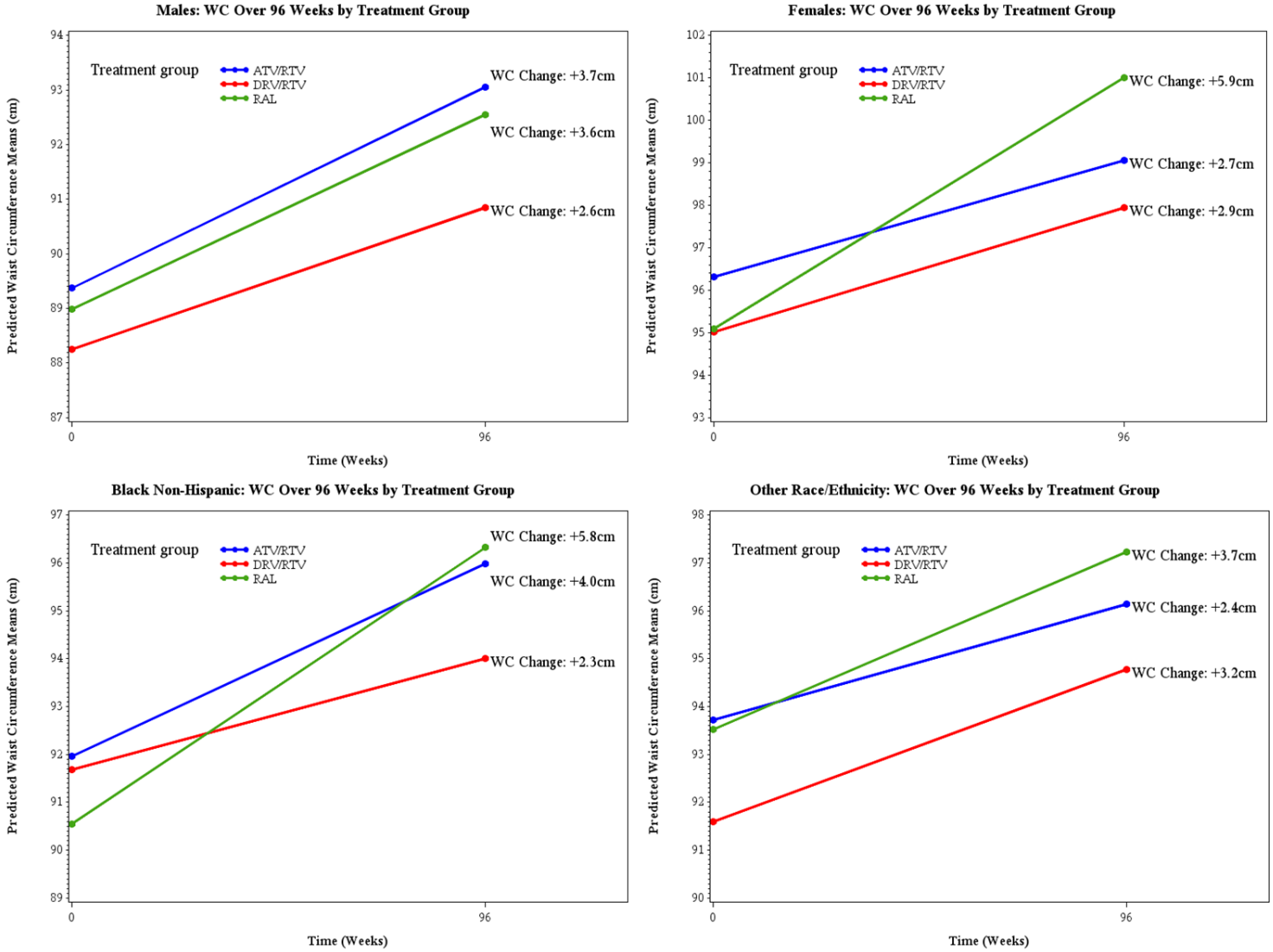
RAL: Raltegravir; ATV/r: Atazanavir/Ritonavir; DRV/r: Darunavir/Ritonavir; PIs: Protease Inhibitors Atazanavir/Ritonavir and Darunavir/Ritonavir; CI: Confidence Interval

Figure 3.1. Changes in waist circumference from baseline to week 96 by treatment group in the ACTG A5257 study population (N=1,809).



RAL: Raltegravir; ATV/r: Atazanavir/Ritonavir; DRV/r: Darunavir/Ritonavir; WC: Waist Circumference

Figure 3.2. Changes in waist circumference from baseline to week 96 by treatment group across sex and race subgroups in the ACTG A5257 study population (N=1,809).



RAL: Raltegravir; ATV/r: Atazanavir/Ritonavir; DRV/r: Darunavir/Ritonavir; WC: Waist Circumference

[a] Waist circumference values for males and females are averaged over race, and values for black and others are averaged over sex.

Table 3.3. Influence analysis examining effect measure modification of treatment by sex and race/ethnicity in predicting waist circumference mean changes for the ACTG A5257 study population (N=1,809).

	Effect Measure Modification			
	Females versus Males		**Black Non-Hispanic versus Other Race/Ethnicity**	
Treatment Comparison	**Differential Mean Change (95% CI)**	**p-value**	**Differential Mean Change (95% CI)**	**p-value**
DRV/r - RAL	-1.54 (-3.79, 0.71)	0.1797	-2.60 (-4.54, -0.66)	0.0088
ATV/r - RAL	-2.30 (-4.60, 0.01)	0.0506	-0.36 (-2.33, 1.62)	0.7227
DRV/r - ATV/r	0.75 (-1.56, 3.07)	0.5234	-2.24 (-4.23, -0.26)	0.0269
PIs - RAL	-1.92 (-3.88, 0.04)	0.0552	-1.48 (-3.17, 0.21)	0.0865

RAL: Raltegravir; ATV/r: Atazanavir/Ritonavir; DRV/r: Darunavir/Ritonavir; PIs: Protease Inhibitors Atazanavir/Ritonavir and Darunavir/Ritonavir; CI: Confidence Interval

Table 3.4. Per-protocol analysis of overall treatment arm differences in waist circumference mean changes from baseline to week 96 and effect measure modification of treatment by sex and race/ethnicity in ACTG A5257 study population (N=1,369).

	Model 1: Overall		Model 2: Effect Measure Modification			
			Females versus Males		Black Non-Hispanic versus Other Race/Ethnicity	
Treatment Comparison	**Differential Mean Change (95% CI)**	**p-value**	**Differential Mean Change (95% CI)**	**p-value**	**Differential Mean Change (95% CI)**	**p-value**
DRV/r - RAL	-1.17 (-2.21, -0.13)	0.0274	-0.99 (-3.49, 1.51)	0.4370	-3.81 (-5.95, -1.67)	0.0005
ATV/r - RAL	-0.45 (-1.53, 0.64)	0.4200	-3.36 (-6.00, -0.72)	0.0127	-0.97 (-3.22, 1.28)	0.3990
DRV/r - ATV/r	-0.73 (-1.83, 0.38)	0.1975	2.37 (-0.36, 5.10)	0.0889	-2.84 (-5.14, -0.54)	0.0154
PIs - RAL	-0.81 (-1.72, 0.099)	0.0806	-2.17 (-4.35, 0.0039)	0.0504	-2.39 (-4.26, -0.52)	0.0123

RAL: Raltegravir; ATV/r: Atazanavir/Ritonavir; DRV/r: Darunavir/Ritonavir; PIs: Protease Inhibitors Atazanavir/Ritonavir and Darunavir/Ritonavir; CI: Confidence Interval

Table 3.5. Intention-to-treat analysis of waist circumference mean changes from baseline across 3 models: complete case analysis, repeated imputed data model, and change score imputed data model in the ACTG A5257 study population (N=1,809).

	Complete Case Analysis		Imputed Data: Repeated Model		Imputed Data: Change Score Model	
Covariate	**Differential Mean Change (95% CI)**	**p-value**	**Differential Mean Change (95% CI)**	**p-value**	**Differential Mean Change (95% CI)**	**p-value**
Treatment						
RAL	--	--	--	--	--	--
ATV/r	-0.34 (-1.39, 0.71)	0.5210	-0.74 (-1.68, 0.21)	0.1253	-0.65 (-1.58, 0.29)	0.1749
DRV/r	-0.70 (-1.75, 0.36)	0.1951	-1.22 (-2.17, -0.28)	0.0114	-1.07 (-2.00, -0.13)	0.0255
PIs	-0.52 (-1.43, 0.39)	0.2643	-0.98 (-1.80, -0.16)	0.0188	--	--
Sex						
Males	--	--	--	--	--	--
Females	0.62 (-0.51, 1.74)	0.2833	0.90 (-0.11, 1.91)	0.0822	0.74 (-0.26, 1.74)	0.1467
Race/Ethnicity						
White Non-Hispanic	--	--	--	--	--	--
Black Non-Hispanic	1.05 -0.03, 2.12)	0.0565	0.70 (-0.29, 1.69)	0.1672	0.61 (-0.38, 1.59)	0.2262
Hispanic	-0.10 (-1.40, 1.20)	0.8772	-0.22 (-1.37, 0.94)	0.7128	-0.17 (-1.32, 0.98)	0.7678
Other	-1.18 (-3.83, 1.46)	0.3804	-1.92 (-4.41, 0.58)	0.1328	-1.94 (-4.39, 0.50)	0.1191
Age (years)	0.0084 (-0.032, 0.049)	0.6854	0.020 (-0.017, 0.057)	0.2877	0.023 (-0.013, 0.060)	0.2096
Baseline BMI (kg/m^2)	0.026 (-0.053, 0.10)	0.5195	0.015 (-0.056, 0.086)	0.6817	0.0044 (-0.066, 0.075)	0.9031
Baseline HIV-1 RNA (log_{10} copies/mL)	1.83 (1.13, 2.54)	<.0001	1.86 (1.23, 2.49)	<.0001	1.70 (1.07, 2.33)	<.0001
Baseline CD4+ (100 cells/mm^3)	-0.65 (-0.91, -0.39)	<.0001	-0.74 (-0.98, -0.50)	<.0001	-0.75 (-0.98, -0.51)	<.0001

RAL: Raltegravir; ATV/r: Atazanavir/Ritonavir; DRV/r: Darunavir/Ritonavir; PIs: Protease Inhibitors Atazanavir/Ritonavir and Darunavir/Ritonavir; CI: Confidence Interval

[a] Model 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 subjects with non-missing data

[c] 'Imputed Data: Repeated Model' is a repeated measures model including a dataset with one iteration of imputed values

[d] 'Imputed Data: Change Score Model' includes estimates summarized over 10 iterations of imputed values and waist circumference change score as the outcome

Table 3.6. Influence analysis of waist circumference repeated imputed data model in ACTG A5257 study population (N=1,809).

