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Metabolic Function and the Prevalence of Lipodystrophy in a Population of HIV-Infected African Subjects Receiving Highly Active Antiretroviral Therapy

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Abstract

Objective—This study measured the prevalence of lipodystrophy and the metabolic effects of highly active antiretroviral therapy (HAART) in HIV-infected African subjects.

Methods—Prevalence was measured in 571 Rwandans receiving HAART for 6 months. Metabolic variables were measured in 100 HIV-positive adults with lipodystrophy, 50 HIV-positive nonlipodystrophic adults, and 50 HIV-negative controls.

Results—A HAART regimen of stavudine, lamivudine, and nevirapine was used by 81.6% of subjects; none received protease inhibitors. Lipodystrophy was observed in 34% (48.5% in urban groups and 17.3% in rural groups) of subjects, with a prevalence of 69.6% in those receiving HAART for >72 weeks. Peripheral lipoatrophy combined with abdominal lipohypertrophy was observed in 72% of lipodystrophic subjects. HIV-positive adults with lipodystrophy had a significantly higher waist-to-hip ratio (WHR; 0.99 ± 0.05 vs. 0.84 ± 0.03 ; $P < 0.0005$) than HIV-positive nonlipodystrophic adults. Total cholesterol concentrations (median [interquartile range], mmol/L) were significantly higher in the HIV-positive adults with lipodystrophy (3.60 [1.38]) than in HIV-positive nonlipodystrophic adults (3.19 [0.65]; $P < 0.005$) and control (3.13 [0.70]; $P < 0.0005$) groups. Impaired fasting glucose was observed in 18% of HIV-positive adults with lipodystrophy, 16% of HIV-positive nonlipodystrophic adults, and 2% of controls, but insulin levels did not differ.

Conclusions—African subjects with lipodystrophy have increased WHR, glucose, and cholesterol levels. Glucose concentrations are also elevated in nonlipodystrophic HIV-positive subjects. Therefore, factors other than body fat redistribution contribute to the glucose intolerance.

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Keywords

Africa; glucose; highly active antiretroviral therapy; lipids; lipodystrophy; prevalence

The use of highly active antiretroviral therapy (HAART) has decreased morbidity and mortality rates associated with HIV infection,¹ but it is associated with body fat redistribution (lipodystrophy) and an increased risk of cardiovascular disease and type 2 diabetes mellitus.² Improved access to World Health Organization (WHO)–recommended HAART in sub-Saharan Africa³ may therefore lead to an increased prevalence of these metabolic disorders. Furthermore, the disfiguring nature of lipodystrophy can compromise HIV serostatus and results in stigmatization and marginalization and can lead to reduced HAART adherence.⁴ Therefore, the present study assessed the prevalence of lipodystrophy and its effects on metabolic function in HAART-treated HIV-positive African subjects.

METHODS

Subjects, Rating of Body Fat Changes, and Anthropometric Analyses

Subjects included in the prevalence study had documented HIV infection, were on WHO-recommended HAART for ≥ 6 months without opportunistic infections, and were between 21 and 50 years of age. Subjects were from the Centre Hospitalier Universitaire de Kigali; Treatment and Research AIDS Center and Center, Hospitalier Universitaire de Butare; and HIV/AIDS clinics of Kimironko, Bilyogo-Nyirama, Kinyinya, and Kacyiru. Ethical permission was obtained from the National Research Ethics Committee, Rwanda, and the University of the Witwatersrand, South Africa. A group of 1356 eligible subjects were contacted, of whom 256 declined to participate and 251 agreed but did not return for data collection, and data for 278 subjects were incomplete and thus not included in the analysis. The total cohort therefore consisted of 571 subjects.

All subjects had weight, height, waist and hip circumference, age, and type and duration of HAART recorded. Subjects completed a lipodystrophy-specific questionnaire self-reporting changes that occurred after initiation of HAART in fat content of the face, dorsocervical region, arms, breasts, abdomen, buttocks, or legs.^{5,6} Subjects rated the severity of fat atrophy and/or fat deposition on a scale of 1 to 4 as absent (score of 1), mild (noticeable on close inspection, score of 2), moderate (readily noticeable by patient or physician, score of 3) or severe (readily noticeable to a casual observer, score of 4).^{5,6} This system was also used to rate overall body fat changes. The ratings of body fat changes were confirmed by a physician, and lipodystrophy was defined as a score of ≥ 2. The questionnaire was administered in the indigenous language Kinyarwanda, which is spoken by all Rwandans, and was explained in detail to ensure that all subjects understood the requirements. Two research assistants trained on proper anatomic placement of the tape, whose measurements were cross-validated on a number of subjects until the variability between duplicate measures were low, assessed anthropometry. Waist circumference was measured using a cloth tape measure halfway between the lowest rib and the iliac crest. Hip circumference was measured at the level of the anterior superior iliac spine when this could be palpated; otherwise, it was measured at the broadest circumference below the waist. The same

research assistants and physicians performed the anthropometric measurements in the rural and urban populations.

