Effect of highly active antiretroviral therapy on fat, lean, and bone mass in HIV-seropositive men and women[1–3]

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ABSTRACT

Background: Alterations in body composition have been reported in HIV-positive adults receiving highly active antiretroviral therapy (HAART), but the magnitude and potential determinants of these changes are unclear.

Objective: We compared total and regional body composition, as measured by dual-energy X-ray absorptiometry, in 203 HIV-positive men and 62 HIV-positive women according to HAART.

Design: This was a cross-sectional analysis of a cohort study of nutrition and HIV infection.

Results: After adjustment for age, weight, race, and exercise habits, total weight and fat mass did not differ significantly in men or women by HAART. Trunk fat was greater in men (1.0 kg; $P < 0.001$) and women (1.4 kg; $P = 0.005$) and leg fat was lower in men (−1.0 kg; $P < 0.001$) and women (−1.5 kg, $P = 0.005$) receiving HAART than in those not. This corresponded to a greater percentage of total fat mass located in the trunk (men: 7.5%, $P < 0.001$; women: 5.1%, $P = 0.02$). Lean mass was also greater with longer duration of HAART in men ($P < 0.002$). In men receiving HAART, total and regional bone mineral content were less than in the men not receiving HAART ($P < 0.001$). These effects increased with longer duration of HAART. Protease inhibitors were associated with the largest differences in regional fat.

Conclusions: HAART is associated with redistribution of fat mass from the legs to the trunk, despite no significant differences in total fat mass or weight. In men, HAART is also associated with a reduction in bone mineral content, suggesting that HAART increases the risk of central obesity and osteoporosis. *Am J Clin Nutr* 2001;74:679–86.

KEY WORDS HIV, human immunodeficiency virus, highly active antiretroviral therapy, HAART, dual-energy X-ray absorptiometry, protease inhibitors, nucleoside reverse transcriptase inhibitors, lipodystrophy, fat redistribution, lean body mass, fat mass, bone mineral content, osteopenia, osteoporosis

INTRODUCTION

Historically, HIV infection has been thought to affect body composition primarily through loss of lean body mass (1–3). However, as the use of highly active antiretroviral therapy (HAART) has become widespread, many patients have reported a new phenomenon of fat redistribution, with central adiposity often accompanied by a peripheral loss of subcutaneous fat (4–6). Such changes were noted primarily in patients receiving protease inhibitor–based HAART, but not exclusively with this therapy (7–12). These changes in body shape have been described in association with every protease inhibitor, in both men and women (4, 10–17). The changes include increased abdominal adiposity, dorsocervical fat accumulation, and breast enlargement (9, 15–20). Peripheral changes include loss of subcutaneous fat in the legs, buttocks, arms, and face, and localized subcutaneous fat pockets (lipomatosis) (4, 20–22). The rate of fat redistribution is reported to differ with nucleoside regimens and to be associated with duration of HIV-positive status and duration of protease inhibitor therapy (23–27). Most studies to date were cross-sectional in design, included small sample sizes, examined white men, and measured isolated aspects of body composition.

Currently, there is considerable variation in the findings of lipodystrophy (4, 7, 9, 10, 13, 15, 23, 28, 29). The effect on whole and regional body composition (both fat and lean mass, separately and in the upper and lower extremities), the relation to HAART and its duration of use, and the relation to HIV infection itself have yet to be clarified. Information on the prevalence and severity of lipodystrophy in women is even more limited.

As early as 1993, before the advent of HAART, alterations in bone turnover and mineral content were reported in HIV-positive adults (30–32). More recently, disturbed bone formation and resorption were reported with the use of protease inhibitors or HAART (33–35; M Romeyn, J Ireland, unpublished observations, 1999). However, little is known about the long-term effects of HIV infection and HAART use on bone health.

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To further investigate these questions, we examined a large, racially diverse cohort of men and women with various medication histories. With use of dual-energy X-ray absorptiometry (DXA), we studied regional differences in body composition—including fat, lean, and bone mass—in individuals receiving or not receiving HAART and specific medications. DXA is a useful method of body-composition assessment in large-scale studies because of its accuracy, availability, ease, and cost (36–39). Although this was a cross-sectional study, we also examined the effect of duration of HAART and its association with body composition.

