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Human immunodeficiency virus (HIV) associated lipodystrophy: The prevalence, severity and phenotypes in patients on highly active anti-retroviral therapy (HAART) in Kenya

Angela Awino McLigeyo[1]*, Godfrey Lule[2], Fredrick C. F Otieno[2], Joshua Kyateesa Kayima[2] and Enoch Omonge[2]

[1]Aga Khan University Hospital, P. O. Box 30270-00100 Nairobi, Kenya.
[2]School of Medicine, College of Health Sciences, University of Nairobi, P. O. Box 19676-00202 Nairobi, Kenya.

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Highly active antiretroviral therapy (HAART) is widely accessible to human immunodeficiency virus (HIV)-infected individuals in Kenya. Their long term use is associated with chronic complications such as lipodystrophy which may lead to stigmatization, reduced self esteem and poor adherence to HAART. This cross-sectional study described the prevalence of lipodystrophy, the phenotypes and severity among adult HIV infected patients on chronic HAART at a HIV clinic in Kenya. Data were collected using an investigator administered questionnaire and anthropometric measurements done using a protocol based on the Third National Health and Nutrition Examination Survey. The prevalence of lipodystrophy was 51.3% (confidence interval (CI) 45.6 to 57.6). Lipoatrophy occurred in 44%, lipohypertrophy in 15% and mixed syndrome in 41% of patients with lipodystrophy. Facial atrophy occurred in 75.7% of patients with lipodystrophy, upper limb atrophy in 48.5%, and lower limb atrophy in 36.8%. Abdominal obesity occurred in 40.4% of patients with lipodystrophy, breast enlargement in 30.9% and dorsocervical fat accumulation in 5.1%. Most patients had severe lipoatrophy, whereas lipohypertrophy was described as mild to moderate using the HIV out-patient study (HOPS) scale. HIV associated lipodystrophy was common in HIV-infected patients on chronic HAART. The main phenotype was lipoatrophy which majority of the patients described as severe.

Key words: Lipodystrophy, highly active anti-retroviral therapy (HAART), nutrition surveys, obesity, abdominal.

INTRODUCTION

Highly active anti-retroviral therapy (HAART) is the standard of care therapy for patients with human immunodeficiency virus (HIV)-1 infection and CD4 counts ≤ 350 cells/mm^3. In Kenya, there has been a dramatic increase in the number of patients accessing antiretroviral therapy from an estimated 3,000 in 2002 to 511,181 in 2011 (Kenya ART Guidelines, 2011). However, viral eradication is not possible with HAART, thus antiretroviral therapy use has to be indefinite for the clinical benefits to be preserved (Hoggs et al., 1998). Prolonged use of HAART has led to recognition of long term complications of these therapies such as lipodystrophy which was first described in HIV-1 infected individuals by Carr et al. (1998). It manifests with distressing morphologic changes in body habitus such as central fat accumulation (lipohypertrophy) evidenced by increased abdominal girth and increased waist to hip ratio, development of a dorsocervical fat pad (buffalo hump), breast enlargement, fat

*Corresponding author. E-mail: awinoligeyo@yahoo.com.

accumulation in the anterior neck and multiple lipomata. Lipodystrophy also manifests with loss of peripheral subcutaneous fat (lipoatrophy) in the face, arms, legs, abdomen and/or buttocks resulting in the appearance of sunken cheeks, exaggerated musculature, bones, arteries and veins occurring most frequently among patients who are responding to HAART. A mixed syndrome has also been reported in patients who exhibit simultaneous fat loss and accumulation at distinct locations of the body (Tien et al., 2003).

