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Article *in* AIDS Research and Human Retroviruses · February 2011

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AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 27, Number 7, 2011

DOI: 10.1089/aid.2010.0272

Regional Anthropometry Changes in Antiretroviral-Naïve Persons Initiating a Zidovudine-Containing Regimen in Mbarara, Uganda

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Abstract

Lipodystrophy is commonly reported in Africa after antiretroviral therapy (ART) is initiated, but few studies have objectively measured changes in body composition. Body composition was determined in 76 HIV-infected participants from Mbarara, Uganda after starting a thymidine-analog regimen, and annual change was determined using repeated measures analysis. We measured skinfolds (tricep, thigh, subscapular, and abdomen), circumferences (arm, hip, thigh, waist), and total lean and fat mass (using bioelectric impedance analysis). A cross-sectional sample of 49 HIV-uninfected participants was studied for comparison. At baseline, most body composition measures were lower in HIV-infected than uninfected participants, but waist circumference was similar. After 12 months on ART, there was little difference in body composition measures between HIV-infected and uninfected participants; median waist circumference appeared higher in HIV-infected participants (79 vs. 75 cm; $p = 0.090$). Among HIV-infected participants, increases were observed in total lean and fat mass, circumference, and skinfold measures; only the increase in tricep skinfold did not reach statistical significance (+1.05 mm; 95% confidence interval: −0.24, 2.34; $p = 0.11$). Regional anthropometry in peripheral and central body sites increased over 12 months after ART initiation in HIV-infected persons from southwestern Uganda, suggesting a restoration to health. Gains in the tricep skinfold, a reliable marker of subcutaneous fat, appeared blunted, which could indicate an inhibitory effect of zidovudine on peripheral subcutaneous fat recovery.

Introduction

Lipodystrophy (or fat distribution changes in peripheral and/or central body sites) is commonly reported in HIV-infected persons in Africa after the initiation of antiretroviral therapy (ART).[1–4] The thymidine analogs stavudine and zidovudine (which are a common component of ART in Africa) have been linked to lipoatrophy or subcutaneous fat loss, the hallmark of the HIV-associated lipodystrophy syndrome, in studies mainly from the United States, Europe, and Australia.[5–10] Lipodystrophy has been associated with decreased quality of life and increased social isolation in sub-Saharan African HIV-infected patients.[11] The stigma associated with these fat changes could lead to decreased adherence to ART, as has been found in studies from the United States and Europe.[12,13]

However, few studies have used objective measures to assess body composition changes in an African HIV population. Most studies from Africa have defined body fat alterations (or lipodystrophy) using subjective criteria of self-report of fat change confirmed by clinical examination.[2,3] Regional anthropometry provides an objective, continuous measure to monitor fat changes at central and peripheral body sites. To our knowledge, only one small study from South

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Africa[14] assessed regional anthropometry changes in HIV-infected persons who were started on a stavudine-containing ART regimen. That study[14] compared anthropometry changes in those with and without lipodystrophy.

The goal of our study was to determine regional anthropometry changes as well as changes in total fat and lean mass measured using bioelectric impedance analysis (BIA) after the initiation of a primarily zidovudine-containing regimen in HIV-infected persons from Mbarara, Uganda. We also compared body composition in HIV-infected participants with controls at baseline.

Materials and Methods

Study population

Between August 2007 and February 2008, a convenience sample of 76 HIV-infected men and women from Mbarara, Uganda, a town in southwestern Uganda, who were newly initiating ART, was recruited from the Uganda AIDS Research on Treatment Outcomes (UARTO) cohort. UARTO is an ongoing prospective observational cohort study of HIV-infected individuals on ART at the Mbarara University of Science and Technology (MUST) HIV clinic. All patients who were scheduled to start ART based on WHO clinical stage and $CD4^+$ T cell count criteria were approached for enrollment into UARTO. We then approached all UARTO participants for enrollment into our substudy during a 6-month time period; the majority of patients approached agreed to participate. All participants were 18 years of age or older, lived within 20 km of the clinic, and none was pregnant or breastfeeding.