	Imputed Data: Repeated Model	
Covariate	**Differential Mean Change (95% CI)**	**p-value**
Treatment		
RAL	--	--
ATV/r	-0.77 (-1.67, 0.13)	0.0945
DRV/r	-1.24 (-2.15, -0.34)	0.0072
PIs	-1.01 (-1.79, -0.22)	0.0117
Sex		
Males	--	--
Females	0.91 (-0.058, 1.87)	0.0654
Race/Ethnicity		
White Non-Hispanic	--	--
Black Non-Hispanic	0.76 (-0.18, 1.71)	0.1132
Hispanic	-0.22 (-1.32, 0.88)	0.6973
Other	-1.93 (-4.31, 0.46)	0.1132
Age (Years)	0.024 (-0.011, 0.059)	0.1740
Baseline BMI (kg/m^2)	-0.020 (-0.088, 0.048)	0.5673
Baseline HIV-1 RNA (log_{10} copies/mL)	1.69 (1.09, 2.30)	<.0001
Baseline CD4+ (100 cells/mm^3)	-0.76 (-0.99, -0.54)	<.0001

RAL: Raltegravir; ATV/r: Atazanavir/Ritonavir; DRV/r: Darunavir/Ritonavir; PIs: Protease Inhibitors Atazanavir/Ritonavir and Darunavir/Ritonavir; CI: Confidence Interval

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

[b] 'Imputed Data: Repeated Model' is a repeated measures model including a dataset with one iteration of imputed values with influential observations removed

Table 3.7. Per-protocol analysis of waist circumference mean changes from baseline to week 96 across repeated and change score imputed data models in ACTG A5257 study population (N=1,369).

	Imputed Data: Repeated Model		Imputed Data: Change Score Model	
Covariate	**Differential Mean Change (95% CI)**	**p-value**	**Differential Mean Change (95% CI)**	**p-value**
Treatment				
RAL	--	--	--	--
ATV/r	-0.80 (-1.82, 0.22)	0.1237	-0.88 (-1.89, 0.14)	0.0912
DRV/r	-1.21 (-2.20, -0.23)	0.0157	-1.31 (-2.29, -0.33)	0.0090
PIs	-1.01 (-1.86, -0.15)	0.0211	--	--
Sex				
Males	--	--	--	--
Females	0.66 (-0.43, 1.74)	0.2354	0.65 (-0.43, 1.73)	0.2400
Race/Ethnicity				
White Non-Hispanic	--	--	--	--
Black Non-Hispanic	0.61 (-0.44, 1.66)	0.2553	0.53 (-0.52, 1.58)	0.3227
Hispanic	0.24 (-1.00, 1.47)	0.7064	0.22 (-1.01, 1.46)	0.7233
Other	-2.05 (-4.61, 0.52)	0.1182	-2.14 (-4.69, 0.40)	0.0982
Age (years)	0.0098 (-0.029, 0.049)	0.6237	0.012 (-0.027, 0.051)	0.5386
Baseline BMI (kg/m^2)	0.029 (-0.046, 0.10)	0.4441	0.020 (-0.055, 0.096)	0.6006
Baseline HIV-1 RNA (log_{10} copies/mL)	1.90 (1.21, 2.59)	<.0001	1.87 (1.19, 2.56)	<.0001
Baseline CD4+ (100 cells/mm^3)	-0.88 (-1.13, -0.63)	<.0001	-0.88 (-1.13, -0.63)	<.0001

RAL: Raltegravir; ATV/r: Atazanavir/Ritonavir; DRV/r: Darunavir/Ritonavir; PIs: Protease Inhibitors Atazanavir/Ritonavir and Darunavir/Ritonavir; CI: Confidence Interval

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

[b] 'Imputed Data: Repeated Model' is a repeated measures model including a dataset with one iteration of imputed values

[c] 'Imputed Data: Change Score Model' includes estimates summarized over 10 iterations of imputed values and waist circumference change score as the outcome

Table 3.8. 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 ACTG A5257 study population (N=1,809).

	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, 1.26)	0.7362	1.05 (0.82, 1.34)	0.6961
DRV/r	0.92 (0.70, 1.21)	0.5470	0.97 (0.76, 1.24)	0.8249
Sex				
Males	--	--	--	--
Females	1.34 (1.00, 1.80)	0.0496	1.36 (1.05, 1.76)	0.0211
Race/Ethnicity				
White Non-Hispanic	--	--	--	--
Black Non-Hispanic	0.99 (0.75, 1.32)	0.9566	0.95 (0.74, 1.23)	0.7034
Hispanic	0.83 (0.59, 1.17)	0.2786	0.74 (0.55, 1.01)	0.0546
Other	0.67 (0.32, 1.42)	0.3013	0.59 (0.29, 1.19)	0.1391
Age (years)	1.01 (0.997, 1.02)	0.1746	1.01 (0.999, 1.02)	0.0778
Baseline BMI (kg/m^2)	1.03 (1.01, 1.05)	0.0037	1.04 (1.02, 1.06)	<.0001
Baseline HIV-1 RNA (log_{10} copies/mL)	1.30 (1.08, 1.57)	0.0058	1.35 (1.14, 1.59)	0.0004
Baseline CD4+ (100 cells/mm^3)	0.88 (0.82, 0.95)	0.0005	0.88 (0.83, 0.94)	0.0001

RAL: Raltegravir; ATV/r: Atazanavir/Ritonavir; DRV/r: Darunavir/Ritonavir; PIs: Protease Inhibitors Atazanavir/Ritonavir and Darunavir/Ritonavir; CI: Confidence Interval

[a] Model 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 subjects with non-missing data

[d] 'Imputed Data' model includes estimates summarized over 10 iterations of imputed values

Table 3.9. Per-protocol analysis examining odds of reporting a higher category of self-reported abdominal size change with imputed data in ACTG A5257 study population (N=1,369).

	Imputed Data	
Covariate	**Odds Ratio (95% CI)**	**p-value**
Treatment		
RAL	--	--
ATV/r	1.05 (0.80, 1.37)	0.7347
DRV/r	0.97 (0.75, 1.26)	0.8377
Sex		
Males	--	--
Females	1.35 (1.02, 1.80)	0.0377
Race/Ethnicity		
White Non-Hispanic	--	--
Black Non-Hispanic	0.95 (0.72, 1.26)	0.7216
Hispanic	0.72 (0.52, 1.00)	0.0518
Other	0.39 (0.17, 0.87)	0.0224
Age (years)	1.01 (0.998, 1.02)	0.1350
Baseline BMI (kg/m^2)	1.04 (1.02, 1.06)	0.0002
Baseline HIV-1 RNA (log_{10} copies/mL)	1.31 (1.09, 1.57)	0.0040
Baseline CD4+ (100 cells/mm^3)	0.87 (0.81, 0.93)	<.0001

RAL: Raltegravir; ATV/r: Atazanavir/Ritonavir; DRV/r: Darunavir/Ritonavir; PIs: Protease Inhibitors Atazanavir/Ritonavir and Darunavir/Ritonavir; CI: Confidence Interval

[a] Model 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] 'Imputed Data' model includes estimates summarized over 10 iterations of imputed values

Chapter 4: Predictors of Severe Weight Gain or Clinically Meaningful Increases in BMI After Antiretroviral Initiation for Treatment of HIV-Infection

4.1 Abstract

Introduction: HIV-infected individuals are increasingly becoming more overweight/obese and gaining unhealthy weight after antiretroviral therapy (ART) initiation. The objective of this study is to understand potential predictors of severe weight/BMI gain.

Methods: A retrospective study was conducted using data from the ACTG A5257 study, where treatment-naïve HIV-infected participants were randomized to one of three regimens including atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), or raltegravir (RAL). Severe weight/BMI gain was defined as two different outcomes: percent weight increase $\geq$ 10%, and an increase in clinical BMI status from study entry to week 96. Logistic regression modeling was used to examine the association between participant demographic/baseline predictors and severe weight/BMI gain. Multiple imputation was used to address missing data. Receiver operating characteristic (ROC) curves were used to compare the models with two types of outcomes.

Results: The analysis included 1,809 participants enrolled in the A5257 study, who were largely male (76%) with a diverse race/ethnicity distribution including 41.9% black non-Hispanic, 34.1% white non-Hispanic, and 21.6% Hispanic individuals. The population had a mean baseline weight of 79 kg and baseline BMI of 26 kg/m^2, with an average increase in weight of 3.8 kg and BMI increase of 1.3 kg/m^2 over 96 weeks. The odds of a severe percent weight gain were 1.55 times higher for black non-Hispanic compared to white non-Hispanic individuals (95% CI: 1.10 to 2.20; p= 0.0129) in the final imputed model. For black compared to white individuals, the odds of an increase in BMI status were 1.48 times higher (95% CI: 1.06 to 2.07; p=0.0223). In

addition, the imputed data analysis showed that for every 1 log (10-fold) increase in HIV-1 RNA, the odds of severe percent weight gain were 2.52 times higher (95% CI: 2.00 to 3.16; $p<0.0001$). For every 100 cell/mm^3 increase in CD4+ count, the odds of severe percent weight gain were 0.78 times lower (95% CI: 0.72 to 0.85; $p<0.0001$). Similar to the percent weight gain outcome, higher baseline HIV-1 RNA (OR: 1.74 (95% CI: 1.41 to 2.15); $p<.0001$) and lower CD4+ levels (OR: 0.80 (95% CI: 0.73 to 0.87); $p<.0001$) were associated with a higher odds of an increase in clinical BMI status at week 96.

Conclusion: Participants presenting with high baseline disease severity before treatment initiation as well as those who were black had an increased odds of severe weight/BMI gain over 96 weeks. Understanding patient characteristics associated with severe weight gain may help with the prevention and management of metabolic complications of HIV-infection and treatment.

4.2 Introduction

With obesity on the rise in the United States, it has also manifested itself as an important health issue in the HIV-infected population. Earlier in the epidemic, wasting was more commonly associated with HIV infection. However, antiretroviral therapy (ART) has helped many underweight individuals regain their weight as a "return to health". On the other hand, this phenomenon of weight gain has brought increased attention in the epidemic towards overweight/obesity, similar to the general population.[78] As of 2007-2008, the prevalence of obesity in the U.S. population was 33.8% and is forecasted to increase to 51% by 2030.[79,80] In a 2008 study of two large Navy clinics, the prevalence of overweight/obesity for HIV patients was 63%, while the prevalence of underweight was only 1%.[78] A study from 2005 examined the prevalence of overweight/obesity in close to 1,700 HIV-infected individuals from various medical locations in Philadelphia, and found that overweight/obesity was much more common than wasting (45% vs. 9%). However, the prevalence was still lower in the HIV population compared to the general Philadelphia population.[81] When comparing HIV-infected adults in the North America AIDS Cohort Collaboration on Research and Design (NA-ACCORD) to matched controls in the United States National Health and Nutrition Examination Survey (NHANES), the difference in obesity prevalence between the two study populations decreased between 1998 and 2010, with 9% obesity prevalence in NA-ACCORD and 22% in NHANES in 1998 becoming and 18% versus 27% in 2010.[82]

For HIV-infected individuals who are underweight, weight gained while on therapy can be beneficial. There is an inverse relationship between weight gain and negative health outcomes, especially mortality, when individuals have severely low BMIs and are underweight.[83,84] However, this benefit of weight gain may not persist in higher BMI groups.

