HIV-ASSOCIATED LIPODYSTROPHY: THE PREVALENCE, ASSOCIATED FACTORS AND METABOLIC ALTERATIONS IN PATIENTS ON LONG TERM ANTIRETROVIRAL THERAPY AT THE KENYATTA NATIONAL HOSPITAL

A dissertation submitted in part fulfilment of the requirements for the degree of Master of Medicine in Internal Medicine, University of Nairobi

by:

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DEDICATION

I dedicate this work to my young family Dennis, Robert and Alexandra for their unwavering support and understanding during this busy period.
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ABBREVIATIONS

AIDS: Acquired Immune Deficiency Syndrome
APROCO: Anti-Protease Cohort
AZT: Zidovudine
BMI: Body Mass Index
CCC: Comprehensive care centre
CD4: Cluster of Differentiation 4
CD8: Cluster of differentiation 8
CRABP-1: Cytoplasmic retinoic acid binding protein-1
CT: Computerised Tomography
DEXA: Dual energy x-ray absorptiometry
d4T: Stavudine
DNA: Deoxyribonucleic Acid
FRAM: Fat Redistribution and Metabolic Change
FFA: Free fatty acids
HAART: Highly Active Anti-Retroviral Therapy
HDL-C: High density lipoprotein cholesterol
HIV: Human Immune deficiency Virus
HOPS: HIV Outpatient Study
IDF: International Diabetes Federation
IFG: Impaired fasting glucose
IFN: Interferon
IQR: Inter-quartile range
KNH: Kenyatta National Hospital
LD: Lipodystrophy
LDL-C: Low density lipoprotein cholesterol
MACS: Multicenter AIDS Cohort Study
MRI: Magnetic Resonance Imaging
MUAC: Mid-upper-arm-circumference
NCEP ATP III: National Cholesterol Education Program/ Adult Treatment Panel III
NHANES: National Health and Nutritional Health Survey
NRTIs: Nucleoside analogue Reverse Transcriptase Inhibitors
NNRTIs: Non Nucleoside analogue Reverse Transcriptase Inhibitor
O1: Opportunistic infection
PI: Protease Inhibitor
PPAR-Y: Peroxisome proliferators activated receptor type gamma
RNA: Ribonucleic Acid
SAT: Subcutaneous adipose tissue
SREBP-1: Sterol regulatory binding protein-1
TC: Total cholesterol
TG: Triglycerides
TNF: Tumour Necrosis Factor
WHO: World Health Organization
WHR: Waist-to-hip ratio
VAT: Visceral adipose tissue
VLDL-TG: Very-low-density lipoproteins-Triglycerides
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I acknowledge the assistance of Mr Oyugi (KAVI) and Mr Franklin Onchiri (KEMRI) in the analysis of my data.
Background: Highly active anti-retroviral therapy (HAART) is widely available to HIV-infected individuals. Long term complications of these therapies such as lipodystrophy are associated with social stigmatization, reduced self esteem and poor adherence to HAART while the associated metabolic dysregulation mainly dyslipidemia and dysglycemia, may lead to premature and accelerated atherosclerosis.

Objective: To determine the prevalence of lipodystrophy and the factors associated with its development among HIV sero-positive patients on highly active anti-retroviral therapy at the Kenyatta National Hospital, Kenya. The associated factors that were assessed include: age, gender, WHO stage of HIV infection at initiation of HAART, CD4 count, type and duration of anti-retroviral therapy, dyslipidemia and dysglycemia.

Design: Cross-sectional prevalence study

Setting: Kenyatta National Hospital, a tertiary health care facility

Subjects: Consenting adults on highly active anti-retroviral therapy for at least six months.

Outcome measures: Prevalence of lipodystrophy; associated factors - age, gender, CD4 cell count, WHO stage of HIV infection at initiation of HAART, combination of and duration of anti-retroviral therapy, metabolic dysregulation such as dyslipidemia defined as presence of any of the following: raised total cholesterol, raised LDL cholesterol, low HDL cholesterol, raised triglycerides; and dysglycemia defined as presence of impaired fasting glucose or diabetes mellitus and the relationship between these factors and lipodystrophy.

Results: Between August and December 2007, 318 patients were screened and 265 recruited of whom 59.6% were female. The overall prevalence of lipodystrophy was 51.3%. Lipoatrophy was the most common phenotype described in 44% of all the patients. Patient age, gender, WHO stage of HIV infection at initiation of HAART, level of baseline and most recent CD4 counts were not associated with the development of lipodystrophy. Use of HAART for 18-36 months was associated with the development of lipodystrophy (p=0.000 OR 2.1 CI 1.2-3.5) as well as use of HAART for longer than 36 months (p=0.000 OR 2.3 CI 1.2-4.6). 52.5% of patients on stavudine based regimen developed lipodystrophy (p= 0.117) and 51.1% of patients on zidovudine based regimen
developed lipodystrophy (p = 0.757). The patients on non-stavudine non-zidovudine based regimen also had significant lipodystrophy (p = 0.000).

Dyslipidemia was found in 55.4% of patients with lipodystrophy and normal lipid levels in 36.4% (p = 0.007 OR 2.2 CI 1.3-4.6). High total cholesterol levels were found in 57% of patients with lipodystrophy and normal levels in 43% (p = 0.008 OR 1.94 CI 1.2-3.2). LDL-cholesterol was raised in 45.9% of patients with lipodystrophy and normal in 54.1% (p = 0.076 OR 1.5 CI 0.95-2.6). HDL levels were low in 45.2% of patients with lipodystrophy and normal in 54.8% (p = 0.257 OR 1.3 CI 0.8-2.2) while triglycerides levels were found to be elevated in 65.9% of patients with lipodystrophy and normal in 34.1% (p = 0.000 OR 3.8 CI 2.3-6.4).

Among patients with lipodystrophy, normal fasting blood sugars were found in 68.9%, impaired fasting blood sugar in 25.1% and diabetes mellitus in 5.1% (p = 0.102). On multivariate analysis, patients who had been on HAART for 18-36 months were 4.4 times more likely to have lipodystrophy than those who had been on HAART for 6-18 months (p < 0.0001) and those who had been on HAART for longer than 36 months were 6.179 times more likely to have lipodystrophy than those who had been on HAART for 6-18 months (p < 0.0001). In addition, patients on HAART who had elevated triglycerides were 2.9 times likely to develop lipodystrophy than those with normal triglycerides (p < 0.0001) and those on HAART who had elevated total cholesterol were 1.28 times likely to develop lipodystrophy than those who had normal total cholesterol (p = 0.388).

Conclusions: Lipodystrophy was common in patients on long term HAART. Most of these patients were on stavudine or zidovudine based combination therapy. Duration of HAART use and elevated triglyceride levels were found to be predictors of lipodystrophy. Age, gender, WHO stage of HIV at initiation of HAART, level of nadir and most recent CD4 count and type of HAART were not significantly associated with lipodystrophy.
1.0 LITERATURE REVIEW

1.1 INTRODUCTION

Highly active anti-retroviral therapy (HAART) is the standard of care therapy for patients with Human Immune Deficiency Virus (HIV) -1 infection. A patient is deemed eligible to initiate therapy if they meet certain criteria set-out in our national guidelines (1).