Studies have shown that patients with lipodystrophy report increased distress due to the cosmetic effects and think that the obvious facial and extremity wasting represents disease progression and a form of involuntary disclosure of HIV status. This has been associated with both short-term and long-term suboptimal adherence to antiretroviral regimens leading to treatment failure (Reynolds et al., 2006). The dysmorphic changes have also been associated with social stigmatization, reduced self esteem, a disruption of sex life and therefore reduced quality of life (Blanch et al., 2004). In addition, HAART-naive patients have been reported as reluctant to initiate treatment with healthcare providers being viewed as ignoring and discrediting patients' distress (Ammassari et al., 2002). The overall prevalence of at least one physical abnormality in various studies is about 50% after 12 to 18 months of therapy (Heath et al., 2002; Galli et al., 2002). In the HIV out-patient study (HOPS), a sub-analysis was performed on 1077 patients visiting out-patient clinics over three month duration. It was reported that 49% of the study population had one or more signs of lipodystrophy. Of the patients, 13.3% had only signs of peripheral fat atrophy, 13.2% had only signs of fat accumulation, and 22.7% had both (Lichtenstein et al., 2001).

In the LIPOCO study, a cross-sectional analysis of 154 men who were part of a French observational cohort, lipodystrophy was observed in 53.25% patients. Investigators classified 15.89% patients in the lipoatrophy group, 4.21% in the obesity group and 18.22% in the mixed group (Saint-Marc et al., 2000).

Diagnosis of HIV-associated lipodystrophy is typically made on clinical grounds. Patient self-reports may be an early and the best indicator of body shape changes, and correlates with physical examination. Case definitions for use as a research tool have been suggested (Carr et al., 2003). Other methods include anthropometric estimates of both visceral adipose tissue (VAT) and subcutaneous adipose tissue though more emphasis has been placed on the prediction of VAT (Zamboni et al., 1998), skin fold thickness to estimate subcutaneous fat, computed tomography (CT) and magnetic resonance imaging (MRI) scans which give objective quantification of fat (Seidel et al., 1990) but requires expert interpretation and are expensive, dual energy X-ray absorptiometry which is suitable for examining subcutaneous fat, but cannot be used to estimate visceral fat, dorsocervical fat and facial fat, and bioelectrical impedance analysis which estimates whole lean body tissue.

HAART is increasingly available and accessible to HIV infected patients in Kenya and has transformed HIV into a chronic manageable disease, but with chronic complications such as lipodystrophy, the cosmetic aspect complications such as lipodystrophy, the cosmetic aspect of which may compromise antiretroviral drug adherence and, ultimately, treatment success. However, there are few studies on lipodystrophy in Africans despite its high prevalence in other societies.

Data from this study will provide a foundation for on-going education to clinicians and patients on the risk factors for these complications and their relationship to antiretroviral therapies.

MATERIALS AND METHODS

Ethical considerations

The study was conducted after approval by the Department of Clinical Medicine and Therapeutics, University of Nairobi, and the Kenyatta National Hospital Scientific and Ethical Review Committee.

Study site

This study was conducted at the HIV out-patient clinic at Kenyatta National Hospital, a tertiary national referral and teaching hospital in Kenya.

Study population

The participants were HIV infected patients, ≥15 years old on HAART for six months or longer seen in the HIV clinic from August, 2007 to August, 2008.

Study design

This was a cross-sectional descriptive study. A study questionnaire was used to collect baseline and clinical data. The assessment of lipodystrophy was determined by self report and physician assessment using a modified version of the lipodystrophy case definition questionnaire (Carr et al., 2003). Anthropometric measurements (height, weight, mid upper arm circumference, waist circumference and hip circumference) were obtained using a standardized protocol based on the Third National Health and Nutrition Examination Survey (NHANES III).

An abdominal circumference of greater than 102 cm for men and 88 cm for women was considered as increase in abdominal girth (Miller et al., 1998). A body mass index more than 25 kg/m^2 was considered overweight. The minimum sample size (n) required to determine the prevalence of lipodystrophy was determined at 265 patients. The criteria for statistical significance was P value <0.05.

Inclusion criteria

HIV infected male and female patients aged 15 years or more and deemed compliant on HAART for six months or more were eligible for this study.

Exclusion criteria

Patients on anabolic steroids or immune-modulatory therapy, those with Cushing's disease or other endocrine disorders, pregnant patients, moribund patients, and patients with malignancy or features of HIV wasting syndrome were excluded.

Patient assessment

The Comprehensive Care Centre operates five days in a week. All patients undergo full evaluation at initial visit consisting of a comprehensive history, including current and prior anti-retroviral therapy, past and current history of opportunistic infections; physical examination and laboratory investigations including full blood count, liver and renal function tests, CD4 and CD8 counts.