One study of an aging HIV-infected cohort found that weight gain after one year of ART initiation was associated with lower mortality for those with an underweight/normal BMI, but not helpful for overweight/obese individuals.[85] Research has shown that weight gain is associated with adverse changes in cardiovascular disease (CVD) risk factors.[86,87] A study examining weight gain one year post ART initiation found an increased risk of CVD for those who had a normal baseline BMI and an increased risk of diabetes for all categories of baseline BMI.[88] The increased health risks from metabolic comorbidities may in fact outweigh the benefits of weight gain for these normal to high BMI individuals.

Severe weight gain has been shown to occur for some individuals after ART initiation, shifting them into higher BMI categories. The study that compared HIV-infected individuals in NA-ACCORD to matched controls in NHANES found that 22% of those with normal baseline BMI had become overweight after ART initiation, and 18% of those with an overweight baseline BMI had become obese. In addition, the Gender, Race And Clinical Experience (GRACE) study, which gave Darunavir/Ritonavir (DRV/r) to treatment-experienced individuals, found that a subset of individuals experienced extreme changes in weight, with weight increases up to 29 kg from baseline to week 48.[89] The objective of this study is to understand the causes of severe weight gain in HIV-infected individuals initiating therapy. This topic is especially important since overweight/obesity prevalence in the HIV-infected population is on the rise.

4.3 Methods

4.3.1 Study Population

A retrospective cohort study was conducted using data from the ACTG A5257 clinical trial and was approved by the Institutional Review Board of the University of California, Los

Angeles. A5257 was a phase III randomized clinical trial comparing antiretroviral treatment regimens including atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), or raltegravir (RAL), each given in combination with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). A total of 1,814 subjects across the United States were enrolled into the A5257 study from May 2009 to June 2013. Detailed information about enrollment, randomization, and inclusion/exclusion criteria can be found in Chapter 3.

4.3.2 Data Collection

Exposures

Demographic data used for these analyses included race/ethnicity, age, and sex, which were collected at baseline. Other exposure variables of interest included baseline BMI (in kg/m^2), CD4+ (in cells/mm^3), and HIV-1 RNA count (in copies/mL). Blood samples were drawn at study entry and sent to core study laboratories for processing. HIV-1 RNA levels were measured using the Abbott RealTime HIV-1 assay at Johns Hopkins University. Flow cytometry was used to phenotype CD4+ T-cells. Laboratory assessment of blood samples has been previously described.[39,42] For the purposes of these analyses, CD4+ count was represented as a continuous variable, with 100 cells/mm^3 as units for better understandability of model coefficients and output. HIV-1 RNA was also a continuous variable that was log base 10 transformed into log HIV-1 RNA count, measured in log copies/mL. Treatment was coded according to the three randomization arms: ATV/r, DRV/r, and RAL.

Outcomes

Severe Percent Weight Increase

Weight (in kg) was collected at week 0 and week 96 of the study. Percent weight change from baseline was used to determine if participants had a severe weight increase over 96 weeks. A severe percent weight increase was defined as having a percent change from baseline equal to or greater than 10%. This cutoff was chosen to represent a clinically meaningful change in weight that would result in metabolic changes and increased CVD risk. This threshold was based on the results from the CARDIA study, which found that a 10-year weight gain of more than 10% was associated with an increased odds of an adverse changes in CVD risk factors of LDL-C, HDL-C, triglycerides, fasting insulin, systolic blood pressure, and diastolic blood pressure for black and white women and men, with the exception of diastolic blood pressure in black men and systolic blood pressure in white men.[86] For the purposes of our study, ≥ 10% change in percent weight from baseline over 96 weeks constituted a severe change in weight for anyone who started at study entry with a normal BMI (18.5-24.9 kg/m^2). Individuals who were underweight (BMI < 18.5 kg/m^2) and moved at least two BMI categories with a weight increase ≥ 10% were also included as having a severe percent weight change outcome.

Increase in Clinical BMI Status

As a sensitivity analysis, the severe weight/BMI gain outcome was also defined using a second method, which involved the clinical categories of BMI: underweight as a BMI below 18.5 kg/m^2, normal weight between 18.5 kg/m^2 - 24.9 kg/m^2, overweight between 25.0 kg/m^2 - 29.9 kg/m^2, and obese at 30.0 kg/m^2 and over.[45] Two additional clinical BMI categories, morbid obesity and super obesity, were added to further break down the individuals who were obese with a BMI ≥ 30.0 kg/m^2. Obesity was redefined as having a BMI between 30.0-39.9 kg/m^2,

morbid obesity was defined as having a BMI between 40.0-49.9 kg/m^2, and super obesity was defined as having a BMI ≥ 50.0 kg/m^2. There is an increased rate of morbid and super obesity occurring in the United States, with potential differences for disease risk in these obese BMI subgroups.[90,91] If an individual had a normal BMI at study entry, and increased one or more BMI categories over 96 weeks, they were considered to have the outcome of an increase in clinical BMI status. If they were underweight and moved at least two BMI categories, they were also included as having an increase in clinical BMI status.

Covariates

Information about substance use, current smoking status, income, and insurance was collected at baseline. These variables were included in the models as potential confounders for the associations between exposures and outcomes of interest. Smoking status at baseline was reported as being a current smoker or not. Illicit drug use included use of cocaine, heroin, amphetamines or other, and was coded as: never used, more than 1 month ago, and within the last month. Drinking status was reported as abstainer, moderate drinker, heavy drinker, and binge drinker. Income was divided into three earning categories: less than $19,999, $20,000 - $49,999, and $50,000 or higher. Insurance status was coded as "Private Insurance" if individuals had some form of private insurance, and "Other" if individuals had types of insurance other than private insurance, including government, out-of-pocket, or some other unknown type.

4.3.3 Data Analysis and Statistical Methods

Logistic regression modeling was used to examine predictors of both severe percent weight increases and increases in clinical BMI status. The predictors examined in this analysis included treatment, sex, race/ethnicity, age, baseline BMI, baseline CD4+, and baseline HIV-1

RNA. Baseline BMI was included as a continuous variable for the model predicting 'severe percent weight increase', and as a categorical predictor with clinical BMI categories for the 'increase in clinical BMI status' outcome. Associations between individual predictors and each of the two definitions for severe weight/BMI gain were examined through univariate logistic regression models. Multivariable models including all predictors of interest were then examined for each weight gain outcome. These models were adjusted for potential confounding from smoking, drinking, illicit drug use, income status, and insurance status. ROC curves were generated to allow for a comparison of the ability of each model to classify individuals as having severe weight/BMI increases and not having these changes. In addition to a complete case analysis, multiple imputation analyses were conducted to account for the missing data created from adjusting for multiple covariates. Fully conditional specification was used to conduct multiple imputation. This analysis included logistic regression results that summarized over 10 iterations of imputed data. Range of area under curve (AUC) values for each iteration of ROC curve were summarized. All analyses were performed using SAS Software, Version 9.4 of the SAS System for Windows (© SAS Institute Inc., Cary, NC).

4.4 Results

4.4.1 Participant Disposition

Our resulting A5257 analysis population consists of the 1,809 HIV-infected adults. Five of the 1,814 individuals that enrolled in the study were excluded due to acute illness, presence of a resistance mutation, or previous use of antiretroviral therapies. Details about participant disposition can be found in Lennox et al. (2014).[39]

4.4.2 Subject Demographics and Baseline Characteristics

Participants included 76% male (N=1,374) and 24% female (N=435) individuals with age ranging from 18 to 76 years and averaging 37 years. The study population had a diverse race/ethnicity distribution of 41.9% black non-Hispanic (N= 757), 34.1% white non-Hispanic (N= 615), and 21.6% Hispanic (N=390) individuals. The participants' baseline HIV disease state included a mean CD4+ level of 308 cells/mm^3 and HIV-1 RNA level of 144,699 copies/mL. Patient demographics and baseline values were balanced between the three randomized treatment arms.[39]

For weight characteristics, the study population had a mean baseline weight of 79 kg and baseline BMI of 26 kg/m^2. The distribution of clinical BMI categories at baseline was 3.4% underweight (BMI < 18.5 kg/m^2), 47.1% normal (BMI 18.5-24.9 kg/m^2), 30.5% overweight (BMI 25-29.9 kg/m^2), 15.8% obese (BMI 30-39.9 kg/m^2), 2.8% morbid obese (BMI 40-49.9 kg/m^2), and 0.4% super obese (BMI $\geq$ 50 kg/m^2). On average over 96 weeks, weight increased for the study population by 3.8 kg and BMI increased by 1.3 kg/m^2. At week 96, the prevalence of overweight/obese BMI categories increased, with an overall distribution 1.6% underweight, 38.6% normal, 35.5% overweight, 19.6% obese, 3.6% morbid obese, and 1.1% super obese.

Those who did not have week 96 follow-up measurements for severe weight/BMI increase outcomes (N=209) showed baseline and demographic characteristics that were generally representative of the study population with follow-up data.

4.4.3 Severe Percent Weight Increase

The distribution of the 'severe percent weight increase' outcome across baseline/ demographic predictors can be found in Table 4.1. Over 96 weeks from study start, 373 (23.3%)

of study participants experienced a severe percent weight increase and 1,227 (76.7%) did not have such a weight gain. The RAL treatment arm had the highest number of severe percent weight outcomes. In addition, those who were female, black non-Hispanic, Hispanic, having higher HIV-1 RNA levels, lower CD4+ levels, older age at study entry, and lower baseline weight and BMI were more likely to experience the severe percent weight outcome.

Crude models examining the association between each individual predictor and outcome revealed that a having higher baseline HIV-1 RNA level, being female compared to male, and black non-Hispanic and Hispanic compared to white non-Hispanic were each significantly associated with a higher odds of severe percent weight increases over 96 weeks (Table 4.2). Having a higher CD4+ level and baseline BMI were significantly associated with a lower odds of a severe percent weight increase. While not statistically significant, it appears that the odds of a severe weight gain while being treated with the protease inhibitors were lower than with raltegravir.