HAART consists of, in most cases regimens that include two Nucleoside analogue Reverse-Transcriptase Inhibitors (NRTIs) and one Non- Nucleoside Reverse Transcriptase Inhibitor (NNRTI) or one or more protease inhibitors (PIs). This combination has both virological and immunological benefits in HIV infection and Acquired Immune Deficiency Syndrome (AIDS) and has resulted in a significant reduction of HIV-1-associated morbidity and mortality (2).

In Kenya, there has been a dramatic increase in the number of patients accessing antiretroviral therapy from an estimated 3,000 in 2002 to 190,000 in 2008 (1). Critical factors in this scale up of antiretroviral therapy have been marked reduction in cost of antiretroviral therapy and expanded availability of resources.

With increased availability of HAART, more attention has focused on the associated drug toxicities for several reasons: First, the severity of the HIV epidemic has led to accelerated licensing of many antiretroviral agents, often with very little known about long-term safety. Second, the sustained benefits of HAART have led to far greater numbers of HIV-1-infected patients receiving at least three drugs for greater periods of time. Third, there are many antiretroviral drugs available in the various drug classes and so the number of possible HAART combinations is huge. Lastly, viral eradication is not possible with HAART, thus antiretroviral therapy use has to be indefinite for the clinical benefits to be preserved (3).

Prolonged use of HAART has in turn led to recognition of long term complications of these therapies such as lipodystrophy which was first described in HIV-1 infected individuals in 1998 (4)). It manifests with distressing morphologic changes in body habitus and is associated with metabolic abnormalities such as hypertriglyceridemia, hypercholesterolemia, insulin resistance (raised C-peptide and insulin concentrations), impaired glucose tolerance and type 2 diabetes mellitus (3). Lipodatrophy has also been associated with low-grade lactic acidemia and hepatic transaminitis(5).
1.2 LIPODYSTROPHIC SYNDROMES IN THE GENERAL POPULATION

The lipodystrophic syndromes are a heterogeneous group of congenital or acquired disorders characterized by either complete or partial lack of adipose tissue (lipoatrophy). In some of these disorders there is also the apparent accumulation of fat in other regions of the body (6).

Table 1; Classification of lipodystrophic disorders (6)

<table>
<thead>
<tr>
<th>Congenital lipodystrophy</th>
</tr>
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<tbody>
<tr>
<td>Total lipoatrophy (Berardinelli-Seip syndrome)</td>
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<tr>
<td>Partial lipoatrophy</td>
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<tr>
<td>Dunnigan variety</td>
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<tr>
<td>Koeberling variety</td>
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<tr>
<td>Lipodystrophy with other dysmorphic features</td>
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<tr>
<td>Other varieties</td>
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<table>
<thead>
<tr>
<th>Acquired Lipodystrophy</th>
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</thead>
<tbody>
<tr>
<td>Total lipoatrophy</td>
</tr>
<tr>
<td>Partial lipoatrophy</td>
</tr>
<tr>
<td>Upper atrophy-lower atrophy</td>
</tr>
<tr>
<td>Dermatome pattern</td>
</tr>
<tr>
<td>HAART associated lipodystrophy</td>
</tr>
<tr>
<td>Localized lipodystrophy</td>
</tr>
<tr>
<td>Drug induced</td>
</tr>
<tr>
<td>Pressure induced</td>
</tr>
<tr>
<td>Panniculitis variety</td>
</tr>
<tr>
<td>Centrifugal variety</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
</tbody>
</table>

Lipodystrophic disorders are rare in the general population. Generalized lipodystrophy maybe congenital or acquired with a prevalence estimated to be less than one case per 1 million people (7). Partial lipodystrophy syndromes are often familial and rare with only a few reported cases (8, 9). Severe cases of lipodystrophy have been associated with severe insulin resistance, severe hyperlipidemia, progressive liver disease, and increased metabolic rate.
Acquired and congenital lipodystrophies may also be associated with proteinuric kidney diseases, and renal biopsy of patients with nephrotic range proteinuria has revealed focal glomerulosclerosis or membranoproliferative glomerulonephritis (10, 11). Localized lipodystrophies are characterized by a loss of subcutaneous fat from small areas of the body but not insulin resistance or other metabolic abnormalities.

1.3 DEFINITION AND BACKGROUND OF HAART-ASSOCIATED LIPODYSTROPHY

Lipodystrophy, sometimes referred to as fat redistribution is common in adults taking protease inhibitors, nucleoside analogue reverse transcriptase inhibitors, or both, for HIV-1 infection (12, 13). Lipodystrophy has been reported to include, singularly or in combination, central fat accumulation (lipohypertrophy) evidenced by increased abdominal girth and increased waist to hip ratio (due to increase in intra-abdominal visceral fat), development of a dorsocervical fat pad (buffalo hump), breast enlargement, fat accumulation in the anterior neck and multiple lipomata (14-17) as well as loss of peripheral subcutaneous fat (lipoatrophy). The latter designation includes subcutaneous fat loss in the face, arms, legs, abdomen and/or buttocks resulting in the appearance of sunken cheeks, exaggerated musculature, bones, arteries and veins. In contrast to traditional wasting syndrome of advanced HIV disease, lipoatrophy is distinguished by preferential loss of fat tissue without substantial loss of lean tissue mass and the fact that it occurs most frequently among patients who are responding to HIV therapy. A mixed syndrome has also been reported in patients who exhibit simultaneous fat loss and accumulation at distinct locations of their body (18-21).

Cross-sectional studies that have included HIV-negative controls have consistently demonstrated lipoatrophy in HIV-infected patients, especially those receiving antiretroviral therapy, but have only inconsistently demonstrated fat accumulation. In the Fat Redistribution and Metabolic Change (FRAM) analysis, HIV-positive men reported more fat loss than controls in all peripheral and most central depots. Peripheral lipoatrophy was more frequent in HIV-positive men than in controls (38.3% vs. 4.6%), whereas central lipohypertrophy was less frequent in the HIV-positive men (40.2% vs. 55.9%). Among HIV-positive men, the presence of central lipohypertrophy was not positively associated with peripheral lipoatrophy (18). The Multicenter AIDS
Cohort (MAC) study also observed that HIV-infection and receipt of HAART had a stronger positive association with lipoatrophy than it did with lipoaccumulation (20).

Longitudinal studies in patients initiating antiretroviral therapy on the other hand, have demonstrated both lipoatrophy and fat accumulation. Mallon et al in a prospective study noted an obvious selective, progressive loss of limb fat whereas both central fat and lean mass were maintained (22). Martinez et al also reported lipoatrophy, central obesity and mixed lipodystrophy in 494 patients on PIs after a median follow-up period of 18 months (23). Mulligan et al, in a randomized trial also found a mixed pattern of central and peripheral fat distribution after initiation of antiretroviral therapy (24).

Lipoatrophy thus, appears to be directly related to antiretroviral therapy; however, it is currently unclear how often fat accumulation represents physiological improvement in the setting of suppressed viral replication versus a pathological response to drug therapy.

Lipodystrophy has also been described as a reciprocal syndrome where fat atrophy at some body sites is associated with body fat accumulation at another site. However, in the (FRAM) analysis, using magnetic resonance imaging (MRI) found that HIV-infected men who had the clinical syndrome of peripheral lipoatrophy had less adipose tissue in both peripheral and central depots than did HIV-infected men without peripheral lipoatrophy. Furthermore, HIV-infected men with or without the clinical syndrome of peripheral lipoatrophy had less adipose tissue in both peripheral and central depots compared with control subjects (18) thus proving this theory wrong.

