Effects of HIV and Antiretroviral Therapy on Resting Energy Expenditure in Adult HIV-Infected Women—A Matched, Prospective, Cross-Sectional Study

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ABSTRACT

Background Several studies have reported increased resting energy expenditure (REE) in people with human immunodeficiency virus (HIV). However, limited data exist on REE in HIV-infected women and the effect of antiretroviral therapy (ART) on REE in this population.

Objective The purpose of this study was to compare REE in healthy controls to adult HIV-infected women classified in three groups: naïve to ART, on ART with virologic suppression, and on ART with an HIV-1 RNA level $\leq 5,000$ copies/mL.

Design After a fast, body composition by bioelectrical impedance analysis and REE by indirect calorimetry were determined. Anthropometric measures were also taken.

Statistical analysis Distributionally appropriate two-sample tests were used for between-group analyses and analysis of covariance was used for confounding adjustment.

Results Eighty-seven women were enrolled and the HIV-infected and control women were matched for age and body mass index. Log-transformed REE was significantly higher in HIV-infected women naïve to ART compared to controls ($7.26 \pm 0.22$ vs $7.14 \pm 0.19; P=0.04$, respectively) and the difference remained significant after adjustment for body cell mass ($P=0.008$). Log-transformed REE was not different in HIV-infected women on ART compared to HIV-infected women naïve to ART ($7.25 \pm 0.25$ vs $7.26 \pm 0.23; P=0.81$, respectively). Adjusting for body cell mass did not change the results ($P=0.56$). Similarly, REE was not different between women naïve to ART and those on ART with undetectable HIV-1 RNA, regardless of adjustment for body cell mass. REE correlated to current and nadir CD4 count and trended toward a negative correlation with HIV-1 RNA levels.

Conclusions We showed that REE is elevated in ART-naïve, HIV-infected women and continues to be elevated when on ART, regardless of virologic suppression, compared to age and body mass index—matched healthy women. This suggests an effect of HIV infection itself and not ART on REE in these HIV-infected women, and should be considered during nutrition assessment and counseling of HIV-infected adult women.
crease with severity of wasting. Both of these studies specifically targeted women with wasting, a diagnosis less common in the current era of highly active antiretroviral therapy (ART). A more recent study by Fitch and colleagues included 283 HIV-infected subjects on ART (51.2% females) and found REE adjusted for fat-free mass to be higher in those with HIV. To our knowledge, no studies have been conducted that dis- ect the effect of HIV infection vs ART. The purpose of our study was to compare REE in HIV-infected women who have never been on ART (naïve group), those on ART with virologic suppres- sion (undetectable group), those on ART with detectable HIV viral loads (detectable group), and HIV-negative, healthy women (control group). We also wanted to determine whether standard energy expenditure equations, the Harris-Benedict and the Mifflin-St Jeor, used for individuals with HIV population correlate with REE determined through indirect calorimetry.

**METHODS**

**Study Design**

We performed a prospective, cross-sectional study of HIV-infected women and healthy controls matched by age and body mass index (BMI) to evaluate whether REE differed. Weight-stable adult, HIV-infected women were recruited between 2004 and 2011 from the John T. Carey Special Immunology Unit, an outpatient HIV clinic in Cleveland, OH. Controls were recruited from healthy volunteers, most of whom were hospital employees. Participants in all groups were excluded if they were taking anabolic agents, stimulants, or any drugs known to alter metabolism. Subjects were also excluded if they had diabetes; an active opportunistic infection; malignancy; hepatic, including chronic hepatitis, or pulmo- nary disease; or were pregnant. This study was approved by the University Hospitals Case Medical Center Institutional Review Board before enrollment of any participants. Each participant signed a written informed consent before enrollment.