Patients eligible for HAART commence treatment and thereafter return to the clinic monthly for review and supply of antiretroviral medication.

Recruitment was done among patients who had been on chronic treatment. The patients were informed about the study and their eligibility assessed. Those who met the inclusion criteria and gave signed informed consent were recruited and the history of their illness was taken. The study questionnaire and lipodystrophy case definition questionnaire were administered by the principal investigator followed by a targeted physical examination and performance of anthropometric measurements.

Sample size calculation

The minimum sample size (n) required to determine the prevalence of lipodystrophy was calculated using the formula:

$$n = \frac{Z2\ Л\ (1- Л)}{d^2}$$

whereby Z value is the upper $\alpha/2$ point of the normal distribution, 1.96; Л is the assumed prevalence. A prevalence of 22% was used from unpublished local data, d = precision, 0.05

Outcomes

Lipodystrophy was defined by at least one of the following features: fat wasting (lipoatrophy) in the face, neck, arms and legs and gluteal regions; fat accumulation (lipohypertrophy) was defined by central obesity (waist circumference of >88 cm in males and >102 cm in females), focal fatty deposits, cervical fat pad enlargement and gynaecomastia; mixed disease was defined as patients with features of both lipoatrophy and lipohypertrophy.

Lipodystrophy was rated using the HOPS scale first by the patient and then by physician examination, as "subtle" (noticeable only if specifically looked for, no change in clothing fit), "moderate" (easily noted by patient or physician, clothing has become loose/tight), or "severe" (obvious to the casual observer, has required a change in clothing size).

Statistical analysis

All data were entered into database using Microsoft excel. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS), version 15.0 and described as means, medians, standard deviation and frequency distributions. The criteria for statistical significance was P value <0.05.

RESULTS

318 HIV-seropositive patients were screened on chronic HAART therapy and excluded 53 (16.6%) patients; 40 had been on HAART for less than 6 months, 5 had opportunistic infections, 3 were moribund, 2 had HIV wasting syndrome, 2 declined consent and 1 had a malignancy. 265 patients were thus enrolled at the Comprehensive Care Centre at the Kenyatta National Hospital.

Patients' baseline characteristics

The mean and median age of the study population was 40.69 and 40 years, respectively. Females constituted 59.6% of the study participants. The mean baseline CD4 count of the study participants was 119 mm^{-3} while CD4 count at the time of study was 335 mm^{-3}. Majority of the patients that is, 194 (73.3%) were in World Health Organization (WHO) stage III and IV at initiation of HAART. The mean duration of treatment of the study participants was 29.7 months with a median of 28 months. One hundred and seventy seven patients (66.8%) had been on HAART for longer than 18 months. Stavudine based regimens were the most commonly used with 188 (70.9%) patients being on this combination and 41 (15.5%) patients being on AZT-based regimen. Twenty six of these patients had switched from a stavudine (d4T) based regimen prior to enrolment into the study. It was also noted that of 36 (13.6%) patients who were on a tenofovir disoproxil fumarate (TDF) based regimen, 30 had switched from a d4T based regimen and 6 from a zidovudine (AZT) based regimen prior to the time of enrolment. Consequently, 244 (92%) of the study participants had used a d4T containing regimen during their follow-up in the clinic. The switches were mainly due to drug toxicity (lipodystrophy and peripheral neuropathy) and treatment failure.(Table 1)

The males weighed more than the females. The mean body mass index (BMI) of the study population was 22.1 kg/m^2. Both median waist circumference and waist to hip ratio (WHR) were within normal at a median of 83.5 cm and 0.89, respectively for males and 84 cm and 0.87, respectively for females. (Table 2)

Lipodystrophy

Among the study participants on chronic HAART therapy, 51.3% (confidence interval (CI) 45.6 to 57.6) had at least one sign of abnormal fat distribution. The concordance between patient self-assessment and physician examination was 96.9%. Lipoatrophy was described in 44%, lipohypertrophy in 15% and mixed syndrome in 41% of patients with lipodystrophy.

Facial fat loss was the commonest sign of lipoatrophy described in 75.7% of patients with fat distribution

Table 1. Demographic characteristics of the study population.