1.4 PREVALENCE OF HAART- ASSOCIATED LIPODYSTROPHY

The overall prevalence of at least one physical abnormality is about 50% after 12-18 months of therapy (25-27).

The Anti- Protease Cohort (APROCO) sub-study of 614 patients by Save’s et al reported a prevalence of 62% for more than one sign of lipodystrophy. Mixed syndrome was more frequent (24%) than isolated peripheral atrophy (21%) or isolated fat accumulation (17%) (28).
In the HIV outpatient 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 (29).

A cross-sectional study of 1359 subjects by Bernasconi et al found that 43% of them had at least one sign of lipodystrophy. Fat wasting (at least one sign) was described in 28% and fat accumulation was described in 30% (30).

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 (31).

A cross-sectional survey of 200 patients done in western Kenya found a total prevalence of 22% with fat accumulation in 14.5%, fat wasting in 4.5% and mixed group were 3% of the population (Diero L, unpublished).

**TABLE 2; Prevalence of lipodystrophy by clinical assessment**

<table>
<thead>
<tr>
<th>Author</th>
<th>Method(s)</th>
<th>Population</th>
<th>n</th>
<th>LD (%)</th>
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<tr>
<td>Van der Valk (Netherlands) 12</td>
<td>PE</td>
<td>HIV positive</td>
<td>175</td>
<td>17</td>
</tr>
<tr>
<td>Chene (France) 57</td>
<td>SR, PE</td>
<td>HIV positive</td>
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<td>31</td>
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<tr>
<td>Lichtenstein (USA) 29</td>
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<td>HIV positive</td>
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<tr>
<td>Blanch (Spain) 58</td>
<td>SR, PE</td>
<td>HIV positive</td>
<td>105</td>
<td>56</td>
</tr>
<tr>
<td>Saves (France) 28</td>
<td>SR, PE, AP</td>
<td>HIV positive</td>
<td>614</td>
<td>62</td>
</tr>
<tr>
<td>Carr 1998 (Australia) 4</td>
<td>SR, PE</td>
<td>HIV positive</td>
<td>116</td>
<td>64</td>
</tr>
<tr>
<td>Carr 1999 (Australia) 32</td>
<td>SR, PE</td>
<td>HIV positive</td>
<td>113</td>
<td>84</td>
</tr>
</tbody>
</table>

SR-Self report, PE-Physical examination, AP-Anthropometric procedures

5
1.5 DYSLIPIDEMIA AND HIV-ASSOCIATED LIPODYSTROPHY

Lipid disturbances are very frequent in patients receiving combination antiretroviral therapy, Save’s et al reported prevalence of hypertriglyceridemia in patients without lipodystrophy, those with 1-3 signs and those with more than 4 signs as 20%, 30%, and 42%, respectively and the prevalences of hypercholesterolemia were 48%, 62%, and 62%, respectively (28). In the LIPOCO study, patients in the lipoatrophy group had significantly elevated levels of plasma triglycerides (31). Samaras et al found hypertriglyceridemia to be twice as prevalent (61%) in patients with lipodystrophy as compared to those without (35%) (33). The pathogenesis of hypertriglyceridemia in HIV-associated lipodystrophy appears to arise predominantly from increased hepatic secretion of VLDL-TG rather than reduced clearance. De novo lipogenesis, resting lipolytic rate and hepatic triglyceride stores are also increased in HIV-associated hypertriglyceridemia. Triglyceride clearance may also be impaired in these patients because of reduced lipoprotein lipase activity; however, this appears to play a minor role (34).

1.6 INSULIN RESISTANCE AND HIV-ASSOCIATED LIPODYSTROPHY

Insulin resistance, worse hyperglycemia and increased risk of type 2 diabetes mellitus have also been associated with receipt of HAART. Insulin resistance and impaired glucose tolerance have been observed with regimens containing protease inhibitors especially indinavir and regimens containing nucleoside reverse transcriptase inhibitors, chiefly stavudine (4, 7). While indinavir has been demonstrated in vitro to have a direct effect on glucose metabolism and may induce insulin resistance by inhibiting glucose movement through the GLUT4 transporter, the emergence of insulin resistance during antiretroviral therapy is a complex process that is not completely understood. Fasting glucose levels from a group of 1,278 men in the MACS cohort showed that 14% of HIV-infected men on antiretroviral therapy had diabetes mellitus compared with 5% in HIV-negative men adjusted for age and body mass index (BMI) (19).

Insulin resistance has been demonstrated in patients with fat redistribution, even in patients not receiving protease inhibitors. In an Australian study on the prevalence of metabolic syndrome in patients on HAART, the prevalence of fasting glucose greater than 5.6 mmol/l was 19% in those with lipodystrophy versus 11% in those without lipodystrophy (33).
In the study by Save’s, the prevalence of glucose alterations was 16% in patients without lipodystrophy, 24% in patients with 1–3 symptoms, and 28% in patients with more than four symptoms of lipodystrophy (28).

In the LIPOCO study, Patients in the obese and mixed lipodystrophy groups had elevated levels of plasma insulin and C-peptide. Visceral adipose tissue measured by CT scan was positively correlated with fasting insulin and the sum of insulin levels (31).

1.7 CLINICAL SIGNIFICANCE OF LIPODYSTROPHY

Reynolds et al studied patient’s perceptions of lipodystrophy syndrome and reported increased distress in HIV-infected individuals on HAART due to the cosmetic effects. Patients also thought that the obvious facial and extremity wasting represented disease progression and a form of involuntary disclosure of HIV-1 status. This was associated with both short-term and long-term suboptimal adherence to antiretroviral regimens leading to virological and even clinical failure (35).

The dysmorphic changes have also been associated with social stigmatization, increased stress, reduced self esteem, a disruption of sex life and therefore reduced quality of life (36). In addition, HAART-naive patients have been reported as reluctant to initiate treatment with healthcare providers being viewed as ignoring and discrediting patients’ distress (37).

Other studies have shown that HIV infected patients are at risk of premature and accelerated atherosclerosis (38, 39). This increased risk has been partly attributed to fat accumulation and fat depletion components of lipodystrophy and the associated metabolic dysregulation which has similar features as those seen in the metabolic syndrome. Samaras K et al in a multicenter cross-sectional study of 788 HIV positive patients, found a prevalence of metabolic syndrome in patients on HAART to be 14% by International Diabetes Federation (IDF) criteria and 18% by National Cholesterol Education Program Adult Treatment Panel III (ATPIII) criteria; Lipodystrophy was present in the majority of patients with metabolic syndrome: 73% by IDF criteria and 79% by ATPIII criteria (33).

Jerico et al also found that 63% of patients with fat-distribution disorders had greater than one metabolic disorder, compared with 48% of patients without lipodystrophy (40).
Patients who experience cardiovascular events however, have been noted to frequently present with a cluster of risk factors and only some are induced or exacerbated by HAART. These patients can benefit from intervention strategies such as dietary modification, physical exercise and lipid lowering therapy to reduce their risk constellation (41).