Metabolic Studies

Metabolic and anthropomorphic variables and blood pressure were obtained from a random group of 100 (60 female) urban-based subjects with moderate to severe lipodystrophy and compared with 50 (30 female) randomly sampled age-, gender-, and body mass index (BMI)-matched urban-based HIV-positive subjects with no lipodystrophy. Both of these groups were selected from the prevalence study cohort. A control group of 50 (30 female) age-, gender-, and BMI-matched HIV-seronegative volunteers with no lipodystrophy was obtained from the urban sites at which the study took place. Pregnant or breast-feeding women were excluded. An overnight fasting blood serum sample was drawn from each subject's arm vein at 7:30 AM using standard laboratory protocols. Blood serum samples were analyzed using a Humalyzer 3000 (Abbott Laboratories, Abbott Park, IL) for total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, and insulin. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula,⁷ and insulin sensitivity assessed using the homeostatic model of assessment (HOMA) method.⁸ The prevalence of impaired fasting glucose (IFG; glucose >5.6 mmol/L⁹) hypertriglyceridemia (triglycerides >1.7 mmol/L¹⁰), and hypercholesterolemia (total cholesterol >5.0 mmol/L¹⁰) was measured in all 3 groups.

Statistical Analyses

Normally distributed variables and variables that could be normalized by means of mathematic transformation were compared across groups using ANOVA. Post hoc analysis was performed on paired means using the Tukey honest significant difference test for unequal sample sizes. Nonparametric data were compared across groups using the Kruskal-Wallis ANOVA. Differences between male and female subjects or between rural and urban groups were analyzed using the Student nonpaired *t* test or the Mann-Whitney *U* test. Spearman correlation was used to assess the relation of HAART duration to metabolic variables. Percentage values were compared using the χ^2 test. Logistic regression was used to determine the principal demographic determinants of lipodystrophy, with HAART duration divided into quartiles and the lowest quartile (quartile 1) used as the reference. Parametric data are expressed in the text and tables as mean $\pm$ SD, whereas nonparametric data are expressed as median (interquartile range). Statistical analyses were performed using Statistica (version 7.1; StatSoft, Tulsa, OK).

RESULTS

HAART Regimens, Anthropometry, and Prevalence of Lipodystrophy

Five HAART regimens were observed: stavudine (d4T), lamivudine (3TC), and nevirapine (NVP) in 81.6% of subjects; zidovudine (AZT), 3TC, and NVP in 10.9%; AZT, 3TC, and efavirenz (EFV) in 4.7%; d4T, 3TC, and EFV in 2.1%; and 3TC, abacavir, and NVP in 0.7%. The percentage of subjects using each regimen did not differ between the rural and urban populations. Lipodystrophy was less common in subjects using regimens containing

EFV (15.4% of 39 subjects) than in subjects not using EFV (35.3% of 532 subjects; $P = 0.01$).

The prevalence of lipodystrophy was 34%, with 26.6% of subjects having moderate to severe lipodystrophy, and was more common in the urban population (48.5%) than in the rural population (17.3%; $P < 0.0005$). When urban and rural data were combined, the prevalence of lipodystrophy was 69.6% in those receiving HAART for >72 weeks. The study population was 73% female, and 25% of male subjects and 37% of female subjects ($P = 0.007$ vs. male subjects) had lipodystrophy. No anthropometric gender differences were noted.

Within the lipodystrophic group, 9% of subjects reported only lipoatrophic changes, 19% reported only lipohypertrophic changes, and 72% reported both types of changes. This was similar in both genders. The regions of the body most commonly affected were the abdomen (in 84% of subjects), legs (70%), face (67%), arms (66%), breast (47%), buttocks (46%), and neck (34%) and were similar for male and female subjects and for urban and rural populations.

Subjects with lipodystrophy had been on HAART for longer and displayed larger waist circumferences but smaller hip circumferences and a larger waist-to-hip ratio (WHR) than subjects without lipodystrophy (Table 1). Rural subjects without lipodystrophy had the lowest BMI.