SUBJECTS AND METHODS

Study design

The subjects in the present study resided primarily in New England and were enrolled in a longitudinal study [Nutrition for Healthy Living (NFHL)] that began in February 1995. They were English-speaking HIV-seropositive men and women aged >18 y. Subjects were recruited through postings in hospitals, health centers, and community centers that serve the HIV-positive population; through community outreach education programs; and by participant referral. Data collection for the NFHL included interviewer-administered questionnaires to collect information about medication and health history. On enrollment in the study, medication history for the previous 12 mo was determined by patient recall. Subjects were telephoned monthly to track subsequent changes in medication and health status. Subjects were seen monthly for 2 baseline appointments, then biannually for the duration of the study. Starting in 1997, DXA scans were conducted on all subjects at specified visits. The protocol was approved by the Tufts University Human Investigation Review Committee and written, informed consent was obtained from all participants. This report is a cross-sectional analysis of all persons ($n = 265$) who underwent a DXA scan before July 22, 1999. If subjects had more than one DXA scan available, the earliest one was used in this study.

Testing protocol

Transverse whole-body scans were obtained by 1 of 3 validated technicians using a QDR2000 scanner (Hologic, Waltham, MA) in the array mode. DXA phantoms were scanned daily to minimize instrument drift as recommended by the manufacturer. DXA was conducted with the subject in a standard supine position, wearing a hospital gown, and after emptying his or her bladder. Data were collected in ≈120 pixel elements per transverse scan with a pixel size of ≈5 × 10 mm. Percentage fat and lean mass were derived for the whole body and for regions of interest by using whole-body software (version 7.10A) provided by the manufacturer. A series of DXA cutoff lines positioned at anatomical markers defined the regions of interest. The trunk was isolated to include the neck, chest, abdomen, and the central portion of the pelvis. Longitudinal cutoff lines positioned between the head of the humerus and scapula at the glenoid fossa isolated the arms (to include the deltoid muscles). A horizontal line positioned at the iliac crest defined the top of the pelvis, with diagonal cutoff lines below the pelvis to bisect both femoral necks and to isolate the legs (to include the upper thighs and lateral portion of the gluteus maximus). Appendicular composition was analyzed by summing the regional data from the 4 extremities.

Antiretroviral drug regimens reported at each visit were classified as HAART or non-HAART. HAART regimens included *1*) 2 protease inhibitors, *2*) 2 nucleoside reverse transcriptase inhibitors (NRTIs) with 1 protease inhibitor, or *3*) 2 NRTIs with 1 nonnucleoside RTI (NNRTI). Determination of no antiretroviral therapy was made if the subject reported no antiretroviral therapy use in the 12 mo before entry into the NFHL study and remained antiretroviral therapy–free through the date of the DXA scan visit. History of AIDS diagnosis included a CD4 count $<200 \times 10^3$ cells/L at the time of any study visit, self-reported occurrence of any AIDS-defining illness, or AIDS diagnosis before or during NFHL participation. HIV RNA was measured with the Roche Amplicor Monitor reverse transcriptase polymerase chain reaction assay (Roche Molecular Systems, Somervillle, NJ) with a lower detection limit of 400 000 copies/L. $CD4^+$ lymphocyte counts were performed by using a specific monoclonal antibody and fluorescence-activated cell sorter analysis (FACScan; Becton-Dickinson, Mansfield, MA).

Statistical analysis

Patients were classified by the medication regimen reported at the time of their DXA scan. Body composition was compared by Student's *t* test, Kruskal-Wallis test, or chi-square test as appropriate between those reporting HAART use and those not reporting HAART. Two-factor analysis of variance determined that no interaction existed between sex and HAART use or HAART duration. Nevertheless, data for each sex were analyzed and are presented separately because of the large differences in normal body composition between men and women and because of controversy regarding differences in lipodystrophy between the sexes.

With use of general linear regression models, adjustments were made for age, participation in strength training, duration of HAART use, race, body mass index (BMI), and total body weight or total body fat, depending on the outcome of interest. The strength-training variable recorded all strength-training exercises performed in the 7 d before the DXA scan. Time per week spent strength training was also reported. All total and regional body-composition measures were adjusted for both the presence (yes or no) and duration (h/wk) of strength training, in separate models. The small number of women in this population who participated in strength training ($n = 4$) did not allow an effect to be determined for women. The HAART duration data were also tested with quadratic and cubic equations to check for linearity. Specific medications taken at the time of the DXA scan were also examined for effects on regional fat mass, with adjustments made for age, participation in strength training, and BMI. Amprenavir and dideoxycytadine were dropped from the analysis because of small sample sizes ($n = 6$ men, 2 women).

All values are presented as means ± SDs if normally distributed or as medians and interquartile ranges if not normally distributed. Results were considered significant if the 2-tailed *P* value was <0.05. All data were analyzed with the SYSTAT 9 statistical package (SPSS, Inc, Chicago).