1.8 RISK FACTORS FOR LIPODYSTROPHY IN HIV

1.8.1 Type of antiretroviral therapy

Nucleoside analogue Reverse Transcriptase Inhibitors
The risk of developing lipoatrophy has been linked repeatedly to the use of NRTIs, especially Stavudine. In the LIPOCO study, the use of Stavudine significantly correlated with wasting in the nucleoside reverse transcriptase inhibitor and protease inhibitor groups when compared with the use of zidovudine. Neither lamivudine nor didanosine use, nor the use of protease inhibitors alone was significantly associated with fat distribution abnormalities or fat wasting (31). In the FRAM analysis, use of the antiretroviral drugs stavudine or indinavir was associated with less leg subcutaneous adipose tissue (SAT) but did not appear to be associated with more visceral adipose tissue (VAT) accumulation(18). Van der Valk et al found an increased risk of lipodystrophy in patients randomized to ritonavir/saquinavir/stavudine than those on Ritonavir/Saquinavir alone (12). In the Swiss HIV cohort study of adverse effects of HAART, use of nucleoside reverse transcriptase inhibitors lamivudine and stavudine were both associated with the development of lipodystrophy (13).

Most NRTI-specific adverse effects are thought to be manifestations of mitochondrial toxicity, resulting from inhibition of mitochondria- specific deoxy-ribonucleic acid (DNA) polymerase gamma, the principal enzyme responsible for mitochondrial DNA replication. This ultimately leads to impaired production of adenosine triphosphate. Mitochondrial depletion and dysfunction have been demonstrated in adipose tissue from HIV-infected adults with lipodystrophy (42, 43). However, more recent evidence suggests that the mitochondrial toxicity of NRTIs may involve not only the depletion of mitochondrial DNA (mtDNA) but also negative effects on the proteins and enzymatic activity of the oxidative-phosphorylation system even prior to such depletion.
Decreased transcription of mitochondrial ribonucleic acid (RNA) without significant depletion of mitochondrial DNA occurs two weeks after initiation of dual-NRTI therapy (zidovudine/lamivudine or stavudine/lamivudine) in HIV-negative controls, suggesting the NRTIs cause mitochondrial dysfunction by means other than through inhibition of DNA polymerase gamma (44).

Newer NRTI agents, abacavir and tenofovir, have not been associated with lipoatrophy. Instead, improvement in both mitochondrial DNA and complex mitochondrial enzyme activity level as well as in the rate of adipocyte apoptosis have been demonstrated following removal of the offending NRTIs and replacement with these newer agents(45).

**Protease inhibitors**

Protease inhibitor use appears to accelerate the rate of development of NRTI-associated lipoatrophy (12). Lipodystrophy has been noted in patients on indinavir, ritonavir, saquinavir (12, 14, and 16). However, this may not be a class effect, as it was not seen in a 48-week trial of atazanavir (46). In vitro, protease inhibitors have been shown to impair adipose cell differentiation. The postulated mechanism is interference with the transcription factor sterol regulatory element-binding protein–1 (SREBP-1). SREBPs have been found to be increased in the nuclei of hepatocytes of animals treated with ritonavir. It has been suggested that PIs inhibit proteases that degrade SREBP (47). Caron (48) analysed the effect of indinavir on adipocyte differentiation and insulin resistance by studying murine preadipocytes that are highly sensitive to insulin. Indinavir did not affect function of the pre-adipocytes but inhibited adipocyte differentiation and caused accumulation of SREBP-1.

Another hypothesis by Carr et al (49) is that Protease inhibitors have a high affinity for the catalytic site of HIV 1 protease and may cause apoptosis of peripheral adipocytes by binding and inhibiting a homologous human protein involved in lipid metabolism namely the C-terminal of the cytoplasmic retinoic acid binding protein type-1 (CRABP-1). CRABP-1 normally binds all retinoic acid, presents it to cytochrome P450 3A isoforms which catalyse its conversion to cis-9-retinoic acid. Cis-9 retinoic acid is the sole ligand for retinoid X receptor which functions as a heterodimer with peroxisome proliferators activated receptor type gamma (PPAR-Y), an adipocyte receptor that regulates peripheral adipocyte differentiation and proliferation. This has been disputed by other studies that found no evidence that PIs acted as PPAR-gamma agonists (50).
1.8.2 Duration of exposure to HAART
The total period of exposure to HAART appears to be relevant to the onset of LD. The majority of cases occur after 3-18 months of exposure (27). Roth et al noted the development of cervical fat pads a median of 22 weeks after initiation of PIs (14). In the Western Australian Cohort Study, the median time from initiation of a PI-containing antiretroviral regimen to clinically apparent peripheral lipoatrophy was 18.5 months for patients receiving stavudine-containing regimens compared with 26 months for patients receiving zidovudine-containing regimens (51). However, combined PI and dual NRTI therapy leads to peripheral lipoatrophy dramatically faster than does dual NRTI therapy alone (12,51). The risk of lipodystrophy increases with both duration of NRTI therapy and duration of PI therapy (51-53). This finding is further supported by the FRAM analysis, in which the duration of treatment with stavudine and the duration of treatment with indinavir were associated with significant decrease in leg subcutaneous adipose tissue (18). The median time of development of LD was 68 weeks in a study by Van der Valk et al (12)

1.8.3 Host factors
Although HIV-associated lipodystrophy is uncommon in the absence of HAART, non-drug factors are also important. Older age has consistently been shown to be associated with increased lipodystrophy risk (54-58). In the FRAM analysis, age was associated with less leg SAT, but more VAT, in HIV-infected subjects (18). Similar findings were noted by Martinez et al in a prospective follow-up of patients on PIs (23). However, body changes occur naturally with aging and body fat distribution abnormalities have also been reported in HIV-1-infected children. Furthermore, age was not found to be associated with lipodystrophy measured by dual energy x-ray absorptiometry (DEXA) in a study of HIV-positive women undergoing HIV therapy (59). Race may be important, with higher rates of lipodystrophy seen in Caucasians (33, 60). Males appear more likely to develop peripheral lipoatrophy, whereas females have greater fat accumulation centrally (31); these findings may reflect differences in baseline body composition. Other studies suggest that higher baseline fat content, greater body mass index heighten the risk for fat accumulation.
1.8.4 Disease factors
The stage of HIV infection may play a role in the pathogenesis of lipoatrophy. Decreased CD4 count at initiation of HIV therapy has been associated with self reported lipoatrophy. In the HIV Outpatient Study (HOPS) cohort of 1077 patients, it was reported that the incidence of lipoatrophy was highest among patients who had a prior CD4+ count of less than 100 cells/μL. The prevalence of moderate to severe atrophy was 30.8% among subjects with minimum and maximum CD4+ counts below 200 cells/μL compared with 3.8% for those with minimum and maximum values all greater than 350 cells/μL. These differences persisted after controlling for time on antiretroviral therapy (29). However, a prospective study, the women’s interagency HIV study reported that objectively measured limb fat loss was associated with higher pre-treatment CD4 cell counts (59). Viral load, duration of HIV infection, prior AIDS diagnosis, immune reconstitution have been cited as important in some studies, but have not been linked consistently to HIV-associated lipodystrophy risk.