Variable	Category	No. of patients	Frequency (%)/ Mean
Age	-	265	40.7
Gender	-	158	59.6
WHO stage	I	24	8.9
	II	47	17.3
	III	99	37.3
	IV	95	36
CD4 counts	Nadir	256	119 mm^{-3}
	Most recent	265	335 mm^{-3}
Duration of HAART (Months)	6 -18	83	31.2
	19 - 36	123	46.4
	> 36	59	22.4
HAART combinations	d4T based	188	70.9
	AZT based	41	15.5
	TDF based	36	13.6

Table 2. Distribution of anthropometric variables of the 265 patients included in the study.

Variable	Median (IQR)	
	Male (n=107)	Female (n=158)
Weight (kg)	64.5 (45-97.5)	62.7 (40.5-96)
Height (cm)	172 (151-188))	166 (149-185)
Waist circumference (cm)	83.5 (61-117)	84 (60-130)
Waist to hip ratio	0.89 (0.72-1.18)	0.87 (0.63-1.30)

abnormalities, followed by fat loss in the arms (48.5%), legs (36.8%), gluteal area (36.8%) and breast (11.8%). Among patients with lipohypertrophy, increased abdominal girth was evident in 40.4% of the patients of whom, 24% had isolated abdominal fat accumulation. Breast enlargement was found in 30.9% of the patients and fat accumulation in the dorsocervical area in 5.1% of the patients (Table 3). There was a high degree of concordance (70 to 97%) between patients and their physicians on the presence of abnormal fat distribution at the different body sites. Most patients had severe lipoatrophy (Figure 1).whereas lipohypertrophy was described as mild to moderate (Figure 2).

DISCUSSION

Lipodystrophy is a well recognized problem in the Western world but with very little data in the African population. There is currently no published data on its prevalence in Kenya. This study was conducted between August 2007 and 2008 at Kenyatta National Hospital, a referral and teaching hospital in Kenya. It comprised 59.6% females (female to male ratio, 1.5:1). Most of the individuals in the study population were young individuals with a median age of 40 years and about 50% aged below 50 years. Females were younger than their male counterparts where 60.7% were below 40 years as compared to 44% of males. These findings reflect the National Acquired Immune Deficiency Syndrome (AIDS) and Sexually Transmitted Infection (STI) Control Programme (NASCOP, 2005) estimates that at least two-thirds of all HIV infected in-dividuals in Kenya are young women in the reproductive age. Therefore, the age and gender distribution of this study population is fairly representative of the sample of HIV-infected patients in Kenya.

The mean BMI was 23.1 kg/m^2; this was within the normal range of 18 to 25 kg/m^2. The median mid-upper arm circumference was 27 cm, the median waist circumference was 84 cm and the median WHR of this population was 0.96. These were similar in both male and

Table 3. Distribution of body sites affected by lipodystrophy.

Change in body fat		Physician assessment (n=136)	
		Lipoatrophy (%)	Lipohypertrophy (%)
Facial fat	Yes	103 (75.7)	5 (3.7)
	No	33 (24.3)	131 (96.3)
Neck	Yes	13 (9.6)	6 (4.4)
	No	123 (90.4)	130 (95.6)
Dorsocervical	Yes	9(6.6)	7 (5.1)
	No	127 (93.4)	129 (94.9)
Breast	Yes	16 (11.8)	42 (30.9)
	No	120 (88.2)	94 (69.1)
Arm	Yes	66 (48.5)	5 (3.7)
	No	70 (51.5)	131 (96.3)
Abdomen	Yes	13 (9.6)	55 (40.4)
	No	123 (90.4)	81 (59.6)
Gluteal fat	Yes	50 (36.8)	6 (4.4)
	No	86 (63.2)	130 (95.6)
Leg fat	Yes	50 (36.8)	4 (2.9)
	No	86 (63.2)	132 (97.1)

