$CD4^+$ Cell Count, Viral Load, and Highly Active Antiretroviral Therapy Use Are Independent Predictors of Body Composition Alterations in HIV-Infected Adults: A Longitudinal Study

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Background. To understand the concurrent effects of human immunodeficiency virus (HIV) infection, the immune system, and antiretroviral therapy on body composition alterations, we examined annualized composition changes in HIV-infected adults who were receiving stable antiretroviral therapy.

Methods. With use of data from the Nutrition For Healthy Living Study, we performed multivariate analyses using longitudinal models to evaluate the relationship of $CD4^+$ cell count, viral load, and highly active antiretroviral therapy (HAART) or antiretroviral therapy (ART) with changes in trunk and extremity composition for 110 men and 42 women who provided data relating to 194 study intervals (i.e., intervals of time between 2 assessment visits). Of these intervals, 165 involved HAART use (89.7% involved protease inhibitor–based regimens), and 29 did not involve HAART use. Patients receiving HAART or ART (who had continuous use during the interval) were compared with HAART- or ART-naive subjects.

Results. The median length of intervals between visits was 12.9 months (interquartile range, 12.1–17.6 months). In models adjusted for HAART or ART use, baseline $CD4^+$ cell count was positively associated with increased trunk fat (mean increase per year, 2.3% per 100 cells/mm^3; 95% confidence interval [CI], 0.7%–3.9%]) and, in men, with increased extremity fat (mean increase per year, 1.8% per 100 cells/mm^3; 95% CI, 0.6%–3.0%). Increase in $CD4^+$ cell count predicted increased extremity lean mass (mean increase per year, 0.6% per 100 cells/mm^3; 95% CI, 0.05%–1.1%). Higher baseline viral load predicted fat loss (trunk fat loss per year, −5.0% per $\log_{10}$ copies/mL; 95% CI, −9.4% to −0.7%; extremity fat loss per year, −3.4% per $\log_{10}$ copies/mL; 95% CI, −6.1% to −0.6%), as did zidovudine use (trunk fat loss per year, −10.8%; 95% CI, −20.4% to −1.4%; extremity fat loss per year, −4.9%; 95% CI, −9.8% to −0.01%). HAART use independently predicted decreased bone mineral content (extremity bone mineral content loss per year, −1.6%; 95% CI, −3.1% to −0.08%) but did not predict changes in fat or lean mass. Receipt of protease inhibitor–based HAART predicted a −1.9% decrease in extremity bone mineral content per year (95% CI, −3.6% to −0.2%), and zidovudine use predicted a −2.6% decrease in trunk bone mineral content per year (95% CI, −4.4% to −0.8%).

Conclusions. Baseline viral load, $CD4^+$ cell count, and change in $CD4^+$ cell count predicted alterations in trunk fat, extremity fat, and lean mass. HAART use and zidovudine use were associated with bone loss, and zidovudine use was associated with fat loss, but HAART use was not associated with fat mass changes.

The complex array of morphologic changes experienced by many HIV-infected individuals continues to puzzle the medical and scientific community. Common changes have been reported to involve fat mass (FM), lean mass (LM), and bone mass (BM) in a variety of patterns and combinations [1, 2]. A cross-sectional, multicenter study (Fat Redistribution and Metabolic

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Change in HIV Infection Study) comparing HIV-infected persons with healthy control subjects using MRI and dual–energy x–ray absorptiometry (DEXA) suggests that central fat accumulation and peripheral fat atrophy occur independently [3]. Body mass index and percentage of body fat have been implicated in changes in FM [4]. Recent cross-sectional and longitudinal studies report that lean mass may be increased in persons receiving HAART [5–7], whereas other studies have not found such an association [8, 9]. A drug initiation study found that some body composition benefits that occurred after initiating antiretroviral therapy were transient [6]. DEXA findings suggest that bone density is low in many individuals who are seropositive for HIV infection [10–12] and that osteopenia may be associated with fat mass abnormalities [13].

A number of difficulties exist in determining the cause of body composition changes. One concern is the best method to determine regional body composition. Specific medications or antiretroviral therapy drug classes (e.g., protease inhibitors [PIs], nucleoside reverse-transcriptase inhibitors [NRTIs], and non-NRTIs [NNRTIs]) and antiretroviral therapy combinations have been reported to affect body shape differently [5, 14–18], and antiretroviral therapy regimens may change for a variety of reasons. Predictors of body shape changes appear to include baseline $CD4^+$ cell count and viral load, as well as change in $CD4^+$ cell count and viral load [4, 6, 14, 19]. Although there is no perfect marker of cumulative disease severity, $CD4^+$ cell count and viral RNA serve as useful surrogate markers of current disease activity and status. Data suggest that body shape changes continue to occur over time [6, 14, 19].

To our knowledge, no published cohort studies have reported the concurrent effects of medications, HIV disease markers, and other cofactors on measures of regional FM, LM, and BM. We longitudinally analyzed a medication-stable cohort of men and women for independent predictors of regional body composition alterations by DEXA.