1.8.5 Genetic predisposition
There is interpatient variability in the development of lipodystrophy and this suggests that those who develop lipodystrophy may have a genetic predisposition to do so. Apolipoprotein E2 is involved in the clearance of triglycerides and those who are homozygous for the E2 genotype are predisposed to develop hyperlipidaemia similar to that of lipodystrophy. HIV-infected patients with this genotype develop marked hyperlipidaemia when treated with PIs (61). However, this only accounts for a small number of those with hyperlipidaemia associated with lipodystrophy.

1.8.6 Cytokine mediated response
Other investigators have suggested that HIV-associated lipodystrophy is an immune reconstitution or cytokine-mediated phenomenon (62). Elevated levels of cytokines as well as macrophages capable of producing such cytokines have been reported in subcutaneous adipose tissue from lipoatrophic subjects. Tumour necrosis factor (TNF) and TNF receptors are increased in HIV-infected patients (63). Ionescu et al. (64) suggest that increased concentrations of proinflammatory cytokines inhibit the production of acylation-stimulating protein (ASP), a protein which upregulates the pathways for glucose uptake and fat deposition in adipocytes; they demonstrated an association between lower limb lipoatrophy and subnormal ASP production.
1.9 DIAGNOSIS OF LIPODYSTROPHY

1.9.1 Clinical:
Diagnosis of HIV-associated lipodystrophy typically is 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 (65) but consensus is lacking and the applicability to clinical practice is unclear.

Anthropometric procedures: Anthropometric estimates of both VAT and SAT have been published, though more emphasis has been placed on the prediction of VAT (66-67).

Skin fold thickness: This is done using skin callipers to estimate subcutaneous fat.

1.9.2 Imaging
CT and MRI scans: These cross-sectional techniques can be used for objective quantification of fat (68). This may be either single slice or whole body imaging. However imaging requires expert interpretation, is relatively expensive, with limited availability and has not been observed to provide a clinical advantage over self report and physical examination assessments perhaps because of the large natural variability in body-fat mass and distribution. CT scanning also entails some radiation exposure. Finally, the sub compartments of SAT and VAT are not homogeneous, and partition based only upon 3-dimensional localization might be overly simplistic.

Dual energy x-ray absorptiometry: This is suitable for examining appendicular fat, which is comprised almost entirely of SAT. Estimation of visceral fat is more difficult since changes in VAT and SAT independently affect trunk fat. Changes in the dorsocervical fat pad or the face cannot be recorded by DEXA.

Bioelectrical impedance analysis (BIA) typically estimates whole lean body tissue (69). Regional-body composition using BIA remains unvalidated.

Ultrasound: Studies on its utility are still ongoing (70)
2.0 JUSTIFICATION OF THE STUDY

There are few studies on lipodystrophy in Africans. Some western studies have reported that lipodystrophy is rare in Africans.

HAART is increasingly available and accessible to HIV-AIDS infected patients and this has transformed AIDS into a chronic manageable disease. This has in turn led to chronic complications such as lipodystrophy in these patients.

Lipodystrophy and associated metabolic abnormalities such as insulin resistance, diabetes mellitus and dyslipidemia may lead to premature and accelerated atherosclerosis especially in the presence of other traditional cardiovascular risk factors.

The cosmetic aspect may compromise antiretroviral drug adherence, and, ultimately, treatment success. Clinicians and patients can benefit from ongoing education regarding the risk of these complications and their relationship to antiretroviral therapies.

3.0 OBJECTIVES

3.1 Broad objectives

To determine the prevalence of lipodystrophy and the factors associated with it in patients on long-term HAART at the Comprehensive Care Centre.
3.2 Specific objectives

1. To determine the prevalence of HIV associated lipodystrophy in patients on HAART attending KNH Comprehensive Care Centre using clinical methods.

2. To describe the different phenotypes of lipodystrophy in patients on HAART at the CCC.

3. To determine the nadir and current CD4 counts, WHO stage of patients and their association with lipodystrophy.

4. To determine the duration and type of antiretroviral therapy associated with lipodystrophy.

5. To describe the metabolic alterations (dyslipidemia and dysglycemia) associated with lipodystrophy.

4.0 MATERIALS AND METHODS

4.1 Study design
Cross-sectional descriptive study.

4.2 Study site
A HIV out-patient clinic (Comprehensive Care Centre, CCC), at Kenyatta National Hospital, a tertiary national referral and teaching hospital.

4.3 Study population
HIV positive patients, older than 15 years, attending the Comprehensive Care Centre, on HAART for six or more months.
4.4 Patient selection

4.4.1 Inclusion criteria

1. Patients aged 15 years or more
2. HIV positive
3. On HAART regimen, regularly reviewed and deemed compliant with treatment for six months or more
4. Signed informed consent

4.4.2 Exclusion criteria

1. Patients on anabolic steroids or immune-modulatory therapy
2. Patients known to have Cushing's disease or other major endocrine disorder
3. Pregnancy
4. Moribund patients with severe diseases such as malignancy
5. Features of HIV wasting syndrome such as unexplained involuntary weight loss of greater than 10% of baseline weight plus chronic diarrhoea, chronic weakness or fever.

4.5 Case definition

Adult

Patients 15 years or older as indicated in their hospital records.

HIV-Seropositive

HIV- infected patients confirmed by a positive ELISA test result, as documented in their clinic records.

Duration of treatment

HAART for a minimum duration of six months.
HAART

HAART will be defined as any combination of at least three drugs from the three classes of anti-retroviral drugs (NRTIs, PIs, NNRTIs) i.e. two Nucleoside analogue Reverse-Transcriptase Inhibitors (NRTIs) and one Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) or one or more protease inhibitors (PI).

4.6 Screening and recruitment

The Comprehensive Care Centre is run five days a week. All patients undergo full evaluation 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 deemed eligible for HAART commence treatment and thereafter are given individualized appointments depending on their clinical condition. They also return to the clinic monthly for 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 taken. The study questionnaire was then administered by the principal investigator followed by a targeted physical examination.

The patients were requested to return the following week after an overnight fast of at least 9-12 hours at which time, blood samples were taken for analysis of lipid profiles and fasting blood sugar. Transport allowance was provided for those patients who returned for the subsequent visit.

4.7 Sampling

Random sampling was done until desired sample size was achieved.
4.8 Sample size

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

\[ n = \frac{Z^2 \pi (1-\pi)}{d^2} \]

Whereby \( Z \) value is the upper \( \alpha /2 \) point of the normal distribution, 1.96. \( \pi \) is the assumed prevalence. A prevalence of 22% used from unpublished local data. 

\( d \) = precision, 0.05,

\[ n = 262 \text{ patients} \]

4.9 Clinical methods

An investigator administered questionnaire was used to collect data.

Patient and physician assessment of lipodystrophy was determined by a modified version of the lipodystrophy case definition questionnaire which is validated (65).

4.9.1 Anthropometric measures

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).

**Height**

Standing height was measured once to the nearest 0.5cm, with patient barefoot, the back square against the wall tape, eyes looking straight ahead, with a set square resting on the scalp and against the wall.

**Weight**

Weight was measured once to the nearest 100 grams using a lever balance, barefoot, in light garments.
Waist circumference
This was measured from subject's right with subject standing, arms slightly away from the body. The right ilium was located and a horizontal mark made just above its uppermost lateral border. This line was crossed with a vertical line mark on mid-axillary line. Tape will be placed on the mark on a level horizontal plane and measures were done in cm to the nearest mm.

