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

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Abstract

Lipohypertrophy in HIV-infected patients is associated with metabolic abnormalities. Raltegravir (RAL) is not known to induce fat changes or severe metabolic perturbations. HIV-infected women with central adiposity and HIV-1 RNA less than 50 copies per milliliter on non-nucleoside reverse transcriptase inhibitor (NNRTI)- or protease inhibitor (PI)-based antiretroviral therapy (ART) continued their nucleoside reverse transcriptase inhibitor (NRTI) backbone and were randomized to switch to open label RAL immediately or after 24 weeks. The primary end point was 24-week between-group change in computed tomography (CT)-quantified visceral adipose tissue (AT) volume. Fasting lipids, glucose, C-reactive protein (CRP), anthropometric measurements, and patient-reported quality of life assessments were also measured. Thirty-six 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, subjects were 75% black or Hispanic, and on 62% PI-based and 38% NNRTI-based regimens. The median age was 43 years, CD4 count 558 cells per microliter, and body mass index (BMI) 32 kg/m^2. After 24 weeks, no statistically significant changes in visceral or subcutaneous AT, anthropometrics, BMI, glucose, or CRP were observed. In subjects receiving RAL, significant improvements in total and LDL cholesterol ($p = 0.04$), 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 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 not AT volumes. Additional insights into AT and metabolic changes in women on RAL will be provided by 48-week follow-up of the immediate-switch arm.

Introduction

In the context of HIV infection, lipodystrophy refers to a spectrum of changes in body fat redistribution that can be categorized as either lipoatrophy (fat loss) or lipohypertrophy (fat gain, particularly truncal fat). Both types of adipose tissue redistribution have specific risk factors and have been associated with metabolic abnormalities, decreased quality of life, medication nonadherence, and depression.[1–10] Optimal treatment regimens for lipoatrophy and lipohypertrophy have not yet been established, and may vary by the type of adipose tissue abnormality.

The prevalence of abdominal adiposity in HIV-infected patients on antiretroviral therapy (ART) has been reported to be 30–70% in some cohorts.[11–16] Lipohypertrophy may be more common in women,[8,11,17–20] and ART may play a role in the pathogenesis of lipohypertrophy,[12,16,20–22] but the contribution of specific antiretroviral agents and classes is less clear.

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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.[23–25] 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 central adiposity and suppressed HIV-1 RNA on stable therapy. The delayed-start design of the study provided for a standard of care control arm during the first 24 weeks, while allowing all subjects to receive open label RAL therapy during weeks 25–48. Computed tomography (CT)-quantified adipose tissue volumes, anthropometric measurements, fasting metabolic parameters, and body image assessments were performed. The 24-week, randomized controlled primary end point results of this intervention are presented here.

Methods

Patient population

Subjects were recruited from five 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 greater than 94 cm or waist-to-hip ratio greater than 0.88),[26] HIV-1 RNA less than 50 copies per milliliter at screening and less than 400 copies per milliliter for the 6 months prior to entry, current ART with a nucleoside reverse transcriptase inhibitor (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.[23] 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" less than 500 copies per milliliter with subsequent resuppression 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 less than 50 copies per milliliter 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 end point 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 400 mg 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 versus continued standard of care (PI or NNRTI).

The primary end point was between-group change in percent visceral adipose tissue volume 24 weeks following a switch to RAL versus 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 h) 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 per milliliter 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 or higher clinical events and grade 2 or higher lab abnormalities necessitated 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 (Phase V Technologies, Wellesley, MA).[27] 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,[26] in which the U.S. Food and Drug Administration defined a between-group difference in VAT of 8% or more 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 end point was also informed by studies of growth hormone releasing factor in HIV lipodystrophy, in which significant reductions in VAT volume were achieved after 26 weeks.[26]

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 end point. A supplemental intent-to-treat analysis and analyses of transformed mean values (versus median) were also performed, and produced similar results (data not shown).

Nonprotocol defined secondary analyses were performed stratifying data by BMI (<30 versus ≥30 kg/m^2) and entry ART regimen (between- and within-group comparisons of PI versus NNRTI). Linear regressions were performed to assess the effects of major confounders including age (<50 versus ≥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).

PRO assessments were analyzed by Phase V Technologies, Inc. according to a standardized, validated protocol.[27] These data are presented as an intent-to-treat analysis, and differ from the as-treated analysis presented for other end points by only two subjects (one in each arm). Similar to the other end points, 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's 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 for Windows™ (version 12, SPSS Inc., Chicago, IL).

