Switch to Raltegravir From Protease Inhibitor or Nonnucleoside Reverse-Transcriptase Inhibitor Does not Reduce Visceral Fat In Human Immunodeficiency Virus-Infected Women With Central Adiposity.
Switch to Raltegravir From Protease Inhibitor or Nonnucleoside Reverse-Transcriptase Inhibitor Does not Reduce Visceral Fat In Human Immunodeficiency Virus-Infected Women With Central Adiposity

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Human immunodeficiency virus-infected women with central adiposity switched to raltegravir-based antiretroviral therapy immediately or after 24 weeks. No statistically significant changes in computed tomography-quantified visceral adipose tissue (VAT) or subcutaneous fat were observed, although 48 weeks of raltegravir was associated with a 6.4% VAT decline. Raltegravir for 24 weeks was associated with improvements in lipids.

**Keywords.** antiretroviral therapy; fat; HIV; raltegravir; visceral; women.

High rates of central adiposity and generalized obesity have been reported in human immunodeficiency virus-infected (HIV+) persons on antiretroviral therapy (ART) [1, 2]. Antiretroviral therapy-related adipose tissue (AT) accumulation in the trunk and viscera (lipohypertrophy) may be more common in HIV+ women [3, 4]; however, the contribution of specific antiretroviral agents and the efficacy of switching ART to improve lipohypertrophy remain uncertain.

We previously reported 24-week results from a randomized clinical trial of switch to raltegravir (RAL)-based ART versus continued protease inhibitor (PI)-based or nonnucleoside reverse-transcriptase inhibitor (NNRTI)-based therapy in HIV+ women with central adiposity on suppressive ART. No statistically significant between-group changes in visceral AT (VAT) or abdominal subcutaneous AT (SAT) were observed, although RAL-treated participants experienced significant reductions in low-density lipoprotein (LDL) and total cholesterol levels [5]. We now report the final, 48-week results from this trial.

**METHODS**

**Patient Population**

Complete enrollment procedures have been described previously [5]. Participants were recruited from 5 North American centers from September 2008 to July 2010, with 48-week follow-up completed in June 2011. All study documents and procedures were approved by the institutional review boards or ethics committees of the participating institutions. All participants provided written informed consent before initiation of study procedures. This trial is registered at clinicaltrials.gov (NCT00656175).

**Study Design**

Participants were randomized 1:1 to continue their NRTIs but switched from PI or NNRTI to open label RAL 400 mg twice daily by mouth at Week 0 (immediate) or 24 (delayed). Delayed-switch participants provided an internal control group for the first 24 weeks. During Weeks 24–48, all participants received RAL.

The primary endpoint was between-group change in percentage of VAT 24 weeks after switch to RAL versus continued PI/NNRTI. Sample size was informed by the US Food and Drug Administration, which defined a ≥8% between-group VAT change as clinically significant [6]. Eighteen women per randomized group provided 80% power to detect a 10% between-group VAT difference at 24 weeks. Secondary endpoints included 48-week follow-up of immediate-switch participants, 24-week (Weeks 24–48) follow-up of delayed-switch participants, 24-week pooled follow-up of all participants (Weeks 0–24 for immediate-switch, Weeks 24–48 for delayed-switch), and measurement of fasting lipids, glucose, and high-sensitivity C-reactive protein (hs-CRP). A Data Safety Monitoring Board performed quarterly reviews without interim data analyses.

**Assessments**

Adipose tissue areas (VAT, SAT, and total AT [TAT]) were measured via single slice L4-L5 computed tomography (CT) scan at

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Weeks 0, 24, and 48. Scans were performed locally but read centrally by a blinded reader at the Tufts University Body Composition Center. Site phantom scans were analyzed by the reading center before initiation of study procedures to ensure between-site scan consistency.

Fasting (>8 hours) glucose, lipoprotein profile, hs-CRP, CD4+ T lymphocyte counts, HIV-1 RNA (assay sensitivity ≤50 copies/mL), and safety evaluations (complete blood count with differential, liver enzymes, serum creatinine, pregnancy test) were measured as per the schedule of events [5]. Laboratory tests were performed 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 ≥2 laboratory abnormalities were reported to the Data Management Center, as required.