Logistic regression was performed to determine the main demographic determinants of lipodystrophy. The model included age, gender, site (urban or rural), and HAART duration. The results demonstrated that rural residence was protective (odds ratio [OR] = 0.20, 95% confidence interval [CI]: 0.12 to 0.32; $P < 0.0001$), whereas longer duration of HAART significantly increased (quartile 2 of HAART duration: OR = 1.81, 95% CI: 0.88 to 3.74, $P = 0.11$; quartile 3: OR = 12.08, 95% CI: 6.53 to 22.35, $P < 0.0001$; and quartile 4: OR = 24.63, 95% CI: 13.13 to 46.21, $P < 0.0001$) the risk of developing lipodystrophy.

Body Composition and Metabolic Variables

Within the metabolic study, statistically significant differences existed between the 3 groups for waist and hip circumferences, WHRs, and serum total cholesterol and plasma glucose concentrations (Table 2). Triglyceride levels were also found to vary across groups by ANOVA ($F = 3.23$, $P < 0.05$), but statistically significant differences between individual subject groups were not observed. If all the ANOVAs were run using only male subjects or only female subjects, the same trends as those described previously were observed. The duration of HAART was shown to be significantly longer in the lipodystrophic HIV-positive group than in the nonlipodystrophic HIV-positive group ($P = 0.001$). No differences were found between these 2 groups for the prevalence of the 5 different HAART regimens, and no differences were noted across these regimens for any of the metabolic or anthropometric variables.

The BMI of the nonlipodystrophic HIV-positive group was significantly higher than that of the other 2 groups (see Table 2); however, univariate correlation analyses demonstrated that

BMI did not correlate with any of the metabolic variables, and thus could not explain any of the significant differences observed for these variables between the 3 subject groups.

Gender differences were also analyzed, and no significant differences were observed for any of the metabolic variables.

The prevalence of IFG levels was found to be 18% in the lipodystrophic group ($P = 0.006$ vs. HIV-negative group), 16% in the nonlipodystrophic group ($P = 0.01$ vs. HIV-negative group), and 2% for the HIV-negative group. The prevalence of hypertriglyceridemia was found to be 9% in the lipodystrophic group and 0% in each of the other 2 subject groups ($P = 0.03$ vs. lipodystrophic group). The prevalence of hypercholesterolemia was found to be 14% in the lipodystrophic group but 0% in each of the other 2 subject groups ($P = 0.006$ vs. lipodystrophic group).

Spearman correlation showed that duration of HAART for all HIV-positive subjects ($n = 150$) did not correlate with triglyceride ($r = 0.05$, $P = 0.56$), cholesterol ($r = 0.11$, $P = 0.18$), HOMA ($r = 0.10$, $P = 0.22$), or glucose ($r = -0.01$, $P = 0.87$) levels.

DISCUSSION

This is the first study to report the prevalence of lipodystrophy in African subjects receiving HAART, and it is the largest study to have analyzed the metabolic and anthropometric effects of WHO-recommended triple therapy. This study used a previously published subjective method for diagnosing lipodystrophy.⁵ The accuracy of such methods has been criticized. Thus, some studies show that patients overreport the level of body fat changes when these are confirmed by a clinician¹¹ or by anthropometric measurements,¹² whereas other studies show that patient self-reporting¹³ or clinical assessment¹⁴ of body fat changes underestimates the prevalence of lipodystrophy when compared with objective measures. We used patient self-reporting and confirmation by a clinician. This is the most widely used method^{5,6,15–17} and has been suggested as the best to use in the absence of objective measures of lipodystrophy.¹⁸ This technique has been used as the method of choice for the development of an objective case definition of lipodystrophy⁶ and has been shown to correlate with objective measures of fat mass (ie, brachial and thigh circumference, echographically assessed perirenal fat diameter).¹⁷

The prevalence of lipodystrophy in HIV-infected subjects in the present study was 34.0%, with 26.6% of all study subjects reporting moderate to severe body fat changes. Previous large studies using HAART without protease inhibitors report a lipodystrophy prevalence of 7% to 46%.^{19–21} This wide range in prevalence levels is attributable to differences in the definition of lipodystrophy and the treatment regimens used.²

The prevalence of lipodystrophy in this study reached 69.6% after 18 months of therapy. Other studies have also shown a relation between HAART duration and lipodystrophy.²² This high prevalence of lipodystrophy may have severe consequences, because it is known that the body shape changes resulting from lipodystrophy can lead to reduced HAART adherence.⁴ The present study indicates that HAART regimens that include EFV, even in the presence of d4T, are associated with a lower prevalence of lipodystrophy. Previous studies

have also shown that nonnucleoside reverse transcriptase inhibitors (NNRTIs) have more favorable effects on body fat redistribution.^{23,24} The number of subjects receiving EFV in the present study was low (n = 39), however.