As part of the substudy, trained research staff interviewed the participants and performed a physical examination, which included anthropometric measurements at the baseline visit (prior to starting ART) and then every 3 months for 12 months. Of the 76 enrolled participants, four did not have any follow up visits: one died, two became pregnant, and one withdrew from the study after the baseline visit. Of the remaining 72 participants, 51 completed the 12 month visit. The primary reason for loss to follow-up was that participants were not able to return during the 12-month window period. We adjusted our analyses to account for loss to follow-up as described below, as those lost patients may have been more likely to have poor health.

A cross-sectional sample of sex-matched HIV-uninfected controls was enrolled as a comparison group. Controls were recruited by outreach workers from the Mulago- Mbarara Teaching Hospitals Joint AIDS Program for routine testing and counseling. HIV-seronegative controls who agreed to participate in the study underwent a brief interview and the same physical examination as the HIV-infected participants. The controls were measured at one point in time in order to provide a reference point for the body composition measures observed in the HIV-infected participants.

Informed consent was obtained from all participants using protocols approved by the Institutional Review Boards (IRB) in both Uganda and the United States.

Body composition measurements

Research staff were trained and certified to perform anthropometry using a standardized protocol.[15] Height and weight were measured to calculate body mass index (BMI) in kilogram per meter squared (kg/m^2). Circumferences of the arm, waist, hip, and mid-thigh were obtained using a Gulick II measuring tape. Skinfolds of the triceps, subscapular, abdomen, and thigh were measured using the Lange skinfold caliper. For all anthropometry measurements, two independent measurements were taken. If the first two measurements were outside of the acceptable range of variance for a particular body area, then a third measurement was taken. The mean of the two closest measures was then used in analysis.

Total lean and fat mass were measured by BIA (Quantum II BIA; RJL Systems, Michigan) using the formulas of Kotler *et al*.[16] The machine was tested for accuracy daily and measurements were taken with participants in the supine position.

Statistical analysis

Summary statistics of demographic and clinical characteristics at baseline were calculated for the HIV-infected and control participants. Body composition characteristics for the HIV-infected participants at baseline and at the 12 month visit were compared to controls at baseline using the Mann–

Table 1. Baseline Characteristics of HIV-Infected and Uninfected Participants

	HIV$^+$	*Control*	p-*value*
n	76	49	
Age (years)	35.5 (30.0, 42.3)	26.0 (22.0, 32.0)	<0.0001
Gender			
Female	45 (59%)	29 (59%)	0.99
Male	31 (41%)	20 (41%)	
Weight (kg)	55.0 (51.0, 61.0)	59.0 (55.0, 64.0)	0.011
Height (cm)	162.1 (157.4, 167.5)	163.0 (156.7, 169.3)	0.98
BMI (kg/m^2)	21.1 (19.4, 23.2)	22.5 (20.7, 24.7)	0.024
Smoking			
Current	9 (12%)	N/A	
Ever	28 (36%)		
Never	49 (63%)		
CD4 cells/μl	132 (92,197)	N/A	
HIV RNA (copies/ml)	97,503 (34,995, 251,906)	N/A	

N/A, data not available in controls.

Whitney *U* test. We also performed age-adjusted comparisons of body composition, since controls were younger than HIV-infected participants.

Among the HIV-infected participants, the annual unadjusted and adjusted mean changes in body composition measures were calculated using repeated measures analyses with random intercepts and random slopes.[17] The slopes of the regression lines were used as estimates for the rates of change of the body composition measurements. Covariates included in the adjusted analysis were age, gender, current smoking, reported history of clinical AIDS, baseline $CD4^+$ T cell count, and HIV RNA. The relationship of time with body composition showed a linear relationship for some regions, but in other instances showed nonlinear relationships; we therefore modeled time using linear splines, with potentially different slopes for 0–6 and 6–12 months. We chose a 6-month cutpoint, because fat recovery has been reported to occur in the first 6 months after starting antiretroviral therapy followed by stabilization of trunk fat and decreases in limb fat.[6]

To account for those with missing body composition measures due to loss to follow-up, we performed analyses using an inverse probability weighting (IPW) approach[18–20] by modeling each participant's probability of having nonmissing body composition at each timepoint. The inverse of this probability was then used as a weight (applied to persons with nonmissing body composition) in the analysis. Multiple imputation using the Markov chain Monte Carlo method for arbitrary missing data was used to impute missing covariates.[21] We also examined interactions of time with gender, history of AIDS, $CD4^+$ T cell count, and HIV RNA.