SUBJECTS AND METHODS

Patients were participants in Nutrition for Healthy Living, an observational cohort study initiated in 1995 to describe the natural history of HIV disease and progression and to determine the role of nutrition. Subjects ⩾18 years old and with all stages of disease were eligible. Recruitment was through advertisements in local newspapers, radio, health clinics, and physician networks in Boston, Massachusetts, and Providence, Rhode Island. Exclusion criteria included pregnancy, severe diarrhea, diabetes, thyroid disease, malignancies other than Kaposi sarcoma, or poor English language fluency at the time of recruitment. Subjects made study visits at ~6-month intervals and completed surveys and 3-day food records and had blood samples drawn at each visit. Since 1997, annual DEXA scans have been conducted. Enrolled subjects continue to receive care from their treating physicians. Additional details of the study have been published elsewhere [8].

All subjects with a minimum of 2 DEXA scans conducted at visits 11–24 months apart between June 1997 and June 2001 who had complete medication information were included in this analysis (figure 1). For a subject to be included, medication status had to be continuous 1 month prior to and throughout the entire interval. If participants were involved in intervention studies affecting nutrition or body composition, data for these intervals and the 6 months after intervention were excluded. Although 291 Nutrition for Healthy Living participants met the 2-DEXA minimum in this time frame, only 110 men and 42 women met inclusion criteria for this analysis. Data available on single individuals over multiple visits were used to create multiple intervals for some of the subjects. These 152 individuals provided data for 194 intervals. Table 1 reports baseline values for subject characteristics. Table 2 reports the body composition characteristics at the start of each interval used in this analysis. HAART users, defined as those reporting continuous use of HAART throughout the interval, were compared with participants who were deemed to be HAART naive on the basis of our data collection. Similarly, for specific medications and medication classes, continuous users of each medication or medication class were compared with those with no prior or current use of the specified medication or medication class reported. Duration of HAART or of antiretroviral therapy was defined as the number of months of previous cumulative use, as determined by self-report at study entry, plus the months to the start of an interval.

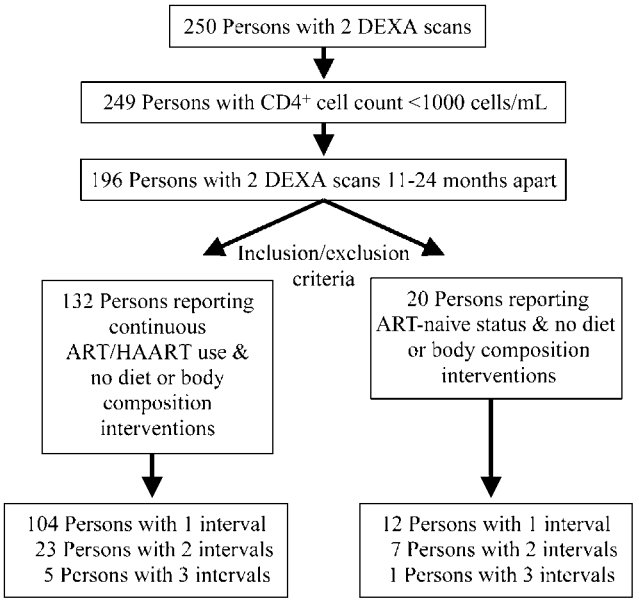

Figure 1. Subject and interval selection. ART, antiretroviral therapy; DEXA, dual-energy x-ray absorptiometry.

Testing protocol. The protocol was approved by the Tufts University Human Investigation Review Committee. Written informed consent was obtained from all participants.

Transverse whole-body DEXA scans were obtained with a single QDR2000 scanner (Hologic) in the array mode, performed by 1 of 3 validated technicians, and followed the prescribed Nutrition for Healthy Living protocol [5]. Whole-body and regional analyses of soft tissues were performed using the QDR2000 product software, version 7.10A (Hologic).

Individual antiretroviral medication use and duration of use were recorded at each visit. Individual antiretroviral drugs were classified by drug class (i.e., PI, NRTI, or NNRTI) and by drug combinations as HAART or non-HAART. HAART regimens included (1) $\geq$2 PIs (PI-based HAART), (2) $\geq$1 PI and $\geq$2 NRTIs (PI-based HAART), (3) $\geq$1 PI, $\geq$1 NRTI, and $\geq$1 NNRTI (mixed HAART), (4) $\geq$2 NRTIs and $\geq$1 NNRTI (NNRTI-based HAART), or (5) $\geq$3 NRTIs (NRTI-based HAART). An antiretroviral therapy user or HAART user was defined as someone reporting continuous antiretroviral therapy or HAART use from the beginning of the interval through the end of the interval. A subject was considered to be antiretroviral therapy naive or HAART naive if there was no antiretroviral therapy or HAART use in the 12 months before entry into the Nutrition for Healthy Living study and none initiated by the date of the final DEXA.

History of AIDS diagnosis included a $CD4^+$ cell count <200 cells/mm^3 at the time of any study visit, self-reported occurrence of any AIDS-defining illness, or AIDS diagnosis before or during participation in the Nutrition for Healthy Living study. HIV RNA level was measured with the Roche Amplicor Monitor RT-PCR assay (Roche Molecular Systems), with a lower limit of detection of 400 copies/mL. Viral loads that were undetectable using this assay were assigned the mean value of 200 copies/mL (i.e., 2.3 $\log_{10}$ copies/mL). $CD4^+$ lymphocyte counts were performed using a specific monoclonal antibody and fluorescence-activated, cell-sorted analysis.