Hip circumference
Hip circumference was done from the patient's right with eyes at the level of hip region and tape placed over the largest part of the hip. Subjects had light clothing and stood, feet together. Measures were done in cm to the nearest mm.

Mid-arm circumference
This was measured standing to the right of the subject with subject standing, arms hanging loose, and relaxed. Steel measuring tape was placed around upper arm skin, perpendicular to long axis of the arm at marked point and the two overlapping ends pulled together.

4.10 Laboratory methods
After an overnight fast of 9-12 hours, about 6ml of venous was taken from all the patients for measurement of lipid profiles and fasting blood glucose. Analysis of the samples was done at the paediatric university laboratory, University of Nairobi using the HUMALYZER 2000 machine.

Serum cholesterol level was determined after enzymatic hydrolysis of cholesterol esters and oxidation to yield hydrogen peroxide. The hydrogen peroxide then combines with 4-aminophenazone to form the indicator quinoneimine which is quantitated at 500nm wavelength (71).

HDL-cholesterol was determined using a direct method with a two reagent format mainly phosphotungstic acid and magnesium chloride. Addition of the first reagent helps in complexing HDL, LDL, VLDL and chylomicron lipoproteins. Addition of a second reagent solubilizes the HDL lipoprotein particles which react with cholesterol esterase and cholesterol oxidase in the presence of chromogens to produce a colour change which was then quantitated (71).
LDL-cholesterol was determined directly using a two-step format. The first reagent aimed at protecting LDL-C from enzymatic processing while addition of a second reagent selectively oxidizes the LDL-C in a colour producing enzymatic reaction (71).

Triglycerides were determined after enzymatic hydrolysis with lipases. The indicator is quinoneimine formed from hydrogen peroxide, 4-aminoantipyrine and 4-chlorophenol under the catalytic influence of peroxidase (71).

Fasting blood glucose was measured by the glucose oxidase method on the medisense glucometer (72).

4.11 Quality Assurance

Commercial reagent kits were used for all biochemical assays. All analyses were performed according to manufacturer's specifications by a competent technologist. Commercial quality control material was included in all analytical runs and results were only be accepted if control samples were within acceptable limits.

5.0 DEFINITION OF STUDY VARIABLES

5.1 Lipodystrophy

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 >88cm in males and > 102cm in females), focal fatty deposits, cervical fat pad enlargement and gynaecomastia. Mixed disease was defined as patients with features of both lipoatrophy and lipohypertrophy

Lipodysrophy was rated using the HIV Outpatient Study (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).
5.2 Anthropometrics
An abdominal circumference of greater than 102 cm for men and 88 cm for women was considered as increase in abdominal girth (73). BMI greater than 25 kg/m² was considered overweight.

5.3 Type of antiretroviral therapy
Was defined as any combination of at least three drugs from the three classes of antiretroviral drugs (NRTIs, PIs, NNRTIs) i.e. two Nucleoside analogue Reverse-Transcriptase Inhibitors (NRTIs) and one Non- Nucleoside Reverse Transcriptase Inhibitor (NNRTI) or one or more protease inhibitors (PI)

5.4 Duration of treatment
This was defined as the cumulative duration of treatment of an individual up to the recruitment day.

5.6 CD4 counts
Nadir CD4 count was defined as the lowest level of CD4 counts that has ever been measured while current CD4 was the value done at the time of the study.

5.7 Dyslipidemia
This was classified as per NCEP/ATP III guidelines (73).

5.7.1 Hypercholesterolemia

Total Cholesterol levels ≥ 5.17 mmol/l

Categories

5.17 - 6.18 mmol/l (Borderline high)
≥6.19 mmol/l (High)

5.7.2 High-Low Density Lipoprotein

LDL Cholesterol levels ≥3.34 mmol/l
3.34 - 4.11 mmol/l (Borderline high)
4.12 - 4.88 mmol/l (High)
>4.9 mmol/l (Very high)

5.7.3 Low High Density Lipoprotein

HDL Cholesterol level <1.03 mmol/l

5.7.4 Hypertriglyceridemia

Triglycerides levels >1.69 mmol/l

5.8 Dysglycemia

Study participants were considered diabetic if:

Self report of diabetes, or

Use of hypoglycaemic medication, or

Fasting plasma glucose (FPG) ≥7.0 mmol/L.

Impaired fasting glucose (IFG) was defined as FPG of 5.6 mmol/L to 6.9 mmol/L.
6.0 DATA MANAGEMENT AND STATISTICAL ANALYSIS

All data were entered into data base using Microsoft excel. Statistical analysis was performed using Statistical Package for Social Sciences, version 15.0 software for windows.

Continuous variables were analysed by descriptive statistics such as means, medians and standard deviation and categorical variables by frequency distributions.

The association between potential determinants and the presence of morphologic changes was examined using a logistic regression model.

Results were presented in form of tables, graphs and pie charts.

The criteria for statistical significance was P value $\leq 0.05$
7.0 ETHICAL CONSIDERATIONS

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

Patients were only included after going through the following consent process:

1. An explanation that the project involved research and the purpose of this research.

2. An explanation of full details of all the tests to be done.

3. A description of the medical and psychological harms and benefits of the study in lay terms.

4. Assured that participation in the study was voluntary, and that they could decline to participate or withdraw from the study without any penalty.

5. Assured that confidentiality would be strictly maintained.

6. Assured of full and free access to their results and that all therapeutic interventions would be made according to accepted standards of practice.
During the period between August and December 2007, a total of 1500 patients attended CCC at Kenyatta National Hospital. 318 patients were screened. To remove confounders of acute changes in body fat, we excluded 51 patients. A total of 265 patients met the inclusion criteria and were recruited.

**Figure 1: Flow chart of Screening and Recruitment**

- 1500 patients attended CCC KNH
- Not on HAART Excluded
- 318 on HAART screened
- Excluded 40 HAART<6 months
  - 5 OI
  - 3 moribund
  - 2 HIV wasting
  - 2 no consent
  - 1 malignancy
- 265 recruited
8.1 BASELINE CHARACTERISTICS

The baseline characteristics of the study participants are depicted in table 3.

Table 3: Baseline characteristics of the 265 study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>ALL Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>265</td>
</tr>
<tr>
<td>Gender:</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>107</td>
</tr>
<tr>
<td>Female</td>
<td>158</td>
</tr>
<tr>
<td>Occupation:</td>
<td></td>
</tr>
<tr>
<td>Self-employed</td>
<td>97</td>
</tr>
<tr>
<td>Employed</td>
<td>97</td>
</tr>
<tr>
<td>Unemployed</td>
<td>62</td>
</tr>
<tr>
<td>Retired</td>
<td>7</td>
</tr>
<tr>
<td>Marital Status:</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>50</td>
</tr>
<tr>
<td>Married</td>
<td>153</td>
</tr>
<tr>
<td>Divorced</td>
<td>7</td>
</tr>
<tr>
<td>Widowed</td>
<td>33</td>
</tr>
<tr>
<td>Separated</td>
<td>20</td>
</tr>
<tr>
<td>Education:</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>5</td>
</tr>
<tr>
<td>Primary</td>
<td>84</td>
</tr>
<tr>
<td>Secondary</td>
<td>135</td>
</tr>
<tr>
<td>Tertiary</td>
<td>34</td>
</tr>
</tbody>
</table>

The mean age of the study population was 40.69 years with a median of 40 years. Majority of the participants were female constituting 158 (59.6%) of the study population. Moreover, 153 (58%) of the study participants were married and 135 (52%) had attained secondary education. One hundred and ninety four (73.8%) of them were formally employed.
8.1.1 CD4 counts

Table 4: Mean nadir and CD4 count at recruitment of the study participants

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 nadir</td>
<td>256</td>
<td>119</td>
</tr>
<tr>
<td>CD4 current</td>
<td>251</td>
<td>335</td>
</tr>
</tbody>
</table>

Among the study participants, the mean baseline CD4 count was 119/mm$^3$. Those with lipodystrophy had lower mean baseline CD4 counts than those with no lipodystrophy. The mean of the most recent CD4 count for the study participants was 335/mm$^3$.