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

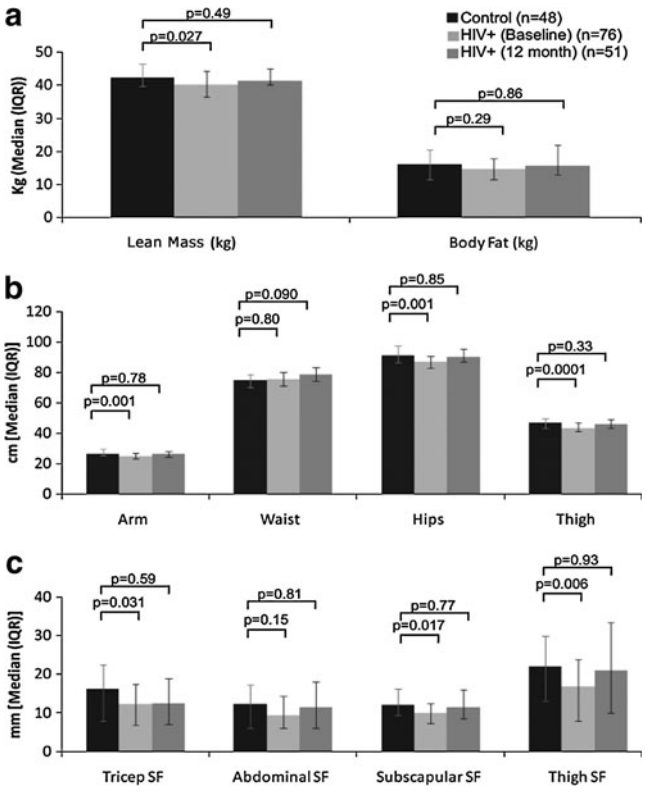

FIG. 1. **(a)** Total lean and fat mass in HIV^+ at baseline and 12 months after initiation of antiretroviral therapy (ART) versus HIV^-. **(b)** Regional circumference measures in HIV^+ at baseline and 12 months after initiation of ART versus HIV^-. **(c)** Regional skinfold measures in HIV^+ at baseline and 12 months after initiation of ART versus HIV^-.

Results

Table 1 shows the baseline characteristics of the 76 HIV-infected participants and 49 HIV-uninfected controls. Women accounted for 59% of the HIV-infected and control participants. HIV-infected participants were older and had lower BMI than controls (median 21.1 vs. 22.5); BMI was in the normal range for both groups. Among the HIV-infected, the median $CD4^+$ T cell count was 132 cells/μl and the median HIV viral load was 97,503 copies/ml. All participants were started on a zidovudine-containing ART regimen except one who was started on a stavudine-containing regimen; all participants were on a nonnucleoside reverse transcriptase inhibitor. The majority (71%) of participants reported taking the same regimen throughout their participation in the study.

At baseline, HIV-infected participants had lower total lean mass than controls. HIV-infected participants also had slightly lower total body fat than controls at baseline (median 14.8 vs. 16.1 kg), but the difference did not reach statistical significance ($p = 0.31$, Fig. 1a). HIV-infected participants also had lower arm, hip, and thigh circumference than controls at baseline, but waist circumference was similar (Fig. 1b). Tricep, subscapular, and thigh skinfolds were also lower in HIV-infected participants at baseline; the abdomen skinfold also appeared to be lower (median 9.3 vs. 12.3 mm), but the difference did not reach statistical significance ($p = 0.15$, Fig. 1c).

After being on ART for 12 months, HIV-infected participants showed statistically significant gains in most regions, such that there was little difference in lean mass or total body fat between HIV-infected participants at month 12 and controls at baseline (Fig. 1a). Similarly, there was little difference in arm, hip, and thigh circumference between HIV-infected and controls, while waist circumference appeared higher than controls (Fig. 1b). Skinfolds for HIV-infected participants at month 12 were not statistically different from controls (Fig. 1c). Triceps skinfold appeared lower at month 12 compared with controls, but the difference did not reach statistical significance. Age-adjusted analyses showed similar results.