Statistical analysis. Under the guidance of a research statistician, statistical analyses were performed using SAS software, versions 8 and 9 (SAS). Subjects' characteristics were tabulated on the basis of the individual's data at the baseline of their first interval, as well as from all included intervals. Binary characteristics were described by $CD4^+$ cell count and by percentage of nonmissing values. Differences between groups were tested for significance using the χ^2 test or, if there were <5 observations in a cell, using the Fisher exact test. Continuous characteristics were expressed as mean ($\pm$SD) or, if the data were highly skewed, as median (interquartile range). Differences between groups were tested for significance using the Student's t test or, if the data were highly skewed, the Wilcoxon rank sum test. All statistical tests were 2-sided, and α was set at 5%.

The units of analysis were intervals, with an interval defined as the time between 2 DEXA scans. To account for the variations in time between the actual DEXA scan dates, data were proportionally adjusted to a 12-month period, and thereby created annualized change. The dependent variable in regression models was annualized percentage change in 6 body composition measures; these included FM, LM, and bone mineral content (BMC) in trunk and extremities (i.e., arms plus legs), as defined by DEXA. All independent variables (i.e., HAART use, HAART class, antiretroviral therapy use, antiretroviral therapy class, baseline $CD4^+$ cell count, baseline viral load, age, sex, strength training, smoking, and dietary intake) were measured at the beginning of the interval, with the exception of annualized change in $CD4^+$ cell count and viral load, which were measured over the interval. The within-person correlations were modeled as first-order autoregressive, to account for decreasing serial correlation. All models were implemented with SAS Proc Mixed (SAS) to allow for multiple intervals per person. All inferences were conducted using the empirical SE to account for within-person correlation [20]. This allows valid statistical inferences to be made using data that come from >1 observation per person.

Model diagnostics—including Cook's distance, deletion of outliers, residual plots, and normal probability plots—were used to check for influential points, nonnormality, nonlinearities, and unequal variances. The stepwise restricted cubic spline [21] was also used to check for nonlinearities.

Multivariate, longitudinal models separately assessing the effect of $CD4^+$ cell count and viral load on change in FM and LM were adjusted for HAART use, age, sex, sex and HAART interaction, energy intake <35 kcal/kg, and strength training. Separate models assessing the effect of $CD4^+$ cell count and viral load on BMC were also adjusted for calcium intake less than the dietary reference index value, vitamin D intake less than the dietary reference index value, and smoking. Interactions of $CD4^+$ cell count and viral load with sex were tested.

In separate multivariate, longitudinal models, we assessed the effect of antiviral medications on body composition adjusted for age, sex, baseline value and change in $CD4^+$ cell count, baseline value and change in viral load, energy intake <35 kcal/kg, calcium intake less than the dietary reference index value, vitamin D intake less than the dietary reference index value, strength training, and smoking, as appropriate. Interactions of medications with sex were tested.

RESULTS

Subjects. One hundred ten men and 42 women (a total of 152 subject) with a total of 194 intervals met inclusion criteria for this analysis. Seventy-six percent of individuals provided 1 interval for analysis, 20% provided 2 intervals, and 4% provided 3 intervals. Table 1 presents the baseline assessments for the participants. In subjects using HAART at baseline, the median

Table 1. Demographic and clinical characteristics of 152 HIV-infected adults enrolled in a longitudinal study of body composition alterations at baseline visit for the first study interval.

Variable	All subjects	Men	Women
No. (%) of subjects	152 (100)	110 (72)	42 (28)
Age, mean years ± SD	42.7 ± 6.9	43.5 ± 6.8[a]	40.7 ± 6.8
Body mass index, mean ± SD	24.9 ± 4.2	24.4 ± 3.8[b]	26.4 ± 4.8
Time since diagnosis, mean years ± SD	7.4 ± 3.6	7.4 ± 3.6	7.3 ± 3.7
Baseline $CD4^+$ cell count, mean cells/mm^3 ± SD	430 ± 227	398 ± 224[b]	522 ± 211
Annualized Δ in $CD4^+$ cell count, mean cells/mm^3 ± SD	−1 ± 125	4 ± 115	−15 ± 152
Viral load, median $\log_{10}$ copies/mL (IQR)	2.3 (2.3–3.8)	2.3 (2.3–3.9)	2.3 (2.3–3.1)
Annualized Δ in viral load, median $\log_{10}$ copies/mL (IQR)	0 (−0.08 to 0.07)	0 (−0.08 to 0.09)	0 (0.0–0.0)
AIDS diagnosis, no. (%) of subjects	82 (54.0)	62 (56.4)	20 (47.6)
Nonwhite ethnicity, no. (%) of subjects	54 (35.5)	32 (29.1)[b]	22 (52.4)
Men who have sex with men, no. (%) of subjects	91 (59.9)	91 (82.7)	NA
History of injection drug use, no. (%) of subjects	15 (9.9)	8 (7.3)	7 (16.7)
Strength training in past week, no. (%) of subjects	37 (24.5)	34 (30.9)[b]	3 (7.3)
Current smoker, no. (%) of subjects	60 (40.0)	34 (31.2)[b]	26 (63.4)

NOTE. Student's *t* test, χ^2 test, Wilcoxon rank sum test, or Fisher exact test were used as appropriate. IQR, interquartile range.