8.1.2 WHO stage at initiation of HAART

Figure 2: WHO stage of HIV infection of the study participants at initiation of HAART

Majority of the patients that is, 194 (73.3%) were in WHO stage III and IV at initiation of HAART. Only 71 (26.7%) patients were in stage I and II.
8.1.3 Duration on HAART

Figure 3: Duration of HAART use by the 265 patients in the study

The mean duration of treatment of the study participants was 29.7 months with a median of 28 months. Amongst the study participants, 177 (66.8%) had been on HAART for longer than 18 months. Only 88 (31.2%) had used HAART for 6-18 months.
At the time of enrolment, 188 (70.9%) patients were on a d4T based regimen.

There were 41 (15.5%) patients on an AZT-based regimen, of which 26 had switched from a d4T based regimen prior to the study.

Of the 36 (13.6%) patients on non-d4T, non-AZT based regimen, 30 patients had switched from a d4T based regimen and 6 from an AZT based regimen prior to the time of enrolment.

Consequently, 244 (92%) of the study participants had used 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.
8.1.5 Anthropometric measurements

Table 5: Anthropometric profiles of the 265 patients included in the study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male (n=107) (median, IQR)</th>
<th>Female (n=158) (median, IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>64.5</td>
<td>62.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172</td>
<td>166</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>83.5</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>61-117</td>
<td>60-130</td>
</tr>
<tr>
<td>Waist to hip ratio</td>
<td>0.89</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>0.72-1.18</td>
<td>0.63-1.30</td>
</tr>
</tbody>
</table>

The males weighed more than the females.
The mean BMI of the study population was 22.1 kg/m$^2$.
Both median waist circumference and waist to hip ratio 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.
LIPODYSTROPHY

Two hundred and sixty five patients who had been on long-term antiretroviral drugs were examined, and 136 (51.3% CI 45.6-57.6) of them had at least one sign of abnormal fat distribution. The concordance between patient self-assessment and physician examination was 96.9%.

Figure 5: Prevalence of lipodystrophy in the study population

![Prevalence of lipodystrophy](image)

Phenotypes

Figure 6: Phenotypes of lipodystrophy described in the study participants

![Phenotypes](image)

Lipoatrophy was described in 44% (n=60), lipohypertrophy in 15% (n=20) and mixed syndrome in 41% (n=56) of patients with lipodystrophy.
Table 6: Body sites affected by lipodystrophy

<table>
<thead>
<tr>
<th>Change in body fat</th>
<th>Physician assessment n=136</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lipoatrophy</td>
</tr>
<tr>
<td><strong>Facial fat</strong></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>103 (75.7%)</td>
</tr>
<tr>
<td>no</td>
<td>33 (24.3%)</td>
</tr>
<tr>
<td><strong>Neck</strong></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>13 (9.6%)</td>
</tr>
<tr>
<td>no</td>
<td>123 (90.4%)</td>
</tr>
<tr>
<td><strong>Dorsocervical</strong></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>9 (6.6%)</td>
</tr>
<tr>
<td>no</td>
<td>127 (93.4%)</td>
</tr>
<tr>
<td><strong>Breast</strong></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>16 (11.8%)</td>
</tr>
<tr>
<td>no</td>
<td>120 (88.2%)</td>
</tr>
<tr>
<td><strong>Arm</strong></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>66 (48.5%)</td>
</tr>
<tr>
<td>no</td>
<td>70 (51.5%)</td>
</tr>
<tr>
<td><strong>Abdomen</strong></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>13 (9.6%)</td>
</tr>
<tr>
<td>no</td>
<td>123 (90.4%)</td>
</tr>
<tr>
<td><strong>Gluteal fat</strong></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>50 (36.8%)</td>
</tr>
<tr>
<td>no</td>
<td>86 (63.2%)</td>
</tr>
<tr>
<td><strong>Leg fat</strong></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>50 (36.8%)</td>
</tr>
<tr>
<td>no</td>
<td>86 (63.2%)</td>
</tr>
</tbody>
</table>

Facial fat loss was the commonest sign of lipoatrophy described in 75.7% of patients with fat distribution 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, thirteen 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. There was a high degree of concordance (70-97%) between patients and their physicians on the presence of abnormal fat distribution at the different body sites.
Severity of lipodystrophy

Severity was graded using the HOPS scale as mild; noticeable only when specifically sought, moderate; readily obvious to the clinician or patient and severe; Obvious to the casual observer.

Most patients had severe lipoatrophy whereas lipohypertrophy was described as mild to moderate.

Figure 7: Severity of lipoatrophy by body site of this population

Figure 8: Severity of lipohypertrophy by body site of the population
### Table 7: Factors associated with lipodystrophy in the 265 study participants

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Prevalence of LD</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>88 (55.6%)</td>
<td>158</td>
<td>0.083</td>
</tr>
<tr>
<td>Male</td>
<td>48 (44.9%)</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-30</td>
<td>10 (37%)</td>
<td>27</td>
<td>0.415</td>
</tr>
<tr>
<td>11-40</td>
<td>59 (50.9%)</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td>11-50</td>
<td>48 (55.2%)</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>&gt;50</td>
<td>16 (45.7%)</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>WHO stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>12 (52.1%)</td>
<td>23</td>
<td>0.059</td>
</tr>
<tr>
<td>II</td>
<td>23 (50%)</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>50 (52.1%)</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>48 (51.6%)</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>HAART duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18</td>
<td>19 (24.7%)</td>
<td>77</td>
<td>0.34 (0.1-0.6)</td>
</tr>
<tr>
<td>18-36</td>
<td>73 (60.8%)</td>
<td>120</td>
<td>2.1 (1.2-3.5)</td>
</tr>
<tr>
<td>&gt;36</td>
<td>39 (67.2%)</td>
<td>58</td>
<td>2.3 (1.2-4.6)</td>
</tr>
<tr>
<td>CD4 nadir</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>108 (52.4%)</td>
<td>206</td>
<td></td>
</tr>
<tr>
<td>&gt;200</td>
<td>22 (44%)</td>
<td>50</td>
<td>0.285</td>
</tr>
<tr>
<td>Current CD4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>25 (43%)</td>
<td>58</td>
<td>0.150</td>
</tr>
<tr>
<td>&gt;200</td>
<td>104 (53.8%)</td>
<td>193</td>
<td></td>
</tr>
</tbody>
</table>

**Gender and lipodystrophy**

Forty eight (35.3%) of the patients with lipodystrophy were males while females were 88 (64.7%). This difference did not attain statistical significance (p=0.083).