Female subjects comprised 73% of the present study population, and this confirms data showing that only 30% of HIV-infected Rwandan patients receiving HAART are male.²⁵ In this study, female subjects tended to have a greater risk of developing lipodystrophy than male subjects, as also demonstrated in a previous study.²⁶ It is not known whether this is attributable to gender-related physiologic differences or to a greater awareness in women of body shape changes.

In the present study, WHR was higher in subjects with lipodystrophy. This was attributable to higher waist and lower hip circumferences, suggesting that lipohypertrophy occurs abdominally, whereas lipoatrophy occurs in the gluteofemoral region. Contradicting this, 2 large studies have shown that in subjects receiving ART, lipoatrophy is common, whereas abdominal lipohypertrophy is equally or less common than in HIV-negative subjects.^{15,16} Both studies included patients on a number of different ART regimens, however, and the HIV-negative populations had higher body weights than the HIV-positive subjects. Furthermore, in female subjects, HAART was actually associated with greater visceral fat mass.¹⁶ The HIV-negative subjects in the current study had much lower WHRs than those with lipodystrophy, suggesting that the increased abdominal obesity is related to HAART rather than to simple restoration to health. Studies have shown that nucleoside reverse transcriptase inhibitors (NRTIs) block adipogenesis²⁷ and cause mitochondrial damage in adipocytes,²⁸ and this may partly explain their lipoatrophic effects. The mechanism underlying lipohypertrophy is not understood, however.

The prevalence of lipodystrophy was higher in urban dwellers than in rural dwellers. One explanation may be the higher BMI of the urban population and the possibility that HAART-associated lipodystrophy is more prevalent in populations with a greater body fat mass. This may be attributable to a higher number of target cells (ie, adipocytes) or the greater ease of identification of lipoatrophy. A study has shown that body fat changes are more likely with increasing BMI in subjects receiving HAART.²⁹

In the present study, subjects with lipodystrophy had significantly higher total cholesterol concentrations and higher prevalences of hypertriglyceridemia and hypercholesterolemia than those without lipodystrophy. This effect may be attributable to increased abdominal fat mass; however, it must be noted that HAART² and d4T in particular³⁰ have been shown to increase serum cholesterol and triglyceride levels.

Fasting plasma glucose levels and the prevalence of IFG were higher in HIV-positive lipodystrophic and non-lipodystrophic patients than in HIV-negative subjects. This suggests that glucose intolerance is not attributable to increased abdominal fat mass but may be related to direct effects of NRTIs and/or NNRTIs. Previous studies have also shown that NRTI use is associated with decreased glucose tolerance.^{19,31} Neither insulin nor HOMA levels were different across the 3 subject groups in the present study. Therefore, HAART

does not seem to be affecting insulin secretion or activity. NRTI treatment has been shown to increase fasting insulin levels in a long-term longitudinal study, however.³²

The present study shows that risk factors for cardiovascular disease and type 2 diabetes are elevated in African subjects receiving HAART that contains NNRTIs and NRTIs. No individuals were noted with diabetes, however, and the positive effects of HAART in terms of reduced morbidity and mortality¹ far outweigh the possible risk of diabetes or cardiovascular disease.³³ Furthermore, a study conducted in Cameroon using the same WHO-recommended HAART regimens demonstrated undetectable viral levels in 80% of subjects after 24 weeks of therapy.³⁴ Nevertheless, the psychologic impact of body fat remodeling and its effects on treatment adherence should not be ignored, particularly in light of the high prevalence of lipodystrophy noted in this and another study in western India, which also used WHO-recommended HAART regimens.¹⁹ Additionally, longitudinal studies should be performed in this population to determine whether diabetes and cardiovascular disease increase in prevalence over extended periods of HAART.

Whether the data obtained in this study are applicable to all Rwandan subjects receiving antiretroviral therapy (ART) is a matter for debate. There are only 2 other studies that have investigated this population, and both displayed a preponderance of female subjects—60%³⁵ and 65%³⁶ compared with 73% in the current study. The median age of 40 years³⁶ was the same for the present study. These data therefore suggest that our cohort may be similar to most Rwandan subjects receiving ART.

