UCLA

UCLA Electronic Theses and Dissertations

Title

A Randomized Trial of Raltegravir Replacement for Protease Inhibitor or Non-Nucleoside Reverse Transcriptase Inhibitor in Human Immunodeficiency Virus-Infected Women with Lipohypertrophy

Permalink

https://escholarship.org/uc/item/0pj7n789

Author

Lake, Jordan Elizabeth

Publication Date

2012

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

A Randomized Trial of Raltegravir Replacement for Protease Inhibitor or Non-Nucleoside

Reverse Transcriptase Inhibitor in Human Immunodeficiency Virus-Infected Women with

Lipohypertrophy

A thesis submitted in partial satisfaction of the requirements

for the degree Master of Science in Clinical Research

by

Jordan Elizabeth Lake

2012

ABSTRACT OF THE THESIS

A Randomized Trial of Raltegravir Replacement for Protease Inhibitor or Non-Nucleoside

Reverse Transcriptase Inhibitor in Human Immunodeficiency Virus-Infected Women with

Lipohypertrophy

by

Jordan Elizabeth Lake

Master of Science in Clinical Research

University of California, Los Angeles, 2012

Professor Robert M Elashoff, Chair

ABSTRACT

Lipohypertrophy is associated with multiple metabolic abnormalities. Raltegravir (RAL) is not

known to induce fat changes or severe metabolic perturbations. HIV-infected women with

lipohypertrophy and HIV-1 RNA <50 copies/mL on NNRTI- or PI-based ART continued their

NRTI backbone and were randomized to switch to open label RAL immediately or after 24

weeks. The primary endpoint was 24-week between-group change in CT-quantified visceral AT

volume. Fasting lipids, glucose, CRP, anthropometric measurements, and patient-reported

quality of life assessments were also measured. Thirty-six evaluable subjects provided 80%

power to detect a 10% between-group difference in visceral AT over 24 weeks. Thirty-seven of

39 enrolled subjects completed Week 24. At entry, 75% were Black or Hispanic, 62% were on

PI-based and 38% NNRTI-based regimens. The median age was 43 years, CD4 count 558

cells/µL, and BMI 32 kg/m^2. After 24 weeks, no statistically significant changes in absolute or

percent visceral or subcutaneous AT, visceral:total AT ratio, anthropometrics, BMI, glucose, or

CRP were observed. In subjects receiving RAL, significant improvements in total and LDL

cholesterol (p=0.04) and self-reported belly size (p=0.02) and composite body size (p = 0.02)

were observed. Body size changes correlated well with percent visceral AT change. No
virologic failures, changes in CD4 count, or RAL-related adverse events occurred. Compared to
continued PI or NNRTI, switch to RAL was associated with statistically significant 24-week
improvements in total and LDL cholesterol but no significant changes in AT volumes.

The thesis of Jordan Elizabeth Lake is approved.

Judith Silverstein Currier

Katrina Mae Dipple

Marc Adam Suchard

Robert M Elashoff, Committee Chair

University of California, Los Angeles

2012

Table of Contents

List of Figures and Tables

Acknowledgements

This work has been submitted to AIDS Patient Care and STDs, and is currently under revision.

Meetings at Which Data Has Been Presented: This data was presented in part at the 13th International Workshop on Adverse Drug Reactions and Co-Morbidities (Rome, Italy, July 14-16, 2011), and the International AIDS Society 6th Conference on HIV Pathogenesis Treatment and Prevention (Rome, Italy, July 17-20, 2011).

J.E. Lake was the primary author, served as Co-Principal Investigator for the protocol, aided in protocol revisions, and contributed to study oversight and data analysis.

G.A. McComsey developed the original study design and protocol with J.S. Currier, served as Co-Principal Investigator for the protocol, and contributed to the analytic plan and manuscript preparation.

T.M. Hulgan was a Co-Investigator and contributed to manuscript preparation.

C.A. Wanke was a Co-Investigator and contributed to manuscript preparation.

A. Mangili was a Co-Investigator and contributed to manuscript preparation.

S.L. Walmsley was a Co-Investigator and contributed to manuscript preparation.

M.S. Boger was a Co-Investigator and contributed to manuscript preparation.

R.R. Turner provided quality of life and body image questionnaires on behalf of Phase V®

Chapter 1: Background

Lipodystrophy: Definition and Prevalence

In the context of HIV infection, the term lipodystrophy refers to a spectrum of changes in body fat redistribution and associated metabolic abnormalities, and is not precise.[1-3] Adipose tissue abnormalities can be categorized as either lipoatrophy (fat loss) or lipohypertrophy (fat gain, particularly truncal fat), with each syndrome having unique risk factors, clinical features, and treatments. Fat redistribution of any type has been reported to range from 2%-84% in HIV-infected subjects,[2-5] with the wide range reflecting a lack of consensus definition and diagnostic criteria. Slightly more precise estimates of abdominal adiposity in HIV-infected patients on antiretroviral therapy (ART) made been made, with prevalence rates of 30-70% reported in some cohorts (a complete list of ART classes and agents discussed in this thesis is provided in **Table 1**).[6-11]

The term lipohypertrophy is generally used to refer to fat accumulation in any or all of the following areas: the abdomen, breasts, posterior neck (buffalo hump), and viscera. In the research setting, it is more specifically defined as a combination of patient-reported fat changes and an increased waist:hip ratio or abdominal circumference. In FDA registration studies of growth hormone releasing factor, minimum circumferences for a diagnosis of lipohypertrophy were defined as abdominal (mid-waist) circumference >95 cm in men and >94 cm in women or waist:hip ratio >0.94 in men and >0.88 in women.[12] Cross-sectional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are the gold standard for measurement of body fat volume.

Lipodystrophy: Risk Factors

Lipohypertrophy may be more common in women, [6,13-17] and has been associated with multiple metabolic abnormalities, decreased quality of life, and depression.[14,18-24] In

observational and cross sectional studies, older age, white race, and more advanced degree of immunosuppression have also been described as risk factors for the development of lipohypertrophy.

ART may play a role in the pathogenesis of lipohypertrophy,[7,11,17,25,26] but the contribution of specific antiretroviral agents and classes is less clear. It is also unclear whether switching ART can significantly improve lipohypertrophy once it has developed. For example, protease inhibitors (PIs) have been implicated as a potential risk factor, however, recent prospective trials in treatment-naïve patients have called into question the role of PIs as a cause of lipohypertrophy. After 48 weeks of tenofovir + lamivudine with either ritonavir-boosted tipranavir- or lopinavir, Carr et al described a decrease in both peripheral and visceral fat across treatment groups.[27] Similarly, 48 weeks of either a tipranavir- or ritonavir/lopinavir-based regimen combined with emtricitabine also demonstrated decreased visceral fat (Carr, 9th IWLADR, 2007, study BI82.33). In AIDS Clinical Trials Group 5142, an efavirenz-based regimen induced the same level of trunk fat increase as that seen in the ritonavir/lopinavir arm,[7] again questioning the role of PIs in inducing the abdominal fat accumulation seen in HIV-infected subjects.

Lipodystrophy: Treatment Options

Although lipohypertrophy is a common and distressing problem for people living with HIV infection, the decision to treat fat redistribution is frequently determined in the context of associated metabolic comorbidities (such as insulin resistance and hyperlipidemia) that can result from a combination of ART and visceral fat accumulation even in the absence of an associated metabolic syndrome. However, metabolic changes and aberrations of fat deposition may independently contribute to increased cardiovascular risk,[7,20,21,28,29] making treatment of these states an important issue in the long-term management of HIV infection.

To date, efforts to combat HIV- and/or ART-related metabolic derangements and changes in fat distribution have met with mixed results. In part, this is due to an incomplete understanding of the mechanisms underlying these changes. Currently, the only FDA-approved treatment for central fat accumulation in HIV-infected patients is growth hormone releasing factor. While growth hormone releasing factor has been shown to decrease visceral adipose tissue and improve lipid profiles in this patient population, it has side effects similar to that of growth hormone, requires injection, and its effects appear to diminish quickly.[30] Similarly, low-dose growth hormone may have a benefit on visceral adipose tissue volume, but short-term negative effects on insulin sensitivity were observed, lipoatrophy worsened, its use requires patients to receive regular subcutaneous injections, and the effects also appear to diminish quickly.[31,32]

Metformin, which is used to improve insulin sensitivity in patients with diabetes and polycystic ovarian syndrome, has been shown in HIV infection to improve visceral fat accumulation but exacerbate peripheral lipoatrophy,[33,34] which may be an independent risk factor for CVD.[29]

Both HIV and ART (specifically PIs and non-nucleoside reverse transcriptase inhibitors) may modulate lipodystrophy via down-regulation of peroxisome proliferator activated receptor-gamma (PPAR-γ).[35,36] Thiazolidinediones, which also activate PPAR-γ, have not been shown to have an effect on visceral fat in the setting of HIV infection,[37-39] and have untoward side effects such as weight gain, fluid retention, and lipid abnormalities. In summary, novel treatments for visceral fat accumulation and its associated metabolic abnormalities in HIV-infected patients on ART are needed.

Raltegravir: Pharmacology and Efficacy

3

Raltegravir is an HIV-1 integrase inhibitor with potent *in vivo* antiviral activity in treatment-naïve and treatment-experienced HIV-infected subjects. In a Phase II trial of 197 treatment-naïve subjects randomized to receive one of 4 doses of raltegravir or efavirenz with tenofovir and emtricitabine, 85-95% of subjects in all raltegravir dose groups achieved an HIV-1 RNA level of <50 copies/mL after 24 weeks.[40] In 167 treatment-experienced subjects given raltegravir 200 mg, 400 mg, or 600 mg given twice daily, raltegravir lowered viral load by at least 2 log10 copies/mL in all subjects within 2 weeks of treatment initiation, with viral loads suppressed to < 50 copies/mL in 56-72% of subjects within 16 weeks.[41]

In the STARTMRK-1 and -2 Phase III trials, subjects were randomized to receive raltegravir 400 mg po bid or efavirenz 600mg daily, each with tenofovir and emtricitabine. After 48 weeks, 86.1% of raltegravir treated subjects achieved an HIV-1 viral load <50 copies/mL compared with 81.9% of efavirenz treated patients, demonstrating raltegravir's non-inferiority to efavirenz in achieving viral suppression. Additionally, the time to achieve viral suppression was shorter for patients on raltegravir than on efavirenz (p<0.0001).[42] In the BENCHMRK-1 and -2 studies, subjects with triple class resistance on optimized background therapy received raltegravir 400mg po bid vs. placebo. At week 16, 77.5% of raltegravir recipients had HIV-1 RNA levels <400 copies/mL compared to 41.9% of placebo recipients (p<0.001) and, at week 48, 62.1% of raltegravir subjects vs. 32.9% of subjects receiving placebo had HIV-1 viral loads <50 copies/mL (p<0.001).[43] In summary, these studies of raltegravir demonstrate excellent efficacy in achieving virologic suppression in both treatment-naïve and treatment-experienced subjects.

