Age-Related Skeletal Muscle Decline Is Similar in HIV-Infected and Uninfected Individuals

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Background. Skeletal muscle (SM) mass decreases with advanced age and with disease in HIV infection. It is unknown whether age-related muscle loss is accelerated in the current era of antiretroviral therapy and which factors might contribute to muscle loss among HIV-infected adults. We hypothesized that muscle mass would be lower and decline faster in HIV-infected adults than in similar-aged controls.

Methods. Whole-body 1H-magnetic resonance imaging was used to quantify regional and total SM in 399 HIV-infected and 204 control men and women at baseline and 5 years later. Multivariable regression identified associated factors.

Results. At baseline and Year 5, total SM was lower in HIV-infected than control men. HIV-infected women were similar to control women at both time points. After adjusting for demographics, lifestyle factors, and total adipose tissue, HIV infection was associated with lower Year 5 SM in men and higher SM in women compared with controls. Average overall 5-year change in total SM was small and age related, but rate of change was similar in HIV-infected and control men and women. CD4 count and efavirenz use in HIV-infected participants were associated with increasing SM, whereas age and stavudine use were associated with decreasing SM.

Conclusions. Muscle mass was lower in HIV-infected men compared with controls, whereas HIV-infected women had slightly higher SM than control women after multivariable adjustment. We found evidence against substantially faster SM decline in HIV-infected versus similar-aged controls. SM gain was associated with increasing CD4 count, whereas stavudine use may contribute to SM loss.

Key Words: Sarcopenia—Lipoatrophy—Fat redistribution—Body composition.

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Despite the introduction of highly active antiretroviral therapy, HIV-infected persons remain at increased risk of non–AIDS-related mortality and morbidity (1,2). It has been reported that many of these conditions appear to occur at an earlier age in HIV-infected persons (3). Skeletal muscle (SM) mass is known to decrease both with advanced age (sarcopenia) and with disease (cachexia), including HIV infection (4). Unintentional weight loss and SM cachexia are associated with increased mortality risk (5–8). Even in the modern highly active antiretroviral therapy era, wasting and weight loss remain common in some HIV-infected patients (7).

It is unknown whether the rate of age-related muscle loss is accelerated in HIV infection and which factors might contribute to muscle loss among HIV-infected adults. In uninfected participants, in the cross-sectional National Health and Nutrition Examination Survey (NHANES) study, dual-energy X-ray absorptiometry (DXA)-measured fat-free mass appeared to remain stable or increase until age 40–45 years and was lower in older ages in both men and women (9). In an uninfected cohort recruited at age 46–80 years, muscle mass declined at a rate of 1%–2% per year (10). In adults aged 70–79 years, Goodpaster and colleagues (11) reported...
a loss of leg lean mass of approximately 1% per year. Another recent study of men older than 50 years (8) found a loss of 92 g (0.16%) per year in total lean mass. Physical activity was controlled for in some (8,10) but not all (9,11) studies.

Few longitudinal studies of lean mass in HIV infection have been conducted in the recent highly active antiretroviral therapy era, and most were small. In one report, 23 clinically stable HIV-infected adults (17 men and 6 women) were studied before and 24 months after initiation of dual nucleoside reverse transcriptase inhibitor–based therapy; lean mass was relatively stable by DXA (0.5 kg decline, \( p = .37 \)) (12). Another 2-year study of 23 HIV-infected men (17 on highly active antiretroviral therapy) and 26 healthy controls found that lean mass tended to increase in HIV-infected (1.3 kg, \( p = .13 \)) and was stable in controls (13). A study of 152 HIV-infected men and women found overall increases in DXA-measured trunk lean mass of 0.9% per year, with little change in extremity lean mass (14). A study of 101 HIV-infected men with lipodystrophy found DXA-measured lean mass stable over 4 years (15). Because both lean and fat mass increase when body weight increases (16–18), potential interactions between lean and fat need to be considered when analyzing and interpreting longitudinal alterations in lean mass.