**Clinical Evaluations**

Participants were weighed on a calibrated digital scale (Cardinal Scale Manufacturing Company) and height was measured with a wall-mounted measuring tape. Temperature was measured using a digital thermometer (Welch Allyn). Waist and hip circum- ferences were measured in triplicate with a tape measure and averaged. Waist measurements were taken at the smallest part of the waist. Hip measurements were taken at the uppermost portion of the hips. Participants were rescheduled if they were fe- brile. Participants were questioned about exercise habits and alcohol, tobacco, and drug use.

**Body Composition**

Body composition was determined by single frequency (50 kHz) bioelectrical impedance analysis (BIA) (Quantum X, RJL Systems). Participants were instructed to come fasting and abstain from caffeine and nicotine for a minimum of 4 hours and from exercise for 12 hours before BIA measurement. Analysis was performed with participants lying flat on an exam- ination table. Electrodes were placed on the right foot at the third metatarsal, at the depression of the ankle, on the right hand on the third finger, and at the radial/carpal depres- sion. Resistance and reactance were measured and entered into the computer program (Cyprus 1.2, RJL Systems) along with height, weight, age, and activity level. Body composition was determined by the Kotler equation.

**REE**

Oxygen consumption (VO2) was measured and energy expendi- ture was calculated with handheld indirect calorimetry (Medgem by HeatheTech, now part of MicroLife Corporation). Again, participants were instructed to come fasting from food, caloric beverages, caffeine, and tobacco for ≥4 hours. Participants were oriented to a temperature neutral room for 10 minutes. A one-time use mouthpiece and nose clip were used and participants were instructed to breathe through their mouths into the self-calibrating Medgem de- vice. Measurement was performed for 10 minutes to assure that a steady state was achieved. VO2 was captured and REE calculated by the Weir equation.

**Laboratory Values**

Current medication, HIV-1 RNA level, CD4 cell count, nadir CD4 cell count, cholesterol, triglycerides, and date of HIV di- agnosis were all obtained by reviewing the patient’s medical records. For HIV-infected women on ART, virologic suppres- sion was defined as plasma HIV-1 RNA <400 copies/mL.

**Statistics**

Demographic characteristics, anthropometric, and laboratory values are described by mean and standard deviation for continuous variables and by frequency and percent for categorical variables by group. Paired t tests or Wilcoxon rank sum tests were used for between-group comparisons as distributionally appropriate for continuous variables and χ2 tests or Fisher’s exact tests as appropriate for categorical variables. To assess the effect of HIV-1 RNA on REE independent of ART, comparison was made between the naïve and control group. To assess the effect of HIV-1 RNA on REE in the HIV-infected group, comparison was made between the combined naïve and detectable groups and the undetectable group. To assess the effect of ART on REE, comparisons were made between the naïve and combined detectable and undetectable groups, and the naïve and undetectable group. Further comparisons included all HIV-infected groups combined and the control group, the combined naïve and detectable groups and the control group, the control and ART-treated groups (combined detectable and undetectable), and the control and undetectable groups. For clarity, groups are referred to by numbers: naïve to ART=1, on ART=2, and control=3. Group 2 was further subdivided based on plasma HIV-1 RNA level: undetectable HIV-1 RNA=2a, detectable HIV-1 RNA=2b. To control for the effect of body cell mass and then body cell mass and anthropometric variables differing between the two groups being compared, multivariable analysis of covariance was performed. Log-transformed REE was used for all comparisons of REE between groups to uphold the assumption of normality. As an exploratory analysis including the HIV-infected partic- ipants only, Spearman correlation coefficients were deter- mined between REE and continuous variables of interest, as well as energy expenditure predicted by the Harris-Benedict and the Mifflin-St Jeor equations. All statistical tests were two-sided with a 0.05 significance level. All analyses were performed using SAS v. 9.2 (SAS Institute).
Table 1. Selected demographic characteristics, anthropometric, and laboratory results of HIV-infected women and controls