RESULTS

Two hundred three men and 62 women were included in this analysis (**Table 1**). The men were ≈3 y older on average ($P < 0.001$). The men had been aware of their positive HIV status for an average of 7.5 y, the women, for 6.9 y (NS). In this ethnically diverse cohort, the racial profile of the female HAART users did

TABLE 1
Characteristics of HIV-positive men and women[1]

	Men (n = 203)		Women (n = 62)	
	No HAART	HAART	No HAART	HAART
n (%)	65 (32)	138 (68)	27 (44)	35 (56)
Age (y)	42.1 ± 7.8	43.2 ± 7.0	39.0 ± 5.0	39.4 ± 7.7
Time HIV positive (y)	7.5 ± 3.7	7.5 ± 3.6	7.0 ± 4.1	6.8 ± 4.2
Race (n)[2]				
Black	26	17	15	17
White	30	105	8	14
Hispanic	5	7	2	4
Other	4	9	2	0
HIV RNA ($\times 10^3$ $\log_{10}$ copies/L)[3]	3.5 (2.9–4.2) [56]	2.7 (2.3–4.0) [123]	3.5 (2.9–4.3) [21]	2.3 (2.3–3.1) [30]
$CD4^+$ ($\times 10^3$ cells/L)	399.7 ± 206.7	409.7 ± 266.7	489.2 ± 414.1	434.7 ±260.1
BMI (kg/m^2)	24.8 ± 3.4	24.3 ± 3.7	24.4 ± 5.4	26.3 ± 6.9
Strength training				
[n (%)]	25 (38.5)	46 (33.3)	2 (7.4)	2 (5.7)
(h/wk)[4]	2.0 ±2.5	2.6 ± 2.3	2.0 ± 0.5	1.8 ± 0.5
Duration of HAART use (mo)[5]	NA	15.1 (<1 to 40)	NA	10.7 (<1 to 28)
Duration of protease inhibitor use (mo)[5]	NA	15.9 (<1 to 40)	2.0	12.0 (<1 to 28)
No antiretroviral therapy [n (%)]	29 (45.3)[6]	0	9 (34.0)	0
AIDS diagnosis [n (%)]	34 (53.0)[7]	117 (85.4)	17 (63.0)	22 (62.9)

[1] $\bar{x}$ ± SD unless indicated otherwise. NA, not applicable; HAART, highly active antiretroviral therapy.
[2] Pearson chi-square for HAART compared with no HAART: men, $P < 0.001$ (df = 5.0).
[3] Median; interquartile range in parentheses; n in brackets.
[4] Among those reporting strength training.
[5] Median; range in parentheses.
[6] Significantly different from women, $P < 0.001$ (Pearson chi-square statistic).
[7] Significantly different from HAART, $P < 0.001$ (Pearson chi-square statistic).

not differ significantly from that of the female nonusers, but white men were more likely to be receiving HAART than were nonwhite men. HIV RNA viral load and CD4 count were available in a subset of 230 subjects and did not differ significantly by HAART use. The median $CD4^+$ lymphocyte counts were 350×10^3 cells/L in men and 400×10^3 cells/L in women, and the median HIV $\log_{10}$ RNA values were 3.31 and 2.92×10^3 $\log_{10}$ copies/L, respectively; both included a wide range of values. The median BMI (in kg/m^2) was 24.1 in men and 24.3 in women and did not differ by HAART use. Strength training was reported by 35% of the men and 6.5% of all women, but did not differ by HAART use. At the time of their DXA scan, 68% of men (n = 138) and 56% of women (n = 35) were receiving HAART. The mean duration of HAART use was 16.3 mo for men (median: 15.1 mo) and 11.2 mo for women (median: 10.7 mo; $P = 0.003$). The median duration of protease inhibitor use was 15.9 mo for men and 12.0 mo for women ($P = 0.002$). In men, a history of an AIDS diagnosis (including a wasting diagnosis) was more prevalent among HAART users than nonusers; this variable did not differ significantly in women.

Crude weight, total fat, and lean mass did not differ significantly between HAART users and nonusers. In the multivariate analyses, weight was compared between persons receiving and not receiving HAART for each sex, with adjustment for age and height. Comparisons of total fat mass were adjusted for age, total weight, and strength training; comparisons of total lean mass and bone mineral content were adjusted for age, height, total weight, and strength training. As expected, women had a greater total fat mass, percentage body fat, trunk fat mass, and leg fat mass than did men. Strength training had a significant effect in the men when included in many models, although hours of training per week did not. There were no significant differences in total lean mass by HAART use in women. In men, HAART was marginally associated with greater total lean mass (1.2 kg; 95% CI: −0.1, 2.4 kg; $P = 0.07$) after further adjustment for strength training.