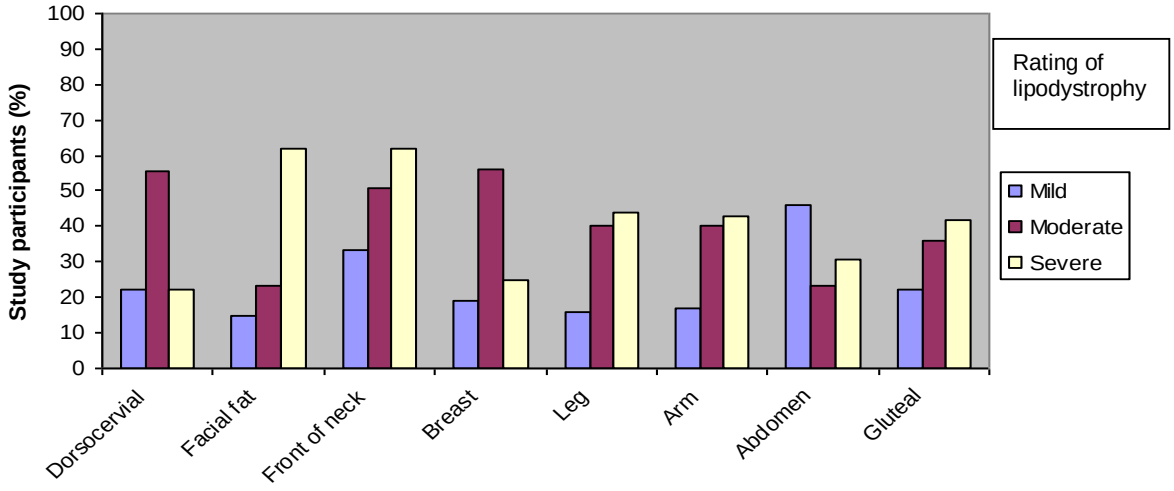

Figure 1. Severity of lipoatrophy by body site of this population.

female patients and within normal. The normal parameters could be a reflection of decreased morbidity as well as the gain of lean tissue mass conferred by the use of HAART and the continuous nutritional assessment and counseling conducted to patients attending our clinics regularly.

In comparison, in the multicenter AIDS cohort study (MACS) cohort, Palella et al. (2004) reported a mean BMI of 25 ± 3 and a mean WRH of 0.95 ± 0.07; the mid upper arm circumference (MUAC) reported 32 ± 4, waist

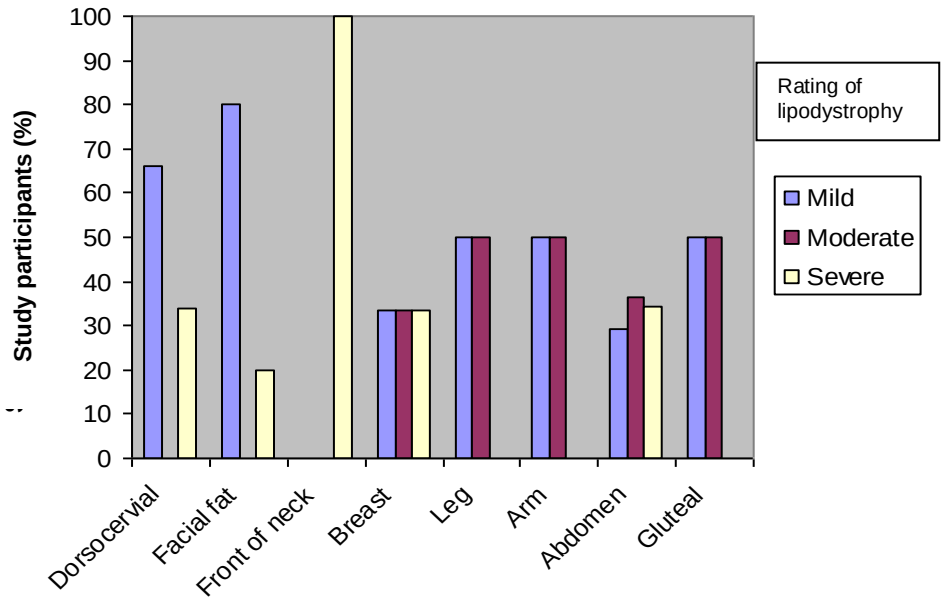

Figure 2. Severity of lipohypertrophy by body site of the population.

circumference of 90 ± 9 and mean weight of 69.6 ± 10.8 using standardized NHANES III protocol. These higher values could be explained by the fact that these measures were done in Caucasian patients who probably started HAART earlier. The lower values in our population may also be explained by the high prevalence of malnutrition in this set-up, genetic make-up and lifestyle influences on body fat composition. In addition, the reduced MUAC could have been lower due to high prevalence of lipoatrophy (44%) in our patients.