### Statistical Analysis
Baseline characteristics were compared using the Mann–Whitney U test and Fisher’s exact test for continuous and categorical variables, respectively. Medians and interquartile ranges are reported for continuous variables, and percentages are

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**Table 1. Baseline Demographic and Clinical Characteristics**

|                      | Immediate | Delayed | Overall |
|----------------------|-----------|---------|---------|
| **Ethnicity**        |           |         |         |
| African American     | 53%       | 65%     | 59%     |
| Hispanic             | 23%       | 10%     | 16%     |
| White                | 18%       | 25%     | 22%     |
| Asian                | 6%        | 0%      | 3%      |
| **Age (years)**      | 41 (39, 47)| 46 (36, 51)| 43 (37, 49) |
| **BMI (kg/m²)**      | 34.7 (28.8, 37.6)| 30.4 (27.7, 35.4)| 32.0 (28.0, 36.5) |
| **Tobacco use (current)** | 24% | 60% | 43% |
| **CD4+ T Lymphocyte count (cells/mm³)** | 563 (447, 747)| 554 (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  | 35%       | 30%     | 32%     |
| Atazanavir           | 6%        | 15%     | 11%     |
| Fosamprenavir/ritonavir | 0% | 5% | 3% |
| Fosamprenavir        | 0%        | 5%      | 3%      |
| Lopinavir/ritonavir  | 18%       | 5%      | 11%     |
| Nelfinavir           | 6%        | 0%      | 3%      |
| **NNRTI**            | n = 6 (35%)| n = 8 (40%)| n = 14 (38%) |
| Efavirenz            | 18%       | 30%     | 24%     |
| Etravirine           | 6%        | 0%      | 3%      |
| Nevirapine           | 12%       | 10%     | 11%     |
| **NRTI**             | n = 17 (100%)| n = 20 (100%)| n = 37 (100%) |
| Abacavir             | 18%       | 25%     | 22%     |
| Lamivudine           | 29%       | 35%     | 32%     |
| Emtricitabine        | 71%       | 65%     | 68%     |
| Tenofovir            | 82%       | 75%     | 78%     |
| **Glucose (mg/dL)**  | 84.0 (78.0, 93.0)| 88.5 (80.0, 97.5)| 87.0 (78.0, 94.0) |
| **Total cholesterol (mg/dL)** | 179.0 (162.0, 206.0)| 199.0 (164.5, 221.5)| 188.0 (162.0, 214.0) |
| **Triglycerides (mg/dL)** | 116.0 (85.0, 144.0)| 129.0 (101.0, 176.0)| 118.0 (92.0, 152.0) |
| **LDL (mg/dL)**      | 113.0 (103.0, 123.0)| 116 (89.0, 138.1)| 115.8 (93.0, 128.0) |
| **HDL (mg/dL)**      | 47.6 (40.2, 57.0)| 49.1 (39.0, 55.0)| 49.0 (40.0, 57.0) |
| **hs-CRP (mg/dL)**   | 2.7 (0.6, 6.0) | 4.7 (0.8, 7.5) | 3.2 (0.6, 6.5) |
| **Diabetes**         | 0%        | 0%      | 0%      |
| **Hyperlipidemia**   | 18%       | 25%     | 22%     |

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; HDL, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

*a* Percentage or median with interquartile range. Mann–Whitney U or Fisher’s exact tests used to test statistical significance for continuous and categorical variables, respectively.

*b* *P* = .05. Otherwise, no statistically significant association between-arm differences.

*c* Defined as self-reported diagnosis or on-therapy at baseline.
reported for categorical data. Comparison of median within- and between-group change scores was performed using the Wilcoxon signed-rank test. The primary analysis was as-treated, excluding participants who did not remain on study drug or have an observed primary endpoint. Supplemental intent-to-treat and log-transformed mean value analyses produced similar results (data not shown). Nonprotocol-defined secondary analyses included stratification by body mass index ([BMI] <30 vs ≥30 kg/m²) and entry ART regimen (PI vs NNRTI). Linear regression assessed confounding effects (age <50 vs ≥50 years, randomization arm, entry ART class, study site, smoking status), but it did not provide additional insight (data not shown). All statistical tests were 2-sided (α = 0.05) without adjustment for multiple testing.

Week 0, 24, and 48 CT scans were not performed on the same scanner for all participants, but phantom scan comparison and sensitivity analysis confirmed that discrepancies were minimal and that no additional statistical correction was needed. Data analysis and management were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Thirty-nine participants enrolled in the study: 37 completed Week 24, 36 completed Week 48, and 1 participant was excluded after Week 24 [5]. Complete baseline characteristics have been described previously [5]. Seventeen participants randomized to immediate-switch, and 20 participants randomized to delayed-switch. Randomized groups were well balanced, except for higher current smoking rates among delayed-switch women (60% vs 24%, P < .05; Table 1). The median age was 43 years, BMI was 32 kg/m², 75% of participants were non-white, 62% were PI-treated (83% ritonavir-boosted), and the most common NRTIs were tenofovir (59%) and emtricitabine (49%). No adverse events occurred.

After 48 weeks, no statistically significant changes in AT or BMI occurred among immediate-switch participants, and the initially observed LDL cholesterol decline did not remain significant (Table 2). However, a nonsignificant VAT decline (−6.4%, P = .85) and a significant hs-CRP decline (−1.0 mg/L, P = .02) were observed. No significant differences in 48-week findings were observed by entry ART regimen.