Regional body composition

The unadjusted total and regional fat, lean, and bone mineral content values for each sex, stratified by HAART use, are shown in **Table 2**. Women receiving HAART tended to have more trunk fat than did women not receiving HAART (NS). Men receiving HAART had significantly less appendicular fat mass and leg fat mass than did men not receiving HAART, and less total and regional bone mineral content. When expressed as a percentage of total mass located below the head, both men and women receiving HAART had a different fat distribution pattern than did those not receiving HAART (**Figure 1**). Otherwise, there were no significant differences in the crude analysis in total or regional body composition by HAART use.

Multivariate analysis of differences in fat mass

After adjustments for age and total fat mass, HAART users had greater trunk fat mass (men: 1.0 kg, 95% CI: 0.6, 1.5 kg, $P < 0.001$; women: 1.4 kg, 95% CI: 0.5, 2.4 kg, $P = 0.005$) and less leg fat mass (men: −1.0 kg, 95% CI: −1.4, −0.6 kg, $P < 0.001$; women: −1.5 kg, 95% CI: −2.6, −0.5 kg, $P = 0.005$) than did nonusers. Arm fat mass did not differ significantly by HAART use. Trunk fat made up a significantly larger percentage of total fat mass below the head in HAART users than in nonusers (men: 7.5%, 95% CI: 4.4%, 10.5%, $P < 0.001$; women: 5.1%, 95% CI: 0.3%, 9.9%, $P = 0.02$), whereas appendicular fat mass accounted for a significantly smaller percentage (men: −7.2%, 95% CI: −9.9%, −4.6%, $P < 0.001$; women: −5.8%, 95% CI: −10.3%, −1.4%, $P = 0.01$) after adjustment for age and total fat mass.

TABLE 2
Comparison of unadjusted body-composition characteristics associated with highly active antiretroviral therapy (HAART) in men and women[1]

	Men			Women		
	No HAART (n = 65)	HAART (n = 138)	P	No HAART (n = 27)	HAART (n = 35)	P
Weight (kg)	75.7 ± 7.8	74.9 ± 7.0	0.66	64.5 ± 16.4	70.0 ± 19.2	0.23
Percentage body fat (%)	21.9 ± 7.6	20.0 ± 7.5	0.09	32.6 ± 9.8	34.8 ± 12.3	0.44
Body mass (kg)						
Total FM	17.0 ± 7.5	15.5 ± 8.1	0.20	22.3 ± 11.6	26.0 ±14.9	0.28
Total LBM	55.9 ± 7.8	56.9 ± 7.9	0.43	40.1 ± 6.2	41.8 ± 7.4	0.33
Total BMC	2.8 ± 0.05	2.5 ± 0.04	0.001	2.2 ± 0.03	2.2 ± 0.04	0.67
Regional body mass						
Trunk FM (kg)	8.0 ± 4.4	8.2 ± 5.0	0.77	9.3 ± 5.8	12.7 ± 8.6	0.07
Trunk LBM (kg)	28.3 ± 4.1	29.0 ± 4.1	0.21	21.1 ± 3.2	22.0 ± 3.7	0.28
Trunk BMC (g)	725 ± 0.02	660 ± 0.02	0.004	553 ± 0.01	582 ± 0.01	0.33
Appendicular FM (kg)	8.1 ± 3.5	6.4 ± 3.7	0.002	12.2 ± 6.1	12.4 ± 6.8	0.89
Appendicular LBM (kg)	23.1 ± 4.1	24.2 ± 39.6	0.72	15.9 ± 3.2	16.5 ± 3.7	0.48
Appendicular BMC (g)	1528 ± 311	1359 ± 0.03	<0.001	1110 ± 0.02	1110 ± 0.02	0.86
Leg FM (kg)	6.2 ± 0.3	4.7 ± 2.9	0.001	9.5 ± 5.0	9.2 ± 5.1	0.82
Leg LBM (kg)	17.4 ± 2.9	17.8 ± 2.9	0.46	12.3 ± 2.7	12.8 ± 2.9	0.52
Leg BMC (g)	1109 ± 0.02	989 ± 0.02	<0.001	826 ± 0.01	820 ± 0.02	0.87

[1]Unadjusted $\bar{x}$ ± SD. FM, fat mass; LBM, lean body mass; BMC, bone mineral content.