Raltegravir: Safety and Tolerability

Raltegravir is generally very well tolerated, with a side effect profile better than or comparable to controls. Among subject-reported side effects, headache, fatigue and dizziness

are common.[41-44] Asymptomatic elevations of creatine kinase have also been described,[44] as have excerbation of depressive symptoms.[45] However, in a recent meta-analysis, no excess of depressive symptoms was observed in subjects receiving raltegravir.[44]

Raltegravir has not been associated with severe metabolic perturbations, including fat changes, during short-term therapy.[42,46,47] Early studies of raltegravir were not powered to assess gender differences in the response to therapy, however, and limited data is available specifically on the metabolic effects of raltegravir in HIV-infected women.

The need for increased knowledge about the safety and tolerability of raltegravir in women, combined with the desire to develop novel therapies for lipohypertrophy and its metabolic consequences in HIV-infected patients was the driving force behind this project. We designed a Phase IIb, randomized, 48-week, open label study to assess the effects of switching from protease inhibitor- or non-nucleoside reverse transcriptase inhibitor-based ART to a raltegravir-based regimen in women with lipohypertrophy and suppressed HIV-1 RNA on stable ART. CT-quantified adipose tissue volumes, anthropometric measurements, fasting metabolic parameters, and body image assessments were performed. The Week 24 primary endpoint results of this intervention are presented in this thesis (**Chapter 2**).

Chapter 2: Primary Endpoint Manuscript

Title: A Randomized Trial of Raltegravir Replacement for PI or NNRTI in HIV-Infected Women with Lipohypertrophy

Authors: Jordan E Lake[1], Grace A McComsey[2], Todd M Hulgan[3], Christine A Wanke[4], Alexandra Mangili[4], Sharon L Walmsley[5], M Sean Boger[6], Ralph R Turner[7], Heather E McCreath[1], and Judith S Currier[1]

Affiliations:

1. Jordan E. Lake, M.D.
   Heather E. McCreath Ph.D.
   Judith S. Currier, M.D., M.Sc.
   Department of Medicine
   University of California, Los Angeles
   Los Angeles, CA USA

2. Grace A. McComsey, M.D.
   Department of Pediatrics and Medicine
   Case Western Reserve University
   Cleveland, OH, USA

3. Todd M. Hulgan, M.D., M.P.H.
   Department of Medicine
   Vanderbilt University
   Nashville, TN, USA

4. Christine A. Wanke, M.D.
   Alexandra Mangili, M.D., M.P.H.
   Department of Medicine
   Tufts University
   Boston, MA, USA

5. Sharon L. Walmsley, M.D., M.Sc.
   Department of Medicine
   University of Toronto
   Toronto, ONT, Canada

6. M. Sean Boger, M.D., Pharm.D.
   Department of Medicine
   Medical University of South Carolina
   Charleston, SC, USA

7. Ralph R. Turner, Ph.D., M.P.H.
   Phase V Technologies, Inc.
   Wellesley, MA, USA

Contact Information:

Corresponding Author:
Jordan E. Lake, M.D.
9911 W. Pico Blvd., Ste. 980
Los Angeles, CA 90035
Phone: 310-557-9679
Fax: 310-557-1899
jlake@mednet.ucla.edu

Alternate Author:
Judith S. Currier, M.D., M.Sc.
9911 W. Pico Blvd., Ste. 980
Los Angeles, CA 90035
Phone: 310-557-1896
Fax: 310-557-1899
jscurrier@medent.ucla.edu

Running Title: Women, Integrase, and Fat Accumulation Trial

ABSTRACT

Lipohypertrophy is associated with multiple metabolic abnormalities. Raltegravir (RAL) is not known to induce fat changes or severe metabolic perturbations. HIV-infected women with lipohypertrophy and HIV-1 RNA <50 copies/mL on NNRTI- or PI-based ART continued their

NRTI backbone and were randomized to switch to open label RAL immediately or after 24 weeks. The primary endpoint was 24-week between-group change in CT-quantified visceral AT volume. Fasting lipids, glucose, CRP, anthropometric measurements, and patient-reported quality of life assessments were also measured. Thirty-six evaluable subjects provided 80% power to detect a 10% between-group difference in visceral AT over 24 weeks. Thirty-seven of 39 enrolled subjects completed Week 24. At entry, 75% were Black or Hispanic, 62% were on PI-based and 38% NNRTI-based regimens. The median age was 43 years, CD4 count 558 cells/μL, and BMI 32 kg/m^2. After 24 weeks, no statistically significant changes in absolute or percent visceral or subcutaneous AT, visceral:total AT ratio, anthropometrics, BMI, glucose, or CRP were observed. In subjects receiving RAL, significant improvements in total and LDL cholesterol (p=0.04) and self-reported belly size (p=0.02) and composite body size (p = 0.02) were observed. Body size changes correlated well with percent visceral AT change. No virologic failures, changes in CD4 count, or RAL-related adverse events occurred. Compared to continued PI or NNRTI, switch to RAL was associated with statistically significant 24-week improvements in total and LDL cholesterol but no significant changes in AT volumes.

Key Words: raltegravir, visceral fat, lipohypertrophy, body image, antiretroviral therapy, women

INTRODUCTION

Abdominal adiposity in HIV-infected patients is common in HIV-infected patients on antiretroviral therapy (ART), with prevalence rates of 30-70% reported in some cohorts.[6-11] Lipohypertrophy, or central fat accumulation, may be more common in women, [6,13-17] and has been associated with multiple metabolic abnormalities, decreased quality of life, and depression.[14,18-24] ART may play a role in the pathogenesis of lipohypertrophy,[7,11,17,25,26] but the contribution of specific antiretroviral agents and classes is less clear. It is also unclear whether

switching ART can significantly improve lipohypertrophy once it has developed.

Raltegravir (RAL) is an HIV-1 integrase inhibitor that has not been associated with severe metabolic perturbations, including fat changes, during short-term therapy. [42,46,47] We designed a Phase IIb, randomized, 48-week, open label study to assess the effects of switching from protease inhibitor (PI)- or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART to a RAL-based regimen in women with lipohypertrophy and suppressed HIV-1 RNA on stable therapy. CT-quantified adipose tissue volumes, anthropometric measurements, fasting metabolic parameters, and body image assessments were performed. The Week 24 primary endpoint results of this intervention are presented here.

METHODS

Patient Population

Subjects were recruited from 5 centers in North America between September 2008 and July 2010. Inclusion criteria initially included: Age 18 or older, documented HIV-1 infection, central fat accumulation (defined similarly to studies of growth hormone releasing factor as waist circumference >94 cm or waist-to-hip ratio >0.88[12]), HIV-1 RNA <50 copies/mL at screening and <400 copies/mL for the 6 months prior to entry, current ART with a nucleoside (NRTI) backbone of tenofovir or abacavir AND emtricitabine or lamivudine PLUS either a PI or NNRTI, no change in ART for 12 weeks prior to screening, and ability and willingness to provide informed consent.

In December 2008, Merck and Co. prematurely terminated their SWITCHMRK protocols (NCT00443703 and NCT00443729) due to increased rates of virologic failure in subjects switching from lopinavir-ritonavir to RAL. Treatment-experienced subjects with underlying NRTI resistance at the time of switch to RAL significantly contributed to observed failure rates. [46] At that time, enrollment into our study was halted and entry criteria revised to require documentation of continuous virologic suppression since ART initiation (HIV-1 RNA "blips" <500

8

copies/mL with subsequent re-suppression were allowed), as well as exclusion of subjects with genotypic or phenotypic resistance to any current ART component, prior use of single or dual NRTI-only regimens, or history of any ART not considered highly active by current standards. Participants were not required to be on their first regimen; however, subjects must not have previously substituted agent(s) secondary to suspected or proven virologic failure. Other reasons for substitution such as medication intolerance, regimen simplification, or subject preference were permitted.

Other exclusion criteria remained unchanged and included: Pregnancy or breastfeeding; current use of metformin, thiazolidinediones, or androgen therapy; use of growth hormone or growth hormone releasing factor in the 6 months prior to screening; change or initiation of lipid-lowering agents in the 3 months prior to randomization; and intent to significantly modify diet or exercise habits during the 48-week study period. Subjects on oral hypoglycemic or lipid-lowering agents at entry were not permitted to titrate doses of these medications while on study.

Enrollment re-opened at all sites in May 2009. Previously enrolled subjects were treated as follows: Subjects randomized to the immediate-switch group who did not meet revised criteria were permitted to stay on RAL if their HIV-1 RNA remained <50 copies/mL and they signed an informed consent incorporating a discussion of the revised risks and benefits (n=13). Subjects randomized to the delayed-switch group were taken off study if they did not meet revised inclusion criteria (n=1). No subjects in the delayed-switch group started RAL prior to revision of entry criteria. All subjects completed the Week 24 primary endpoint in January 2011, and the study concluded in June 2011 when the last subject completed the Week 48 evaluations (as per protocol).

All study documents and procedures were approved by the institutional review boards of the participating institutions, and all subjects provided written informed consent prior to initiation of study procedures. Procedures were performed in accordance with the ethical standards of

the responsible committee on human experimentation and with the Helsinki Declaration of the World Medical Association.

Study Design

Subjects were randomized 1:1 to continue their NRTI backbone and switch to open label RAL 400mg twice daily by mouth either at study entry (immediate-switch) or at week 24 (delayed-switch). Subjects randomized to delayed-switch provided an internal control group of subjects on continued PI or NNRTI therapy for the first 24 weeks. During Weeks 24-48, all subjects received RAL.