[a] Statistically significant difference between men and women ($P < .05$).
[b] Statistically significant difference between men and women ($P \leq .01$).

time of continuous HAART use prior to the initial assessment visit was 15.3 months (interquartile range, 7.0–26.7 months). Median interval length was 12.9 months (interquartile range, 12.1–17.6 months). Of the 165 HAART-use intervals, 89.7% of these involved regimens that were PI-based HAART; 29 were non-HAART intervals.

Table 1 shows differences between men and women in the cohort. On the basis of 3-day food record from their initial visit, women were more likely to report insufficient calcium intake (69.1% did not meet the dietary reference index value, compared with 34.6% of men; $P < .001$) and insufficient energy intake (i.e., <35 kcal/kg of body weight) (69.1% of women vs. 30.9% of men; $P < .001$) (data not shown). There were no statistically significant differences by sex, except that women were less likely to use HAART (76.2% vs. 90.9%; $P = .02$), more likely to use non-HAART antiretroviral therapies (23.8% vs. 8.2%; $P = .009$) (data not shown), and had been receiving HAART for a shorter duration (median duration, 6.8 vs. 15.2 months; $P = .02$) than were men. Baseline regional body composition differed by sex (table 2); women had nearly double the FM, two-thirds the LM, and less BMC than men ($P <$ .001 for all). No differences in annualized percentage change

Table 2. Baseline values and changes in regional body composition as assessed by dual-energy x-ray absorptiometry after the first study interval for 152 HIV-infected adults enrolled in a longitudinal study of body composition alterations.

	Unadjusted baseline value, median kg (IQR)			Unadjusted annualized percentage change, mean % ± SD		
	All subjects (n = 152)	Men (n = 110)	Women (n = 42)	All (n = 152)	Men (n = 110)	Women (n = 42)
Fat mass						
Extremities[a]	6.7 (4.1–10.4)	5.3 (3.8–7.6)[b]	11.8 (8.7–16.3)	−3.9 ± 20.0	−5.3 ± 19.0	−0.31 ± 22.4
Trunk	8.2 (4.6–11.6)	6.8 (3.9–10.1)[b]	11.2 (8.0–16.7)	4.4 ± 35.1	4.1 ± 30.9	5.2 ± 44.8
Lean body mass						
Extremities[a]	22.9 (18.8–26.4)	24.8 (22.0–27.5)[b]	16.0 (14.5–18.6)	0.33 ± 5.6	−0.32 ± 4.8	2.0 ± 7.0
Trunk	27.2 (23.5–30.8)	29.3 (26.5–32.0)[b]	21.0 (19.3–23.5)	0.96 ± 4.1	0.65 ± 4.0	1.8 ± 4.2
Bone mineral content						
Extremities[a]	1.3 (1.1–1.5)	1.4 (1.3–1.5)[b]	1.1 (1.0–1.2)	−0.71 ± 4.03	−0.67 ± 4.2	−0.82 ± 3.7
Trunk	0.65 (0.57–0.73)	0.67 (0.58–0.75)[b]	0.57 (0.51–0.61)	−0.05 ± 5.4	0.78 ± 5.0[c]	−2.3 ± 5.9

NOTE. Student's *t* test, χ^2 test, Wilcoxon rank sum test, or Fisher exact test were used as appropriate. IQR, interquartile range.

[a] Determined by the sum of arms plus legs to as defined by dual-energy x-ray absorptiometry scan.
[b] Statistically significant difference between men and women ($P < .001$).
[c] Statistically significant difference between men and women ($P = .003$).

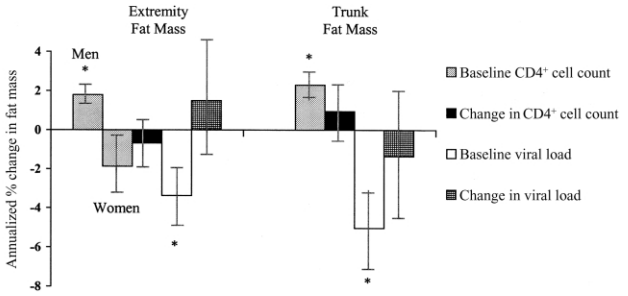

Figure 2. Effects of baseline value and change in $CD4^+$ cell count and viral load on fat mass, as assessed by dual-energy x-ray absorptiometry. Data are expressed as the estimate of coefficient (±SE) for annualized percentage change in fat mass from the beginning of an interval, adjusted for a theoretical 1-year period, per 100 cells/mm^3 and per $\log_{10}$ copies/mL, respectively. Effects of baseline $CD4^+$ cell count on extremity fat mass are shown as separate bars for men and women because of statistically significant interaction; in men, the association is statistically significant ($P = .005$). Separate models were run for the 4 predictors of interest: baseline $CD4^+$ cell count, change in $CD4^+$ cell count, baseline viral load, and change in viral load. Each model was adjusted for HAART, age, sex, and the combination of sex and HAART. In addition, the model was adjusted for caloric intake <35 g/kg. The interaction between sex and the predictor of interest was tested for each model. For extremity fat mass, the interaction of sex and baseline $CD4^+$ cell count was statistically significant ($P = .04$). *Bars,* standard error. *$P < .05$.

in regional body composition were observed between men and women, except for trunk BMC ($P = .003$) (table 2).