After adjusting for all covariates, the association between severe percent weight gain and being black non-Hispanic, baseline HIV-1 RNA, and baseline CD4+ levels remained statistically significant for both the complete case analysis and imputed data analysis (Table 4.2). The AUC value from the ROC curve for the complete case analysis model was 0.78, showing reasonable predictive accuracy for the model (Figure 4.1). For the imputed data analysis, for every 1 log (10-fold) increase in baseline HIV-1 RNA, the odds of severe percent weight gain were 2.52 times higher (95% CI: 2.00 to 3.16; $p<0.0001$). For every 100 cell/mm^3 increase in baseline CD4+ count, the odds of severe percent weight gain were 0.78 times lower (95% CI: 0.72 to 0.85; $p<0.0001$). The odds of a severe percent weight increase are 1.55 times higher for black compared to white individuals (95% CI: 1.10 to 2.20; $p= 0.0129$). The imputed data analysis also

showed that the protective association between ATV/r versus RAL became statistically significant, with the odds of severe percent weight gain for the ATV/r arm being 0.72 times the odds for the RAL arm (95% CI: 0.53 to 0.99; p=0.0427). The odds ratio results for DRV/r versus RAL were similar but not statistically significant (OR: 0.74 [95% CI 0.54 to 1.01]; p=0.0555). The range of AUC values from the 10 iterations of the imputation analysis were 0.7715 - 0.7745, which were similar to the complete case analysis.

4.4.4 Increase in Clinical BMI Status

For the analysis examining the 'increase in clinical BMI status' outcome, 8 individuals with a baseline BMI of super obese ($\geq$50 kg/m^2) were excluded because by definition of this outcome, it was not possible for these individuals to have an increase in BMI status as they were already in the highest category of BMI at study entry.

At week 96, 361 (22.7%) of A5257 study participants experienced an increase in clinical BMI status and 1,231 (77.3%) did not experience such a gain in BMI (Table 1). Similar to the severe percent weight gain outcome, those treated with raltegravir, female, black non-Hispanic, having higher HIV-1 RNA levels, lower CD4+ levels, and having older age at study entry were more likely to have an increase in clinical BMI status from study entry. Baseline weight and BMI values were similar across outcomes.

Crude models found significant associations for sex, black non-Hispanic and Hispanic race/ethnicities, baseline HIV-1 RNA levels, and baseline CD4+ levels (Table 4.3). For the adjusted models, categorical baseline BMI was excluded as a predictor as the most extreme BMI categories had very small sample sizes and unstable estimates. The final imputed data model found the association between being Hispanic and an increase in clinical BMI status was no

longer significant, and there was an additional significant association found for treatment with DRV/r (Table 4.3). The odds of an increase in clinical BMI status with DRV/r treatment was 0.72 times lower than the odds with RAL treatment (95% CI: 0.53 to 0.98; p=0.0381). For black non-Hispanic individuals compared to white non-Hispanic individuals, the odds of an increase in BMI status was 1.48 times higher (95% CI: 1.06 to 2.07; p=0.0223). Similar to the severe percent weight gain outcome, higher baseline HIV-1 RNA (OR: 1.74 [95% CI: 1.41 to 2.15]; p<.0001) and lower CD4+ levels (OR: 0.80 [95% CI: 0.73 to 0.87]; p<.0001) were associated with a higher odds of an increase in clinical BMI status at week 96. The range of AUC values from the imputation analysis were 0.7132 - 0.7172, which were similar to the complete case analysis value of 0.72 shown in Figure 4.2.

4.5 Discussion

Our study examined predictors of severe weight gain in an HIV-infected cohort beginning ARV treatment, and demonstrated that contemporary ARV therapies, gender, race/ethnicity, baseline BMI, and baseline disease status are associated with severe increases in weight/BMI over 96 weeks. This study used two definitions of severe weight gain: severe percent weight increase and increase in clinical BMI status. The ROC curves for both models showed similar predictive accuracy, with the severe percent weight increase model being marginally stronger.

From the analysis results adjusting for all covariates for both definitions of the outcome, it appears that treatment with a protease inhibitor may be protective against severe weight/BMI gain compared to treatment with the integrase inhibitor raltegravir. ATV/r compared to RAL was significantly associated with a lower odds of a severe increase in percent weight, while DRV/r

had a protective effect of almost the same magnitude as well. For the clinically meaningful increase in BMI status outcome, DRV/r compared to RAL was significantly associated with lower odds of BMI gain, while the association between ATV/r and RAL remained protective but non-significant. Previous research has shown that boosted protease inhibitor use for both 6 and 24 months after therapy initiation has been associated greater increases of BMI when compared to NRTI-, NNRTI-, and PI-based regimens.[92] Another study found that treatment with the PIs ATV/r and Lopinavir was associated with a higher odds of weight gain ≥ 5 kg when also compared with other PIs, NRTIs, and NNRTIs.[69] Although PIs may have been previously found to be associated with greater weight increases, they may be more beneficial concerning weight outcomes when compared to integrase inhibitors such as raltegravir. As discussed in detail in Chapter 3, RAL was associated with larger increases in waist circumference, and therefore potential abdominal fat increases, compared to ATV/r and DRV/r.[40]

We could not confirm an association between baseline age and BMI with severe weight/BMI gain, however, other studies have found that a lower baseline weight/BMI was associated with greater gains of weight.[85,93] Our results were not statistically significant but did show a protective direction for increases in BMI against percent weight gain. This may be due to a greater reconstitution of health after initiating therapy for those with lower BMI/weights at baseline. In addition, other studies have found a greater weight gain was associated with an age of 35 years compared to younger or older individuals.[82]

Our study results also indicated that black non-Hispanic race/ethnicity was significantly associated with an increased odds of severe weight/BMI gain. A study of non-underweight participants of the South Texas HIV Cohort examined weight changes across subject characteristics. At baseline, minority patients were more likely to be overweight/obese regardless

of health insurance type. Their study results also revealed a significant interaction between race/ethnicity and insurance status in predicting weight gain, with uninsured minorities (Hispanic or black non-Hispanic) having almost three times the odds of significant weight gain (≥3% annual BMI increase) compared to insured white non-Hispanic individuals.[94] After adjusting for insurance status in both our analyses, being black non-Hispanic remained a significant predictor of weight gain over 96 weeks. Further research is needed to understand why this race/ethnicity group may be particularly afflicted by weight gain after ART initiation. In the general population, black non-Hispanic and Hispanic individuals have a higher risk of being obese compared to white non-Hispanics.[77,91,95] Another study found that For HIV-infected individuals, African American women may be at higher risk for obesity.[81] We could not confirm an association between sex and weight gain in our study.

A strong association between baseline disease state before ART initiation and increased odds of severe weight/BMI gain was also found in our study. All models from both analyses defining the two outcomes of severe weight/BMI gain consistently demonstrated that a higher baseline viral load and lower CD4+ count predicted increased weight gain over the course of the study. Previous studies have reported mixed results concerning the association between these laboratory values and weight gain. However, the directionality of the results can often be distinguished by whether these measurements were time-updated and post ART initiation versus baseline and before start of treatment. Studies that found an association between higher CD4+ and lower HIV-1 RNA and weight gain did not measure these values pre-treatment.[78,93] Other research that reported an association between higher disease severity including lower CD4+ and higher viral load levels, and increased risk of weight gain measured these values pre-treatment.[82,85,92] Only one study reports that post-treatment levels of high CD4+ were protective

against weight gain ≥ 5 kg and high viral load was associated with weight gain ≥ 5 kg.[69] Guehi et al. (2016) report that an increase in CD4+ of 50 cells/mm^3 over 24 months was associated with becoming overweight/obese, and suggest the possibility of general immune reconstitution promoting weight gain.[96] As explained in Chapter 3, higher disease severity at baseline may be associated with exacerbated adipose tissue inflammation and expansion, which may potentially also lead to a gain in weight. If advanced disease state before start of therapy is associated with fat gain, as our results indicate, then this supports the advantages of initiating ART earlier.

Some study limitations include that 11.6% of participants in the A5257 study did not have weight/BMI follow-up measurements, and therefore, could not be assessed for the severe weight gain outcome. As mentioned in the results, the missing individuals were relatively similar concerning baseline/demographic characteristics compared to the individuals with follow-up measurements. In addition, while our study did include a substantial follow-up time of 96 weeks, a longer duration may have allowed for latent weight changes to emerge in the study population. The study also did not collect exercise and diet information on participants, which would have given us more insight into understanding the potential risk factors of weight gain in HIV-infected individuals. Strengths of our study include that this was prospectively collected clinical trial data where weight changes were monitored over 96 weeks. In addition, we were able to examine associations between pre-treatment risk factors and post-ART weight gains. Our large sample size, including a racially and ethnically diverse population with both males and females allowed us to examine several predictors of severe weight gain.

4.6 Conclusion

Overweight/obesity is becoming an increasingly important issue in the current HIV treatment era, as opposed to earlier periods of the HIV epidemic that were marked by underweight/wasting. Recent research has shown that more individuals are gaining an 'unhealthy' amount of weight after beginning antiretroviral therapy, with those of normal weight transitioning into higher weight categories. HIV-infected individuals appear to be at an elevated risk of CVD, warranting further research on adverse weight outcomes that may increase their risk of metabolic complications.[4,5,24] Understanding patient characteristics linked with extreme weight increases, such as disease severity, may help clinicians optimize treatment approaches with an eye towards preventing such adverse changes in health. Certain race/ethnicity minority groups may also have particular proclivity to weight increases, manifesting a need for additional focus on investigating such complications in these populations.

4.7 Tables and Figures

Table 4.1. Demographic and baseline characteristics of A5257 study population across severe percent weight increase and increase in clinical BMI status outcomes (N=1,809).