Among the HIV-infected participants, statistically significant 12 month gains were seen in total lean and fat mass (Fig. 2). Circumferences and most skinfolds also showed statistically significant increases from baseline (Fig. 3). While a small increase in the tricep skinfold was seen, the change after 12 months did not reach statistical significance (1.05 mm, 95% CI -0.24, 2.34, $p = 0.11$). When we examined the mean annual change using an observed case approach instead of the IPW approach, we observed similar findings.

We also found statistically significant gender–time interactions for several regions. Compared to the baseline measurement, women had larger increases in the thigh, abdomen, and subscapular skinfolds, whereas the increase in men was not statistically significant ($p < 0.01$, gender by time interaction; thigh, women: +10.14, 95% CI: 7.14, 13.13 vs. men: +1.87; 95% CI: -1.59, 5.33; abdomen, women: +4.75, 95% CI: 2.39, 7.12 vs. men: +0.49, 95% CI: -2.26, 3.23; subscapula, women: +4.88, 95% CI: 2.87, 6.89 vs. men: +0.60, 95% CI:

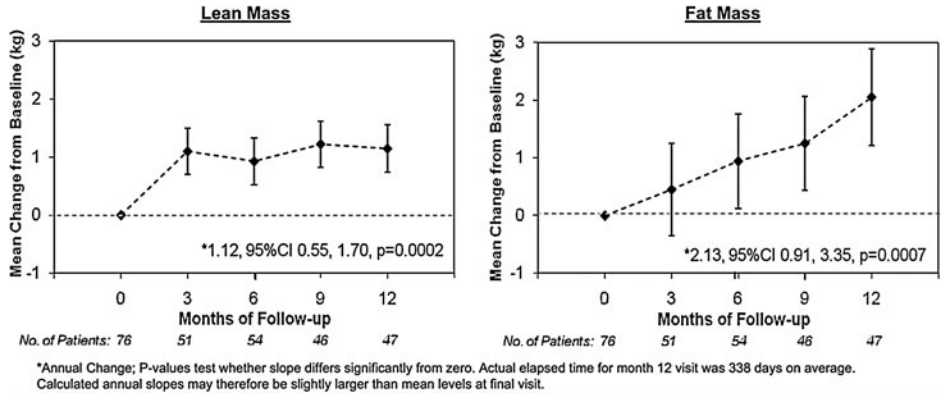

FIG. 2. Mean annual change from baseline of total lean and fat mass in HIV$^+$ participants after initiation of ART. At each follow-up visit, the mean change from baseline is plotted with the 95% confidence interval (CI).