No large nationally representative study has compared SM changes over several years in a population of HIV-infected and control participants. The aim of this analysis was to determine the rate of SM change and factors associated with SM after 5 years of follow-up in the Study of Fat Redistribution and Metabolic Change in HIV infection (FRAM), a large, nationally representative multi-ethnic cohort of HIV-infected and control men and women, in which regional adipose tissue (AT) distribution and changes in AT over time have been studied (19–21). We hypothesized that muscle mass would be lower and decline faster in HIV-infected adults than in similar-aged controls.

METHODS

The FRAM study was initially designed to evaluate the prevalence and correlates of changes in fat distribution, insulin resistance, and dyslipidemia in a representative sample of HIV-infected participants and HIV-seronegative controls in the United States. The methods used in the FRAM study have been described in detail previously (22).

Study Population

HIV-infected participants were recruited from 16 HIV or infectious disease clinics or cohorts. HIV diagnosis was determined at each individual clinical site. Control participants were recruited from two centers from the Coronary Artery Risk Development in Young Adults (CARDIA) study (23). CARDIA participants were originally recruited as a sample of healthy 18- to 30-year-old Caucasian and African American men and women from four cities in 1985–1986 for a longitudinal study of cardiovascular risk factors, with population-based recruitment in three cities and recruitment from the membership of a prepaid health care program in the fourth city. Body mass index (BMI) in the CARDIA population and within each group is very similar to NHANES. FRAM recruited CARDIA participants enrolled in an ancillary study, the Visceral Fat and Metabolic Rate in Young Adults (VIM) Study (24). The VIM ancillary study recruited participants from two of the four CARDIA centers in 1995–1996. The VIM ancillary study enrolled approximately 100 CARDIA participants from each of the race and gender groups with BMI distributed equally above and below race- and gender-specific medians of the population-based CARDIA study.

FRAM Year 5 retention outcomes for participants initially enrolled have been reported (2). At the second exam (Year 5), 261 HIV-infected participants and 14 controls could not be recontacted, 128 HIV-infected participants and 6 controls were deceased, and 213 HIV-infected participants and 36 controls declined to enroll. Compared with those who were either alive or had unknown vital status at Year 5, those who died were older, more often African American, and had a higher prevalence of smoking, detectable HIV RNA, hepatitis C, history of AIDS, and more kidney disease and inflammation (25).

The Year 5 follow-up exam included 581 HIV-infected participants and 241 controls with baseline measures. Three control participants were excluded because Year 5 review indicated that they were now taking antiretroviral (ARV) medications. HIV and control participants were excluded if they had contraindications to MRI, such as metal implants, claustrophobia, or weight greater than 136 kg and height greater than 196 cm as per specifications of the scanner manufacturers. We report here on the subset of 399 HIV-infected participants and 204 controls who had SM measured at both time points. Because a greater percentage of HIV-infected participants did not have measured MRI and were more likely to be deceased by the second exam, we adjusted analyses as described below to address the concern of selection bias. Institutional review boards at all sites approved the protocols for both FRAM exams.

Magnetic Resonance Imaging

Whole-body magnetic resonance imaging (MRI) was performed to quantify regional and total SM and AT volumes, as described in detail previously (11,19,22,26). All scans were read by the same analyst at the Obesity Research Center, St. Luke’s-Roosevelt Hospital, New York, NY. Imaging techniques and anatomical sites (based on bone landmarks) were identical between HIV-infected and control participants. In the baseline FRAM exam, SM volume included intermuscular AT. At the Year 5 exam, SM and intermuscular AT (27) were measured separately. We
Therefore added intermuscular AT to SM at Year 5 to enable proper comparison of baseline and Year 5 SM measures.

Anatomic sites considered in this analysis were: legs, lower trunk (abdomen and back), upper trunk (chest and back), and arms. MRI reproducibility averaged 0.7% for SM and 1.1% for AT (26). Volumes were converted to mass, assuming a density of 0.92 kg/L for fat and 1.04 kg/L for muscle (26). SM and AT measures were adjusted for height and frame size (measured by elbow breadth), as described below. We did not adjust to BMI, as BMI is influenced by the phenomenon being studied: quantity of lean.