Predictors of Regional Body Composition Changes

Examining all 194 intervals (unadjusted interval data not shown), the cohort experienced an average annual loss of 3.6% of extremity FM ($P = .011$), with greater changes seen in men. Increases in trunk FM were not significant ($P = .66$). Trunk LM (nonfat, nonbone mass) increased 0.9% per year ($P = .002$), whereas extremity LM did not change. Small decreases in extremity BMC were not statistically significant. Women had a statistically significant annual loss of trunk BMC (mean unadjusted change [±SD] in women, −1.5% ± 5.6%; mean unadjusted change [±SD] in men, 0.94% ± 5.0%; $P = .004$ for sex interaction).

Baseline $CD4^+$ cell count. Figures 2–4 illustrate adjusted models examining $CD4^+$ cell count and viral load effects on regional changes. A positive linear relationship existed between change in trunk fat and baseline $CD4^+$ cell count, with a 2.3% annualized mean increase in trunk fat per 100 $CD4^+$ cells/mm^3 (95% CI, 0.7%–3.9%; $P = .006$). The relationship between extremity FM and baseline $CD4^+$ cell count varied by sex ($P = .02$ for sex interaction). Baseline $CD4^+$ cell count predicted a 1.8% annualized mean increase in extremity FM per 100 $CD4^+$ cells/mm^3 in men only (95% CI, 0.6%–3.0%; $P = .005$); for women, the association was not statistically significant ($P = .18$). Baseline $CD4^+$ cell count was not associated with changes in LM or BMC.

Change in $CD4^+$ cell count. Extremity LM increased with changes in $CD4^+$ cell count from baseline (mean increase per year, 0.59% per 100 cells/mm^3; 95% CI, 0.05%–1.1%; $P = .03$).

Baseline viral load. Higher viral load at baseline predicted a subsequent loss of extremity FM (mean decrease per year, −3.4% per $\log_{10}$ copies/mL; 95% CI, −6.1% to −0.6%; $P = .02$) and trunk FM (mean decrease per year, −5.0% per $\log_{10}$ copies/mL; 95% CI, −9.4% to −0.7%; $P = .03$).

Change in viral load. No association was found between change in viral load and regional body composition changes.

Use of HAART or antiretroviral therapy. Table 3 shows the association between use of specific antiretroviral therapy and HAART regimens and body composition changes in adjusted models. HAART use (found in 146 intervals) was associated with a mean annual 1.6% loss of extremity BMC in both sexes (95% CI, −3.1% to −0.08%; $P = .04$) and a mean 2.5% annualized LM increase in women (95% CI, 0.5%–4.6%; $P = .02$) but with no other body composition changes.

Increased extremity LM (mean increase per year, 2.8%; 95% CI, 0.1%–5.6%; $P = .04$) was associated with NNRTI-based HAART regimens, but the number of intervals analyzed was very small (16 of 169 intervals analyzed involved NNRTI-based HAART regimens). PI-based HAART (used in 92 of 169 intervals) was associated with extremity BMC loss (mean decrease per year, −1.9%; 95% CI, −3.6% to −0.2%; $P = .03$), but no other HAART regimen had this association.

Zidovudine use (found in 60 of 103 intervals analyzed) was associated with an annual decrease in extremity FM (mean decrease per year, −4.9%; 95% CI, −9.8% to −0.01%; $P = .049$) and trunk FM (mean decrease per year, −10.8%; 95% CI, −20.4% to −1.4%; $P = .02$). Zalcitabine use was associated with a decrease in trunk FM, and stavudine use was not. Use of lamivudine (found in 117 of 127 intervals) was associated with increased trunk LM (mean increase per year, 3.0%; 95% CI, 0.1%–5.8%; $P = .04$). Although few individuals were receiving didanosine (found in 27 of 137 intervals), use of the agent was associated with a decrease in trunk LM (mean decrease per year, −6.4%; 95% CI, −10.3% to −2.5%; $P = .002$) in women only. Zidovudine use (found in 60 of 103 intervals) was associated with an annual decrease in trunk BMC (mean decrease per year, −2.6%; 95% CI, −4.4% to −0.8%; $P = .005$). The use of stavudine (found in 69 of 130 intervals) was associated with an increase in trunk BMC (mean increase per year, 2.0%; 95% CI, 0.4%–3.6%; $P = .01$).