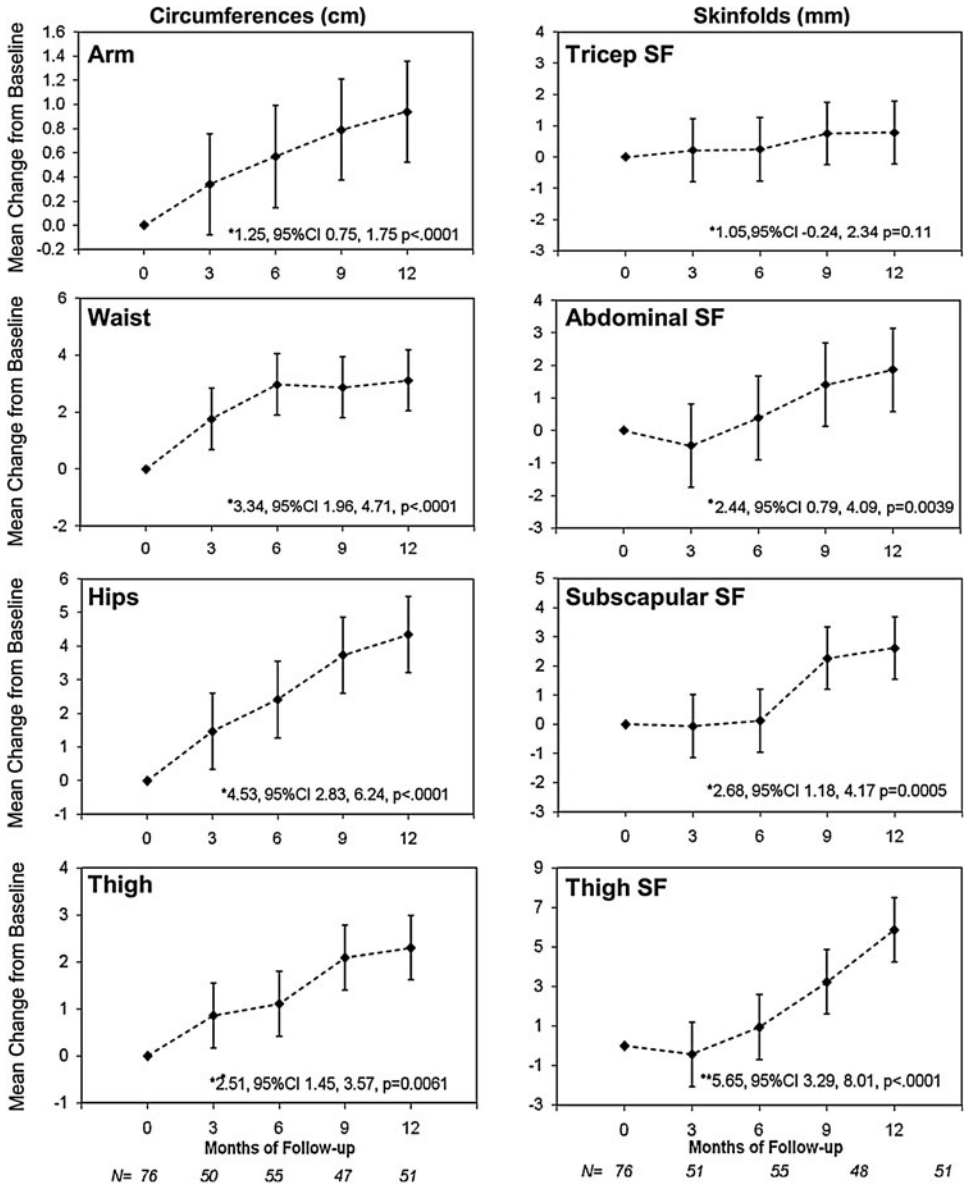

FIG. 3. Mean annual change from baseline for circumferences and skinfolds at each follow-up visit in HIV$^+$ participants after initiation of ART. At each follow-up visit, the mean change from baseline is plotted with the 95% confidence interval (CI).

Table 2. Mean Semiannual Change in Body Composition by Follow-up Time Period: 0–6 Months and 6–12 Months

	0–6 months			*6–12 months*			
	Mean semiannual change	*95% CI*	p-*value*	*Mean semiannual change*	*95% CI*	p-*value*	*0–6 vs. 6–12 months* p-*value*
Lean mass (kg)	1.11	0.64, 1.59	<0.0001	−0.18	−0.90, 0.55	0.63	0.016
Fat mass (kg)	1.38	0.48, 2.27	0.0029	0.79	−0.50, 2.08	0.23	0.53
Circumferences (cm)							
Arm	0.77	0.33, 1.21	0.0007	0.43	−0.02, 0.88	0.061	0.37
Waist	3.17	1.96, 4.37	<0.0001	−0.36	−1.77, 1.04	0.61	0.0017
Hip	3.04	1.90, 4.17	<0.0001	1.25	−0.06, 2.57	0.062	0.046
Thigh	1.39	0.65, 2.14	0.0003	1.09	−0.02, 2.20	0.055	0.69
Skinfolds (mm)							
Tricep	0.26	−0.71, 1.24	0.60	0.87	−0.43, 2.17	0.19	0.52
Abdominal	0.28	−1.08, 1.65	0.68	2.37	0.83, 3.92	0.0027	0.084
Subscapular	0.51	−0.62, 1.64	0.38	2.52	1.10, 3.95	0.0006	0.057
Thigh	0.59	−1.05, 2.24	0.48	5.97	3.47, 8.48	<0.0001	0.0028

Semiannual change is calculated from repeated measures model with IPW to adjust for loss to follow-up.

−1.71, 2.91). The tricep skinfold showed similar changes in men and women. Women were also more likely to have significant increases in the chest and hip circumference than men (data not shown). Mean annual increases in arm and waist circumference were similar in men and women.