**Other Measurements**

Height and weight were measured by standardized protocols. Frame size (28) was assessed by measuring right elbow breadth with a bicondylar Vernier caliper (±0.1 cm). Standardized questionnaires were used to determine demographic characteristics; medical history; HIV risk factors; and use of alcohol, tobacco, and illicit drugs (22,23). Research associates interviewed participants and reviewed medical charts regarding ARV medication use. A diagnosis of AIDS was made by history of opportunistic infection or CD4 count <200 c/µL.

Hepatitis C RNA testing was performed on frozen sera using the Bayer Versant 3.0 branched DNA (bDNA) assay (Leverkusen, Germany) in the entire cohort. CD4 lymphocyte count and percent, HIV RNA level in HIV-infected participants, and other blood specimens were analyzed in a single centralized laboratory (Covance, Indianapolis, IN). Insulin resistance was calculated using the homeostasis model assessment from fasting glucose (milligrams per deciliter) and insulin (micromvits per milliliter) concentrations as: (insulin × glucose)/405. Cystatin C was measured in previously frozen sera stored at −70°C, using a particle-enhanced immunonephelometric assay (BNII nephelometer; Dade Behring Inc., Deerfield, IL).

**Statistical Methods**

Analyses that compared characteristics of HIV-infected and control groups using t tests. SM changes from baseline to the 5-year follow-up exam were compared using a paired t test within HIV-infected and control groups separately. Spread in 5-year SM change between HIV-infected and control participants was compared using Levene’s test for equality of variance.

We analyzed SM using multivariable linear regression with robust standard errors (30,31) with Year 5 SM or SM change as the dependent variable. All analyses were adjusted for height, frame size, and quadratic terms for height and frame size, except where indicated otherwise. Separate models were constructed, controlling sequentially for (a) HIV status and demographic factors, (b) lifestyle factors, and (c) AT, because subcutaneous AT changes are prevalent in HIV infection and differ between men and women (19–21). To ensure that models were not overfit, we built parsimonious models using a backward stepwise procedure. We also examined associations of homeostasis model assessment and cystatin C with SM in exploratory analyses. Age, gender, and race were included in every model. Interactions of HIV status, gender, ethnicity, and age with SM were assessed and included if they reached statistical significance. The linearity assumption was tested for continuous measures by adding quadratic terms to the models (p > .4 for all linear models of change in SM shown) and by examining generalized additive models (32). We also analyzed relative percentage change in SM, defined as log(follow-up SM) minus log(baseline SM), which is less skewed than percentage change and which downweights exceptionally large values of SM.

Candidate lifestyle factors assessed that might affect SM included physical activity, tobacco use, alcohol use, adequate food intake, and illicit drug use. We considered baseline, Year 5, and changes from baseline as candidates in our models. Candidate HIV-specific factors (tested only for HIV models) included AIDS diagnosis, reported HIV duration, HIV RNA level (log 10), current and nadir CD4 count (log 2), hepatitis C infection (by RNA), days since last opportunistic infection, recent opportunistic infection status (last 100 days), and HIV risk factors. In multivariable models controlling for the above factors, we evaluated ever use, duration on, and duration off each individual ARV drug and ARV class as previously defined (19).

Multiple imputation utilizing the Markov chain Monte Carlo method for arbitrary missing data was used to impute missing covariate values (33). HIV-infected participants were missing MRI more often than controls due in part to higher rates of death and loss to follow-up between exams, as described elsewhere (2). To mitigate potential selection bias, we therefore adjusted estimates using an inverse probability weighting approach (34) by modeling each
participant’s probability of having non-missing SM using logistic regression analysis. The inverse of this probability was used as a weight (applied to participants with measured SM) in multivariable regression analyses.

All analyses were conducted using the SAS system, version 9.2 (SAS Institute, Inc., Cary, NC).

**Results**

**Participants**

MRI-measured SM was available on 603 participants whose demographic and baseline characteristics are presented in Table 1. Within the age range of controls (33–45 years), HIV-infected and control participants were similar in age, height, and percentage of Caucasians and African Americans, but HIV-infected participants were more often men (67% vs 51%) through the design of the controls. At baseline, control participants weighed more and had higher BMI.