In the delayed-switch arm, switch to RAL at Week 24 was associated with an increase in the percentage of SAT (3.4%, P = .05) and a BMI (0.6 kg/m², P = .05). Significant declines in total cholesterol, LDL cholesterol, and high-density lipoprotein cholesterol were observed, with a trend seen for triglycerides. Unlike immediate-switch participants [5], lipid declines after switch to RAL seemed to be driven by switch from NNRTI rather than PI, although participant numbers were small in this subgroup analysis. A similar phenomenon was observed for SAT (PI: −0.1%, P = .52; NNRTI: 8.8%, P = .05).

### Table 2. Median Changes in Adipose Tissue, Anthropometrics, and Laboratory Values After Switch to Raltegravir

|                          | Week 0–48 Changes |                                           | Week 24–48 Changes |                                           | Pooled 24-Week Changes |                                           |
|--------------------------|-------------------|------------------------------------------------|-------------------|------------------------------------------------|------------------------|------------------------------------------------|
|                          | Immediate         | Within-Group Value | P Value | Delayed                          | Within-Group Value | P Value | Immediate 0–24 wks | Within-Group Value | P Value | Delayed 24–48 wks | Within-Group Value | P Value |
| N                        | 17                | 19                                                              | 36                      |
| BMI (kg/m²)              | −0.1 (−0.9, 0.4)  | .52                                                             | .06 (0.0, 1.6)       | .05                                                             | .03 (−0.2, 1.1)      | .05                                                             |
| Waist-to-hip ratio       | −0.01 (−0.04, 0.02) | .24                                                             | 0.0 (−0.02, 0.01)  | .47                                                             | 0.0 (−0.02, 0.02)   | .50                                                             |
| TAT (cm²)                | −16.5 (−52.5, 17.2) | .40                                                             | 26.5 (−24.7, 31.0) | .28                                                             | 8.9 (−33.6, 30.1)   | 1.00                                                             |
| SAT (cm²)                | −17.8 (−30.3, 28.1) | .57                                                             | 13.4 (−5.2, 36.0)  | .10                                                             | 0.8 (−26.0, 31.6)   | .59                                                             |
| VAT (cm³)                | −11.7 (−17.4, 13.3) | .68                                                             | 2.8 (−18.9, 11.1)  | .64                                                             | −4.4 (−18.9, 13.1)  | .51                                                             |
| VAT/SAT                  | −0.01 (−0.04, 0.04) | .86                                                             | −0.01 (−0.06, 0.01) | .23                                                             | −0.02 (−0.05, 0.02) | .30                                                             |
| VAT/TAT                  | −0.01 (−0.02, 0.03) | .96                                                             | 0.0 (−0.03, 0.01)  | .26                                                             | 0.01 (−0.03, 0.01)  | .30                                                             |
| %VAT change              | −6.4 (−15.6, 12.5) | .85                                                             | −1.8 (−12.3, 11.4) | .70                                                             | −3.3 (−12.3, 12.1)  | .60                                                             |
| %SAT change              | −2.9 (−9.7, 5.9)   | .46                                                             | 3.4 (−1.4, 9.4)    | .05                                                             | −5.6 (7.2, 0.4)     | .47                                                             |
| CD4+ T Lymphocyte count (cells/mℓ) | 46.0 (−10.0, 61.0) | .16                                                             | 42.0 (−26.0, 133.0) | .08                                                             | 5.0 (−29.0, 62.0)   | .27                                                             |
| Glucose (mg/dL)          | 4.0 (0.0, 8.0)    | .13                                                             | 0.5 (−6.0, 5.0)    | .85                                                             | 0.0 (−6.0, 5.0)     | .70                                                             |
| Total cholesterol (mg/dL) | −14.0 (−29.0, 6.0) | .01                                                             | −20.0 (−47.0, −2.0) | < .001                                                          | −17.0 (−31.0, −2.0) | < .0001                                                         |
| Triglycerides (mg/dL)    | −1.0 (−21.0, 9.0) | .32                                                             | −27.5 (−42.0, 8.0) | .07                                                             | −18.0 (−42.0, 8.0)  | < .01                                                         |
| LDL cholesterol (mg/dL)  | −2.0 (−28.8, 3.2) | .16                                                             | −6.2 (−23.0, 0.0)  | .01                                                             | −9.1 (−23.9, 1.6)   | < .01                                                         |
| HDL cholesterol (mg/dL)  | −4.0 (−9.6, 3.0)  | .25                                                             | −4.3 (−6.0, −1.0)  | .03                                                             | −2.6 (−6.0, 0.4)    | .03                                                             |
| hs-CRP (mg/L)            | −1.0 (3.2, 0.0)   | .02                                                             | −0.4 (−1.4, 2.2)   | 1.00                                                             | −0.2 (−1.9, 0.5)    | .34                                                             |