<table>
<thead>
<tr>
<th></th>
<th>Naive (group 1; n=25)</th>
<th>Undetectable (group 2a; n=25)</th>
<th>Detectable (group 2b; n=12)</th>
<th>Control (group 3; n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>40.20±10.10</td>
<td>42.50±10.00</td>
<td>41.30±8.80</td>
<td>39.60±10.90</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>4 (16)</td>
<td>3 (12)</td>
<td>2 (17)</td>
<td>13 (52)</td>
</tr>
<tr>
<td>African American</td>
<td>21 (84)</td>
<td>21 (84)</td>
<td>10 (83)</td>
<td>11 (44)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>1 (4)</td>
</tr>
<tr>
<td><strong>Current smoker</strong></td>
<td>14 (56)</td>
<td>8 (32)</td>
<td>6 (50)</td>
<td>3 (12)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>31.90±10.80</td>
<td>30.90±8.50</td>
<td>26.00±8.00</td>
<td>27.10±6.00</td>
</tr>
<tr>
<td><strong>BCM</strong></td>
<td>25.80±5.40</td>
<td>27.00±4.50</td>
<td>29.40±4.80</td>
<td>28.70±4.20</td>
</tr>
<tr>
<td><strong>Fat (%)</strong></td>
<td>43.50±12.70</td>
<td>41.90±10.50</td>
<td>33.20±13.50</td>
<td>38.30±9.80</td>
</tr>
<tr>
<td><strong>WHR</strong></td>
<td>0.85±0.10</td>
<td>0.89±0.06</td>
<td>0.85±0.04</td>
<td>0.82±0.11</td>
</tr>
<tr>
<td><strong>CD4 (cells/mL³)</strong></td>
<td>517±283</td>
<td>679±366</td>
<td>155±145</td>
<td>—</td>
</tr>
<tr>
<td><strong>Nadir (cells/mL³)</strong></td>
<td>440±203</td>
<td>225±194</td>
<td>56±50</td>
<td>—</td>
</tr>
<tr>
<td><strong>HIV-1 RNA (copies/mL)</strong></td>
<td>53,856±101,490</td>
<td>114±136</td>
<td>96,758±93,712</td>
<td>—</td>
</tr>
<tr>
<td><strong>HIV duration (mo)</strong></td>
<td>45±47.80</td>
<td>108.20±70.80</td>
<td>121.10±55.20</td>
<td>—</td>
</tr>
<tr>
<td><strong>Cholesterol (mg/dL)⁹</strong></td>
<td>173±34.70</td>
<td>201±40.10</td>
<td>164±31.20</td>
<td>—</td>
</tr>
<tr>
<td><strong>Triglycerides (mg/dL)⁹</strong></td>
<td>110±49</td>
<td>157±101</td>
<td>218±230</td>
<td>—</td>
</tr>
<tr>
<td><strong>On PI⁹</strong></td>
<td>—</td>
<td>17 (68)</td>
<td>8 (67)</td>
<td>—</td>
</tr>
<tr>
<td><strong>On NNRTI⁹</strong></td>
<td>—</td>
<td>7 (28)</td>
<td>3 (25)</td>
<td>—</td>
</tr>
</tbody>
</table>

With 25 participants in each of the naïve, undetectable, and control groups, we had 80% power to detect a difference in REE means of 40.4, a clinically significant difference, assuming a common standard deviation of 50 using a two-group t test with a 0.05 two-sided significance level.

**RESULTS**

**Patients’ Characteristics**

Eighty-seven women (62 HIV-infected and 25 controls) were enrolled and completed the study evaluations. Table 1 details the demographic characteristics, anthropometric, and laboratory data by study group. Overall, the HIV-infected women and the control group were well matched by age and BMI, and there were no statistically significant differences between groups in any of the comparisons made with regard to these variables. Overall, the mean age was 40.85±10.04 years and the mean BMI was 29.43±8.71. There were proportionally more African-American participants and current smokers in the HIV-infected groups when compared with controls. None of the subjects identified as Hispanic or Latino. Anthropometric data were largely similar between groups, except as outlined here.