**Comparison of Baseline and Year 5 Muscle Mass in HIV-Infected and Control Participants**

Mean SM at baseline and Year 5 in HIV-infected and control participants, restricted to the age range of controls (age 33–45 years at baseline) and adjusted as described in the Methods section, are shown in Figure 1. HIV-infected men had lower mean total SM compared with control men at both baseline (29.0 vs 31.4 kg, \( p < .0001 \)) and Year 5 (28.8 vs 31.6 kg, \( p < .0001 \)). By comparison, HIV-infected women and control women had similar mean total SM at baseline (26.3 vs 25.5 kg, \( p = .23 \)) and Year 5 (26.5 vs 26.2 kg, \( p = .64 \)).

Because HIV infection remained associated with lower SM in men at year 5 in men, we examined models of Year 5 total SM to determine whether differences between HIV-infected and control participants remained after multivariable adjustment (Table 2). After multivariable adjustment for demographic factors (age, sex, and race), HIV-infected men averaged \( −3.3 \) kg lower SM compared with control men (\( p < .0001 \)), but SM was similar in HIV-infected and control women.

![Figure 1. Comparison of total skeletal muscle at baseline and year 5 by HIV status and gender. Solid symbol = HIV + patients and open symbol = control. Skeletal muscle is adjusted for height and frame size as described in the Methods section. Age restricted and opportunistic infection excluded. HIV versus control \( t \) test of HIV versus control at baseline (FRAM1) and Year 5 (FRAM2).](https://academic.oup.com/biomedgerontology/article-abstract/66A/3/332/600940)
Comparison of Changes in Muscle Mass of HIV-Infected and Control Participants

The distribution of change in total SM between baseline and Year 5 is shown in Figure 2. Because similar distributions for SM change were seen in men and women (data not shown), analysis of change was pooled. Overall, the average change in absolute SM for HIV-infected and control participants was small (−0.28 kg, p < .0001). Further adjustment for total AT attenuated the HIV association in men to −1.3 kg, p = .020. In women, HIV infection was associated with 1.2 kg higher SM (p = .022) in fully adjusted models that included AT. The test for HIV by gender interaction was statistically significant in all models. Similar results were found for regional SM (data not shown). Results were also similar in separate sensitivity analyses: (a) without multiple imputation or adjustment for selection bias and (b) using the full age range in the HIV sample (19–76 years at baseline).

In a sensitivity analysis, we restricted the age in the multivariable model analysis to HIV-infected and control participants in the same age range; we also found little women (only 0.23 kg higher in HIV-infected women, p = .68). The HIV association in men was somewhat attenuated after adjusting for demographic and lifestyle factors (−2.8 kg, p < .0001). Further adjustment for total AT attenuated the HIV association in men to −1.3 kg, p = .020. In women, HIV infection was associated with 1.2 kg higher SM (p = .022) in fully adjusted models that included AT. The test for HIV by gender interaction was statistically significant in all models. Similar results were found for regional SM (data not shown). Results were also similar in separate sensitivity analyses: (a) without multiple imputation or adjustment for selection bias and (b) using the full age range in the HIV sample (19–76 years at baseline).

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We also sought to determine whether there was evidence for accelerated SM loss in HIV-infected participants. Baseline age was negatively associated with SM change in both HIV-infected and control participants (Figure 3), meaning that on average younger participants experienced SM gains and older participants experienced SM losses. We therefore modeled the difference in 5-year SM change between HIV-infected and control participants, with separate estimates for different ages (Table 3). After multivariable adjustment for demographics, the expected 5-year SM changes from baseline for individuals aged 35, 40, and 45 years at baseline were small, and none of the differences between HIV and controls in expected SM change reached statistical significance. Estimated 5-year SM change for a 35-year-old participant was +0.75 kg (p = .020) in controls and +0.28 kg (p = .34) in HIV-infected patients. Expected SM change for a 40-year-old participant was +0.19 kg (p = .39) in controls and −0.14 kg (p = .61) in HIV participants. Expected SM change for a 45-year-old participant was −0.36 kg (p = .27) in controls and −0.55 kg (p = .055) in HIV participants.