Randomization occurred via random number generation by the data management center. Randomization numbers were distributed to the sites from the data management center in sealed envelopes, which were only opened by the site study coordinator or principal investigator after a subject successfully met all inclusion and no exclusion criteria. Blinding of subjects did not occur, as randomization required switching a subject's ART to RAL vs. continued standard of care (PI or NNRTI).

The primary endpoint was between-group change in percent visceral adipose tissue volume 24 weeks following a switch to RAL vs. continued PI or NNRTI. A Data Safety Monitoring Board was convened and performed quarterly reviews without interim data analyses.

Assessments

Adipose tissue volumes [visceral (VAT), subcutaneous (SAT), and total (TAT)] were measured via single slice L4-L5 CT scan at Weeks 0 and 24. Scans were performed locally, but standardized and read centrally by a blinded reader at the Tufts University Body Composition Center. Phantom scans were generated by the sites prior to initiation of study procedures. These scans were analyzed by the reading center to ensure between-site scan consistency.

Anthropometric measurements (waist, hip, and neck circumferences) were performed according to AIDS Clinical Trials Group standards (https://actgnetwork.org/committees/resource/site-management-clinical-care/training-subcommittee) at Weeks 0, 12, and 24.

Fasting (>8 hours) glucose, lipoprotein profile, high sensitivity C-reactive protein (hs-CRP), and CD4 cell counts were assessed at Weeks 0, 12, and 24. HIV-1 RNA (assay sensitivity ≤50 copies/mL required) was measured at screening and Weeks 4, 8, 12, and 24. All other safety evaluations were performed at Weeks 0, 4, 8, 12, 18, and 24 and included complete blood count with differential, chemistry panel including liver enzymes and serum creatinine, a pregnancy test (where applicable), and Center for Epidemiologic Studies Depression (CES-D) scales. These labs were performed at the individual sites in real-time and according to local standards.

Adverse events were graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (Version 1.0, December 2004). All ≥Grade 3 clinical events and ≥Grade 2 lab abnormalities obligated reporting to the Data Management Center. Pregnancy obligated reporting to the study team, the sponsor, and the Antiretroviral Pregnancy Registry, as well as discontinuation of study treatment.

Patient-reported outcomes (PRO) were performed at Weeks 0 and 24 using the validated Body Image Impact scale from the Phase V® Technologies Health Outcomes Information System. [48] Subjects self-reported their current body image at each time point in relationship to a subject-perceived "healthy look," as well as their level of body image distress.

Statistical Analysis

Sample size for this study was informed by studies of growth hormone releasing factor in HIV lipodystrophy, [12] in which the U.S. Food and Drug Administration defined a between-group

change in VAT of ≥8% as clinically significant. An estimated sample size of 18 women per randomization group provided 80% power to detect a 10% difference (chosen to achieve greater than the defined minimum clinical significance) in VAT at 24 weeks between the RAL-treated patients and those remaining on a PI or NNRTI. The 24-week primary endpoint was also informed by studies of growth hormone releasing factor in HIV lipodystrophy, in which subjects significant reductions in VAT volume were acheived after 26 weeks.[12]

Baseline characteristics of the treatment groups were compared using the Mann-Whitney U-test for continuous variables and the Fisher's exact test for categorical variables. Median values and interquartile ranges (IQR) are reported for continuous variables, and percentages for categorical data.

Comparison of median between-group 24-week change scores for all adipose tissue volumes, anthropometric measurements, lab values, and CES-D scores were performed using the Wilcoxon sign-rank test. The primary analysis was as-treated, excluding subjects who did not remain on the study regimen and/or did not have an observed primary endpoint. A supplemental intent-to-treat analysis and analyses of transformed mean values (vs. median) were also performed, and produced similar results (data not shown).

Non-protocol defined secondary analyses were performed stratifying data by BMI (<30 vs. ≥30kg/m^2) and entry ART regimen (between- and within-group comparisons of PI vs. NNRTI). Linear regressions were performed to assess the effects of major confounders including age (<50 vs. ≥50 years), randomization arm, entry ART class, study site, and current smoking status (data not shown). All statistical tests were two-sided with a nominal p level of 0.05. Analyses were exploratory without adjusting for multiple testing.

Week 0 and 24 CT scans could not be performed on the same scanner for all subjects. The reading center determined the discrepancies were minimal (based on phantom scan comparison), and that no additional statistical correction factors were required for these subjects

or to correct for differences between sites. This was confirmed by sensitivity analysis. Data

analysis and management was performed using SAS 9.2 (SAS Institute, Inc., Cary, NC, USA).

PRO assessments were analyzed by Phase V® Technologies, Inc. (Wellesley,

Massachusetts, USA) according to a standardized, validated protocol. [48] These data are

presented as an intent-to-treat analysis, and differ from the as-treated analysis presented for

other endpoints by only two subjects (one in each arm). Similar to the other endpoints, intent-to-

treat results are not expected to vary significantly from the as-treated analysis.

The 24-week change score was used as the basic unit of analysis for all PRO

parameters. Absolute difference scores were calculated to reflect the absolute change towards

"my healthy look" as positive values on the bidirectional Body Size Evaluation scale.

Within-group comparisons were performed using the Student paired t-test, between-

group comparisons using the Mann Whitney test, and sample comparability by the Kolmogorov-

Smirnov test. Spearman correlation coefficients were reported for linear tests of correlation with

VAT volume. Partial correlations were conducted using Pearson coefficients. All PRO analyses

were conducted using SPSS for Windows™ (Version 12).

RESULTS

Patient Population

Sixty-one subjects were screened, 39 enrolled, and 37 completed the Week 24 primary

endpoint (**Figure 1**). The most common reasons for screen failure were: Not meeting minimum

waist circumference and/or waist-to-hip ratio criteria (n=4), unwillingness to comply with study

procedures (n=4), and having a detectable HIV-1 RNA at screening (n=4). One subject

withdrew due to perceived RAL intolerance (see Adverse Events below). A second subject

withdrew after randomization and prior to initiating RAL due to unrelated health concerns that

limited her ability to participate.

Complete demographic and baseline clinical characteristics are provided in **Table 2**. Of the 37 subjects included in the as-treated analysis, 17 were randomized to immediate-switch, and 20 to delayed-switch. At baseline, both study groups were well balanced, although the delayed-switch group had a higher rate of current tobacco use (24% vs. 58%). The median age was 43 years, BMI 32 kg/m^2, and 75% of subjects self-identified as Black or Hispanic. Sixty-two percent of subjects were on a PI at entry (vs. 38% NNRTI), and the most commonly reported NRTIs were tenofovir (59%) and emtricitabine (49%). Subjects were not asked to keep food and exercise diaries. No subject reported initiation or change of dosing of lipid- (n=7 at baseline) or glucose- (n=0 at baseline) lowering agents during the 24-week follow-up period.

Adipose Tissue Volumes

After 24 weeks the immediate-switch group lost 3.6% VAT, whereas the delayed-switch group gained 1.9% (median between-group change=5.4%, between-group p=0.43**, Figure 2a**). Individual subject-level VAT changes are provided in **Figures 2b and 2c**. Additionally, there were no statistically significant changes in SAT, TAT, or VAT:TAT ratio (**Table 3**). Similar changes in AT volumes were seen in a subgroup analysis of subjects with BMI<30 and when the analysis was stratified by entry ART class (PI vs. NNRTI). No significant changes in weight, BMI, or anthropometric measurements were observed.

Body Image Impact

At baseline, subjects reported high rates of body dysmorphia and distress, with a disproportionate focus on belly dysmorphia compared to other body parts. Of the three patient-reported belly scales (size, appearance distress, and current look), mean belly size evaluation indicated subject perception of a larger than "healthy look" (mean score of 62.2 vs. a normalized mean of 50) accompanied by significant levels of belly appearance distress (p<0.001). When

14

asked to select the profile they most felt represented their current appearance, 49% of subjects ranked their belly profile in the 2 most extreme of 6 categories of increased abdominal girth; similarly, the mean profile was significantly higher than the midpoint profile (p=0.03).

After 24 weeks, significant improvements in self-reported belly size (p=0.02) and composite body size (p=0.02) evaluation were seen in the immediate-switch group, while no significant changes were seen in the delayed-switch group (belly size p=0.91, body size p=0.83). In the immediate-switch group, percent change in VAT significantly correlated with change in belly size evaluation (r=-0.571, p=0.03), belly appearance distress (r=-0.647, p=0.01), and composite body appearance distress (r=-0.645, p=0.01) after controlling for baseline VAT and PRO measures. No significant correlations existed in the delayed-switch group.

Lipids

Fasting lipid results are summarized in **Table 3**. Statistically significant improvements in median total (TC) and low-density lipoprotein (LDL) cholesterol were seen in subjects switching to RAL compared to stable or worsening profiles in subjects remaining on PI or NNRTI (TC: -17.0mg/dL vs. -1.0mg/dL, between-group p=0.04; LDL: -12.0mg/dL vs. 3.0mg/dL, IQR (-9.0, 16.0), between-group p=0.04; (**Figure 3**). These improvements were disproportionately attributable to subjects switching from PIs to RAL (TC: PI -24.0mg/dL vs. NNRTI -7.5mg/dL, between-group p=0.08; LDL: PI -19.5mg/dL vs. NNRTI -3.5mg/dL, between-group p=0.21).

A 16.0mg/dL reduction in triglycerides was observed in patients switching to RAL compared to a 3.0mg/dL increase in subjects remaining on a PI or NNRTI (between-group p=0.26). No statistically significant changes in high-density lipoprotein cholesterol were observed (RAL -1.3mg/dL, PI or NNRTI 3.0mg/dL, between-group p=0.22).

15

Glucose and hs-CRP

No significant change in fasting glucose or hs-CRP was observed between or within groups (glucose: RAL -2.0mg/dL vs. PI or NNRTI -1.0mg/dL, between group p=0.86; hs-CRP: RAL -0.01mg/L vs. PI or NNRTI -0.20mg/L, between group p=0.78).

Adverse Events

No RAL-related Grade 3 or 4 adverse events were reported. All Grade 1 or 2 adverse events were determined to be unrelated or probably unrelated to RAL (in the immediate-switch group), and did not occur more frequently in the immediate- than the delayed-switch group. One subject withdrew during the first week of RAL therapy after developing a Grade 1 facial rash. The rash was determined to be unrelated to RAL by the site investigator, but the subject declined to continue RAL and withdrew from the study. No deaths or virologic failures occurred in either group.