When we analyzed the semiannual rate of body composition change (Table 2), the total lean and fat mass both increased significantly in the first 6 months after starting ART. In the second 6 months, the amount of total lean mass appeared to stabilize and the increase in total fat mass was not statistically different. Circumferences of the arm, waist, hip, and thigh increased significantly in the first 6 months of ART. In the second 6 months, the increases in the arm, hip, and thigh circumference were not statistically significant and the waist circumference appeared to stabilize during the second 6 months. By contrast, skinfolds of the tricep, abdomen, subscapula, and thigh changed little in the first 6 months. In the second 6 months, skinfolds in all four sites increased, but the change in the tricep skinfold did not reach statistical significance.

Discussion

Using anthropometry to examine regional body composition changes (as opposed to a dichotomous outcome based upon self-report and clinical examination), we made several noteworthy observations in our study of Ugandan HIV-infected persons after initiation of a zidovudine-containing regimen. First, we found that total lean and fat mass as well as regional circumferences and skinfolds in peripheral and central body sites increased over the 12-month period on ART, suggesting restoration to health. Second, the increase in the tricep skinfold was blunted, which could indicate a zidovudine effect on peripheral subcutaneous fat recovery. Finally, we observed temporal differences in fat and lean mass recovery. Increases in lean mass and circumferences occurred early (first 6 months); by contrast, there was little increase in any of the skinfolds (which are thought to be a reliable measure of subcutaneous fat) until after 6 months of ART.

Our observations of an increase in peripheral and central body fat measured using anthropometry are consistent with studies from the United States and Australia.[6–8] However, we found mean annual increases over the 12-month period; other studies[6,7] reported trunk and limb fat increases [measured by dual-energy x-ray absorptiometry (DXA)] that appeared to peak 16 to 32 weeks after a stavudine- or zidovudine-containing regimen was started. Subsequent decreases in limb fat (thought to be due to the thymidine analogs) to levels near or below baseline levels and stabilization in trunk fat were observed after 48 weeks of therapy. A similar pattern was seen when circumferences of peripheral sites (thigh, arm, hip) and waist were studied.[7] A possible reason for the difference between our study and those studies is that our participants had lower baseline $CD4^+$ T cell counts and BMI. Our participants were also mostly on a zidovudine-containing regimen, whereas in other studies, patients were mostly on a stavudine-containing regimen[6]; stavudine has been shown to cause greater limb fat loss than zidovudine in some studies.[9,10] Interestingly, a South African study[14] of 42 HIV-infected patients with mean $CD4^+$ T cell count of 93 cells/μl found increases (waist, hip circumference, and tricep skinfold) that appeared to peak later (41–59 weeks after starting a stavudine-containing regimen). These findings suggest that regardless of the type of thymidine analog used, before direct effects of the drugs on adipose tissue can be observed, a threshold amount of fat and thus longer restoration to health (and fat recovery) period is needed. Sex differences may also account for some of these differences due to the large proportion of women included in African studies.

Our findings that the increase in tricep skinfold was blunted over the 12-month period is also consistent with the South African study.[14] In that study, only the tricep skinfold declined to below baseline values by 111 weeks of follow-up. These studies suggest that similar to studies from the United States, Europe, and Australia,[5–10] the thymidine analogs (stavudine and zidovudine) are associated with lipoatrophy or fat loss, particularly in peripheral body sites. Unexpectedly, we did not find that the increase in the thigh skinfold was blunted over time, possibly because we followed patients for

only a 12-month period. A U.S. study found that mean decreases in the thigh skinfold were not observed until after 12 months on a zidovudine-containing regimen, but mean decreases were observed in the tricep skinfold within the first 12 months on therapy.[8] The timing of fat loss associated with thymidine analogs may differ in the upper and lower extremity.

Interestingly, we observed that the increase in lean mass and circumferences (especially the waist) occurred mostly in the first 6 months after initiating ART, whereas there was little change in any skinfold measure during the same period. Similar changes have been observed in studies of women with anorexia nervosa in the initial weight recovery period.[22–24] In these studies, central fat accumulation occurred at a greater rate than in healthy age-matched controls, while peripheral fat remained lower than or about the same as in controls. Some have hypothesized that the chronic nutritional deprivation associated with anorexia may lead to altered growth hormone secretion or hypercortisolemia that may influence central fat distribution during recovery.[25] In contrast to our study, a consistent increase in muscle mass was not observed in these studies, likely because our patients had lower lean mass (from muscle wasting or cachexia) resulting from advanced HIV infection. The findings in anorexic patients could suggest that some reports of lipodystrophy in Africa are partly explained by the natural course of fat recovery after restoration to health, as opposed to a direct drug effect. Further study is needed to understand the mechanisms underlying the differences in timing of recovery of lean mass and fat mass in the viscera and subcutaneous compartments in HIV-infected men and women (particularly in food insecure settings) and its long-term implications.