After further multivariable adjustment for physical activity, smoking, and change from baseline in total AT, the differences in SM between HIV and control narrowed and decreased in statistical significance. Expected 5-year SM change in 35-year-old HIV-infected participants was −0.19 kg lower than controls (p = .64), −0.064 kg lower at age 40 years (p = .84), and +0.067 kg higher at age 45 years (p = .86).

In a sensitivity analysis, we restricted the age in the multivariable model analysis to HIV-infected and control participants in the same age range; we also found little

Table 2. Multivariable Linear Regression Analysis of Year 5 Muscle Mass by HIV Status

<table>
<thead>
<tr>
<th>HIV+ (n = 240)</th>
<th>Controls (n = 204)</th>
<th>p Value</th>
<th>HIV+ (n = 161)</th>
<th>Controls (n = 105)</th>
<th>p Value</th>
<th>HIV+ (n = 79)</th>
<th>Controls (n = 99)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total SM (kg), M ± SD</td>
<td>28.1 ± 4.5</td>
<td>28.8 ± 4.8</td>
<td>&lt;.0001</td>
<td>28.8 ± 4.6</td>
<td>31.6 ± 4.8</td>
<td>&lt;.0001</td>
<td>26.5 ± 5.2</td>
<td>26.2 ± 4.7</td>
</tr>
<tr>
<td>Adjusted for demographics</td>
<td>−1.79 (−2.64 to −0.95)</td>
<td>&lt;.0001</td>
<td>−3.34 (−4.50 to −2.18)</td>
<td>&lt;.0001</td>
<td>0.23 (−0.87 to 1.32)</td>
<td>.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for Demographic + lifestyle</td>
<td>−2.78 (−3.97 to −1.59)</td>
<td>&lt;.0001</td>
<td>1.07 (−0.037 to 2.18)</td>
<td>.058</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>−0.24 (−1.09 to 0.61)</td>
<td>.58</td>
<td>−1.33 (−2.46 to −0.21)</td>
<td>.020</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Demographic, lifestyle, AT)†</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: Results above are age restricted and OI excluded. Outcome is raw SM; model controls for height, frame size, and quadratic terms. Covariates were selected from Year 5 exam. Bolded p-values denote statistical significance. AT = adipose tissue; CI = confidence interval; OI = opportunistic infection; SM = skeletal muscle.

† Mean ± SD for SM is adjusted for height, frame size, and quadratic terms, as in Figure 1.
Factors Associated With Muscle Mass in HIV-Infected Participants

We used multivariable analysis to identify factors that were independently associated with 5-year change in total SM (Table 4). Overall, the average change in SM was nearly zero (Figure 2), although there was a broad distribution of change. We adjusted for demographics, lifestyle factors, HIV-related factors, and AT. After adjustment, aging was associated with decreased change in SM, whereas physical activity and increases in CD4 were associated with increased change in SM. Among those with no stavudine exposure, the average change in SM was +0.18 kg, but each year of exposure was associated with a larger SM loss (−0.22 kg/year, \( p = .0061 \)). By contrast, longer exposure to efavirenz was associated with smaller SM loss (+0.15 kg/year, \( p = .047 \)). Increases in total AT were strongly associated with increased change in SM. There were no statistically significant interactions between age and demographics, lifestyle factors, AT, or HIV-specific factors.

Discussion

In this study of MRI-measured total body SM mass, we found that age-associated SM changes occurred at a similar rate over 5 years in HIV-infected adults as it did in similar-aged HIV-negative controls. Even after multivariable adjustment, estimates for SM change were similar between younger (35–40 years) as well as older (40–45 years) HIV-infected participants and controls. These data suggest that over 5 years, the typical rate of age-associated SM loss is not greater or accelerated in 33- to 45-year-old HIV-infected adults in the era of modern ARV therapy.

There were differences between men and women in the association of HIV infection with SM levels at both exams. After controlling for age, race, lifestyle factors, and adiposity, HIV-infected men had less total SM than control men at baseline, and their SM remained lower than in controls after 5 years. It is likely that some of the HIV effect on SM may strongly associated with higher SM. Results were similar when stratified by gender, although the indinavir association was stronger in men.