**Effect of HIV Infection on REE Independent of ART (Comparing Group 1 vs Group 3).** Demographics and anthropometric data were similar between groups, with the exception of a larger body cell mass in group 3 (45.82±9.28 lb vs 45.4±5.29 lb; P=0.04 for group 1 vs group 3, respectively). Log-transformed REE (Table 2) was significantly higher in group 1 compared to the group 3 (7.26±0.22 vs 7.14±0.19; P=0.04 for group 1 vs group 3, respectively) and the difference remained significant after adjustment for body cell mass (P=0.008).
Table 2. Mean resting energy expenditure and mean log-transformed resting energy expenditure in HIV*infected women and controls

<table>
<thead>
<tr>
<th></th>
<th>Naïve (group 1; n=25)</th>
<th>Undetectable (group 2a; n=25)</th>
<th>Detectable (group 2b; n=12)</th>
<th>Control (group 3; n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REE</strong> (kcal/d)</td>
<td>1,465 ± 342</td>
<td>1,508 ± 361</td>
<td>1,331 ± 386</td>
<td>1,284 ± 240</td>
</tr>
<tr>
<td>Log-transformed REE</td>
<td>7.26 ± 0.23</td>
<td>7.29 ± 0.22</td>
<td>7.16 ± 0.28</td>
<td>7.14 ± 0.19</td>
</tr>
<tr>
<td>Harris Benedict Equation (kcal/d)</td>
<td>1,577 ± 322</td>
<td>1,502 ± 245</td>
<td>1,408 ± 238</td>
<td>1,477 ± 170</td>
</tr>
<tr>
<td>Mifflin-St Jeor Equation (kcal/d)</td>
<td>1,506 ± 354</td>
<td>1,415 ± 267</td>
<td>1,324 ± 266</td>
<td>1,413 ± 188</td>
</tr>
<tr>
<td>Difference between REE and HBE* (%)</td>
<td>9.40 ± 15.80</td>
<td>1.80 ± 13.60</td>
<td>9.10 ± 13.90</td>
<td>17.20 ± 15.70</td>
</tr>
<tr>
<td>Difference between REE and MSJE** (%)</td>
<td>4 ± 16.30</td>
<td>-4.50 ± 12.90</td>
<td>1.80 ± 11.20</td>
<td>11.80 ± 15.40</td>
</tr>
</tbody>
</table>

*HIV = human immunodeficiency virus.

**REE = resting energy expenditure.

Effect of Detectable HIV Viral Load on REE in HIV-Infected Subjects (Comparing HIV-Infected Groups 1+2b vs Group 2a). Demographics and anthropometric data were similar between groups, with the exception of waist-to-hip ratio (WHR) (0.85 ± 0.08 vs 0.89 ± 0.06; P=0.04 for combined groups 1+2b vs group 2a, respectively). Log-transformed REE was not different between groups (7.23 ± 0.25 vs 7.29 ± 0.22; P=0.3 for combined groups 1+2b vs group 2a, respectively) and adjusting for body cell mass (P=0.1) or body cell mass WHR (P=0.52) did not make a difference.

Effect of ART on REE in HIV-Infected Subjects (Comparing Group 1 vs Group 2 and Group 1 vs Group 2a). We assessed the effect of ART on REE by first comparing REE between group 1 (n=25) and ART-treated women (group 2; n=37). Demographics and anthropometric data were similar between these two groups. Also, log-transformed REE was not statistically different between groups (7.26 ± 0.23 vs 7.25 ± 0.25; P=0.81 for group 1 vs group 2, respectively), and adjusting for body cell mass did not change the results (P=0.56).

Because having detectable HIV-1 RNA on ART usually indicates suboptimal adherence to ART, we also compared REE in group 1 vs 2a. Demographics and anthropometric data were similar between these two groups. Log-transformed REE was significantly different between groups (7.26 ± 0.23 vs 7.29 ± 0.22; P=0.65 for group 1 vs 2a, respectively) and adjusting for body cell mass did not change the results (P=0.25).