DISCUSSION

After 24 weeks, no statistically significant differences in any AT parameter were observed between women switching to RAL vs. continued PI or NNRTI, although a slight decrease in VAT (3.6%) was observed in the RAL group compared to a 1.9% increase in subjects continuing PI or NNRTI.

In the SPIRAL study, subjects on a suppressive, ritonavir-boosted, PI-based regimen were randomized to switch to RAL vs. continued PI. After 48 weeks, PI-treated patients experienced significant increases in CT-quantified total abdominal and visceral AT, whereas RAL-treated subjects experienced no significant AT changes. Similar to our study, no statistically significant between-arm changes were observed. [49] The 48-week follow-up of our participants will allow us to observe whether significant within group AT changes will emerge in the immediate-switch

16

group. While an observed benefit on VAT would be an important positive finding, failure to show a significant VAT improvement will also be important to our understanding of the possible contribution of ART classes to lipohypertrophy, and would be consistent with findings from the SPIRAL study.

Body image impact measures improved in subjects switched to RAL. While sample size limited our ability to detect between-group differences, within-group improvements in body image and body distress (with a focus on belly distress) were observed in the immediate- but not delayed-switch groups after 24 weeks. Importantly, changes in VAT volume correlated significantly with improvements in belly size and distress after controlling for baseline VAT and PRO scores, possibly suggesting the improvements observed in the RAL-treated group reflected an underlying change in clinical status rather than an unrelated subjective assessment.

In this study, statistically significant improvements in median total and LDL cholesterol were observed in subjects switching to RAL, with the effect size dominated by subjects switching from a PI to RAL. These results are in keeping with those observed in the SWITCHMRK and SPIRAL trials, [46,50] although statistically significant improvements in triglyceride levels were not seen in our study. Importantly, more women in our study were on atazanavir (predominantly ritonavir-boosted) than PIs more commonly associated with lipid abnormalities (such as lopinavir/ritonavir), highlighting the potential benefit of switching to RAL from any PI.

Most importantly, switch to RAL was safe in this cohort of women, and was not associated with an increased risk of virologic failure or emergence of new adverse events. Although women at risk for underlying ART resistance were excluded from participation in this study, our findings reinforce the virologic safety of RAL in patients with minimal treatment experience.

Our study has several important limitations. First, the high prevalence of obesity in this cohort (median BMI 32kg/m^2) likely limited our ability to see the desired treatment effect, an improvement in HIV-related lipohypertrophy rather than generalized obesity, and the study was

not powered to observe a smaller improvements in VAT in the number of women with BMI<30 (n=14/37). Second, due to the small sample size and relatively short length of follow-up, targeting a 10% between-group difference in VAT over 24 weeks may have been overly ambitious. Accordingly, an overall between-group VAT difference of 5.4% was observed after 24 weeks, and it is possible that longer follow-up would have allowed for greater between-group differences to emerge. Third, this study was not designed to assess the potential contribution of NRTIs to lipohypertrophy, nor can we exclude the NRTI backbone as a confounding factor. Fourth, the PRO results observed in the immediate-switch group could have been influenced by the open label study design. We acknowledge that self-reported assessments are subject to bias, and while the validated Phase V® Technologies PRO assessment tool is designed to minimize the introduction of biases, we cannot rule out this possibility. Similarly, we cannot rule a potential influence of the open-label design on patient behavior, as subjects did not keep diet and exercise diaries (although no significant change in weight or BMI was observed). Finally, safety concerns following closure of the SWITCHMRK protocols obligated us to limit inclusion to women with the lowest risk of virologic failure following a switch to RAL. These restrictions may limit the generalizability of our results to the larger population of women on ART with lipohypertrophy, and may have excluded some women with lipohypertrophy secondary to prolonged antiretroviral exposure.

CONCLUSION

Switching to raltegravir was safe and well tolerated. No statistically significant improvement in VAT or other AT parameters was seen 24 weeks following a switch to RAL vs. continued PI or NNRTI in virologically-suppressed, HIV-infected women with lipohypertrophy. Significant improvements in total and LDL cholesterol were observed, mainly in subjects switching from a PI to RAL. The planned 48-week follow-up will help determine whether

additional metabolic or AT changes can occur with continued RAL therapy in this group of HIV-infected women.

ACKNOWLEDGEMENTS

Meetings at Which Data Has Been Presented: This data was presented in part at the 13th International Workshop on Adverse Drug Reactions and Co-Morbidities (Rome, Italy, July 14-16, 2011), and the International AIDS Society 6th Conference on HIV Pathogenesis Treatment and Prevention (Rome, Italy, July 17-20, 2011).

J.E. Lake was the primary author, served as Co-Principal Investigator for the protocol, aided in protocol revisions, and contributed to study oversight and data analysis.

G.A. McComsey developed the original study design and protocol with J.S. Currier, served as Co-Principal Investigator for the protocol, and contributed to the analytic plan and manuscript preparation.

T.M. Hulgan was a Co-Investigator and contributed to manuscript preparation.

C.A. Wanke was a Co-Investigator and contributed to manuscript preparation.

19

A. Mangili was a Co-Investigator and contributed to manuscript preparation.

S.L. Walmsley was a Co-Investigator and contributed to manuscript preparation.

M.S. Boger was a Co-Investigator and contributed to manuscript preparation.

R.R. Turner provided quality of life and body image questionnaires on behalf of Phase V® Technologies, Inc., performed quality of life and body image endpoint data analysis, and contributed to manuscript preparation.

H.E. McCreath served as Data Manager and contributed to data analysis and manuscript preparation.

J.S. Currier obtained funding for the study, developed the original study design and protocol with G.A. McComsey, was Co-Principal Investigator of the protocol, and contributed to manuscript development.

DISCLOSURES

Conflicts of Interest: J.E. Lake has provided consulting services to Merck and Co. **G.A. McComsey** has served as a scientific advisor or speaker for Bristol Myers Squibb, GlaxoSmithKline, Abbott, Tibotec, and Gilead Sciences, has received research grants from Bristol Myers Squibb, GlaxoSmithKline, Abbott, Merck, and Gilead Sciences, and is currently serving as the DSMB Chair for a Pfizer-sponsored study. **T.M. Hulgan** has received a research grant from Merck and Co. **C.A. Wanke** has received grant funding from GlaxoSmithKline and Theratechnologies, and served as an event adjudicator for a Pfizer study. **A. Mangili** is currently the Medical Director for HIV/Endocrinology at EMD Serono, Inc., but performed this work independently of this position through her affiliation with Tufts University. **S.L. Walmsley** has provided consulting services to Merck and Co., and received a research grant from Merck Frosst Canada Ltd. to help support this work. She has also served as an advisor and speaker to Abbott, Tibotec, Bristol Myers Squibb, ViiV Healthcare, and Gilead Sciences. **M.S. Boger,**

Table 1. Antiretroviral Classes and Their Agents*

Class	Agent
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	Abacavir
	Lamivudine
	Emtricitabine
	Tenofovir
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Efavirenz
	Etravirine
	Nevirapine
Protease Inhibitors (PIs)	Ritonavir
	Atazanavir
	Fosamprenavir
	Lopinavir
	Nelfinavir
Integrase Inhibitors (IIs)	Raltegravir

*Restricted to classes and agents mentioned in this thesis.

Figure 1: Enrollment and Disposition


```
                    ┌──────────────────┐
                    │   61 screened    │───────────────────────┐
                    └──────────────────┘                       │
                             │                                 ▼
                             ▼                    ┌─────────────────────────────┐
                    ┌──────────────────┐          │   18 screen failures        │
                    │   39 enrolled    │          │ • 4 did not meet            │
                    └──────────────────┘          │   minimum waist             │
                             │                     │   circumference or          │
              ┌──────────────┴─────────────┐      │   waist/hip ratio           │
              ▼                            ▼       │ • 4 unwilling to comply     │
  ┌────────────────────┐      ┌────────────────────┐ │   with study procedures  │
  │ 18 randomized      │      │ 21 randomized      │ │ • 4 detectable viral loads│
  │ to immediate switch│      │ to delayed switch  │ │ • 1 prior virologic failure│
  └────────────────────┘      └────────────────────┘ │ • 1 AST/ALT out of       │
         │                           │               │   range                  │
  ┌──────────────┐        ┌──────────────┐           │ • 1 incompatible NRTI    │
  │ 1 withdrawal │◄───    │ 1 withdrawal │           │   backbone               │
  │(unrelated    │        │(transportation│          │ • 1 history of resistance│
  │ Grade 1      │        │  issues)      │          │   to current NRTI        │
  │ adverse event)│       └──────────────┘           │ • 1 history of dual      │
  └──────────────┘                                    │   nucleoside therapy     │
         ▼                           ▼                │ • 1 deportation          │
  ┌────────────────┐      ┌────────────────┐          └─────────────────────────────┘
  │ 17 completed   │      │ 20 completed   │
  │ primary endpoint│     │ primary endpoint│          ┌─────────────────────────────┐
  └────────────────┘      └────────────────┘          │   4 screened                │
                                                       │   successfully but          │
                                                       │   declined to enroll        │
                                                       │ • 1 started RAL outside     │
                                                       │   of the study              │
                                                       │ • 1 moved to Germany        │
                                                       │ • 2 declined to provide     │
                                                       │   reasons for withdrawal    │
                                                       │   of consent                │
                                                       └─────────────────────────────┘
```

AST=aspartate transaminase, ALT=alanine transaminase
NRTI=nucleoside reverse transcriptase inhibitor

Table 2. Demographic and clinical baseline characteristics[a]