Factors Associated With Change in Muscle Mass in HIV-Infected Participants

We used multivariable analysis to identify factors that were independently associated with 5-year change in total SM (Table 4). Overall, the average change in SM was nearly zero (Figure 2), although there was a broad distribution of change. We adjusted for demographics, lifestyle factors, HIV-related factors, and AT. After adjustment, aging was associated with decreased change in SM, whereas physical activity and increases in CD4 were associated with increased change in SM. Among those with no stavudine exposure, the average change in SM was +0.18 kg, but each year of exposure was associated with a larger SM loss (−0.22 kg/year, \( p = .0061 \)). By contrast, longer exposure to efavirenz was associated with smaller SM loss (+0.15 kg/year, \( p = .047 \)). Increases in total AT were strongly associated with increased change in SM. There were no statistically significant interactions between age and demographics, lifestyle factors, AT, or HIV-specific factors.

Table 3. Estimated 5-Year Change in Total SM (kg) by HIV Status (not age restricted)

<table>
<thead>
<tr>
<th>Baseline Age</th>
<th>Age 35</th>
<th></th>
<th>Age 35</th>
<th></th>
<th>Age 35</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 204)</td>
<td>+0.75 (0.12 to 1.38)</td>
<td>.020</td>
<td>+0.19 (−0.24 to 0.62)</td>
<td>.39</td>
<td>−0.36 (−1.00 to 0.28)</td>
<td>.27</td>
</tr>
<tr>
<td>HIV+ (n = 399)</td>
<td>+0.28 (−0.29 to 0.85)</td>
<td>.34</td>
<td>−0.14 (−0.67 to 0.39)</td>
<td>.61</td>
<td>−0.55 (−1.11 to 0.0052)</td>
<td>.052</td>
</tr>
<tr>
<td>HIV vs control (demographic adjusted)*</td>
<td>−0.47 (−1.27 to 0.33)</td>
<td>.25</td>
<td>−0.33 (−0.93 to 0.28)</td>
<td>.29</td>
<td>−0.19 (−0.97 to 0.59)</td>
<td>.64</td>
</tr>
<tr>
<td>HIV vs control (fully adjusted)†</td>
<td>−0.19 (−1.00 to 0.61)</td>
<td>.64</td>
<td>−0.064 (−0.67 to 0.54)</td>
<td>.84</td>
<td>0.067 (−0.66 to 0.79)</td>
<td>.86</td>
</tr>
</tbody>
</table>

Notes: Estimated 5-year change for those aged 35, 40, and 45 years at baseline from pooled not age-restricted HIV versus control models. Estimates are from linear models not models stratified by age. CI = confidence interval; SM = skeletal muscle.

Outcome: \( 5 \times \) (raw change in total SM)/(years between exams).

*Model is SM change = HIV + demographics (age, race, and gender).
†Model is SM change = HIV + demographics + lifestyle (Year 5) + change in AT.
be mediated by lifestyle factors and especially the decreased adiposity of lipoatrophy. However, despite the significant attenuation of the HIV effect in men when controlling for lifestyle and especially AT, there is an additional effect of HIV in men, beyond what these factors reflect. By contrast, HIV-infected women, who start with greater AT, appeared to have greater total SM at Year 5 compared with control women after multivariable adjustment, with little attenuation when adjusting for AT. These findings are consistent with the previously published hypothesis that the greater AT mass at baseline in women protects against subsequent loss of SM (35–37).

Regardless, comparisons by sex indicated that over 5 years, the average change in SM in HIV-infected men and women was similar to control men and women over the examined control age range. In HIV-infected participants, we found that an increase in CD4 count over the 5 years of study was a strong predictor of more gain/less loss in SM (and conversely CD4 decrease was associated with more loss/gain in SM). This might have been expected because low CD4+ T-cell count and high plasma HIV viremia are associated with a lower muscle protein synthesis rate, and ARV therapy–induced improvements in immune and virologic status increase muscle protein synthesis and reduce some aspects of muscle proteolysis (38,39), although the precise molecular level regulator is not clear.