Other Comparisons between Healthy Controls and HIV-Infected Subjects

All HIV-Infected Groups Combined vs Control (Comparing Groups 1+2 vs Group 3). Demographics and anthropometric data were similar between groups, with the exception of WHR (0.87 ± 0.08 vs 0.82 ± 0.11; P=0.001 for groups 1+2 vs group 3, respectively). Log-transformed REE was significantly higher in groups 1+2 compared to group 3 (7.26 ± 0.24 vs 7.14 ± 0.19; P=0.03, respectively) and the difference remained significant after adjusting for body cell mass (P=0.0006) and body cell mass and WHR (P=0.01).

Detectable HIV Viral Load vs Controls (Comparing Groups 1+2b vs Group 3). Demographics and anthropometric data were similar between groups with the exception of WHR (0.85 ± 0.08 vs 0.82 ± 0.11; P=0.03 for groups 1 and 2b vs 3, respectively). Log-transformed REE was not significantly different between groups (7.23 ± 0.25 vs 7.14 ± 0.19; P=0.19, for groups 1+2b vs group 3, respectively); however, the difference became significant after adjusting for body cell mass (P=0.009) and remained when adjusting for body cell mass and WHR (P=0.03).

Control vs HIV-infected on ART (Comparing Group 3 vs Group 2). Demographics and anthropometric data were similar between groups, with the exception of WHR (0.82 ± 0.11 vs 0.89 ± 0.06; P=0.0002 for group 3 vs group 2, respectively). Log-transformed REE was not statistically different between groups (7.14 ± 0.19 vs 7.25 ± 0.25; P=0.07 for group 3 vs group 2, respectively); however, the difference became significant after adjusting for body cell mass (P=0.0008) and remained when adjusting for body cell mass and WHR (P=0.03).

Control vs HIV-Infected on ART with Virologic Suppression (Comparing Group 3 vs Group 2a). Demographics and anthropometric data were similar between groups, with the exception of WHR (mean=0.82 ± 0.11 vs 0.89 ± 0.06; P=0.0002 for group 3 vs 2a, respectively). Log-transformed REE was significantly greater in the undetectable group (7.14 ± 0.19 vs 7.29 ± 0.22; P=0.01 for group 3 vs 2a, respectively). The difference remained significant after adjustment for body cell mass (P=0.0003) and body cell mass and WHR (P=0.02).

Correlation Analysis

Table 3 shows the correlation coefficients between REE and several continuous variables. In the HIV-infected women, REE was positively correlated with BMI, WHR, body cell mass, fat, and both current and nadir CD4 counts. REE was not correlated with age, HIV-1 RNA level, HIV duration, total cholesterol, or triglyceride levels. Predicted energy expenditure, using the Harris-Benedict and the Mifflin-St Jeor equations,
positively correlated with REE ($r=0.79; P<0.0001$ and $r=0.78; P<0.0001$, respectively).

**DISCUSSION**

For the first time, we show that REE is significantly different between HIV-infected women naive to ART compared to age and BMI-matched healthy controls. In addition, there was no difference in REE by ART status or detectable HIV-1 RNA level. This suggests that the differences seen in REE are the result of HIV infection itself and not to ART.

Interestingly, in an exploratory analysis including just the HIV-infected women, HIV-1 RNA levels were not correlated with REE. This supports the findings of the Grinspoon study.9 CD4 cell count was positively correlated with REE in our study.

Another important finding of our study was that measured REE was strongly correlated with both the Harris-Benedict and Mifflin-St Jeor equations used to predict energy expenditure (see Table 3). This supports the findings of Lane and Provost-Craig, who found that the Harris-Benedict equation was found as well.10 This is of practical significance for registered dietitians who perform nutritional assessments because this indicates that these equations still accurately predict REE needs. An appropriate activity factor can be applied to determine total energy expenditure.

The mechanism of increased REE is not fully understood. While cytokines have been indicated for a reduction in appetite and elevated REE in certain disease states, there was no correlation between tumor necrosis factor-α and REE in a study of HIV-infected women by Lane and Provost-Craig.10

The half-life of serum cytokines is relatively short and, therefore, may explain the results of the Lane and Provost-Craig study.