Adjusted models found no effect on regional FM attributable to use of any individual PI (table 3), but saquinavir use (found in 28 of 91 intervals) and ritonavir use (found in 24 of 92

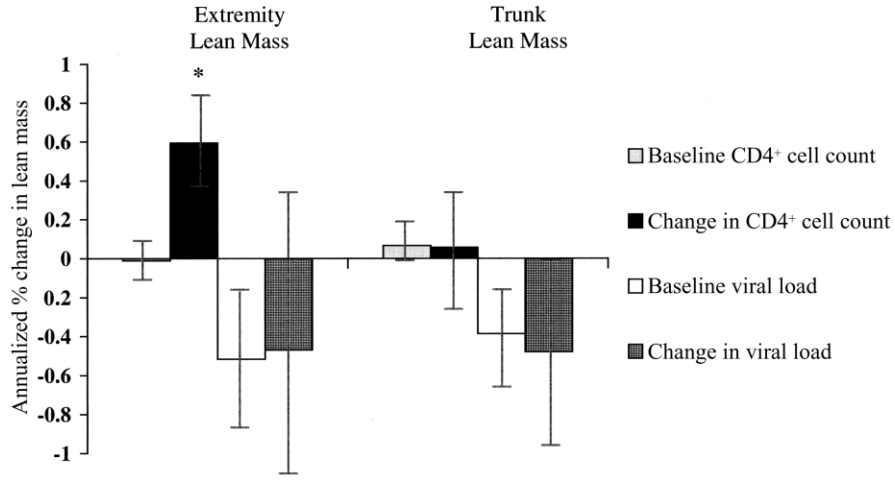

Figure 3. Effects of baseline value and change in CD4+ cell count and viral load on lean mass, as assessed by dual-energy x-ray absorptiometry. Data are expressed as the estimate of coefficient (± SE) for annualized percentage change in lean mass from the beginning of an interval, adjusted for a theoretical 1-year period, per 100 cells/mm^3 and per $\log_{10}$ copies/mL, respectively. Separate models were run for the 4 predictors of interest: baseline CD4+ cell count, change in CD4+ cell count, baseline viral load, and change in viral load. Each model was adjusted for HAART, age, sex, and the combination of sex and HAART. In addition, the model was adjusted for caloric intake <35 g/kg. The interaction between sex and the predictor of interest was tested for each model. *Bars,* standard error. *$P < .05$.

intervals) were each associated an annualized decrease in extremity LM (mean decrease per year, −1.4% [95% CI, −2.7% to −0.7%] and −1.8% [95% CI, −3.2% to −0.4%], respectively; $P = .04$ and $P = .01$, respectively). Nelfinavir use (found in 43 of 98 intervals) was associated with a 2.2% annualized increase in extremity BMC (95% CI, 1.2%–3.2%; $P < .001$).

Low energy intake predicted a large loss of trunk fat (coefficient range, −7.8% to −17.1% per year; $P < .05$ for all) in models examining the effect of viral load change, HAART use, and the PIs ritonavir, indinavir, nelfinavir, and saquinavir and was retained in these models. Cigarette smoking was associated with annual decreases in BMC in the trunk (coefficient range,

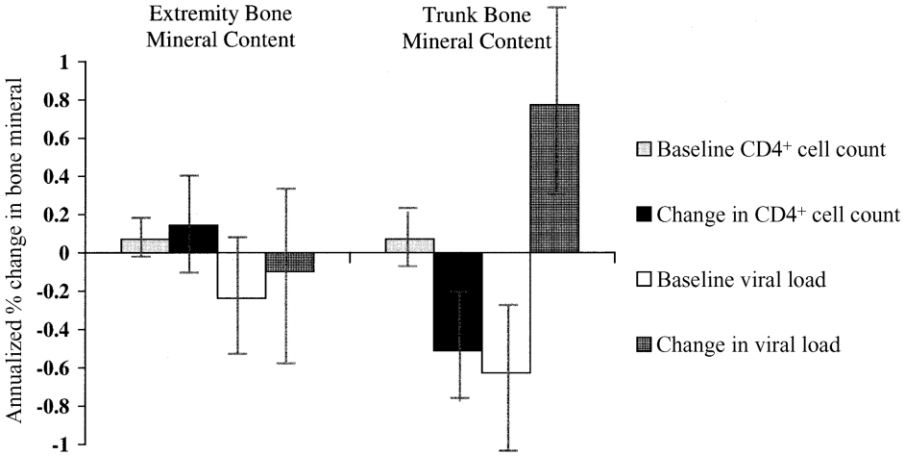

Figure 4. Effects of baseline value and change in CD4+ cell count and viral load on bone mineral content, as assessed by dual-energy x-ray absorptiometry. Data are expressed as the estimate of coefficient (± SE) for annualized percentage change in bone mineral content from the beginning of an interval, adjusted for a theoretical 1-year period, per 100 cells/mm^3 and per $\log_{10}$ copies/mL, respectively. Separate models were run for the 4 predictors of interest: baseline CD4+ cell count, change in CD4+ cell count, baseline viral load, and change in viral load. Each model was adjusted for HAART, age, sex, and the combination of sex and HAART. In addition, the model was adjusted for smoking status, vitamin D intake less than the dietary reference intake value, and calcium intake less than the dietary reference intake value. The interaction between sex and the predictor of interest was tested for each model. For the covariate of smoking status, there was a statistically significant association with change in extremity bone mineral content ($P < .001$ for all) and trunk bone mineral content ($P \leq .03$). *Bars,* standard error. *$P < .05$.