We found that higher CD4 count and indinavir exposure were associated with greater Year 5 SM, even after controlling for total AT. The indinavir finding appears to contradict in vitro and rodent findings, where indinavir exposure acutely reduced SM protein synthesis and impaired protein translation initiation and efficiency in cultured C2C12 myocytes and in rats (40). Although the positive association of CD4 count with SM is not novel (4,14,41), we find no other reports in the literature of a positive relationship of indinavir with muscle mass. We cannot rule out confounding factors in those who were able to continue longer use of indinavir. Of note, unlike stavudine and efavirenz, indinavir did not show an independent association with SM change.

After adjustment, exposure to stavudine was associated with more loss in SM, whereas efavirenz was associated with smaller losses in SM. The association of stavudine use with lower SM even after multivariable adjustment for AT raises the question of other toxic effects of stavudine, perhaps on nerve or muscle. Laboratory animals (42,43) and HIV-seronegative adults (44) exposed to a short course of stavudine experience sustained adverse effects on SM mitochondrial DNA copy number, biogenesis, and function, but their relationship to muscle protein mass has not been reported. We are unaware of any data on the effect of efavirenz on SM. In contrast, the Nutrition For Healthy Living Study found little association of stavudine with lean body mass changes (14) and did not report on efavirenz use.

There are some limitations to our study. At baseline, the HIV-infected participants spanned a wider age range (19–76 years) than the controls (33–45 years). This limits our ability to compare the estimated rates of SM change in HIV+ versus control in older participants. This was an observational study, so we cannot infer a causal link between stavudine, efavirenz, or indinavir use with SM amounts or changes. The findings suggest against SM declining substantially faster in HIV-infected adults than in similar-aged controls. The broad confidence intervals in Table 2 leave open some possibility that clinically relevant SM loss may be accelerated in HIV-infected adults. However, the distribution of SM change was much broader in HIV-infected men and women compared with controls, even in age-restricted analyses. These data suggest that greater weight loss does occur in a subset of HIV-infected participants, and the multivariable analysis supports the concept that weight change is related to CD4 count. An additional limitation is that the SM measure at baseline included intramuscular AT, whereas at Year 5 SM and intermuscular AT were measured separately. We dealt with this
by adding intermuscular AT to SM to make the Year 5 measurement comparable to baseline. Although we controlled for physical activity, we were unable to control for muscle strength or quality. Previous studies have found that muscle function may be more important than mass in predicting morbidity and mortality (11, 45, 46). We also did not assess for the frailty-related phenotype, which is increased in HIV infection (47); the frailty-related phenotype is strongly associated with low CD4 count, consistent with our finding of a positive association of change in CD4 count with change in SM. Finally, there may have been incomplete or inadequate control for factors that may confound or explain the association between HIV infection and SM. For example, we did not measure gonadal steroid levels, which decline with age and are lower in HIV infection.

A major strength of our study is the comparison of SM change over 5 years directly measured using MRI in HIV-infected and control adults. This allowed us to account for normal SM changes with aging. The controls were enrolled in the VIM substudy (24) of the CARDIA cohort, where the average BMI is similar to that of the nationally representative sample of NHANES. A further strength of our study is the ability to adjust for AT amount and changes, which influence SM.

In conclusion, 5 years after the first exam in the FRAM study, average change in SM was similar in HIV-infected and control participants. HIV-infected men had lower SM compared with control men, even after controlling for demographics, lifestyle factors, and AT. HIV-infected women had similar or slightly higher SM than control women. We found suggestive evidence against substantially accelerated SM loss in HIV infection. HIV-infected participants were more prone to gain as well as lose SM compared with controls. Increased CD4 count was associated with more SM gain/less loss and decreased CD4 count with more loss/less gain. Given that an increase in CD4 count is an indication of the effectiveness of ARV therapy and a decrease in CD4 an indication of failure of ARV therapy, our data support the concept that effective ARV therapy has an important impact on changes in SM. As HIV muscle loss and wasting 5% or more have been associated with morbidity and mortality (8), the long-term consequences of the wide spectrum of SM loss or gain found here need additional study.

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Conflict of Interest
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Supplementary Material
Supplementary material can be found at: [http://biomed.gerontologyjournals.org/]

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References