	Severe Percent Weight Increase		Increase in Clinical BMI Status	
Characteristics	**Yes**	**No**	**Yes**	**No**
Overall [N(%)]	373 (23.3)	1227 (76.7)	361 (22.7)	1231 (77.3)
Treatment [N(%)]				
ATV/r	114 (21.6)	415 (78.4)	117 (22.3)	408 (77.7)
RAL	144 (26.5)	399 (73.5)	136 (25.1)	405 (74.9)
DRV/r	115 (21.8)	413 (78.2)	108 (20.5)	418 (79.5)
Sex [N(%)]				
Male	269 (22.1)	947 (77.9)	260 (21.4)	953 (78.6)
Female	104 (27.1)	280 (72.9)	101 (26.7)	278 (73.3)
Race/Ethnicity [N(%)]				
White non-Hispanic	98 (17.9)	450 (82.1)	94 (17.2)	453 (82.8)
Black non-Hispanic	178 (26.9)	484 (73.1)	163 (24.9)	492 (75.1)
Hispanic	90 (26.0)	256 (74.0)	99 (28.6)	247 (71.4)
Other	5 (12.2)	36 (87.8)	4 (9.8)	37 (90.2)
HIV-1 RNA Level [N(%)]				
< 100,000 copies/mL	154 (13.9)	952 (86.1)	177 (16.1)	921 (83.9)
≥ 100,000 copies/mL	219 (44.3)	275 (55.7)	184 (37.2)	310 (62.8)
CD4+ Level [N(%)]				
≥ 350 cells/mm^3	86 (13.1)	569 (86.9)	97 (14.9)	555 (85.1)
< 350 cells/mm^3	287 (30.4)	658 (69.6)	264 (28.1)	676 (71.9)
HIV-1 RNA Level (log_{10} copies/mL) [Mean (SD, range)]	5.1 (0.7, 3.1-6.6)	4.5 (0.7, 2.4-6.3)	4.9 (0.7, 2.8-6.6)	4.5 (0.7, 2.4-6.3)
CD4+ Level (cells/mm^3) [Mean (SD, range)]	198 (181, 3-889)	340 (183, 2-1610)	216 (182, 3-795)	333 (187, 2-1610)
Age (years) [Mean (SD, range)]	39 (11, 18-76)	38 (11, 18-72)	39 (11, 18-76)	37 (11, 18-74)
BMI (kg/m^2) [Mean (SD, range)]	25.2 (5.6, 15.6-64.2)	26.5 (6.0, 15.2-61.5)	26.2 (5.5, 15.6-49.7)	26.0 (5.6, 15.2-49.7)
Weight (kg) [Mean (SD, range)]	75.5 (17.6, 42.5-169.6)	79.8 (18.7, 37.6-194.5)	78.2 (17.3, 42.5-163.7)	78.4 (17.8, 37.6-163.7)

RAL: Raltegravir; ATV/r: Atazanavir/Ritonavir; DRV/r: Darunavir/Ritonavir

Table 4.2. Crude and adjusted logistic regression models predicting severe percent weight increase from week 0 to week 96 in the ACTG A5257 study population (N=1,809).

	Crude		Adjusted			
			Complete Case Analysis		Imputed Data Analysis	
Covariate	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Treatment						
RAL	--	--	--	--	--	--
ATV/r	0.76 (0.57, 1.01)	0.0574	0.77 (0.54, 1.12)	0.1751	0.72 (0.53, 0.99)	0.0427
DRV/r	0.77 (0.58, 1.02)	0.0705	0.81 (0.56, 1.17)	0.2512	0.74 (0.54, 1.01)	0.0555
Sex						
Males	--	--	--	--	--	--
Females	1.31 (1.01, 1.70)	0.0454	1.24 (0.84, 1.83)	0.2876	1.35 (0.97, 1.89)	0.0742
Race/Ethnicity						
White Non-Hispanic	--	--	--	--	--	--
Black Non-Hispanic	1.69 (1.28, 2.23)	0.0002	1.74 (1.17, 2.58)	0.0058	1.55 (1.10, 2.20)	0.0129
Hispanic	1.61 (1.17, 2.23)	0.0038	1.13 (0.71, 1.79)	0.6034	0.99 (0.67, 1.48)	0.9757
Other	0.64 (0.24, 1.67)	0.3588	0.78 (0.27, 2.32)	0.6593	0.50 (0.17, 1.45)	0.2021
Age (years)	1.01 (0.998, 1.02)	0.1252	1.01 (0.996, 1.03)	0.1597	1.01 (0.99, 1.02)	0.2859
Baseline BMI (kg/m^2)	0.96 (0.94, 0.98)	0.0004	0.99 (0.96, 1.02)	0.5408	0.98 (0.96, 1.01)	0.1767
Baseline HIV-1 RNA (log_{10} copies/mL)	3.45 (2.84, 4.19)	<.0001	2.89 (2.20, 3.80)	<.0001	2.52 (2.00, 3.16)	<.0001
Baseline CD4+ (100 cells/mm^3)	0.62 (0.58, 0.67)	<.0001	0.80 (0.73, 0.89)	<.0001	0.78 (0.72, 0.85)	<.0001

RAL: Raltegravir; ATV/r: Atazanavir/Ritonavir; DRV/r: Darunavir/Ritonavir; CI: Confidence Interval

[a] Severe percent weight increase outcome includes individuals with a normal baseline BMI whose 96 week increase in weight was ≥ 10%, or individuals with an underweight baseline BMI that increased at least two clinical BMI categories and had a weight increase ≥ 10%

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

[c] 'Complete Case Analysis' model includes all subjects with non-missing data

[d] 'Imputed Data Analysis' includes logistic regression estimates summarized over 10 iterations of imputed values

Table 4.3. Crude and adjusted logistic regression models predicting increase in clinical BMI status from week 0 to week 96 in the ACTG A5257 study population (N=1,809).

	Crude		Adjusted			
			Complete Case Analysis		Imputed Data Analysis	
Covariate	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Treatment						
RAL	--	--	--	--	--	--
ATV/r	0.85 (0.64, 1.13)	0.2739	0.91 (0.64, 1.29)	0.5792	0.84 (0.62, 1.13)	0.2457
DRV/r	0.77 (0.58, 1.03)	0.0737	0.76 (0.53, 1.09)	0.1380	0.72 (0.53, 0.98)	0.0381
Sex						
Males	--	--	--	--	--	--
Females	1.33 (1.02, 1.74)	0.0347	1.23 (0.86, 1.78)	0.2613	1.24 (0.91, 1.69)	0.1828
Race/Ethnicity						
White Non-Hispanic	--	--	--	--	--	--
Black Non-Hispanic	1.60 (1.20, 2.12)	0.0012	1.57 (1.07, 2.30)	0.0199	1.48 (1.06, 2.07)	0.0223
Hispanic	1.93 (1.40, 2.67)	<.0001	1.45 (0.94, 2.25)	0.0926	1.45 (0.996, 2.11)	0.0527
Other	0.52 (0.18, 1.50)	0.2260	0.62 (0.20, 1.92)	0.4083	0.45 (0.15, 1.35)	0.1556
Age (years)	1.01 (0.999, 1.02)	0.0653	1.01 (0.99, 1.02)	0.2739	1.01 (0.997, 1.02)	0.1617
Baseline HIV-1 RNA (log_{10} copies/mL)	2.32 (1.94, 2.77)	<.0001	2.01 (1.56, 2.58)	<.0001	1.74 (1.41, 2.15)	<.0001
Baseline CD4+ (100 cells/mm^3)	0.69 (0.64, 0.74)	<.0001	0.84 (0.76, 0.92)	0.0004	0.80 (0.73, 0.87)	<.0001

RAL: Raltegravir; ATV/r: Atazanavir/Ritonavir; DRV/r: Darunavir/Ritonavir; CI: Confidence Interval

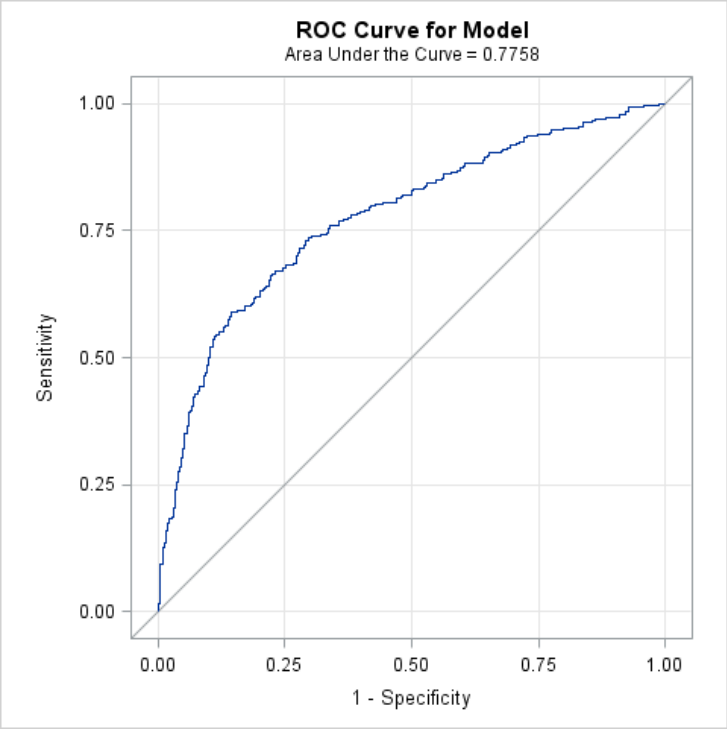
[a] Increase in clinical BMI status outcome includes individuals with a normal baseline BMI that increased at least one clinical BMI category over 96 weeks, or individuals with a underweight baseline BMI that increased at least two clinical BMI categories

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

[c] 'Complete Case Analysis' model includes all subjects with non-missing data

[d] 'Imputed Data Analysis' includes logistic regression estimates summarized over 10 iterations of imputed values

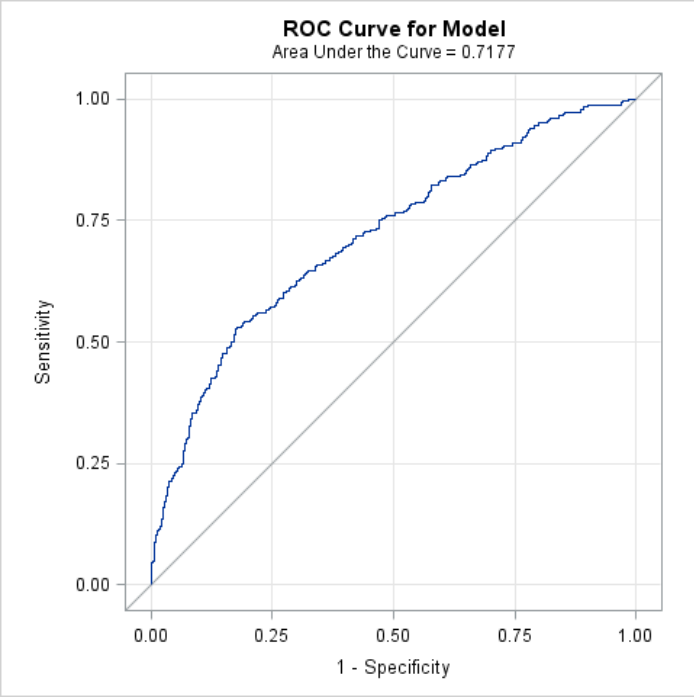
Figure 4.1. Receiver operator characteristic (ROC) curve examining sensitivity and 1-specificity across various thresholds for the model predicting severe change in percent weight from baseline to week 96 of the ACTG A5257 study population (N=1,809).