Results

Patient population

Sixty-one subjects were screened, 39 enrolled, and 37 completed the week 24 primary end point (Fig. 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 1. 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% versus 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 (versus 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.

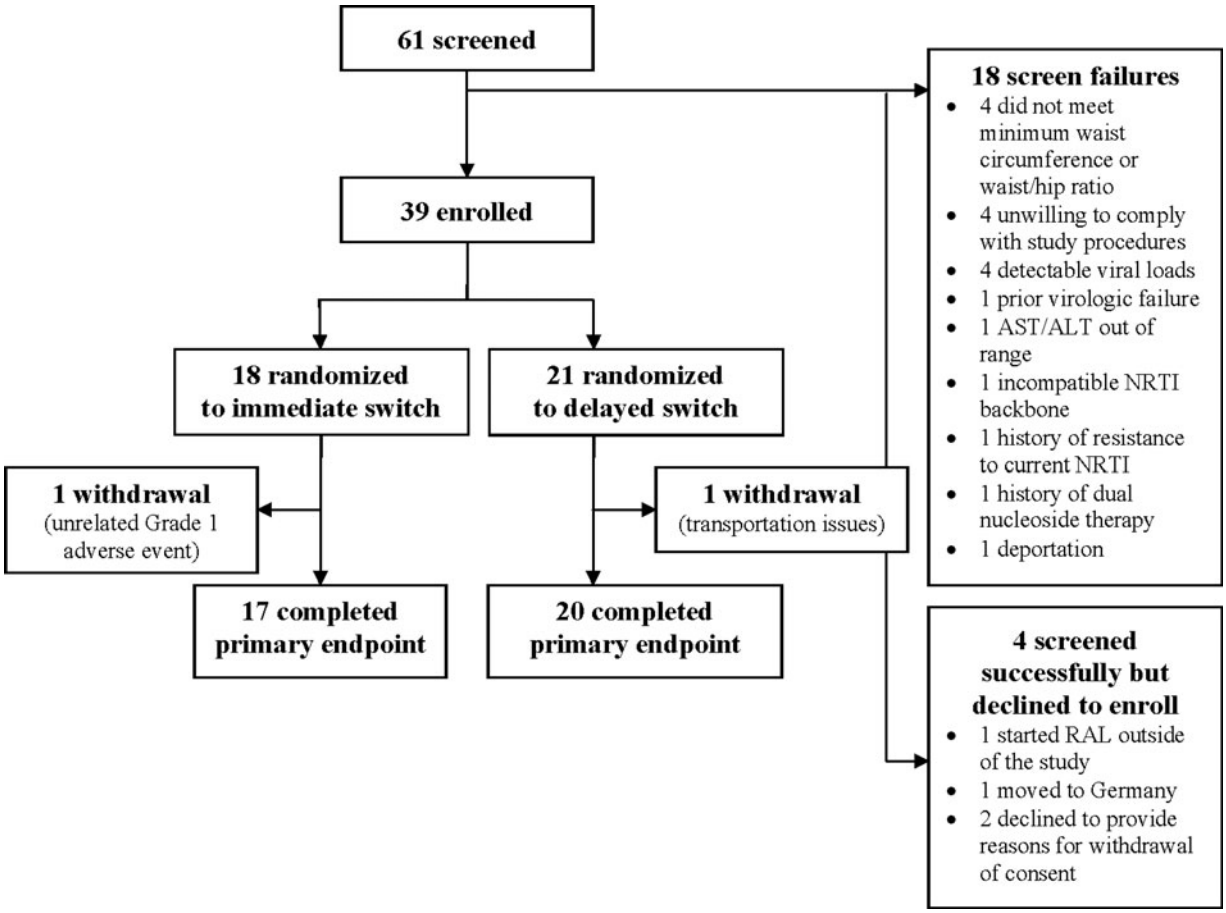

FIG. 1. Enrollment and disposition. AST, aspartate transaminase; ALT, alanine transaminase; NRTI, nucleoside reverse transcriptase inhibitor.