	Immediate	Delayed	**Overall**
Ethnicity	N=17	N=20	**N=37**
African-American	53%	65%	**59%**
Hispanic	23%	10%	**16%**
White	23%	25%	**24%**
Asian	6%	0%	**3%**
Age (years)	41 (39, 47)	44 (36, 51)	**43 (37, 49)**
Weight (kg)	88.7 (81.0, 105.0)	78.6 (71.4, 100.5)	**84.4 (73.6, 105.0)**
BMI (kg/m^2)	34.6 (28.8, 37.6)	30.4 (27.7, 35.4)	**32.0 (27.9, 36.5)**
Tobacco Use (Current)[b]	24%	58%	**42%**
CD4 count (cells/uL)	563 (447, 747)	553 (354, 770)	**558 (422, 747)**
PI	N=11 (65%)	N=12 (60%)	**N=23 (62%)**
Atazanavir/ritonavir	6	6	**12**
Atazanavir	1	3	**4**
Fosamprenavir/ritonavir	1	1	**2**
Fosamprenavir	0	1	**1**
Lopinavir/ritonavir	2	1	**3**
Nelfinavir	1	0	**1**
NNRTI	N=6 (35%)	N=8 (40%)	**N=14 (38%)**
Efavirenz	3	7	**10**
Etravirine	1	0	**1**
Nevirapine	2	1	**3**
NRTI Backbone	N=17 (100%)	N=20 (100%)	**N=37 (100%)**
Abacavir	4	5	**9**
Lamivudine	5	7	**12**
Emtricitabine	8	10	**18**
Tenofovir	10	12	**22**
Fat Gain on ART (self report)			
Neck	59%	35%	**46%**
Arms	59%	50%	**54%**
Breasts	62%	37%	**49%**
Legs	41%	35%	**38%**
Other (including abdomen)	65%	80%	**73%**
VAT (cm^2)	145 (105, 154)	138 (93, 154)	**138 (100.0, 154)**
SAT (cm^2)	450 (381, 687)	420 (342, 587)	**431 (343, 606)**
TAT (cm^2)	586 (518, 830)	512 (463, 711)	**543 (464, 750)**
VAT:TAT	0.20 (0.18, 0.26)	0.20 (0.17, 0.30)	**0.20 (0.17, 0.28)**
Neck Circumference (cm)	36.8 (35.7, 37.5)	36.4 (34.5, 38.0)	**36.8 (34.5, 37.7)**
Waist Circumference (cm)	106.0 (102.0, 121.0)	102.4 (99.2, 113.0)	**105.5 (99.5, 118.0)**
Hip Circumference (cm)	117.5 (102.1, 127.0)	106.5 (102.1, 124.4)	**115.5 (102.1, 127.0)**
Waist-Hip Ratio	0.95 (0.90, 0.99)	0.96 (0.93, 1.02)	**0.95 (0.92, 1.00)**
Glucose (mg/dL)	84.0 (78.0, 93.0)	87.0 (79.0, 98.0)	**86.5 (78.0, 94.0)**
Total Cholesterol (mg/dL)	179.0 (162.0, 206.0)	199.0 (173.0, 223.0)	**192.5 (164.5, 216.0)**
Triglycerides (mg/dL)[c]	116.0 (85.0, 144.0)	123.0 (101.0, 176.0)	**117.0 (91.0, 153.0)**
LDL (mg/dL)	113.0 (103.0, 123.0)	116.0 (93.0, 142.0)	**115.9 (93.5, 130.0)**
HDL (mg/dL)	47.6 (40.2, 57.0)	49.1 (39.0, 57.0)	**49.0 (39.5, 57.0)**
hs-CRP (mg/L)	2.7 (0.6, 6.0)	3.5 (0.6, 7.7)	**3.1 (0.6, 6.9)**
Diabetes[d]	0%	0%	**0%**
Hyperlipidemia[d]	18%	25%	**22%**

[a]Percent or median with interquartile range. Mann-Whitney U-test used to test statistical significance for continuous variables. Fisher's exact test used to test statistical significance for categorical variables.

[b]p=0.03. Otherwise, no statistically significant between arm differences (p<0.05).

[c]No significant difference after exclusion of outlier.

[d]Defined as self-reported diagnosis or on lipid-lowering therapy at baseline.

BMI=body mass index; PI=protease inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; VAT=visceral adipose tissue; SAT=subcutaneous adipose tissue; TAT=total adipose tissue; LDL=low-density lipoprotein cholesterol; HDL=high-density lipoprotein cholesterol

Figure 2. Median (by group) and subject-level 24-week percent adipose tissue changes

    A. Median 24-week percent adipose tissue changes

    B. VAT line drawing for immediate switch

    C. VAT line drawing for delayed switch
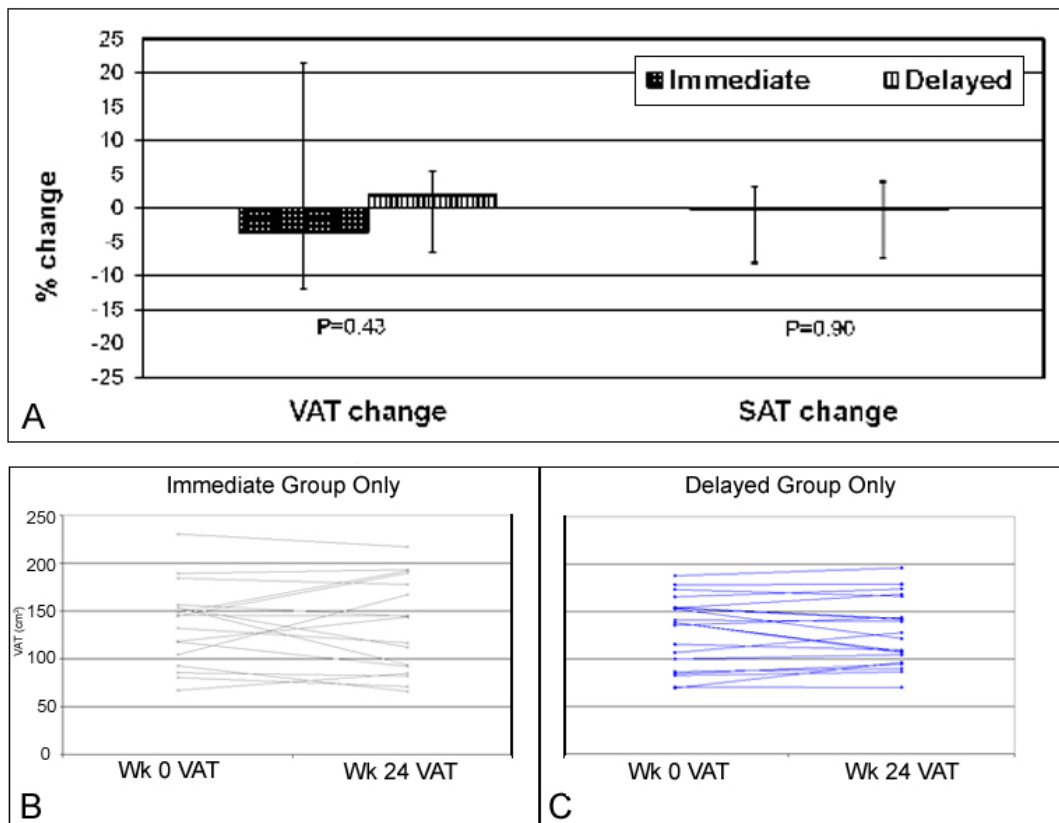
VAT=visceral adipose tissue; SAT=subcutaneous adipose tissue

Table 3. Twenty-four week change in anthropometrics, adipose tissue and lipid profiles[a]

| 24-week Median Change (IQR)	Raltegravir (n=17)	Control (n=20)	P value (Raltegravir vs. Control)
Weight (kg)	0.2 (-1.3, 0.9)	-0.2 (-3.2, 1.4)	0.47
BMI (kg/m^2)	0.1 (-0.4, 0.4)	-0.1 (-1.3, 0.5)	0.40
Neck circumferemce (cm)	-0.1 (-0.3, 0.2)	-0.2 (-0.5, 0.1)	0.41
Waist circumference (cm)	-0.7 (-3.5, 2.0)	-0.9 (-4.7, 1.0)	0.59
Hip circumference (cm)	0.0 (-1.3, 1.2)	0.0 (-2.5, 1.5)	0.91
Waist:hip ratio	0.00 (-0.02, 0.01)	-0.01 (-0.04, 0.01)	0.34
% VAT	-3.6 (-11.9, 21.6)	1.9 (-6.4, 5.5)	0.43
VAT (cm^2)	-6.6 (-15.5, 17.6)	1.8 (-9.3, 8.1)	0.52
%SAT	-0.1 (-8.0, 3.2)	-0.01 (-7.4, 4.0)	0.93
SAT (cm^2)	-0.5 (-31.2, 20.1)	-3.4 (-40.5, 20.5)	0.85
TAT (cm^2)	-12.6 (-35.0, 22.8)	1.2 (-50.8, 23.3)	0.90
VAT: TAT	-0.01 (-0.03, 0.04)	0.01 (-0.01, 0.02)	0.39
Total cholesterol (mg/dL)	**-17.0 (-31.0, -7.0)**	**-1.0 (-14.0, 17.0)**	**0.04**
LDL (mg/dL)	**-12.0 (-23.9, 1.6)**	**3.0 (-9.0, 16.0)**	**0.04**
HDL (mg/dL)	-1.3 (-5.0, 2.0)	2.20 (-4.0, 7.0)	0.22
Triglycerides (mg/dL)	-16.0 (-29.0, 2.0)	3.0 (-50.0, 24.0)	0.26

[a]Percent or median with interquartile range reported. Wilcoxon sign-rank test used to test for statistical significance.