[a] Severe percent weight increase outcome includes individuals with a normal baseline BMI whose 96 week increase in weight was ≥ 10%, or individuals with an underweight baseline BMI that increased at least two clinical BMI categories and had a weight increase ≥ 10%

[b] ROC curve derived from 'Complete Case Analysis' model including all subjects with non-missing data

Figure 4.2. Receiver operator characteristic (ROC) curve examining sensitivity and 1-specificity across various thresholds for the model predicting increase in clinical BMI status from baseline to week 96 of the ACTG A5257 study population (N=1,809).



[a] Increase in clinical BMI status outcome includes individuals with a normal baseline BMI that increased at least one clinical BMI category over 96 weeks, or individuals with a underweight baseline BMI that increased at least two clinical BMI categories

[b] ROC curve derived from 'Complete Case Analysis' model including all subjects with non-missing data

Chapter 5: Summary and Public Health Implications

With the knowledge obtained from this dissertation, we gained additional insights into understanding body fat composition changes in HIV patients on ARV therapies.

In order to assess changes in body fat composition in HIV-infected individuals, a method of measurement is needed that is simple, affordable, and reproducible. CT and DXA scans today are commonly used as diagnostic or monitoring tools for specific medical conditions. However, various factors such as cost, necessity of a trained technician to operate the machines and experienced medical professionals to interpret the results, as well as concerns about exposure to radiation, limit their use as routine tools in a physician's arsenal for tracking changes in their patient's physical health and vital signs. Observing changes in body composition is especially important for HIV-infected patients, who are at a higher risk of metabolic abnormalities and cardiovascular disease.

The first study verified that self-reported fat gain and waist circumference are correlated with CT and DXA measurements. These more simple forms of body fat assessment could potentially be adopted by clinicians as valid measures of fat gain for HIV-infected patients undergoing ARV therapy. More accessible and simpler methods of assessing abdominal fat accumulation will be especially valuable in resource-limited settings that do not have access to extensive laboratory tests.

In addition, it is important for clinicians to understand what characteristics of their patients can lead to abdominal fat accumulation after initiating therapy. From the findings of the second study, we see that contemporary ARV treatment effects appear to be modified by sex and race/ethnicity. Further research is needed to understand why these treatment effects vary by these demographic subgroups. Disease severity appears to be strongly associated with abdominal

changes, which would supports the advantages of initiating treatment as early as possible. In addition, both WC and self-reported changes could potentially be used for monitoring of patient heath, further illustrating the usefulness of these more accessible measurement tools.

Given the elevated CVD risk with HIV-infection and the increasing prevalence of obesity and weight gain in the HIV-infected population, it is important to understand causes of severe weight gain in individuals beginning therapy. The third study found that baseline disease status as well as race/ethnicity appear to be associated with severe weight gain for this population. Understanding patient characteristics linked with extreme weight increases may help with the management of metabolic complications. Clinicians could potentially optimize treatment approaches to avoid weight increases and associated increases in cardiovascular risk factors in individuals who may be predisposed to excess gain after therapy initiation.

Chapter 6: References

1. Mahy M, Autenrieth CS, Stanecki K, Wynd S. Increasing trends in HIV prevalence among people aged 50 years and older: evidence from estimates and survey data. AIDS 2014;28(4):S453–9.

2. Fact sheet [Internet]. [cited 2015 Aug 25];Available from: http://www.unaids.org/en/resources/campaigns/2014/2014gapreport/factsheet

3. HIV Among People Aged 50 and Over | Age | HIV by Group | HIV/AIDS | CDC [Internet]. [cited 2015 Aug 25];Available from: http://www.cdc.gov/hiv/group/age/olderamericans/index.html

4. Cheruvu S, Holloway CJ. Cardiovascular disease in human immunodeficiency virus Internal Medicine Journal Volume 44, Issue 4. Internal Medicine Journal 1;44(4):315–24.

5. Esser S, Gelbrich G, Brockmeyer N, Goehler A, Schadendorf D, Erbel R, Neumann T, Reinsch N. Prevalence of cardiovascular diseases in HIV-infected outpatients: results from a prospective, multicenter cohort study. Clin Res Cardiol 2012;102(3):203–13.

6. Stein JH, Hsue PY. Inflammation, immune activation, and CVD risk in individuals with HIV infection. JAMA 2012;308(4):405–6.

7. Strategies for Management of Antiretroviral Therapy (SMART) Study Group, El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, Babiker A, Burman W, Clumeck N, Cohen CJ, Cohn D, Cooper D, Darbyshire J, Emery S, Fätkenheuer G, Gazzard B, Grund B, Hoy J, Klingman K, Losso M, Markowitz N, Neuhaus J, Phillips A, Rappoport C. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med 2006;355(22):2283–96.

8. Wada NI, Jacobson LP, Margolick JB, Breen EC, Macatangay B, Penugonda S, Martínez-maza O, Bream JH. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. AIDS 2015;29(4):463–71.

9. Hadigan C, Meigs JB, Wilson PWF, D'Agostino RB, Davis B, Basgoz N, Sax PE, Grinspoon S. Prediction of Coronary Heart Disease Risk in HIV-Infected Patients with Fat Redistribution. Clin Infect Dis 2003;36(7):909–16.

10. Riddler SA, Smit E, Cole SR, Li R, Chmiel JS, Dobs A, Palella F, Visscher B, Evans R, Kingsley LA. Impact of HIV infection and HAART on serum lipids in men. JAMA 2003;289(22):2978–82.

11. Friis-Møller N, Reiss P, Sabin CA, Weber R, Monforte A, El-Sadr W, Thiébaut R, De Wit S, Kirk O, Fontas E, Law MG, Phillips A, Lundgren JD, Group DS. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med 2007;356(17):1723–35.

12. Iloeje U, Yuan Y, L'Italien G, Mauskopf J, Holmberg S, Moorman A, Wood K, Moore R. Protease inhibitor exposure and increased risk of cardiovascular disease in HIV-infected patients. HIV Medicine 2005;6(1):37–44.

13. Domingo P, Estrada V, López-Aldeguer J, Villaroya F, Martínez E. Fat redistribution syndromes associated with HIV-1 infection and combination antiretroviral therapy. AIDS Rev 2012;14(2):112–23.

14. Hughes-Austin J, Larsen B, Allison M. Visceral Adipose Tissue and Cardiovascular Disease Risk. Curr Cardiovasc Risk Rep 2013;7(2):95–101.

15. Wronska A, Kmiec Z. Structural and biochemical characteristics of various white adipose tissue depots Acta Physiologica Volume 205, Issue 2. Acta Physiologica 1;205(2):194–208.

16. Karastergiou K, Fried SK. Multiple adipose depots increase cardiovascular risk via local and systemic effects. Curr Atheroscler Rep 2013;15(10):361.

17. Després JP. Body fat distribution and risk of cardiovascular disease: an update. Circulation 2012;126(10):1301–13.

18. Demerath EW. Causes and consequences of human variation in visceral adiposity. Am J Clin Nutr 2010;91(1):1–2.

19. Lake JE, Wohl D, Scherzer R, Grunfeld C, Tien PC, Sidney S, Currier JS. Regional fat deposition and cardiovascular risk in HIV infection: the FRAM study. AIDS Care 2011;23(8):929–38.

20. Scherzer R, Heymsfield SB, Lee D, Powderly WG, Tien PC, Bacchetti P, Shlipak MG, Grunfeld C. Decreased limb muscle and increased central adiposity are associated with 5-year all-cause mortality in HIV infection. AIDS 2011;25(11):1405–14.

21. Guaraldi G, Stentarelli C, Zona S, Orlando G, Carli F, Ligabue G, Lattanzi A, Zaccherini G, Rossi R, Modena MG, Alexopoulos N, Palella F, Raggi P. Lipodystrophy and anti-retroviral therapy as predictors of sub-clinical atherosclerosis in human immunodeficiency virus infected subjects. Atherosclerosis 2010;208(1):222–7.

22. Guaraldi G, Zona S, Orlando G, Carli F, Ligabue G, Fiocchi F, Rossi R, Modena MG, Raggi P. Progression of coronary artery calcium in men affected by human immunodeficiency virus infection. Int J Cardiovasc Imaging 2011;28(4):935–41.

23. Grunfeld C, Rimland D, Gibert CL, Powderly WG, Sidney S, Shlipak MG, Bacchetti P, Scherzer R, Haffner SM, Heymsfield SB. 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(3):283–90.

24. Currier JS, Lundgren JD, Carr A, Klein D, Sabin CA, Sax PE, Schouten JT, Smieja M, 2 for WG. Epidemiological Evidence for Cardiovascular Disease in HIV-Infected Patients and Relationship to Highly Active Antiretroviral Therapy. Circulation 2008;118(2):e29–35.

25. McComsey GA, Kitch D, Sax PE, Tebas P, Tierney C, Jahed NC, Myers L, Melbourne K, Ha B, Daar ES. 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(2):185–96.

26. Martinez E, Gonzalez-Cordon A, Ferrer E, Domingo P, Negredo E, Gutierrez F, Portilla J, Curran A, Podzamczer D, Ribera E, Murillas J, Bernardino JI, Santos I, Carton JA, Peraire J, Pich J, Deulofeu R, Perez I, Gatell JM, Martínez E, Gatell JM, Arnaiz JA, Beleta H, Garcia D, Pich J, Pejenaute A, Ramos N, Pérez I, Arcaina P, Giner L, Moya S, Pampliega M, Portilla J, Barrera G, Podzamczer D, Rozas N, Saumoy M, Ferrer E, Asensi V, Cartón JA, Gatell JM, González-Cordón A, Pérez I, Martínez E, Masiá M, Padilla S, Ramos JR, Robledano C, Gutiérrez F, Puig J, Negredo E, Arribas JR, Castro JM, Bernardino JI, Sanz J, Santos I, Cairó M, Velli P, Dalmau D, Lamas A, Martí-Belda P, Dronda F, Blanco JR, Gutierrez M, Mateo MG, Domingo P, Losada E, Prieto A, Antela A, Murillas J, Aguilar A, Peraire J, Vargas M, Viladés C, Vidal F, Crespo M, Curran A, Ribera E, Arnaiz JA, Beleta H, Garcia D, Pejenaute A, Ramos N, Pich J. Differential Body Composition Effects of Protease Inhibitors Recommended for Initial Treatment of HIV Infection: A Randomized Clinical Trial. Clin Infect Dis 2014;ciu898.

27. Katzmarzyk PT, Heymsfield SB, Bouchard C. Clinical utility of visceral adipose tissue for the identification of cardiometabolic risk in white and African American adults123. Am J Clin Nutr 2013;97(3):480–6.

28. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu C-Y, Vasan RS, Murabito JM, Meigs JB, Cupples LA, D'Agostino RB, O'Donnell CJ. Abdominal Visceral and Subcutaneous Adipose Tissue Compartments Association With Metabolic Risk Factors in the Framingham Heart Study. Circulation 2007;116(1):39–48.