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 $p = 0.43$, Fig. 2A). Individual subject-level VAT changes are provided in Figs. 2B and C. Additionally, there were no statistically significant changes in SAT, TAT, VAT:SAT ratio, or VAT:TAT ratio (Table 2). Similar changes in AT volumes were seen in a subgroup analysis of subjects with BMI less than 30 and when the analysis was stratified by entry ART class (PI versus 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 versus a normalized mean of 50) accompanied by significant levels of belly appearance distress ($p < 0.001$). When 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 2. 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: −17.0 mg/dL versus −1.0 mg/dL, between-group $p = 0.04$; LDL: −12.0mg/dL versus 3.0 mg/dL, between-group $p = 0.04$; Fig. 3). These improvements were disproportionately attributable to subjects switching from PIs to RAL (TC: PI −24.0 mg/dL versus NNRTI −7.5 mg/dL, between-group $p = 0.08$; LDL: PI

Table 1. 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/μL)	563 (447, 747)	553 (354, 770)	558 (422, 747)
Time on ART (years)	5.1 (3.1, 7.1)	2.7 (1.6, 6.3)	3.7 (2.4, 7.1)
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:SAT	0.25 (0.22, 0.35)	0.25 (0.20, 0.42)	0.25 (0.21, 0.38)
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.

[c]No significant difference after exclusion of outlier.

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

BMI, body mass index; ART, antiretroviral therapy; PI, protease inhibitor; NNRTI, nonnucleoside 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.

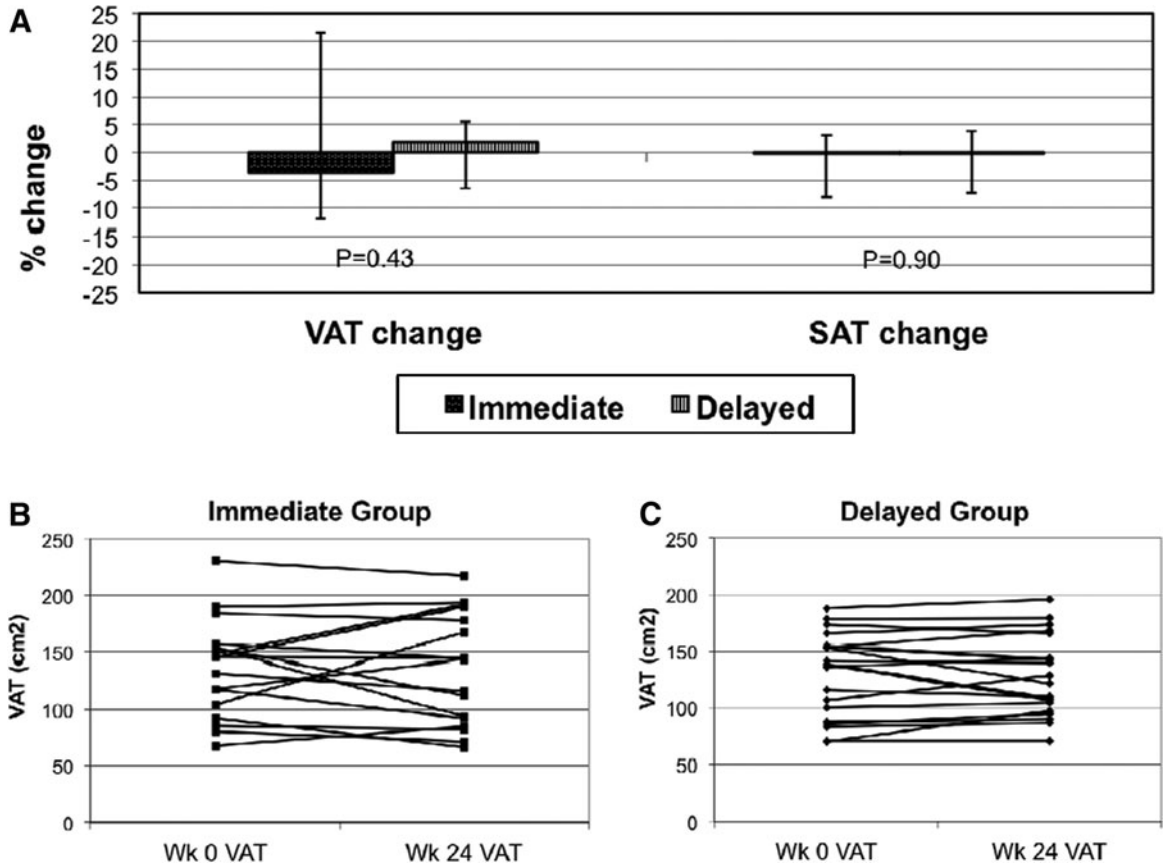

FIG. 2. Median (by group) and subject-level 24-week adipose tissue changes. (**A**) Median 24-week percent adipose tissue changes. (**B**) VAT line drawing for immediate switch. (**C**) VAT line drawing for delayed switch. VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

Table 2. 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:SAT	−0.02 (−0.05, 0.06)	0.01 (−0.02, 0.04)	0.46
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.