The overall prevalence of HIV associated lipodystrophy in HAART treated patients was 51.3% (CI 45.6 to 57.6) discerned on physical examination. This high prevalence was expected due to patient treatment with stavudine and zidovudine which are implicated in the etiology of lipodystrophy from majority of studies (Van der Valk et al., 2001; Fellay et al., 2001; Saint-Marc et al., 2000).

In Rwanda, a multicenter study in 571 patients reported a prevalence of 48.5% in urban population and 17.3% in rural groups (Mutimura et al., 2007). Our study was done in an urban set-up and the higher prevalence may have been due to influence of diet, lifestyle and behavioral choices on the development of lipodystrophy.

A cross-sectional analysis done on 1077 patients belonging to the HOPS cohort who had been on HAART for 3 years, Lichtenstein et al. (2001) found a prevalence of 49%. This study was similar to ours in using patient report and physician examination to diagnose lipodystrophy.

Peripheral lipoatrophy was the most common phenotype occurring in 44% of our patients. Facial atrophy was reported in 75.7%, arm atrophy in 48.5%, leg and buttock atrophy in 36.8% of patients with peripheral lipoatrophy. Most of the patients described the wasting as severe. This is a cause for concern, because it can impact on adherence due to effect of these body changes on cosmesis as well as increased stigmatization.

The Rwanda study (Mutimura et al., 2007) reported facial, arm, leg and gluteal atrophy in 67, 66, 70, and 46%, respectively. The differences in the prevalence may be due to other environmental and genetic factors.

The simultaneous presence of peripheral lipoatrophy and lipohypertrophy (mixed disease) was common in our study (41%). This is similar to the prevalence reported in the HOPS cohort of 46.2% but much lower than in the Rwanda study (Mutimura et al., 2007) in which mixed syndrome was the most common phenotype occurring in 72% of the study population. These findings of mixed disease suggest that lipoatrophy and lipohypertrophy should be assessed together when describing the prevalence or incidence of lipodystrophy syndrome.

Lipohypertrophy was found in 15% of our study population and was the least common phenotype diagnosed. Abdominal adiposity was the most often reported form of lipohypertrophy found in 40.4% of patients with lipohypertrophy followed by gynecomastia in 30.9% and buffalo hump in 5.1%. Fat accumulation in the neck was commonly reported as severe while the other areas of lipohypertrophy involvement were reported as mild to moderate. Thirteen patients had isolated increase in abdominal girth and were analyzed alongside those with several signs.

The high prevalence of central obesity in this study sounds the drum beat for the clinician to assess for other risk factors for cardiovascular disease and thereafter incorporate therapeutic lifestyle measures in the management

of these patients.

Our findings compare well with those reported by the MACS in USA (Palella et al., 2004) which used anthropometric assessment in a case control study of HIV infected and non-infected patients. Among those on HAART, MACS reported facial atrophy in 42%, increased abdominal girth in 42%; buttock, leg and arm atrophy in 36, 34 and 29%, respectively. 12% of the patients had a buffalo hump.

In the Rwanda study (Mutimura et al., 2007), abdominal obesity was found in 84% of the study participants and gynecomastia in 47%. The differences may be due to differences in the methodology of the two studies. Our study used waist circumference to define increase in abdominal girth, while the Rwanda study used WHR. Waist circumference is known to be a more sensitive and specific measure of visceral adiposity than WHR (Zamboni et al., 1998).

The limitation of this study is that we were unable to perform imaging techniques such as CT and MRI scans due to their high costs. These scans are better in quantifying the changes in body fat. HIV associated lipodystrophy was common in HIV infected patients on long term HAART at Kenyatta National Hospital with the main phenotype being lipoatrophy.

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