Table 3. Effect of antiretroviral therapy on annualized percentage change in regional body composition of HIV-infected adults receiving stable medication regimens.

Comparison group to by class	Total no. of intervals in the analysis	Intervals with continuous regimen use to no. (%) of total intervals	Annualized percentage change in regional body composition to estimate of coefficient (95% CI)[a]					
			Extremity fat mass	Trunk fat mass	Extremity lean body mass	Trunk lean body mass	Extremity bone mineral content	Trunk bone mineral content
By type of regimen								
HAART vs. HAART naive	170	146 (85.9)	−2.2 (−8.8 to 4.3)	2.3 (−5.0 to 9.6)	0.03 (−1.8 to 1.9)	Men: −0.98 (−2.0 to 0.2); women: 2.5 (0.5–4.6)[b]	−1.6 (−3.1 to −0.08)[b]	−0.10 (−1.9 to 1.7)
PI-based HAART vs. HAART naive	169	92 (54.4)	−2.0 (−9.5 to 5.4)	6.0 (−2.8 to 14.8)	0.30 (−1.7 to 2.3)	0.83 (−0.6 to 2.3)	−1.9 (−3.6 to −0.2)[b]	−0.09 (−2.1 to 1.9)
Mixed HAART vs. HAART naive	169	37 (21.9)	−1.4 (−8.8 to 6.0)	3.9 (−4.8 to 12.6)	−1.5 (−3.7 to 0.7)	−0.78 (−2.2 to 0.7)	−1.4 (−3.2 to 0.4)	0.78 (−1.2 to 2.8)
NNRTI-based HAART vs. HAART naive	169	16 (9.5)	−5.4 (−15.1 to 4.2)	3.1 (−8.0 to 14.3)	2.8 (0.1–5.6)[b]	1.2 (−0.6 to 3.1)	−0.70 (−2.7 to 1.3)	−1.6 (−4.5 to 1.2)
By drug								
Specific PI-based HAART vs. all other PI-based HAART naive								
Nelfinavir	98	43 (43.9)	−2.7 (−9.5 to 4.1)	0.87 (−7.5 to 9.3)	0.89 (−0.8 to 2.5)	0.56 (−0.8 to 1.9)	2.2 (1.2–3.2)[c]	0.02 (−1.7 to 1.7)
Indinavir	87	31 (35.6)	6.1 (−1.1 to 13.3)	4.9 (−4.1 to 13.8)	0.08 (−1.6 to 1.8)	−0.41 (−1.8 to 1.0)	−0.06 (−1.2 to 1.1)	0.26 (−1.8 to 2.4)
Saquinavir	91	28 (30.8)	−0.75 (−8.0 to 6.5)	−5.3 (−14.0 to 3.4)	−1.4 (−2.7 to −0.7)[b]	0.36 (−1.1 to 1.8)	−1.3 (−3.0 to 0.4)	0.43 (−1.6 to 2.4)
Ritonavir	92	24 (26.1)	−0.26 (−8.3 to 7.8)	−7.9 (−18.8 to 3.1)	−1.8 (−3.2 to −0.4)[b]	−0.26 (−1.5 to 1.0)	−1.6 (−3.4 to 0.1)	−0.67 (−3.0 to 1.6)
Specific NRTI-based HAART vs. all other NRTI HAART								
Lamivudine	127	117 (92.1)	−9.3 (−24.2 to 5.7)	−18.5 (−41.5 to 4.4)	1.8 (−0.13 to 3.7)	3.0 (0.10–5.8)[b]	−0.67 (−3.5 to 2.2)	−0.92 (−4.7 to 2.8)
Zidovudine	103	60 (58.3)	−4.9 (−9.8 to −0.01)[b]	−10.8 (−20.1 to −1.4)[b]	0.66 (−1.02 to 2.3)	0.88 (−0.39 to 2.1)	−1.2 (−2.4 to 0.10)	−2.6 (−4.4 to −0.8)[c]
Stavudine	130	69 (53.1)	−0.11 (−5.8 to 5.6)	2.9 (−6.1 to 11.9)	0.12 (−1.4 to 1.6)	−0.17 (−1.3 to 1.0)	−0.39 (−1.4 to 0.62)	2.0 (0.42– 3.6)[b]
Didanosine	137	27 (19.7)	0.70 (−8.5 to 9.9)	−3.6 (−17.1 to 9.9)	0.08 (−1.8 to 2.0)	Men: 0.66 (−0.94 to 2.3); women: −6.4 (−10.3 to −2.5)[c]	−0.26 (−1.9 to 1.4)	0.54 (−1.5 to 2.6)
Zalcitabine	141	6 (4.3)	−4.8 (−11.8 to 2.3)	−14.1 (−25.7 to −2.6)[b]	−1.3 (−3.1 to 0.5)	Men: 0.70 (−0.34 to 1.7); women: −3.4 (−6.8 to −0.03)[b]	−1.0 (−2.7 to 0.7)	0.90 (−3.0 to 4.8)