29. Guaraldi G, Zona S, Orlando G, Carli F, Ligabue G, Fiocchi F, Rossi R, Modena MG, Raggi P. Progression of coronary artery calcium in men affected by human immunodeficiency virus infection. Int J Cardiovasc Imaging 2011;28(4):935–41.

30. Amato MC, Guarnotta V, Giordano C. Body composition assessment for the definition of cardiometabolic risk. J Endocrinol Invest 2013;36(7):537–43.

31. Després JP, Prud'homme D, Pouliot MC, Tremblay A, Bouchard C. Estimation of deep abdominal adipose-tissue accumulation from simple anthropometric measurements in men. Am J Clin Nutr 1991;54(3):471–7.

32. Direk K, Cecelja M, Astle W, Chowienczyk P, Spector TD, Falchi M, Andrew T. The relationship between DXA-based and anthropometric measures of visceral fat and morbidity in women. BMC Cardiovasc Disord 2013;13:25.

33. Rankinen T, Kim SY, Pérusse L, Després JP, Bouchard C. The prediction of abdominal visceral fat level from body composition and anthropometry: ROC analysis. Int J Obes Relat Metab Disord 1999;23(8):801–9.

34. Pouliot MC, Després JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994;73(7):460–8.

35. Tungsiripat M, O'Riordan MA, Storer N, Harrill D, Ganz J, Libutti D, Gerschenson M, McComsey GA. Subjective clinical lipoatrophy assessment correlates with DEXA-measured limb fat. HIV Clin Trials 2009;10(5):314–9.

36. Abrahams Z, Dave JA, Maartens G, Lesosky M, Levitt NS. The development of simple anthropometric measures to diagnose antiretroviral therapy-associated lipodystrophy in resource limited settings. AIDS Res Ther 2014;11:26.

37. Belloso WH, Quirós RE, Ivalo SA, Perman MI, Galich AM, Stern LD, Barcán LA. Agreement analysis of variables involved in lipodystrophy syndrome definition in HIV-infected patients. J Acquir Immune Defic Syndr 2003;32(1):104–11.

38. Richard H. Haubrich, S.A. Riddler, G. DiRienzo, Y. Zheng, W.G. Powderly, K.W. Garren, D.L. Butcher, J.F. Rooney, J.W. Mellors, D.V. Havlir. Clinical Associations of Extremity Fat Loss from ACTG 5142: A Prospective, Randomized, Phase III Trial of NRTI-, PI-, and NNRTI-sparing Regimens for Antiretroviral Therapy (ART) of Naive, HIV-1 infected Subjects [Internet]. Boston, United States: 2008 [cited 2014 Aug 27]. Available from: http://www.natap.org/2008/CROI/croi_61.htm

39. Lennox JL, Landovitz RJ, Ribaudo HJ, Ofotokun I, Na LH, Godfrey C, Kuritzkes DR, Sagar M, Brown TT, Cohn SE, McComsey GA, Aweeka F, Fichtenbaum CJ, Presti RM, Koletar SL, Haas DW, Patterson KB, Benson CA, Baugh BP, Leavitt RY, Rooney JF, Seekins D, Currier JS. 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(7):461–71.

40. Ofotokun I, Na LH, Landovitz RJ, Ribaudo HJ, McComsey GA, Godfrey C, Aweeka F, Cohn SE, Sagar M, Kuritzkes DR, Brown TT, Patterson KB, Para MF, Leavitt RY, Villasis-Keever A, Baugh BP, Lennox JL, Currier JS, Team for the ACTG (ACTG) A, Saemann M, Baer J, Koletar S, Meixner L, Seefried E, Bailey V, Basham R, Currin D, Chicurel-Bayard M, Spitz T, Frain J, Lindsey E, James T, Putnam B, Basler C, Dube MP, Santos B, Daar E, Shaik S, Tebas P, Thomas A, Bedimo R, Mba M, Cohn D, Moran F, Bagur JLS, Dueño IB, Taiwo B, Berzins B, Chang E, Palmer M, Adams M, Hurley C, Lane T, Dam CV, Tashima K, Patterson H, Rio C del, Patrick E, Markowitz N, Brar I, Arduino RC, Martinez ML, Kim R, Smith Y, Bolivar H, Fischl MA, Telzak E, Cindrich R, Sax P, Keenan C, Whitely K, Davis T, MacArthur RD, Farrough M, Aberg JA, Cespedes MS, Dunaway S, Storey S, Gallant J, Wiggins I, Sha B, Navarro V, Watson V, Nixon D, Luetkemeyer A, Dwyer J, Allen K, Walton P, Kumar P, Timpone J, McKellar M, Granholm J, Yin MT, Torres M, Valle S, Slamowitz D, Davis CE, Blattner WA, Linus B, Albrecht M, Megill C, Hughes V, Flynn T, Sbrolla A, Riddler S, Klevens L. 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(12):1842–51.

41. Stein JH, Brown TT, Ribaudo HJ, Chen Y, Yan M, Lauer-Brodell E, Mccomsey GA, Dubé MP, Murphy RL, Hodis HN, Currier JS. Ultrasonographic measures of cardiovascular disease risk in antiretroviral treatment-naïve individuals with HIV infection. AIDS 2013;27(6):929–37.

42. Kelesidis T, Tran TTT, Stein JH, Brown TT, Moser C, Ribaudo HJ, Dube MP, Murphy R, Yang OO, Currier JS, McComsey GA. Changes in Inflammation and Immune Activation With Atazanavir-, Raltegravir-, Darunavir-Based Initial Antiviral Therapy: ACTG 5260s. Clin Infect Dis 2015;61(4):651–60.

43. Brown TT, Chen Y, Currier JS, Ribaudo HJ, Rothenberg J, Dubé MP, Murphy R, Stein JH, McComsey GA. Body Composition, Soluble Markers of Inflammation, and Bone Mineral Density in Antiretroviral Therapy-Naïve HIV-1 Infected Individuals. J Acquir Immune Defic Syndr 2013;63(3):323–30.

44. McComsey GA, Moser C, Currier J, Ribaudo HJ, Paczuski P, Dubé MP, Kelesidis T, Rothenberg J, Stein JH, Brown TT. Body Composition Changes after Initiation of Raltegravir or Protease Inhibitors: ACTG A5260s. Clin Infect Dis 2016;

45. About Adult BMI | Assessing Your Weight | Healthy Weight | DNPAO | CDC [Internet]. [cited 2015 Jul 14];Available from: http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/

46. Tien PC, Benson C, Zolopa AR, Sidney S, Osmond D, Grunfeld C. The study of fat redistribution and metabolic change in HIV infection (FRAM): methods, design, and sample characteristics. Am J Epidemiol 2006;163(9):860–9.

47. 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(1):72–8.

48. Krul AJ, Daanen HAM, Choi H. Self-reported and measured weight, height and body mass index (BMI) in Italy, the Netherlands and North America. The European Journal of Public Health 2011;21(4):414–9.

49. Falutz J, Rosenthall L, Kotler D, Zona S, Guaraldi G. Surrogate markers of visceral adipose tissue in treated HIV-infected patients: accuracy of waist circumference determination. HIV Med 2014;15(2):98–107.

50. Janiszewski PM, Ross R, Despres J-P, Lemieux I, Orlando G, Carli F, Bagni P, Menozzi M, Zona S, Guaraldi G. Hypertriglyceridemia and Waist Circumference Predict Cardiovascular Risk among HIV Patients: A Cross-Sectional Study. PLoS One [Internet] 2011 [cited 2015 Nov 6];6(9). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3178598/

51. Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, Kahn R. Waist circumference and cardiometabolic risk: a consensus statement from Shaping America's

Health: Association for Weight Management and Obesity Prevention; NAASO, The Obesity Society; the American Society for Nutrition; and the American Diabetes Association. Am J Clin Nutr 2007;85(5):1197–202.

52. Jaime PC, Florindo AA, Latorre M do RD de O, Segurado AAC. Central obesity and dietary intake in HIV/AIDS patients. Revista de Saúde Pública 2006;40(4):634–40.

53. Leclercq P, Goujard C, Duracinsky M, Allaert F, L'Henaff M, Hellet M, Meunier JP, Carret S, Thevenon J, Ngo Van P, Pialoux G. 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 Research and Human Retroviruses 2012;29(5):761–8.

54. Moyle G, Moutschen M, Martínez E, Domingo P, Guaraldi G, Raffi F, Behrens G, Reiss P. Epidemiology, assessment, and management of excess abdominal fat in persons with HIV infection. AIDS Rev 2010;12(1):3–14.

55. Cabrero E, Griffa L, Burgos A. 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 and STDs 2010;24(1):5–13.

56. Martinez E, Gonzalez-Cordon A, Ferrer E, Domingo P, Negredo E, Gutierrez F, Portilla J, Curran A, Podzamczer D, Ribera E, Murillas J, Bernardino JI, Santos I, Carton JA, Peraire J, Pich J, Deulofeu R, Perez I, Gatell JM, Group on behalf of the AS, Martínez E, Gatell JM, Arnaiz JA, Beleta H, Garcia D, Pich J, Pejenaute A, Ramos N, Pérez I, Arcaina P, Giner L, Moya S, Pampliega M, Portilla J, Barrera G, Podzamczer D, Rozas N, Saumoy M, Ferrer E, Asensi V, Cartón JA, Gatell JM, González-Cordón A, Pérez I, Martínez E, Masiá M, Padilla S, Ramos JR, Robledano C, Gutiérrez F, Puig J, Negredo E, Arribas JR, Castro JM, Bernardino JI, Sanz J, Santos I, Cairó M, Velli P, Dalmau D, Lamas A, Martí-Belda P, Dronda F, Blanco JR, Gutierrez M, Mateo MG, Domingo P, Losada E, Prieto A, Antela A, Murillas J, Aguilar A, Peraire J, Vargas M, Viladés C, Vidal F, Crespo M, Curran A, Ribera E, Arnaiz JA, Beleta H, Garcia D, Pejenaute A, Ramos N, Pich J. Differential Body Composition Effects of Protease Inhibitors Recommended for Initial Treatment of HIV Infection: A Randomized Clinical Trial. Clin Infect Dis 2015;60(5):811–20.

57. Stanley TL, Grinspoon SK. Body Composition and Metabolic Changes in HIV-Infected Patients. J Infect Dis 2012;205(Suppl 3):S383–90.

58. Jemsek JG, Arathoon E, Arlotti M, Perez C, Sosa N, Pokrovskiy V, Thiry A, Soccodato M, Noor MA, Giordano M. 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(2):273–80.