IQR=interquartile range; BMI=body mass index; VAT=visceral adipose tissue;

SAT=subcutaneous adipose tissue; TAT=total adipose tissue; LDL=low-density lipoprotein cholesterol; HDL=high-density lipoprotein cholesterol

Figure 3. Median 24-week lipid changes
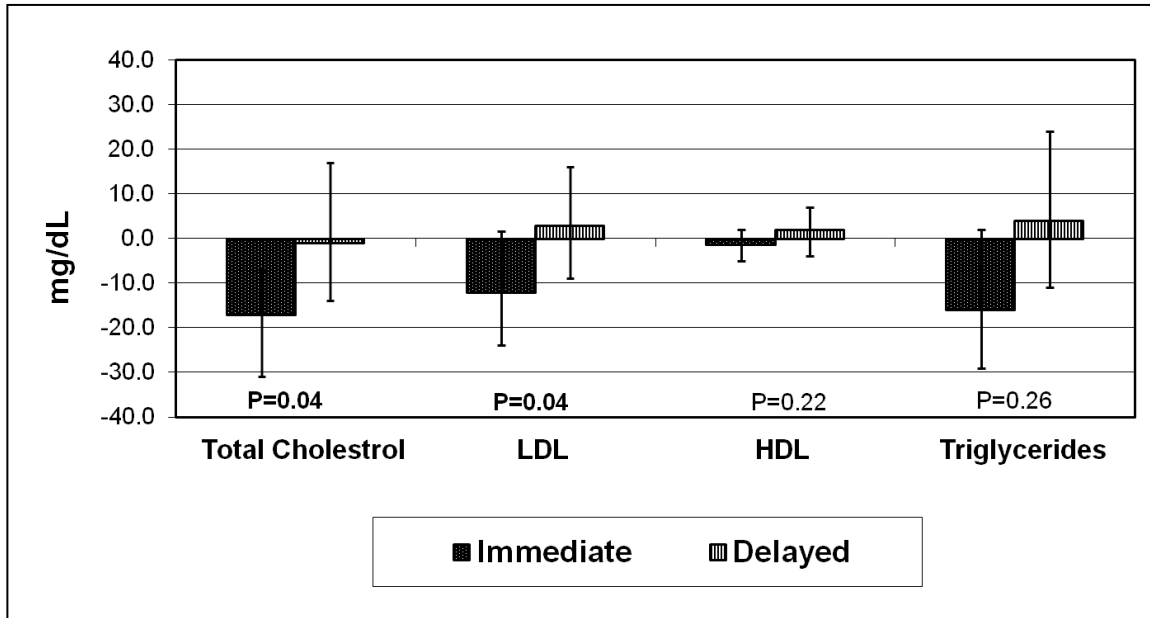
LDL=low-density lipoprotein; HDL=high-density lipoprotein

Chapter 3: Statistical Appendix

ELABORATION ON DESIGN METHODOLOGY

Selection of Delayed-Start Study Design

Antiretroviral therapy (ART) has advanced significantly in the last 20 years, with tolerable, effective regimens available to most patients. Additionally, because such therapies exist, patients are often resistant to participating in placebo-controlled studies, and asking subjects to participate in placebo-controlled studies of ART would be unethical. Selection of the delayed-start design provided for a control (standard of care) arm and allowed all subjects to receive the intervention. As the subjects were receiving life-saving therapies not provided by the study (entry ART regimen/nucleoside backbone), the study arms could not be blinded.

Adjustment for Change of Inclusion Criteria

As noted in Chapter 2, release of the SWITCHMRK results led to tightening of inclusion and exclusion criteria for this study. Fourteen of 37 subjects were enrolled prior to the revision. Because the revised criteria were more rigid than the original criteria, and because all subjects continuing on study post-revision met the revised criteria (n=13), we did not feel that the enrolled subject population changed enough to warrant statistical adjustment. As noted in the Limitations section of Chapter 2, the revised inclusion and exclusion criteria may have led to selection of a subject population with limited generalizability, but subjects enrolled pre- and post-revision were similar.

Selection of the Primary Endpoint

The primary endpoint was between-group change in percent visceral adipose tissue (VAT) volume 24 weeks following a switch to RAL vs. continued PI or NNRTI, with clinical significance defined as a ≥8% between group change in VAT. This definition of clinical

significance was defined by the FDA in the context of growth-hormone releasing factor registration trials (Falutz, 2007). However, the definition of clinical significance should apply to any therapy designed to induce VAT loss and not vary by intervention, making extrapolation of this definition to our study reasonable.

ELABORATION ON STATISTICAL METHODOLOGY

Primary Endpoint Analysis

Median between group 24-week change scores were calculated for all adipose tissue volumes, anthropometric measurements, lab values, and CES-D scores. Subjects served as their own controls. The Wilcoxon sign-rank test was chosen over the paired t-test given the non-normal distribution of some variables. All statistical tests were two-sided with a nominal p level of 0.05. All secondary analyses were exploratory without adjusting for multiple testing.

Given the small sample size and the increased risk of underestimating any potential treatment effect with an intent-to-treat analysis, a protocol defined as-treated analysis was performed. Only one subject in each arm did not complete the primary endpoint, making the as-treated and supplemental intent-to-treat analyses nearly identical.

A comparison of mean 24-week change scores was also calculated, and produced similar results (**Table 4**). Distribution of the data (medians or means) was not skewed sufficiently so as to warrant log transformation of raw data.

Table 4: CARE 001 Mean (Standard Deviation) 24-week Change Scores

	Arm A-Immediate	Arm B-Delayed	P value
VAT (cm^2)	-0.9 (31.8)	-1.1 (16.2)	0.52
% VAT	0.5 (25.6)	0.9 (14.3)	0.43
SAT (cm^2)	-8.7 (30.2)	-14.7 (53.5)	0.85
% SAT	-1.8 (6.94)	-2.7 (11.3)	0.90
TAT (cm^2)	-9.7 (37.3)	-15.7 (56.5)	0.90
%TAT	-1.6 (7.4)	-2.5 (9.0)	0.85
VAT:TAT	0.00 (0.05)	0.00 (0.03)	0.39
Weight (kg)	0.1 (2.2)	-1.5 (4.0)	0.47
BMI (kg/m^2)	0.1 (0.8)	-0.6 (1.6)	0.39
Waist (cm)	-0.8 (3.1)	-2.9 (6.4)	0.59
Hip (cm)	-0.1 (2.7)	-0.7 (3.2)	0.91
Waist:hip ratio	-0.01 (0.03)	-0.02 (0.04)	0.34
Neck (cm)	-0.1 (0.9)	-0.4 (0.9)	0.41
Total cholesterol (mg/dL)	-16.7 (34.1)	-3.6 (26.0)	**0.04**
LDL cholesterol (mg/dL)	-8.2 (23.3)	3.0 (20.5)	0.26
HDL cholesterol (mg/dL)	-1.5 (7.5)	1.6 (9.0)	**0.04**
Triglycerides (mg/dL)	-18.2 (39.5)	-36.4 (159.4)	0.22
Glucose (mg/dL)	-1.6 (8.8)	0.4 (12.1)	0.86
CRP (μg/L)	-1.1 (6.4)	-3.0 (11.9)	0.78

Non-protocol defined secondary analyses were performed stratifying data by BMI (<30 vs. ≥30kg/m^2) and entry ART regimen (between- and within-group comparisons of PI vs. NNRTI). The degree of morbid obesity in our cohort was not expected, and obesity could not be expected to improve with a switch from PI or NNRTI to RAL. Therefore, of comparison of outcomes between subjects with BMI <30 vs. ≥30kg/m^2 was warranted (**Table 5**).

Table 5: CARE 001 Median 24-Week Change Scores Restricted to BMI<30kg/m^2

	Arm A-Immediate	Arm B-Delayed	P value
VAT (cm^2)	3.7 (-25.5, 25.6)	0.5 (-11.5, 8.1)	0.52
% VAT	2.0 (-21.7, 21.6)	0.3 (-7.5, 6.0)	0.43
SAT (cm^2)	-0.5 (-18.5, 10.3)	-11.9 (-23.8, 5.6)	0.55
% SAT	-0.1 (-6.7, 4.2)	-3.5 (-5.5, 2.0)	0.90
TAT (cm^2)	25.1 (-45.1, 37.4)	-7.6 (-43.3, 10.2)	0.90
%TAT	4.7 (-12.3, 8.7)	-1.7 (-8.8, 2.2)	0.85
VAT:TAT	-0.03 (-0.03, 0.04)	0.01 (-0.01, 0.02)	0.39
Weight (kg)	0.9 (0.9, 1.8)	0.4 (-2.3, 1.0)	0.47
BMI (kg/m^2)	0.4 (0.3, 0.7)	0.1 (-0.8, 0.4)	0.39
Waist (cm)	0.6 (-3.9, 2.0)	-1.0 (-3.8, 1.1)	0.59
Hip (cm)	1.2 (0.8, 1.6)	-0.1 (-1.5, 2.1)	0.91
Waist:hip ratio	-0.02 (-0.05, 0.01)	-0.008 (-0.02, 0.0007)	0.34
Neck (cm)	-0.1 (-0.3, -0.1)	-0.3 (-0.5, 0.1)	0.41
Total cholesterol (mg/dL)	-31.0 (-32.0, -28.0)	8.0 (-7.0, 17.0)	**0.03**
LDL cholesterol (mg/dL)	-31.0 (-32.0, -28.0)	6.5 (3.0, 16.4)	**0.03**
HDL cholesterol (mg/dL)	-2.0 (-4.0, 2.0)	7.0 (3.0, 11.0)	0.19
Triglycerides (mg/dL)	-18.0 (-60.0, -6.0)	7.5 (-32.5, 19.0)	0.35
Glucose (mg/dL)	-4.0 (-14.0, 8.0)	1.0 (-3.0, 5.0)	0.85
CRP (μg/L)	0.0 (-1.1, 0.1)	-0.2 (-0.4, 0.0)	0.67

Additionally, entry ART regimen was a potential confounder, as subjects on PIs may not receive equivalent benefits from switching to RAL compared to subjects on an NNRTI at entry. This was born out in differential 24-week changes in lipids by ART entry regimen. The complete analysis stratified by entry ART is presented here (**Tables 6 and 7**).