It is noteworthy that we observed a gender-by-time interaction, where women had significant increases in most skinfold and circumference measures and men showed small increases over time. A study of postrenal transplant patients also found that women gained fat mass faster than men.[26] Furthermore, a small retrospective study comparing HIV-infected persons before the advent of HAART to HIV-infected persons after the advent of HAART found that most of the weight difference in men was accounted for by the change in lean mass, whereas in women, most of the weight difference was accounted for by a change in fat mass.[27] Differences in sex steroid levels between men and women have been postulated as a reason. In our population, other unmeasured factors such as social and cultural factors as well as access to food might also be possible explanations for this finding. Sex differences in recovery of total and regional fat warrant study in a larger cohort of HIV-infected men and women.

The limitations of our study include the small sample size and the relatively short follow-up period, which did not allow us to fully differentiate the restoration to health phase from the potential longer term effects of zidovudine in our population. We also were not able to assess body composition changes in controls over a similar 12-month period. We did not study the potential metabolic consequences of these body fat changes, because baseline fasting glucose and lipid values from these participants and limited fasting data over the 12 month period were well within the normal range (data not shown). While anthropometry is prone to some measurement variability, it is the most cost-effective method for obtaining objective and continuous measures of fat in resource-limited settings where direct measures of fat such as MRI, CT, or DXA scanning are not feasible.

In conclusion, regional anthropometry in peripheral and central body sites increased over a 12-month period after zidovudine-containing ART initiation in a cohort of HIV-infected persons from southwestern Uganda. This suggests a restoration to health that may be more prolonged than previously reported in resource-rich countries. Gains in tricep skinfold, a reliable marker of subcutaneous fat, appeared blunted, which could suggest an inhibitory effect of zidovudine on peripheral subcutaneous fat recovery. Further studies over a longer period of time in a large cohort of HIV-infected men and women compared to controls are needed to fully understand the body composition changes and potential metabolic consequences after the initiation of ART. Comparative studies with HIV-infected persons from resource-rich countries may also elucidate how environmental and nutritional factors may have an impact on the rate of recovery of lean and fat mass after initiation of ART.

Acknowledgments

The authors would like to acknowledge the contributions of Annet Kawuma and Heather Southwell to this research. This work was supported in part by a Center for AIDS Research pilot grant: P30AI027763-15, K23 AI-66943, and ROI MH-54907.

Author Disclosure Statement

No competing financial interests exist.

References

1. Bussmann H, Wester CW, Thomas A, *et al.:* Response to zidovudine/didanosine-containing combination antiretroviral therapy among HIV-1 subtype C-infected adults in Botswana: Two-year outcomes from a randomized clinical trial. J Acquir Immune Defic Syndr 2009;51(1):37–46.
2. Mutimura E, Stewart A, Rheeder P, and Crowther NJ: Metabolic function and the prevalence of lipodystrophy in a population of HIV-infected African subjects receiving highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2007;46(4):451–455.
3. van Griensven J, De Naeyer L, Mushi T, *et al.:* High prevalence of lipoatrophy among patients on stavudine-containing first-line antiretroviral therapy regimens in Rwanda. Trans R Soc Trop Med Hyg 2007;101(8):793–798.
4. Mercier S, Gueye NF, Cournil A, *et al.:* Lipodystrophy and metabolic disorders in HIV-1-infected adults on 4- to 9-year antiretroviral therapy in Senegal: A case-control study. J Acquir Immune Defic Syndr 2009;51(2):224–230.
5. Mallal SA, John M, Moore CB, James IR, and McKinnon EJ: Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. AIDS 2000;14(10):1309–1316.
6. Mallon PW, Miller J, Cooper DA, and Carr A: Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy. AIDS 2003;17(7):971–979.
7. Mulligan K, Parker RA, Komarow L, *et al.:* Mixed patterns of changes in central and peripheral fat following initiation of antiretroviral therapy in a randomized trial. J Acquir Immune Defic Syndr 2006;41(5):590–597.