Multivariate analysis of differences in lean mass

After adjustment for age, weight, height, and participation in strength training, trunk lean mass (0.8 kg; 95% CI: 0.1, 1.5 kg; P = 0.03) and leg lean mass (0.4 kg; 95% CI: −0.05, 0.9 kg; P = 0.09) tended to be greater in male HAART users than in male nonusers. However, appendicular lean mass (as the sum of arms and legs) did not differ significantly by HAART use in the men. In the women, HAART use was not associated with a significant effect on total or regional lean mass.

Multivariate analysis of differences in bone mineral content

After adjustment for age, height, weight, race, and strength training, differences in bone mineral content were evident when comparing men receiving HAART with those not receiving HAART, with less total (−179.2 g; 95% CI: −201.5, −155.9 g), trunk (−51.8 g; 95% CI: −23.2, −82.4 g), appendicular (−117.5 g; 95% CI: −168.8, −68.4 g), and leg bone mineral content (−83.1 g; 95% CI: −122.5, −45.5 g) (all $P \leq 0.001$) in men receiving HAART. There were no significant differences in bone mineral content by HAART use among the women.

Effect of duration of HAART use

The self-reported duration of HAART use was associated with differences in regional fat mass, lean mass, and bone mineral content in men and regional fat mass in women (**Table 3**). The effect on body composition increased linearly with greater duration of treatment. Analyses of total fat mass and lean mass were adjusted for age, total body weight, height, and participation in strength training. Analysis of bone mineral content was adjusted for age, total body weight, height, race, and participation in strength training. Analyses of regional fat variables were adjusted for age, total fat mass, and participation in strength training.

Fat mass

Duration of HAART use was associated with fat alterations in men, including decreased total fat mass (−103.7 g/mo), increased trunk fat mass (43.3 g/mo), and decreased appendicular fat mass (−44.6 g/mo) (Table 3). The effect of HAART duration on appendicular fat was found only in the legs (−42.3 g/mo) and not the arms. In men, a 0.34% monthly increase in the percentage of total fat mass found in the trunk (P < 0.001) was accompanied a 0.35% monthly decrease in the percentage of total fat mass found in the legs (P < 0.001) (data not shown). In women, the duration of HAART use was associated with increased trunk fat mass (71.1 g/mo), decreased appendicular fat mass (−73.9 g/mo), and decreased leg fat mass (−75.7 g/mo). The percentage of total fat mass found in the legs was inversely associated with treatment duration (−0.23%/mo; P < 0.001), but the percentage of fat mass in the trunk was not (P = 0.22) (data not shown).

Lean mass

In men, total lean mass increased per month of HAART use (111.6 g/mo), including an increase in both trunk lean (55.8 g/mo) and appendicular lean (52.8 g/mo) mass (Table 3). Appendicular lean mass increases occurred in both the legs (40.2 g/mo) and arms (12.5 g/mo). There were no significant differences in regional

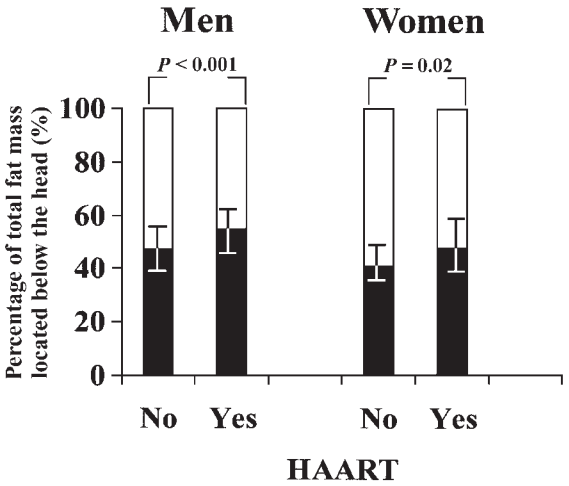

FIGURE 1. Unadjusted mean (±SD) distribution of body fat in the appendages (□) and trunk (■) in HIV-positive men (n = 203) and women (n = 62) in relation to highly active antiretroviral therapy (HAART) use. P values are by t test.

TABLE 3
Effect of the duration of highly active antiretroviral therapy (HAART) on lean body mass, fat mass, and bone mineral content in men and women