Table 6: CARE 001 Median (Interquartile Range) 24-Week Change Scores Within Arm by Baseline ARV

	Arm A-PI	Arm A-NNRTI	P value	Arm B-PI	Arm B-NNRTI	P value
VAT (cm^2)	-6.6 (-26.7, 17.6)	-6.3 (-12.5, 44.7)	0.42	3.7 (-4.0, 11.5)	-5.5 (-21.7, 6.2)	0.19
% VAT	-3.6 (-26.9, 21.6)	-5.8 (-11.9, 30.8)	0.61	3.8 (-2.7, 7.3)	-3.6 (-14.1, 5.5)	0.35
SAT (cm^2)	-0.5 (-31.2, 26.0)	-9.6 (-33.4, 20.1)	0.92	-14.2 (-50.3, 20.5)	4.9 (-32.7, 20.1)	0.70
% SAT	-0.12 (-8.2, 4.0)	-2.8 (-8.0, 3.2)	0.92	-3.0 (-7.4, 4.0)	1.7 (-9.4, 4.0)	0.76
TAT (cm^2)	-15.8 (-35.0, 22.8)	13.9 (-52.7, 29.5)	0.55	1.1 (-41.2, 25.5)	0.0 (-54.2, 22.6)	0.76
%TAT	-2.4 (-6.8, 2.5)	1.6 (-8.5, 5.4)	0.48	0.2 (-5.5, 3.7)	-0.01 (-10.8, 4.3)	0.76
VAT:TAT	-0.01 (-0.04, 0.04)	-0.01 (-0.01, 0.05)	0.32	0.01 (0.00, 0.02)	0.00 (-0.03, 0.01)	0.28
Weight (kg)	-0.5 (-1.8, 0.9)	0.8 (0.0, 1.8)	0.37	-0.4 (-3.2, 1.2)	0.2 (-3.8, 1.4)	0.67
BMI (kg/m^2)	-0.2 (-0.7, 0.4)	0.3 (0.0, 0.7)	0.37	-0.2 (-1.3, 0.4)	0.1 (-1.4, 0.5)	0.62
Waist (cm)	-1.5 (-3.5, 0.6)	1.7 (-3.9, 3.6)	0.23	0.1 (-6.4, 1.9)	-1.2 (-2.6, -0.1)	0.59
Hip (cm)	0.0 (-2.0, 1.5)	0.3 (-0.2, 1.0)	1.00	0.2 (-1.4, 1.7)	-0.8 (-3.6, 1.4)	0.56
Waist:hip ratio	-0.01 (-0.05, 0.02)	0.01 (0.00, 0.02)	0.19	0.00 (-0.04, 0.01)	-0.01 (-0.02, 0.00)	0.88
Neck (cm)	0.0 (-0.3, 0.6)	-0.5 (-1.0, 0.2)	0.23	-0.2 (-1.2, 0.0)	-0.1 (-0.4, 0.3)	0.39
Total cholesterol (mg/dL)	-24.0 (-31.0, -7.0)	-7.5 (-15.0, 5.0)	0.14	1.0 (-17.0, 13.0)	3.5 (-7.5, 7.5)	0.62
LDL cholesterol (mg/dL)	-19.5 (-31.0, 1.6)	-3.5 (-12.0, 6.7)	0.37	-1.1 (-15.5, 13.5)	9.0 (3.0, 16.0)	0.12
HDL cholesterol (mg/dL)	-1.3 (-5.0, 2.0)	-2.0 (-9.4, 6.0)	0.76	1.5 (-5.0, 5.9)	4.5 (-0.5, 10.0)	0.23
Triglycerides (mg/dL)	-28.0 (-60.0, -14.0)	10.0 (-4.0, 40.0)	**0.01**	-5.0 (-32.0, 24.0)	7.5 (-53.0, 35.5)	0.93
Glucose (mg/dL)	-2.0 (-4.0, 6.0)	-2.0 (-14.0, 5.0)	0.48	-1.5 (-9.0, 4.0)	1.5 (-6.0, 9.5)	0.56
CRP (μg/L)	0.1 (-4.4, 0.4)	-0.2 (-1.9, 0.0)	0.95	-0.2 (-1.7, 0.0)	-0.6 (-4.2, 0.1)	0.61

Table 7: CARE 001 Median (Interquartile Range) 24-Week Change Scores Within Baseline ARV by Arm

	Pi-Arm A	PI-Arm B	P value	NNRTI-Arm A	NNRTI-Arm B	P value
VAT (cm^2)	-6.6 (-26.7, 17.6)	3.7 (-4.0, 11.5)	0.27	-6.3 (-12.5, 44.7)	-5.5 (-21.7, 6.2)	0.61
% VAT	-3.6 (-26.9, 21.6)	3.8 (-2.7, 7.3)	0.27	-5.8 (-11.9, 30.8)	-3.6 (-14.1, 5.5)	0.88
SAT (cm^2)	-0.5 (-31.2, 26.0)	-14.2 (-50.3, 20.5)	1.00	-9.6 (-33.4, 20.1)	4.9 (-32.7, 20.1)	1.00
% SAT	-0.12 (-8.2, 4.0)	-3.0 (-7.4, 4.0)	0.85	-2.8 (-8.0, 3.2)	1.7 (-9.4, 4.0)	0.90
TAT (cm^2)	-15.8 (-35.0, 22.8)	1.1 (-41.2, 25.5)	0.46	13.9 (-52.7, 29.5)	0.0 (-54.2, 22.6)	0.61
%TAT	-2.4 (-6.8, 2.5)	0.2 (-5.5, 3.7)	0.42	1.6 (-8.5, 5.4)	-0.01 (-10.8, 4.3)	0.61
VAT:TAT	-0.01 (-0.04, 0.04)	0.01 (0.00, 0.02)	0.20	-0.01 (-0.01, 0.05)	0.00 (-0.03, 0.01)	0.70
Weight (kg)	-0.5 (-1.8, 0.9)	-0.4 (-3.2, 1.2)	0.62	0.8 (0.0, 1.8)	0.2 (-3.8, 1.4)	0.48
BMI (kg/m^2)	-0.2 (-0.7, 0.4)	-0.2 (-1.3, 0.4)	0.54	0.3 (0.0, 0.7)	0.1 (-1.4, 0.5)	0.40
Waist (cm)	-1.5 (-3.5, 0.6)	0.1 (-6.4, 1.9)	0.88	1.7 (-3.9, 3.6)	-1.2 (-2.6, -0.1)	0.24
Hip (cm)	0.0 (-2.0, 1.5)	0.2 (-1.4, 1.7)	0.88	0.3 (-0.2, 1.0)	-0.8 (-3.6, 1.4)	0.90
Waist:hip ratio	-0.01 (-0.05, 0.02)	0.00 (-0.04, 0.01)	0.85	0.01 (0.00, 0.02)	-0.01 (-0.02, 0.00)	0.16
Neck (cm)	0.0 (-0.3, 0.6)	-0.2 (-1.2, 0.0)	0.15	-0.5 (-1.0, 0.2)	-0.1 (-0.4, 0.3)	0.48
Total cholesterol (mg/dL)	-24.0 (-31.0, -7.0)	1.0 (-17.0, 13.0)	0.06	-7.5 (-15.0, 5.0)	3.5 (-7.5, 7.5)	0.20
LDL cholesterol (mg/dL)	-19.5 (-31.0, 1.6)	-1.1 (-15.5, 13.5)	0.14	-3.5 (-12.0, 6.7)	9.0 (3.0, 16.0)	**0.04**
HDL cholesterol (mg/dL)	-1.3 (-5.0, 2.0)	1.5 (-5.0, 5.9)	0.62	-2.0 (-9.4, 6.0)	4.5 (-0.5, 10.0)	0.17
Triglycerides (mg/dL)	-28.0 (-60.0, -14.0)	-5.0 (-32.0, 24.0)	0.06	10.0 (-4.0, 40.0)	7.5 (-53.0, 35.5)	0.80
Glucose (mg/dL)	-2.0 (-4.0, 6.0)	-1.5 (-9.0, 4.0)	0.90	-2.0 (-14.0, 5.0)	1.5 (-6.0, 9.5)	0.56
CRP (μg/L)	0.1 (-4.4, 0.4)	-0.2 (-1.7, 0.0)	0.71	-0.2 (-1.9, 0.0)	-0.6 (-4.2, 0.1)	0.90

To further address pertinent confounders, a logistic regression model was built to assess the effects of age (<50 vs. ≥50 years), randomization arm (immediate vs. delayed), entry ART class (PI vs. NNRTI), and smoking status (current vs. ex/never). These results are displayed in **Table 8**. Performance site was considered but did not improve the model, and sensitivity analysis did not suggest an effect by site.

Table 8: CARE 001 Multivariable Regression Models for 24-Week Change Scores

	Arm A		On PI		Age>50		Current Smoker	
Change in:	β	P value	β	P value	β	P value	β	P value
CD4	-68.3	0.11	-5.3	0.90	-14.8	0.79	-5.8	0.90
Weight (kg)	1.7	0.15	-0.2	0.83	**3.3**	**0.03**	**-2.6**	**0.05**
BMI (kg/m2)	0.7	0.12	-0.1	0.84	**1.3**	**0.03**	**-1.0**	**0.04**
Waist (cm)	1.0	0.61	-0.1	0.95	0.7	0.77	-3.7	0.08
Hip (cm)	0.1	0.96	1.1	0.31	1.6	0.27	**-2.5**	**0.04**
Neck (cm)	0.5	0.14	0.1	0.71	0.5	0.27	0.2	0.53
Waist:hip ratio	0.01	0.60	-0.01	0.63	-0.01	0.65	-0.01	0.55
Total fat (cm2)	8.3	0.64	-0.8	0.96	35.4	0.13	-22.1	0.26
SAT (cm2)	5.1	0.75	1.1	0.95	34.8	0.10	-30.1	0.09
VAT (cm2)	3.4	0.72	-1.9	0.83	0.7	0.96	8.1	0.43
VAT:Total ratio	0.00	0.80	-0.01	0.66	-0.01	0.79	0.02	0.16
%VAT change	2.4	0.77	-0.2	0.98	4.1	0.68	4.2	0.62
% SAT change	0.3	0.94	1.5	0.67	5.6	0.22	-6.0	0.12
Glucose (mg/dL)	-4.4	0.29	2.4	0.54	0.7	0.89	-6.1	0.17
Cholesterol (mg/dL)	4.0	0.68	-9.0	0.33	**28.5**	**0.04**	19.2	0.07
Triglycerides (mg/dL)	47.7	0.29	13.3	0.76	29.8	0.50	52.5	0.28
LDLv(mg/dL)	-1.7	0.83	-9.8	0.19	18.2	0.07	7.2	0.39
HDL (mg/dL)	-0.1	0.84	-1.4	0.64	5.1	0.21	2.0	0.57
hsCRP (μg/L)	-0.1	0.99	3.4	0.35	-4.6	0.33	-0.6	0.89

Due to the small sample size, the regression model covariates were also analyzed as bivariable regressions. Significant outcomes are presented here (**Table 9**).

Table 9: CARE 001 Bivariable Regression Models for 24-Week Change Scores*

	Arm		On PI		Age>50		Current Smoker	
Change in:	β	P value	β	P value	β	P value	β	P value
Weight (kg)	1.63	0.14	-0.83	0.47	1.21	0.38	-1.9	0.09
Cholestrol	-13.51	0.18	-8.12	0.43	**38.6**	**0<.001**	**27.4**	**<0.01**
Triglycerides	17.97	0.64	17.87	0.65	44.52	0.36	48.90	0.21
LDL	-11.49	0.12	-10.67	0.17	**24.6**	**<0.01**	13.9	0.07
HDL	-3.11	0.26	-1.57	0.58	**6.6**	**0.05**	3.80	0.17

*Only values with p<0.10 listed.