The presence of opportunistic infections can elevate REE; however, the subjects in our study were asymptomatic and did not have secondary infections. Other mechanisms investigated have included lipodystrophy, with some studies indicating an elevation in REE with lipodystrophy16,17 and one indicating a decrease.18 None of our study participants had the diagnosis of lipodystrophy at enrollment. However, WHR was measured, with the HIV-infected women having a significantly higher WHR than the control group; WHR was correlated with REE, although to a lesser degree than other variables, in our study sample ($r=0.37542; P<0.0037$). Lipatrophy has been found to elevate REE in a mostly male population,19 although this variable was not assessed in our study.

As in other studies, we found a strong correlation between body cell mass and REE ($r=0.73497; P<0.0001$). BMI and fat mass were also correlated with REE ($r=0.76238; P<0.0001$; $r=0.73209; P<0.0001$, respectively).

Because early aging is an area of intense investigation and concern in HIV, our findings may have significant clinical implications. A widely accepted theory associates the production of reactive oxygen species, and the resultant oxidative stress, to aging.20-22 Because anywhere from 0.2% to 2% of oxygen reduced in the mitochondria is converted to reactive oxygen species,22,23 it is reasonable to postulate that those with increased REE have, over time, a greater absolute production of reactive oxygen species if tissue oxygen concentration also increases.22 This could lead to more oxidative stress if the amount generated exceeds the cell’s ability to repair such damage.24 Our group has shown that increased oxidative stress, as measured by F2-isoprostanes, is present in HIV and is associated with lipatrophy.25 Interestingly, two studies in healthy adults have linked a high REE with increased mortality.26,27 Restricted feeding in humans and animals has been shown to decrease both REE and oxidized DNA.28 One study in HIV-infected men found beneficial effects on oxidative defense with antioxidant supplementation. It has yet to be shown whether the same effect is seen in women with HIV,29 a possible future direction for study.

The limitations of the present study include the use of BIA measurements instead of dual energy x-ray absorptiometry, the lack of consideration of menstrual cycle in the women studied, and a minimum fasting duration of 4 hours. However, most of the women in the present study came to the study visit in the morning after an overnight fast, increasing the fasting duration to at least 8 hours. In addition, the effects of a meal on metabolism tend to wear off after 4 to 5 hours.30 Due to the potential variability of hydration status throughout the menstrual cycle,31 BIA would ideally be performed when each woman was on a predetermined day of the menstrual cycle.

The authors are aware of the discussion regarding the use of single vs dual and multiple frequency BIA and the limitations of the single frequency method. The significance of the results was found in all but one analysis before adjustment for body cell mass. The subjects in this study were weight stable, increasing the accuracy of the estimation of body cell mass with the single-frequency method. Of note, a Grinspoon study found that single-frequency BIA, dual-energy x-ray absorptiometry, and skinfold measurements were highly correlated.
CONCLUSIONS
We showed that REE is elevated in ART-naïve HIV-infected women and continues to be elevated when on effective ART, regardless of virologic suppression, when compared to age- and BMI-matched healthy women. This suggests an effect of HIV infection itself and not ART on REE. The exact mechanism by which this occurs is unknown, but could be due to heightened inflammation or immune activation, which occurs in HIV infection. Longitudinal studies of ART initiation incorporating REE measurements are needed to fully assess the effect of HIV infection, with its resulting oxidative stress and heightened inflammation, on REE. In addition, the effect of specific antiretrovirals on REE has never been assessed and should be planned in future large ART initiation studies.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST
G. A. McComsey has served as a scientific advisor or speaker for Bristol Myers Squibb, GlaxoSmithKline, and Tibotec; has received research grants from Bristol Myers Squibb, GlaxoSmithKline, Merck, and Gilead Sciences; and is currently serving as the DSMB Chair for a Pfizer-sponsored study. No potential conflict of interest was reported by the other authors.

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