8. Shlay JC, Sharma S, Peng G, Gibert CL, and Grunfeld C: Long-term subcutaneous tissue changes among antiretroviral-naive persons initiating stavudine, zidovudine, or abacavir with lamivudine. J Acquir Immune Defic Syndr 2008;48(1):53–62.
9. FRAM Study Investigators: Fat distribution in men with HIV infection. J Acquir Immune Defic Syndr 2005;40(2): 121–131.
10. FRAM Study Investigators: Fat distribution in women with HIV infection. J Acquir Immune Defic Syndr Hum Retrovirol 2006;42(5):562–571.
11. Mutimura E, Stewart A, and Crowther NJ: Assessment of quality of life in HAART-treated HIV-positive subjects with body fat redistribution in Rwanda. AIDS Res Ther 2007;4:19.
12. Ammassari A, Murri R, Pezzotti P, *et al.:* Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. J Acquir Immune Defic Syndr 2001;28(5):445–449.
13. Duran S, Saves M, Spire B, *et al.:* Failure to maintain long-term adherence to highly active antiretroviral therapy: The role of lipodystrophy. AIDS 2001;15(18):2441–2444.
14. George JA, Venter WD, Van Deventer HE, and Crowther NJ: A longitudinal study of the changes in body fat and metabolic parameters in a South African population of HIV-positive patients receiving an antiretroviral therapeutic regimen containing stavudine. AIDS Res Hum Retroviruses 2009;25(8):771–781.
15. Tien PC, Benson C, Zolopa AR, Sidney S, Osmond D, and Grunfeld C: The study of fat redistribution and metabolic change in HIV infection (FRAM): Methods, design, and sample characteristics. Am J Epidemiol 2006;163(9):860–869.
16. Kotler DP, Burastero S, Wang J, and Pierson RN, Jr: Prediction of body cell mass, fat-free mass, and total body water with bioelectrical impedance analysis: Effects of race, sex, and disease. Am J Clin Nutr 1996;64(3 Suppl):489S–497S.
17. Laird NM and Ware JH: Random-effects models for longitudinal data. Biometrics 1982;38(4):963–974.
18. Hernan MA, Brumback B, and Robins JM: Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology 2000;11(5): 561–570.
19. Matsuyama Y: Sensitivity analysis for the estimation of rates of change with non-ignorable drop-out: An application to a randomized clinical trial of the vitamin D3. Statist Med 2003; 22(5):811–827.
20. Robins JM and Finkelstein DM: Correcting for noncompliance and dependent censoring in an AIDS clinical trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics 2000;56(3):779–788.
21. Shafer JL: Multiple Imputation: A primer. Stat Methods Med Res 1999;8:3–15.
22. Grinspoon S, Thomas L, Miller K, Pitts S, Herzog D, and Klibanski A: Changes in regional fat redistribution and the effects of estrogen during spontaneous weight gain in women with anorexia nervosa. Am J Clin Nutr 2001;73(5):865–869.
23. Iketani T, Kiriike N, Nagata T, and Yamagami S: Altered body fat distribution after recovery of weight in patients with anorexia nervosa. Int J Eat Disord 1999;26(3):275–282.
24. Mayer L, Walsh BT, Pierson RN, Jr, *et al.:* Body fat redistribution after weight gain in women with anorexia nervosa. Am J Clin Nutr 2005;81(6):1286–1291.
25. de Alvaro MT, Munoz-Calvo MT, Barrios V, *et al.:* Regional fat distribution in adolescents with anorexia nervosa: Effect of duration of malnutrition and weight recovery. Eur J Endocrinol 2007;157(4):473–479.
26. Coroas A, Oliveira JG, Sampaio S, *et al.:* Nutritional status and body composition evolution in early post-renal transplantation: Is there a female advantage? Transplant Proc 2005;37(6):2765–2770.
27. Kotler DP, Rosenbaum K, Wang J, and Pierson RN: Studies of body composition and fat distribution in HIV-infected and control subjects. J Acquir Immune Defic Syndr Hum Retrovirol 1999;20(3):228–237.

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