In summary, significant care was taken to understand the population of women enrolled in this trial, and the effects of a switch to RAL vs. continued PI or NNRTI in these patients with

central fat accumulation and virologic suppression on ART. This data corroborates other data suggesting a benefit of a switch to RAL on lipids, but did not demonsrate an improvement in VAT in this group of women over 24 weeks. Further study is needed to determine whether additional metabolic benefits can be obtained from RAL therapy in HIV-infected women.

REFERENCES

1.   Bacchetti P, Gripshover B, Grunfeld C, et al. Fat distribution in men with HIV infection. J Acquir Immune Defic Syndr 2005;40:121-31.

2.   Carr A. HIV lipodystrophy: risk factors, pathogenesis, diagnosis and management. AIDS 2003;17 Suppl 1:S141-8.

3.   Miller J, Carr A, Emery S, et al. HIV lipodystrophy: prevalence, severity and correlates of risk in Australia. HIV Med 2003;4:293-301.

4.   Gervasoni C, Ridolfo AL, Trifiro G, et al. Redistribution of body fat in HIV-infected women undergoing combined antiretroviral therapy. AIDS 1999;13:465-71.

5.   Saves M, Raffi F, Capeau J, et al. Factors related to lipodystrophy and metabolic alterations in patients with human immunodeficiency virus infection receiving highly active antiretroviral therapy. Clin Infect Dis 2002;34:1396-405.

6.   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;40:1837-45.

7.   Haubrich RH, Riddler SA, DiRienzo AG, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. AIDS 2009;23:1109-18.

8.   Dube MP, Komarow L, Mulligan K, et al. Long-term body fat outcomes in antiretroviral-naive participants randomized to nelfinavir or efavirenz or both plus dual nucleosides. Dual X-ray absorptiometry results from A5005s, a substudy of Adult Clinical Trials Group 384. J Acquir Immune Defic Syndr 2007;45:508-14.

9.   Pujari SN, Dravid A, Naik E, et al. Lipodystrophy and dyslipidemia among patients taking first-line, World Health Organization-recommended highly active antiretroviral therapy regimens in Western India. J Acquir Immune Defic Syndr 2005;39:199-202.

10.   Mutimura E, Stewart A, Rheeder P, Crowther NJ. Metabolic function and the prevalence of lipodystrophy in a population of HIV-infected African subjects receiving highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2007;46:451-5.

11.   Wohl DA, Brown TT. Management of morphologic changes associated with antiretroviral use in HIV-infected patients. J Acquir Immune Defic Syndr 2008;49 Suppl 2:S93-S100.

12.   Falutz J, Allas S, Blot K, et al. Metabolic effects of a growth hormone-releasing factor in patients with HIV. N Engl J Med 2007;357:2359-70.

13.   Andany N, Raboud JM, Walmsley S, et al. Ethnicity and gender differences in lipodystrophy of HIV-positive individuals taking antiretroviral therapy in Ontario, Canada. HIV Clin Trials 2011;12:89-103.

14.   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 STDS 2010;24:5-13.

15.   Heath KV, Chan KJ, Singer J, O'Shaughnessy MV, Montaner JS, Hogg RS. Incidence of morphological and lipid abnormalities: gender and treatment differentials after initiation of first antiretroviral therapy. Int J Epidemiol 2002;31:1016-20.

16.   Galli M, Veglia F, Angarano G, et al. Gender differences in antiretroviral drug-related adipose tissue alterations. Women are at higher risk than men and develop particular lipodystrophy patterns. J Acquir Immune Defic Syndr 2003;34:58-61.

17.   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;48:1323-6.

18.   Crane HM, Grunfeld C, Harrington RD, Uldall KK, Ciechanowski PS, Kitahata MM. Lipoatrophy among HIV-infected patients is associated with higher levels of depression than lipohypertrophy. HIV Med 2008;9:780-6.

19.   Falutz J. Therapy insight: Body-shape changes and metabolic complications associated with HIV and highly active antiretroviral therapy. Nat Clin Pract Endocrinol Metab 2007;3:651-61.

20.   Currier J, Scherzer R, Bacchetti P, et al. Regional adipose tissue and lipid and lipoprotein levels in HIV-infected women. J Acquir Immune Defic Syndr 2008;48:35-43.

21.   Wohl D, Scherzer R, Heymsfield S, et al. The associations of regional adipose tissue with lipid and lipoprotein levels in HIV-infected men. J Acquir Immune Defic Syndr 2008;48:44-52.

22.   Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S. Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. Metabolism 1987;36:54-9.

23.   Grunfeld C, Rimland D, Gibert CL, et al. Association of upper trunk and visceral adipose tissue volume with insulin resistance in control and HIV-infected subjects in the FRAM study. J Acquir Immune Defic Syndr 2007;46:283-90.

24.   Carr DB, Utzschneider KM, Hull RL, et al. Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. Diabetes 2004;53:2087-94.

25.   Brown TT, Chu H, Wang Z, et al. Longitudinal increases in waist circumference are associated with HIV-serostatus, independent of antiretroviral therapy. AIDS 2007;21:1731-8.

26.   McComsey GA, Kitch D, Sax PE, et al. Peripheral and central fat changes in subjects randomized to abacavir-lamivudine or tenofovir-emtricitabine with atazanavir-ritonavir or efavirenz: ACTG Study A5224s. Clin Infect Dis;53:185-96.

27.   Carr A, Ritzhaupt A, Zhang W, et al. Effects of boosted tipranavir and lopinavir on body composition, insulin sensitivity and adipocytokines in antiretroviral-naive adults. AIDS 2008;22:2313-21.

28.   Mulligan K, Grunfeld C, Tai VW, et al. Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. J Acquir Immune Defic Syndr 2000;23:35-43.

29.   Lake JE, Wohl D, Scherzer R, et al. Regional fat deposition and cardiovascular risk in HIV infection: the FRAM study. AIDS Care;23:929-38.

30.   Falutz J, Allas S, Mamputu JC, et al. Long-term safety and effects of tesamorelin, a growth hormone-releasing factor analogue, in HIV patients with abdominal fat accumulation. AIDS 2008;22:1719-28.

31.   Lo J, You SM, Canavan B, et al. Low-dose physiological growth hormone in patients with HIV and abdominal fat accumulation: a randomized controlled trial. JAMA 2008;300:509-19.

32.   Macallan DC, Baldwin C, Mandalia S, et al. Treatment of altered body composition in HIV-associated lipodystrophy: comparison of rosiglitazone, pravastatin, and recombinant human growth hormone. HIV Clin Trials 2008;9:254-68.

33.   Hadigan C, Corcoran C, Basgoz N, Davis B, Sax P, Grinspoon S. Metformin in the treatment of HIV lipodystrophy syndrome: A randomized controlled trial. JAMA 2000;284:472-7.

34.   Kohli R, Shevitz A, Gorbach S, Wanke C. A randomized placebo-controlled trial of metformin for the treatment of HIV lipodystrophy. HIV Med 2007;8:420-6.

35.   Caron M, Vigouroux C, Bastard JP, Capeau J. Antiretroviral-Related Adipocyte Dysfunction and Lipodystrophy in HIV-Infected Patients: Alteration of the PPARgamma-Dependent Pathways. PPAR Res 2009;2009:507141.

36.   Lemoine M, Capeau J, Serfaty L. PPAR and Liver Injury in HIV-Infected Patients. PPAR Res 2009;2009:906167.

37.   Gelato MC, Mynarcik DC, Quick JL, et al. Improved insulin sensitivity and body fat distribution in HIV-infected patients treated with rosiglitazone: a pilot study. J Acquir Immune Defic Syndr 2002;31:163-70.

38.   Slama L, Lanoy E, Valantin MA, et al. Effect of pioglitazone on HIV-1-related lipodystrophy: a randomized double-blind placebo-controlled trial (ANRS 113). Antivir Ther 2008;13:67-76.

39.   Mulligan K, Yang Y, Wininger DA, et al. Effects of metformin and rosiglitazone in HIV-infected patients with hyperinsulinemia and elevated waist/hip ratio. AIDS 2007;21:47-57.

40.   Markowitz M, Morales-Ramirez JO, Nguyen BY, et al. Antiretroviral activity, pharmacokinetics, and tolerability of MK-0518, a novel inhibitor of HIV-1 integrase, dosed as monotherapy for 10 days in treatment-naive HIV-1-infected individuals. J Acquir Immune Defic Syndr 2006;43:509-15.

41.   Grinsztejn B, Nguyen BY, Katlama C, et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. Lancet 2007;369:1261-9.

42.   Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet 2009;374:796-806.

43.   Steigbigel RT, Cooper DA, Kumar PN, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. N Engl J Med 2008;359:339-54.

44.   Teppler H, Brown DD, Leavitt RY, et al. Long-term safety from the raltegravir clinical development program. Curr HIV Res;9:40-53.

45.   Harris M, Larsen G, Montaner JS. Exacerbation of depression associated with starting raltegravir: a report of four cases. AIDS 2008;22:1890-2.

46.   Eron JJ, Young B, Cooper DA, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. Lancet 2010;375:396-407.

47.   Lennox JL, Dejesus E, Berger DS, et al. Raltegravir versus Efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. J Acquir Immune Defic Syndr 2010;55:39-48.

48.   Turner R. The impact of recombinant human growth hormone (r-hGH) on body image and health-related quality of life (HRQOL) in patients with HIV-associated adipose redistribution syndrome (HARS). Antiviral Therapy 2006;11.

49.   Curran A SM, Martinez E, Larrouse M, Podzamezer D, Ocana I, Lonca M, Gatell J, Ribera E, and SPIRAL Study Group Changes in body composition after switching from PI/r to RAL in virologically suppressed HIV-1+ patients: SPIRAL LIP Substudy. Abstracts from the 18th Conference on Retroviruses and Opportunistic Infections February 27-March 2, 2011 Boston, MA, USA 2011:413.

50.   Saumoy M OJ, Martinez E, Llibre J, Ribera E, Knobel H, Podzamczer D Comprehensive lipid evaluation in patients switching from PI/r-based cART to a RAL-based cART: The SPIRAL Substudy. . Abstracts from the 18th Conference on Retroviruses and Opportunistic Infections February 27-March 2, 2011 Boston, MA, USA 2011:402.