These results demonstrate for the first time that the use of HAART in an African population, particularly in an urban setting, leads to a high prevalence of lipodystrophy and to similar metabolic and anthropometric changes to those observed in “developed world” populations. These data highlight the need for the development of inexpensive and accessible treatments for the reduction of lipodystrophy and its negative effects on HAART adherence.

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TABLE 1
Anthropometry and HAART Duration in Subjects With and Without Lipodystrophy in Rural and Urban Populations

Variables	Subjects With Lipodystrophy			Subjects Without Lipodystrophy		
	Urban (n = 148)	Rural (n = 46)	Combined (n = 194)	Urban (n = 157)	Rural (n = 220)	Combined (n = 377)
Age (y)	39.3 ± 7.8	39.6 ± 7.9	39.4 ± 7.8	38.3 ± 6.7	37.9 ± 8.3	38.1 ± 7.6
HAART (wk)	68 (24) ^{*†}	72 (32) ^{*†}	68.0 (24.0) [§]	44.0 (8.0)	44.0 (10.0)	44.0 (8.0)
BMI	22.5 ± 2.2 [‡]	22.4 ± 2.2	22.5 ± 2.2	23.2 ± 3.1 [‡]	21.8 ± 2.7	22.4 ± 3.0
Waist (cm)	86.2 ± 6.1 ^{*†}	86.5 ± 5.8 ^{*†}	86.3 ± 6.0 [§]	76.0 ± 6.5	75.9 ± 5.8	75.9 ± 6.1
Hip (cm)	87.4 ± 6.5 ^{*†}	88.5 ± 6.0	87.7 ± 6.4 [§]	90.5 ± 7.1	90.6 ± 6.4	90.6 ± 6.7
WHR	0.99 ± 0.05 ^{*†}	0.98 ± 0.06 ^{*†}	0.99 ± 0.05 [§]	0.84 ± 0.03	0.84 ± 0.03	0.84 ± 0.03

Data expressed as mean ± SD or median (interquartile range).

^{*} $P < 0.0005$ vs. urban without lipodystrophy;

[†] $P < 0.0005$ vs. rural without lipodystrophy;

[‡] $P < 0.05$ vs. rural without lipodystrophy;

[§] $P < 0.0005$ vs. combined without lipodystrophy.

TABLE 2

Subjects' Body Composition and Metabolic Parameters

Variables	HIV Positive With Lipodystrophy	HIV Positive Without Lipodystrophy	HIV-Negative Volunteers
Age (y)	37.7 ± 6.2	37.7 ± 6.3	37.7 ± 5.7
BMI	24.2 ± 2.9	25.8 ± 2.8 [*]	24.2 ± 2.4 [§]
HAART duration (wk)	58 (48)	48 (24) [†]	—
Waist circumference (cm)	91.7 ± 7.7	85.0 ± 7.0 [†]	83.1 ± 4.6 [†]
Hip circumference (cm)	93.1 ± 7.2	100.3 ± 4.3 [†]	98.9 ± 4.2 [†]
WHR	0.99 ± 0.04	0.85 ± 0.07 [†]	0.84 ± 0.05 [†]
Total cholesterol (mmol/L)	3.60 (1.38)	3.19 (0.65) [‡]	3.13 (0.70) [†]
HDL (mmol/L)	1.27 (0.26)	1.29 (0.28)	1.31 (0.26)
LDL (mmol/L)	2.06 (1.16)	2.02 (1.24)	2.07 (1.10)
Triglyceride (mmol/L)	1.37 (0.43)	1.14 (0.38)	1.16 (0.38)
Glucose (mmol/L)	4.77 (1.00)	4.91 (0.67)	4.33 (0.55) ^{*,§}
Insulin (pmol/L)	46.9 (40.2)	36.0 (26.6)	49.7 (18.9)
HOMA	1.41 (1.37)	1.17 (0.79)	1.43 (0.78)
Systolic BP (mm Hg)	124.5 (17.5)	124.5 (18.0)	121.5 (18.0)
Diastolic BP (mm Hg)	83.0 (13.5)	84.5 (11.0)	79.0 (11.0)

Data expressed as mean ± SD or median (interquartile range).

^{*} $P < 0.05$;

[†] $P < 0.0005$ vs. lipodystrophic group;

[‡] $P < 0.005$;

[§] $P < 0.05$ vs. HIV-positive, no lipodystrophy group.

BP indicates blood pressure.