	Men (n = 203)			Women (n = 62)		
Dependent variable	Effect/mo of HAART	95% CI	P^1	Effect/mo of HAART	95% CI	P^1
Fat mass (g/mo HAART)						
Total[2]	−103.7	(−164.1, −43.3)	<0.001	−49.5	(−195.7, 96.7)	0.51
Trunk[3]	43.3	(23.7, 62.9)	<0.001	71.1	(7.6, 134.6)	0.03
Appendicular[3]	−44.6	(−64.4, −24.8)	<0.001	−73.9	(−131.8, −0.1)	0.03
Leg[3]	−42.3	(−60.6, −24.1)	<0.001	−75.7	(−143.0, −8.4)	0.03
Arm[3]	−2.2	(−6.7, 2.3)	0.33	1.9	(−19.3, 23.1)	0.87
Lean body mass (g/mo HAART)[2]						
Total	111.6	(52.6, 170.6)	0.001	50.4	(−92.5, 193.3)	0.49
Trunk	55.8	(21.7, 89.9)	0.002	32.3	(−48.5, 113.1)	0.44
Appendicular	52.8	(21.8, 83.8)	0.001	12.7	(−62.4, 87.8)	0.74
Leg	40.2	(18.4, 62.0)	<0.001	7.0	(−48.7, 62.7)	0.81
Arm	12.5	(0.7, 24.3)	0.04	5.7	(−17.0, 28.4)	0.63
Bone mineral content (g/mo HAART)[4]						
Total	−5.7	(−9.6, −1.8)	0.005	0.8	(−6.2, 7.7)	0.83
Trunk	−1.9	(−3.2, −0.7)	0.003	0.5	(−2.0, 3.0)	0.70
Appendicular	−3.7	(−5.8, −1.3)	0.002	−1.3	(−2.3, 4.9)	0.48
Leg	−2.7	(−4.4, −1.0)	0.003	−0.7	(−3.4, 2.0)	0.60
Arm	−0.9	(−1.7, −0.2)	0.01	−0.6	(−1.7, 0.6)	0.31

[1] P for whether the effect/mo of HAART is significantly different from zero.
[2] Adjusted for age, total weight, and strength training.
[3] Adjusted for age, fat weight, and strength training.
[4] Adjusted for age, total weight, height, and strength training.

lean mass proportions associated with HAART duration in men. No significant differences were found in total lean body mass or the lean distribution pattern in association with treatment duration in women.

Bone mineral content

Bone mineral content decreased monthly in small, but significant, amounts from all regions of the body in men receiving HAART (Table 3). Total bone mineral content was reduced 5.7 g/month of HAART, seen in the trunk (−1.9 g/mo) and appendages (−3.7 g/mo), with legs contributing −2.7 g/mo and arms −0.9 g/mo. No significant differences were found in total or regional bone mineral content in association with HAART duration in women.

Effect of specific medications

Among HAART nonusers, specific NRTI use was not associated with regional fat mass differences in men or women, although the effects of lamivudine (3TC; n = 20) and didanosine (DDI; n = 2) on appendicular fat were nearly significant in men (**Table 4**). Amounts of appendicular fat were lower in men receiving each protease inhibitor–based HAART regimen than in men not receiving HAART. A similar effect size was seen with all protease inhibitors, and significant differences in trends were seen with all effects except trunk fat increases with indinavir and melfinavir. In women, only indinavir use was predictive of trunk and appendicular fat differences. Among the NNRTIs, nevirapine use was associated with less appendicular fat in men receiving HAART than in nonusers.

DISCUSSION

The sex and race distributions of the population studied were similar to those in the Massachusetts Department of Public Health AIDS surveillance data: for sex, 80% male and 20% female in the Department of Public Health data and 76.6% male and 23.4% female in the NFHL; for race, 56% white, 24% black, and 20% other in the Department of Public Health data and 59.3% white, 28.3% black, and 12.4% other in the NFHL. In our cohort, regional fat distribution patterns were different in men and women receiving HAART than in those not, and this effect increased with duration of treatment. The differences in effect between men and women may be attributable to the smaller sample size of women because tests for a sex × HAART interaction were not significant. Although some previous studies showed increased trunk fat (13), increased proportion of trunk fat (10), or reduced peripheral fat (4, 23) with HIV infection, this is the first study to strongly show true fat redistribution from the periphery to the trunk in men and women, in a time-dependent manner, without substantial changes in total fat or weight.

In men receiving HAART, treatment was associated with more total and regional lean mass and less total and regional bone mineral content. To our knowledge, such opposing changes in bone content and lean mass have not been reported before. The differences were not attributable to age, weight, height, BMI, body fat, race, duration of HIV infection, or involvement in strength training. In this cohort, 35% of all men reported current strength training, which was shown previously to decrease fat and increase lean and bone mass (40). Viral load, when included in models, was not a significant predictor of differences in body composition (data not shown). Although our study was cross-sectional, the large number and variety of subjects involved, the length of time the subjects were seropositive, and the duration of treatment strengthen these conclusions.