NOTE. This table summarizes many adjusted models. Sample sizes vary from model to model, because each analysis includes only subject files that have complete covariate data and meet all inclusion criteria. A subject was considered to be in the ART group or HAART group if they reported continuous ART or HAART use from the beginning of the interval through the end of the interval. A subject was considered to be ART or HAART naive if the subject reported no ART or HAART use in the 12 months prior to entry into the Nutrition for Healthy Living Study and did not receive ART or HAART through the end of the interval. PI-based HAART was defined as ⩾2 PIs or 1 PI and 2 NRTIs. Mixed HAART was defined as ⩾1 NRTI, 1 PI, and 1 NNRTI. NNRTI-based HAART was defined as ⩾1 NNRTI and 2 PIs. 3-NRTI HAART was defined as ⩾3 NNRTIs. ART, antiretroviral therapy; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

[a] Models were adjusted for sex, age, $CD4^+$ cell count baseline value, change in $CD4^+$ cell count, viral load baseline value, change in viral load, energy intake <35 g/kg, and strength training. Bone mineral content models were also adjusted for smoking, calcium intake less than the dietary reference intake value, and vitamin D intake less than the dietary reference intake value. Drug/sex interactions were tested for all drugs.

[b] $P \leqslant .05$ by Student's t test, χ^2 test, Fisher's exact test, or Wilcoxon rank sum test, as appropriate.

[c] $P \leqslant .01$ by Student's t test, χ^2 test, Fisher's exact test, or Wilcoxon rank sum test, as appropriate.

−1.4% to −2.3%) and extremities (coefficient range, −1.1% to −3.2%). In the HAART model, each year of age predicted a more rapid decrease in trunk LM (mean decrease per year, −0.05%; 95% CI, −0.09% to −0.006%; $P = .03$).

DISCUSSION

With the advent of new and effective antiretroviral therapies, immune restoration and viral suppression are now possible in HIV-infected adults in the United States. As a result, it has been difficult to determine which medication and host factors are associated with the varying aspects of body composition alterations. Many previously reported analyses did not use continuous or objective measures of change, have been cross-sectional, have not included HAART-naive persons for comparison, did not look directly at the effects of $CD4^+$ cell counts or viral loads after adjustment, or did not consider such behaviors as dietary intake and smoking [6, 7, 14, 22]. Although case reports and initiation studies have implicated the introduction of HAART in rapidly inducing body-shape changes in some people, it remains unclear whether these changes continue to evolve with continuous HAART or antiretroviral therapy use. We offer exploratory findings from a longitudinal examination of regional body composition changes in a large cohort of HAART or antiretroviral therapy–experienced and –naive men and women, and we demonstrate ongoing changes in individuals receiving stable therapies.

This analysis confirms an average annual loss of extremity fat in the cohort. DEXA cannot distinguish between upper and lower trunk fat, nor can it distinguish between the visceral and subcutaneous compartments of the abdomen, but total trunk fat changes were not found. Most importantly, disease status was associated with regional body changes, because a lower baseline $CD4^+$ cell count ($P \leqslant .006$) or a higher baseline viral load ($P \leqslant .03$) predicted a greater loss of trunk and limb fat. HAART use or its duration did not contribute to change. Of interest, zidovudine but not stavudine was associated with loss of limb and trunk fat. Because of the time frame in which data were collected, we were unable to determine the effect of some individual medications, including abacavir and the NNRTIs. These findings agree with the current literature that suggests lipoatrophy is the unique physical manifestation of HIV infection, and they support the findings from our group and others that disease status is involved [4, 6, 19, 23–25]. However, it remains impossible to separate the individual effects of antiretroviral therapy agents, because they are used in combination.

Changes in LM have been less well investigated in the HAART era. An early report from our group found that, after HAART initiation, weight increased, and LM did not [8], but our later reports found greater LM in individuals receiving HAART than in others [5]. The current longitudinal study confirms that ongoing improvement in $CD4^+$ cell count was concurrent with gains in extremity LM, perhaps because the latter reflects improved health, nutrition, and mobility that may occur with an improvement in $CD4^+$ cell count.

It appears that both medication and modifiable lifestyle factors altered bone health in our cohort. HAART use and PI use remained associated with bone mineral loss, even after adjustment for the strong effects of numerous well-known osteopenia cofactors. Other significant risk factors included cigarette smoking and dietary practices. The literature has been conflicted about the prevalence of predictors of BMC changes [12, 26–29]. Our analysis supports the involvement of antiretroviral therapy, as well as known risk factors, reinforcing the need for additional longitudinal studies that account for diet, cigarette smoking, and medications concurrently.

Although a cohort such as this does not allow us to examine the changes induced by the introduction of HAART (as would be possible in a randomized control trial), our data do assist in understanding the real-world situation for many patients who experience ongoing body changes over time while receiving treatment. Though our numbers were small for some analyses, statistical differences were apparent. These findings suggest the importance of peak viral load and nadir $CD4^+$ cell count on the subsequent loss of fat, a concurrence in the improvements in $CD4^+$ cell count and LM, and the primary influences of medications and traditional risk factors in bone demineralization. Many details about HIV-associated body composition alterations remain unanswered, but this work confirms the growing body of evidence that such changes are multifactorial.

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