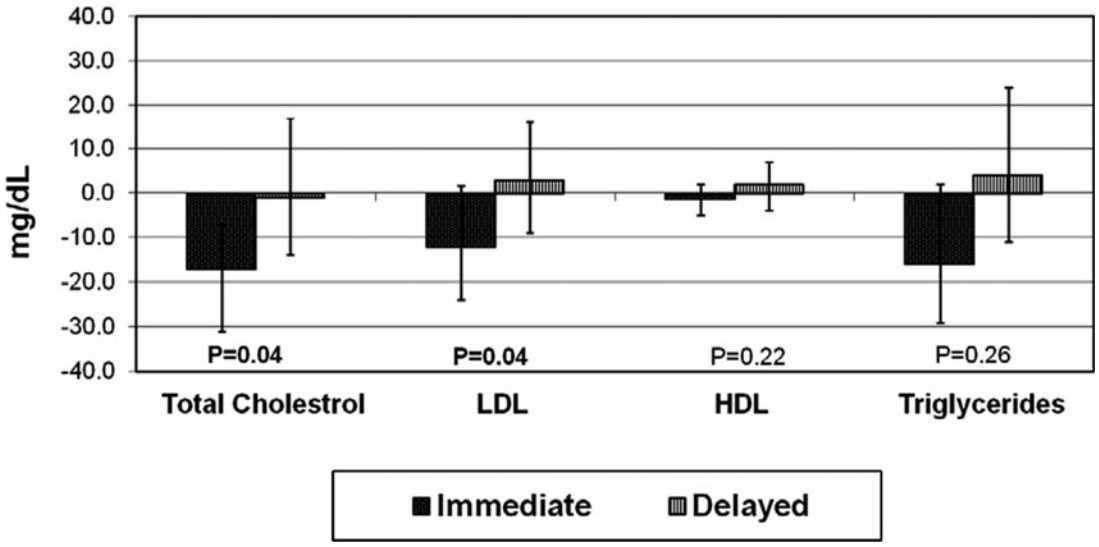

FIG. 3. Median 24-week lipid changes. LDL, low-density lipoprotein; HDL, high-density lipoprotein.

−19.5 mg/dL versus NNRTI −3.5 mg/dL, between-group $p = 0.21$).

A 16.0 mg/dL reduction in triglycerides was observed in patients switching to RAL compared to a 3.0 mg/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 −1.3 mg/dL, PI or NNRTI 3.0 mg/dL, between-group p = 0.22).

Glucose and hs-CRP

No significant change in fasting glucose or hs-CRP was observed between or within groups (glucose: RAL −2.0 mg/dL versus PI or NNRTI −1.0 mg/dL, between group $p = 0.86$; hs-CRP: RAL −0.01 mg/L versus PI or NNRTI −0.20 mg/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 versus 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 versus 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.[28] 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 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,[23,29] 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 generalized obesity in this cohort (median

BMI 32 kg/m^2) likely limited our ability to see the desired treatment effect, an improvement in HIV-related lipohypertrophy, and the study was not powered to observe smaller improvements in VAT in the number of women with BMI less than 30 ($n = 14/37$). This limitation is the result of having a minimum waist circumference and/or waist-to-hip ratio as an entry criterion (designed to target subjects with isolated abdominal adiposity) without defining a maximum BMI to prevent the inclusion of subjects with generalized obesity. The severity of obesity in our cohort is apparent in the baseline VAT:SAT ratio (immediate-switch group: mean 0.29 ± 0.17, Delayed-switch group: mean 0.31 ± 0.16, means and standard deviations provided for comparison with growth hormone releasing factor data), which differs drastically from that in the studies of growth hormone releasing factor (tesamorelin group: mean 1.27 ± 1.61, placebo group: mean 1.18 ± 1.58).[26]

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. However, due to the delayed-start design of this study, no control group exists beyond 24 weeks, and 48-week follow-up will only allow for additional information on continued RAL in the immediate-switch group.

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.

Switching to RAL was safe and well tolerated. No statistically significant improvement in VAT or other AT parameters was seen 24 weeks following a switch to RAL versus 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.

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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, C.A. Wanke, A. Mangili, S.L. Walmsley, and M.S. Boger were all Co-Investigators 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.

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, R.R. Turner, and H.E. McCreath have no conflicts of interest to report. J.S. Currier received a research grant for the conduct of this study through the Merck and Co. Investigator-Initiated Studies Program.

Author Disclosure Statement

No competing financial interests exist.

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