59. Vrouenraets S, Wit F, Fernandez Garcia E, Moyle G, Jackson A, Allavena C, Raffi F, Jayaweera D, Mauss S, Katlama C, Fisher M, Slama L, Hardy W, DeJesus E, van Eeden A, Reiss P, for the 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 Medicine 2011;12(10):620–31.

60. Moyle GJ, Hardy H, Farajallah A, DeGrosky M, McGrath D. 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(4):287–96.

61. Lennox JL, Dejesus E, Berger DS, Lazzarin A, Pollard RB, Ramalho Madruga JV, Zhao J, Wan H, Gilbert CL, Teppler H, Rodgers AJ, Barnard RJO, Miller MD, Dinubile MJ, Nguyen B-Y, Leavitt R, Sklar P, 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(1):39–48.

62. Rockstroh JK, Lennox JL, DeJesus E, Saag MS, Lazzarin A, Wan H, Walker ML, Xu X, Zhao J, Teppler H, DiNubile MJ, Rodgers AJ, Nguyen B-Y, Leavitt R, Sklar P. 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(8):807–16.

63. McComsey G, Rightmire A, Wirtz V, Yang R, Mathew M, McGrath D. 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(9):1323–6.

64. Martínez E, Mocroft A, García-Viejo MA, Pérez-Cuevas JB, Blanco JL, Mallolas J, Bianchi L, Conget I, Blanch J, Phillips A, Gatell JM. Risk of lipodystrophy in HIV-1-infected patients treated with protease inhibitors: a prospective cohort study. The Lancet 2001;357(9256):592–8.

65. Joly V, Flandre P, Meiffredy V, Leturque N, Harel M, Aboulker J-P, Yeni P. Increased risk of lipoatrophy under stavudine in HIV-1-infected patients: results of a substudy from a comparative trial. AIDS 2002;16(18):2447–54.

66. Jacobson DL, Knox T, Spiegelman D, Skinner S, Gorbach S, Wanke C. 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(12):1837–45.

67. Andany N, Raboud JM, Walmsley S, Diong C, Rourke SB, Rueda S, Rachlis A, Wobeser W, Macarthur RD, Binder L, Rosenes R, Loutfy MR. Ethnicity and gender differences in lipodystrophy of HIV-positive individuals taking antiretroviral therapy in Ontario, Canada. HIV Clin Trials 2011;12(2):89–103.

68. Silverberg MJ, Jacobson LP, French A, Witt MD, Gange SJ. Age and Racial / Ethnic Differences in the Prevalence of Reported Symptoms in HIV-Infected Persons on Antiretroviral Therapy. J Pain Symptom Manage 2009;38(2):197–207.

69. Nguyen A, Calmy A, Schiffer V, Bernasconi E, Battegay M, Opravil M, Evison J-M, Tarr P, Schmid P, Perneger T, Hirschel B, the Swiss HIV Cohort Study. Lipodystrophy and weight changes: data from the Swiss HIV Cohort Study, 2000–2006. HIV Medicine 2008;9(3):142–50.

70. Foulkes AS, Wohl DA, Frank I, Puleo E, Restine S, Wolfe ML, Dube MP, Tebas P, Reilly MP. Associations among race/ethnicity, ApoC-III genotypes, and lipids in HIV-1-infected individuals on antiretroviral therapy. PLoS Med 2006;3(3):e52.

71. Engelson ES, Kotler DP, Tan Y, Agin D, Wang J, Pierson RN, Heymsfield SB. Fat distribution in HIV-infected patients reporting truncal enlargement quantified by whole-body magnetic resonance imaging. Am J Clin Nutr 1999;69(6):1162–9.

72. Miller J, Carr A, Emery S, Law M, Mallal S, Baker D, Smith D, Kaldor J, Cooper D. HIV lipodystrophy: prevalence, severity and correlates of risk in Australia. HIV Medicine 2003;4(3):293–301.

73. Savès M, François R, Jacqueline C, Rozenbaum W, Ragnaud J-M, Perronne C, Basdevant A, Leport C, Geneviève C, Group AC (APROCO) S. Factors Related to Lipodystrophy and Metabolic Alterations in Patients with Human Immunodeficiency Virus Infection Receiving Highly Active Antiretroviral Therapy. Clin Infect Dis 2002;34(10):1396–405.

74. Damouche A, Lazure T, Avettand-Fènoël V, Huot N, Dejucq-Rainsford N, Satie A-P, Mélard A, David L, Gommet C, Ghosn J, Noel N, Pourcher G, Martinez V, Benoist S, Béréziat V, Cosma A, Favier B, Vaslin B, Rouzioux C, Capeau J, Müller-Trutwin M, Dereuddre-Bosquet N, Le Grand R, Lambotte O, Bourgeois C. Adipose Tissue Is a Neglected Viral Reservoir and an Inflammatory Site during Chronic HIV and SIV Infection. PLoS Pathog 2015;11(9):e1005153.

75. Kredel LI, Siegmund B. Adipose-Tissue and Intestinal Inflammation – Visceral Obesity and Creeping Fat. Front Immunol [Internet] 2014 [cited 2016 Apr 11];5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4174117/

76. Drouet M, Dubuquoy L, Desreumaux P, Bertin B. Visceral fat and gut inflammation. Nutrition 2012;28(2):113–7.

77. Finkelstein JL, Gala P, Rochford R, Glesby MJ, Mehta S. HIV/AIDS and lipodystrophy: Implications for clinical management in resource-limited settings. J Int AIDS Soc [Internet] 2015 [cited 2015 Jul 3];18(1). Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4297925/

78. Crum-Cianflone N, Tejidor R, Medina S, Barahona I, Ganesan A. Obesity among HIV Patients: The Latest Epidemic. AIDS Patient Care STDS 2008;22(12):925–30.

79. Flegal KM, Carroll MD, Ogden CL, Curtin LR. PRevalence and trends in obesity among us adults, 1999-2008. JAMA 2010;303(3):235–41.

80. Finkelstein EA, Khavjou OA, Thompson H, Trogdon JG, Pan L, Sherry B, Dietz W. Obesity and Severe Obesity Forecasts Through 2030. American Journal of Preventive Medicine 2012;42(6):563–70.

81. Amorosa V, Synnestvedt M, Gross R, Friedman H, MacGregor RR, Gudonis D, Frank I, Tebas P. A tale of 2 epidemics: the intersection between obesity and HIV infection in Philadelphia. J Acquir Immune Defic Syndr 2005;39(5):557–61.

82. Koethe JR, Jenkins CA, Lau B, Shepherd BE, Justice AC, Tate JP, Buchacz K, Napravnik S, Mayor AM, Horberg MA, Blashill AJ, Willig A, Wester CW, Silverberg MJ, Gill J, Thorne JE, Klein M, Eron JJ, Kitahata MM, Sterling TR, Moore RD, North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). Rising Obesity Prevalence and Weight Gain Among Adults Starting Antiretroviral Therapy in the United States and Canada. AIDS Res Hum Retroviruses 2016;32(1):50–8.

83. Madec Y, Szumilin E, Genevier C, Ferradini L, Balkan S, Pujades M, Fontanet A. Weight gain at 3 months of antiretroviral therapy is strongly associated with survival: evidence from two developing countries. AIDS 2009;23(7):853–61.

84. Koethe JR, Lukusa A, Giganti MJ, Chi BH, Nyirenda CK, Limbada MI, Banda Y, Stringer JSA. Association between weight gain and clinical outcomes among malnourished adults initiating antiretroviral therapy in Lusaka, Zambia. J Acquir Immune Defic Syndr 2010;53(4):507–13.

85. Yuh B, Tate J, Butt AA, Crothers K, Freiberg M, Leaf D, Logeais M, Rimland D, Rodriguez-Barradas MC, Ruser C, Justice AC. Weight Change After Antiretroviral Therapy and Mortality. Clin Infect Dis 2015;civ192.

86. Norman JE, Bild D, Lewis CE, Liu K, West DS. The impact of weight change on cardiovascular disease risk factors in young black and white adults: the CARDIA study. Int J Obes Relat Metab Disord 2003;27(3):369–76.

87. Czernichow S, Mennen L, Bertrais S, Preziosi P, Hercberg S, Oppert J-M. Relationships between changes in weight and changes in cardiovascular risk factors in middle-aged French subjects: effect of dieting. Int J Obes Relat Metab Disord 2002;26(8):1138–43.

88. Achhra AC, Mocroft A, Reiss P, Sabin C, Ryom L, de Wit S, Smith CJ, d'Arminio Monforte A, Phillips A, Weber R, Lundgren J, Law MG, D:A:D Study Group. Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study. HIV Med 2016;17(4):255–68.

89. Currier JS, Martorell C, Osiyemi O, Yin MT, Ryan R, De La Rosa G, Mrus J. Effects of Darunavir/Ritonavir-Based Therapy on Metabolic and Anthropometric Parameters in Women and Men Over 48 Weeks. AIDS Patient Care STDS 2011;25(6):333–40.

90. Sturm R. Increases in morbid obesity in the USA: 2000–2005. Public Health 2007;121(7):492–6.

91. Sturm R, Hattori A. Morbid Obesity Rates Continue to Rise Rapidly in the US. Int J Obes (Lond) 2013;37(6):889–91.

92. Tate T, Willig AL, Willig JH, Raper JL, Moneyham L, Kempf M-C, Saag MS, Mugavero MJ. HIV infection and obesity: Where did all the wasting go? Antivir Ther 2012;17(7):1281–9.

93. Crum-Cianflone N, Roediger MP, Eberly L, Headd M, Marconi V, Ganesan A, Weintrob A, Barthel RV, Fraser S, Agan BK, the Infectious Disease Clinical Research Program HIV Working Group. Increasing Rates of Obesity among HIV-Infected Persons during the HIV Epidemic. PLoS ONE 2010;5(4):e10106.

94. Taylor BS, Liang Y, Garduño LS, Walter EA, Gerardi M, Anstead GM, Bullock D, Turner BJ. High Risk of Obesity and Weight Gain for HIV-Infected Uninsured Minorities. J Acquir Immune Defic Syndr 2014;65(2):e33–40.

95. Centers for Disease Control and Prevention (CDC). Differences in prevalence of obesity among black, white, and Hispanic adults - United States, 2006-2008. MMWR Morb Mortal Wkly Rep 2009;58(27):740–4.

96. Guehi C, Badjé A, Gabillard D, Ouattara E, Koulé SO, Moh R, Ekouevi D, Ahibo H, N'Takpé JB, Menan GK, Deschamps N, Lecarrou J, Eholié S, Anglaret X, Danel C. High prevalence of being Overweight and Obese HIV-infected persons, before and after 24 months on early ART in the ANRS 12136 Temprano Trial. AIDS Res Ther [Internet] 2016 [cited 2016 Apr 14];13. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4768327/