Bold text represents statistically significant findings (P < .05). Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SAT, subcutaneous adipose tissue; TAT, total adipose tissue; VAT, visceral adipose tissue.
In a pooled analysis of 24-week data after switch to RAL (Weeks 0–24 for immediate-switch, Weeks 24–48 for delayed-switch), a significant BMI increase (0.3 kg/m², P = .05) was observed that was driven by switch from NNRTI (0.7 kg/m², P = .03) versus PI (0.2 kg/m², P = .56; between-group, P = .08). Of note, no significant AT changes accompanied the observed BMI change. Significant declines in all lipid parameters were also observed, but lipid changes did not vary significantly by entry ART type.

**DISCUSSION**

No statistically significant AT changes were observed 24 or 48 weeks after switch to RAL in this group of HIV+ women with central adiposity on suppressive ART. Although not statistically significant (given our power to detect a ≥10% change), women receiving RAL for 48 weeks did experience a 6.4% median VAT decline that was progressive throughout the 48-week observation period. Because VAT changes of as little as 5% are believed to affect risk for metabolic syndrome [7], the 6.4% observed VAT decline could have an associated clinical benefit. Supporting this hypothesis is the 48-week hs-CRP decline also observed in this group. Larger studies with longer follow-up time are needed to determine whether this finding can be confirmed, whether continued VAT improvements are seen with longer RAL exposure, and/or whether an associated clinical benefit can be defined.

Switch to RAL was also associated with significant lipid declines that occurred in both PI- and NNRTI-treated women. Although lipid reductions have previously been reported after switch from PI- and NNRTI-based therapy to RAL [8–13], our study is the first to specifically report this finding among women, many with generalized obesity, and to definitively report similar lipid declines among women switching from PI and NNRTI.

Finally, we observed small increases in TAT, SAT, and BMI in the delayed-switch group and BMI in the pooled analysis that appeared to be driven by switch from NNRTI to RAL. These AT increases in delayed-switch participants differ from the declines originally observed among immediate-switch women 24 weeks after switch to RAL [5]. An obvious physiologic explanation is not apparent, but these AT changes were small, may not be clinically significant, and, except for BMI, did not reach statistical significance. In addition, the BMI increase in the pooled analysis (which was accompanied by a nonsignificant SAT decrease) could result from an increase in lean mass, which we were unable to assess. More importantly, BMI increases after switch to RAL have only previously been reported in persons switching for virologic failure or from thymidine analog NRTI [14, 15].

**CONCLUSIONS**

This study has several limitations, most notably is a small sample size, which increases the risk of type II error and prevents measurement of small but potentially clinically significant VAT changes. In addition, the study was not powered to look at subgroups, and, although the pooled 24-week analysis improved power to assess some endpoints, results may be confounded by the time lag between switches to RAL. Finally, some women had generalized obesity (rather than isolated lipohypertrophy), which could not be expected to improve with ART switch. Despite these limitations, results from this randomized controlled trial provide important insight into the use of RAL in women on PI- and NNRTI-based ART. Although switch to RAL was not associated with statistically significant improvements in central adiposity in this study, the small observed VAT and hs-CRP decline after 48 weeks of RAL, and the significant lipid declines may be useful in minimizing cardiovascular risk, particularly in the growing, obese HIV+ population.

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**Potential conflicts of interest.** J. E. L. has provided consulting services to Gilead Sciences and GlaxoSmithKline. G. A. M. has served as a scientific advisor or speaker for Bristol Myers Squibb, GlaxoSmithKline, Abbvie, Tibotec, and Gilead Sciences, has received research grants from Bristol Myers Squibb, GlaxoSmithKline, Abbvie Merck, and Gilead Sciences, and is currently serving as the Data Safety Monitoring Board Chair for a Pfizer-sponsored study. T. H. served as Principal Investigator of a research grant to his institution from Merck and Co. C. A. W. has received grant funding from GlaxoSmithKline and Theratechnologies and served as an event adjudicator for a Pfizer study. A. M. is currently the Clinical Research Physician at Novartis Vaccines, but she performed this work independently of this position through her affiliation with Tufts University. S. L. W. has provided consulting services to Merck and Co., and she received a research grant from Merck Frosst Canada Ltd. to help support this work. She has also served as an advisor and speaker to Abbvie, Janssen, Bristol Myers Squibb, Viiv Healthcare, and Gilead Sciences. J. S. C. received a research grant for the conduct of this study through the Merck and Co. Investigator-Initiated Studies Program.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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