In contrast with the subjects in several earlier studies, the subjects in the present study were not selected for weight or body-composition changes or signs or symptoms of fat redistribution or lipodystrophy. The current lack of a standard definition and

TABLE 4
Comparison of regional body fat in men and women exposed and unexposed to specific medications[1]

	Men (n = 203)						Women (n = 62)					
Medication	Exposed	Unexposed	Median duration of medication	Body region	Difference	P	Exposed	Unexposed	Median duration of medication	Body region	Difference	P
	n	n	mo		kg		n	n	mo		kg	
NRTIs												
AZT	27	38	24.6	Trunk	0.4 ± 0.7[2]	0.57	10	17	20.2	Trunk	−0.5 ± 1.0	0.60
				Append	−0.6 ± 0.6	0.36				Append	−1.5 ± 1.2	0.22
3TC	20	45	18.2	Trunk	−0.5 ± 0.8	0.56	9	18	12.0	Trunk	−0.5 ± 1.0	0.61
				Append	−1.2 ± 0.6	0.07				Append	−1.0 ± 1.2	0.41
D4T	12	53	13.2	Trunk	0.5 ± 0.9	0.57	6	21	16.2	Trunk	0.5 ± 1.1	0.67
				Append	−0.6 ± 0.8	0.46				Append	0.1 ± 1.5	0.94
DDI	2	63	6.1	Trunk	2.7 ± 2.1	0.20	1	26	24.0	Trunk	4.4 ± 2.4	0.08
				Append	3.1 ± 1.7	0.08				Append	4.2 ± 3.1	0.19
Protease inhibitors												
Indinavir	47	65	14.9	Trunk	0.3 ± 0.5	0.53	13	27	6.2	Trunk	2.1 ± 1.0	0.04
				Append	−2.0 ± 0.5	<0.001				Append	−2.6 ± 1.1	0.02
Nelfinavir	45	65	12.0	Trunk	0.6 ± 0.6	0.32	9	27	12.0	Trunk	−0.1 ± 0.9	0.90
				Append	−1.0 ± 0.5	0.04				Append	−0.3 ± 1.0	0.79
Saquinavir	34	65	8.2	Trunk	1.5 ± 0.6	0.02	7	27	12.0	Trunk	0.5 ± 1.1	0.67
				Append	−1.3 ± 0.5	0.07				Append	−1.7 ± 1.3	0.11
Ritonavir	28	65	10.5	Trunk	1.1 ± 0.7	0.09	6	27	13.9	Trunk	1.2 ± 1.3	0.38
				Append	−1.3 ± 0.6	0.02				Append	−1.7 ± 1.4	0.25
NNRTIs												
Nevirapine	21	65	11.0	Trunk	0.6 ± 0.7	0.42	8	27	6.9	Trunk	0.5 ± 1.1	0.70
				Append	−1.9 ± 0.6	0.003				Append	−1.7 ± 1.6	0.29
Efavirenz	10	65	3.0	Trunk	1.1 ± 1.0	0.26	2	26	2.5	Trunk	−1.2 ± 2.4	0.62
				Append	−0.1 ± 0.8	0.89				Append	−0.9 ± 3.0	0.76
Delavirdine	4	65	6.0	Trunk	1.8 ± 1.5	0.23	1	27	15.4	Trunk	1.9 ± 2.4	0.44
				Append	−2.2 ± 1.3	0.08				Append	0.9 ± 3.0	0.77

[1] The model was adjusted for BMI, age, and strength training (yes or no). 3TC, lamivudine; Append, appendages (arms and legs); AZT, zidovudine; D4T, stavudine; DDI, didanosine; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor. Exposed was defined as follows: for protease inhibitors, taking the named protease inhibitor (HAART user); for NRTIs, taking the named NRTI (HAART nonuser); and for NNRTIs, taking the named NNRTI (HAART user). Unexposed (for all comparisons) was defined as follows: not taking the specifically named drug (HAART nonuser).
[2] Estimate ± SE.

criteria for lipodystrophy make comparisons between our and previous studies difficult. Nevertheless, we found that the fat distribution pattern differed significantly by HAART use. The association of fat mass and treatment duration found in our study supports the recent longitudinal and cross-sectional results reported by Carr et al (4, 23), who found duration of protease inhibitor use in men to be associated with lower total fat mass, less appendicular fat, and greater trunk fat. In contrast with our study, a recent comparison between HIV-seropositive persons receiving HAART and those studied before receiving HAART reported differences in overall body composition, but not in fat distribution patterns (29). This finding may have been due to the use of anthropometry, a less precise method than DXA.

Peripheral fat wasting may not be as apparent in women as in men because women normally have more appendicular fat. Bernasconi et al (41) reported partial lipodystrophy to be common in women, with fat atrophy of the upper body (including the face) and a sparing effect in the lower extremities. This was not the case in our female population. In the present analysis, women had twice the leg fat of men, and the absolute effect of HAART on leg fat was greater in women than in men. Because women store a greater percentage of their fat reserves in the legs, a greater amount of regional fat mass must be lost before fat wasting is clinically apparent and leg muscles or veins are prominent. However, these changes in leg fat are evident with the use of DXA.

Our results also differ from other recently published studies (29) in that the duration of HAART use was associated with increased lean mass in men. These differences in lean body mass may have been due to differences in eating habits or levels of daily activity, despite adjustment for strength training. For example, Silva et al (42) found an increased daily energy intake of 915.5 kJ/d (219 kcal/d) (P = 0.01) in a longitudinal study of adults from this cohort after they began receiving protease inhibitors. Monkemuller et al (43) reported a marked decrease in the prevalence of gastrointestinal opportunistic infections in those receiving HAART, which may result in fewer days with gastrointestinal symptoms, less limitation of energy intake, and better nutrient absorption.

We found no significant differences in trunk or appendicular fat according to specific NRTI medication use. An important feature of this analysis is that patients receiving an NRTI were compared with patients not receiving the NRTI but who were also not receiving HAART. We chose this approach to remove the potential confounding effect of HAART on the NRTI-fat association. NRTIs are components of most HAART regimens, but the question

of interest was whether they themselves are associated with fat redistribution. For analyses of protease inhibitor and NNRTI use and regional fat distribution, the comparison group was also patients not receiving HAART so that the reference group was the same across the 3 drug classes.

Although mean duration of treatment was greatest with NRTI use, individual NRTIs were not associated with significant differences in either trunk or appendicular fat in men or women after adjustment for age, BMI, and strength training (Table 4). Despite other analyses suggesting that stavudine (D4T) plays a role in fat redistribution (11, 13), we did not find this to be true. It may be the combination of D4T in HAART or D4T as a marker of successful viral suppression that is associated with regional fat change. Each of the protease inhibitors, however, was associated with a similar effect on appendicular fat. Although the sample size in women was very small for each drug, the estimate of effect size was similar to those seen in the men. There was greater variability among the NNRTIs: sample sizes were small in both sexes and the estimates of effect size were probably unstable. In addition, NNRTI use is probably confounded by concurrent or previous exposure to protease inhibitors as part of HAART regimens.

Several potential limitations of this study should be considered. First, DXA was used as a compromise between more expensive imaging methods (computed tomography and magnetic resonance imaging) and less accurate assessment methods (anthropometry and bioelectrical impedance). DXA has been validated for measurement of total-body soft tissue composition of lean and fat mass in persons with HIV infection and in other populations (4, 23, 38, 39, 44–46). The use of DXA for regional analysis has several limitations, however. First, trunk image analysis by DXA is complicated by a combination of asymmetry of the visceral organs, rib bone patterns, lung tissue, air space, and respiratory motion (47). Second, in the arms, the total tissue available for analysis is relatively small, making the error proportionally large. Third, facial wasting is a commonly reported symptom of fat redistribution, but DXA does not quantify facial fat. Fourth, total body scans may have difficulty quantifying soft tissue in the neck area (another body site of reported fat abnormalities). Fifth, DXA has not been validated for regional bone mass. Nevertheless, there is no evidence that DXA is biased in persons receiving HAART.

The results of this study do not prove causality by HAART regimens. Shifts in regional body composition attributed to HAART could also be related to viral suppression, immune reconstitution, cytokine production, severity of the underlying HIV infection, self-selection for HAART continuation, and other undetermined factors. Despite multivariate adjustment, the possibility of treatment bias remains, in that those receiving HAART may have had more advanced disease. As in other studies, we cannot exclude the possibility that prior disease severity increased the risk of subsequent fat redistribution. In this study, a greater proportion of HAART users than nonusers had received a diagnosis of AIDS, although the number of years the subjects knew themselves to be HIV seropositive were similar. We also do not have information on the indication for HAART initiation, pretreatment CD4 counts, disease stage, or viral load response. This underscores the need for longitudinal studies and baseline studies before the initiation of HAART.

The mechanism of the syndrome of central adiposity remains elusive. The major emphasis in studying this syndrome has been on abdominal adiposity, but our findings suggest that peripheral fat wasting, primarily in the legs; lean mass increases; and decreases in bone mineral content are as strongly associated with HAART use in a diverse HIV-seropositive population. Thus, in future studies, it will be important to separately analyze arms and legs, as well as fat, lean, and bone mass, in the study of this syndrome.

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