Lipoatrophy occurred in similar proportion in both males and females, described in 31 males and 30 females. Lipohypertrophy and mixed syndrome were more common in females. Lipohypertrophy occurred in 16 (76.2%) females and 5 (23.8%) males while mixed syndrome was seen in 45 (78.9%) females and 12 (21.1%) males.
**Age and lipodystrophy**

Lipodystrophy occurred with equal frequency in all age groups as depicted in the table 7 above. There was no significant association between age and lipodystrophy.

**WHO stage and lipodystrophy**

Lipodystrophy was seen in 52.1%, 50%, 52.1% and 51.6% of patients in WHO stage I, II, III, and IV respectively as depicted in table 7.

Most of the patients with lipodystrophy were in WHO stage III and IV but there was no significant association between lipodystrophy and WHO stage at initiation of HAART.

**Duration of HAART and lipodystrophy**

A longer duration of therapy was found to be significantly associated with the development of lipodystrophy with 19 patients (24.7%), 73 patients (60.8%) (OR 2.06; CI 1.21-3.51, p value 0.004) and 39 patients (67.2%) (OR 2.34; CI 1.21-1.46, p value 0.006) having lipodystrophy at 6-18, 18-36 and >36 months of treatment respectively.

Increasing duration of HAART use was associated with increased frequency of lipodystrophy.

**CD4 count and lipodystrophy**

A low baseline CD4 count at onset of HAART was not associated with development of lipodystrophy. One hundred and eight (52.4%) patients with baseline CD4 <200/mm$^3$ developed lipodystrophy compared to 22 patients (44%) with CD4 greater than 200/mm$^3$ (p value 0.285)

Likewise adequate immune reconstitution or failure to reconstitute the immunity was not found to be significantly associated with lipodystrophy. One hundred and four (53.8%) of the patients with CD4 greater than 200/mm$^3$ developed lipodystrophy compared to 25 patients(43.1%) with CD4 less than 200/mm$^3$. 
**Type of HAART and lipodystrophy**

Most of our patients were on a d4T based regimen. 128 patients (52.5%) on a d4T based regimen developed lipodystrophy versus 38.1% of those who had never used a d4T based regimen. The association did not reach significant proportions. Similarly 51.1% of patients who were on AZT based regimen developed lipodystrophy compared to 51.3% of those who had never used AZT. Over 90% of patients who were on a non d4T, non AZT based regimen had lipodystrophy. The explanation for this could be that these patients switched to second line regimens following development of toxicity from the first line anti-retroviral drugs.

**Table 8: Type of HAART used by patients with lipodystrophy**

<table>
<thead>
<tr>
<th>HAART combination</th>
<th>Prevalence of lipodystrophy</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>d4T based regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever used</td>
<td>128 (52.5%)</td>
<td>244</td>
<td>0.144</td>
</tr>
<tr>
<td>Never used</td>
<td>8 (38.1%)</td>
<td>21</td>
<td></td>
</tr>
</tbody>
</table>

| AZT based regimen                 |                            |       |         |
| Ever used                         | 21 (51.1%)                 | 41    | 0.748   |
| Never used                        | 115 (51.3%)                | 224   |         |

| Non d4T, non AZT based regimen    |                            |       |         |
| Ever used                         | 33 (91.7%)                 | 36    | 0.000   |
| Never used                        | 103 (45%)                  | 229   |         |
DYSLIPIDEMIA

Dyslipidemia was found in 211 (79.6%) patients, of whom 41.7% were males and 58.3% were females.

Table 9: Metabolic variables of the 265 study participants

<table>
<thead>
<tr>
<th>Variable (mmol/l)</th>
<th>Male (n=107)</th>
<th>Female (n=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC Mean ± s.d</td>
<td>5.2±1.38</td>
<td>5.35±1.32</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5.08 (2.15-10.08)</td>
<td>5.16 (2.54-9.87)</td>
</tr>
<tr>
<td>HDL-C Mean ± s.d</td>
<td>1.097±0.39</td>
<td>1.179±0.44</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.08 (0.24-2.67)</td>
<td>1.11 (0.20-3.03)</td>
</tr>
<tr>
<td>LDL-C Mean ± s.d</td>
<td>3.28±1.26</td>
<td>3.18±1.25</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3.03 (1.08-7.92)</td>
<td>3.02 (0.08-7.67)</td>
</tr>
<tr>
<td>TG Mean ± s.d</td>
<td>2.00±1.54</td>
<td>2.21±1.79</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.62 (0.49-10.6)</td>
<td>1.70 (0.47-11.26)</td>
</tr>
<tr>
<td>FBS Mean ± s.d</td>
<td>5.5 ± 2.1</td>
<td>5.18±0.9</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5.4 (2.8-20.1)</td>
<td>5.1 (3-9.3)</td>
</tr>
</tbody>
</table>

The median total cholesterol, HDL-cholesterol, LDL-cholesterol were within normal in both male and female patients.

Median triglycerides were marginally elevated in females but normal in males. Median fasting blood sugar was normal in both groups.
Types of dyslipidemia

Figure 9: Prevalence of dyslipidemia in the study population

High total cholesterol: Elevated total cholesterol (>5.17mmol/l) was found in 129 (48.6%) of the study participants of whom 68 (25.6%) had borderline high total cholesterol (5.17-6.18 mmol/l) and 61 (23%) had high total cholesterol (>6.19mmol/l).

High LDL-cholesterol: Elevated LDL-cholesterol (>3.34mmol/l) was found in 107 (40.3%) of the study participants of whom 47 (17.7%) had borderline high (3.34-4.11 mmol/l), 35 (13.2%) had high (4.13-4.88mmol/l) and 25 (9.4%) had very high (>4.90mmol/l) LDL- cholesterol.

Low HDL-cholesterol: Low HDL-cholesterol levels (<1.03 mmol/l) was found in 110 (41.5%) of the study participants.

High triglycerides: High triglyceride levels (>1.69mmol/l) was found in 131 (49.4%) of the study participants. 57 (21.5%) had borderline high triglyceride levels (1.69-2.25 mmol/l) and 74 (27.9%) had high triglyceride levels (>2.26mmol/l).
**Dyslipidaemia and lipodystrophy**

**Table 10: Association between dyslipidaemia and lipodystrophy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prevalence of lipodystrophy</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia</td>
<td>117 (55.4%)</td>
<td>211</td>
<td></td>
</tr>
<tr>
<td>No dyslipidemia</td>
<td>19 (35.1%)</td>
<td>54</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Dyslipidemia was found in 117 (55.4%) patients with lipodystrophy and normal lipids in 18 (34.6%) patients with lipodystrophy. Dyslipidemia was significantly associated with lipodystrophy (p=0.007 OR 2.2 CI 1.3-4.6).

**Table 11: Types of dyslipidemia associated with lipodystrophy**

<table>
<thead>
<tr>
<th>Type of lipid</th>
<th>Prevalence of lipodystrophy</th>
<th>Total</th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercholesterolemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>77 (57%)</td>
<td>136</td>
<td>1.94 (1.2-3.2)</td>
<td>0.008</td>
</tr>
<tr>
<td>Normal</td>
<td>59 (43%)</td>
<td>136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High LDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>62 (45.9%)</td>
<td>136</td>
<td>1.5 (0.95-2.6)</td>
<td>0.076</td>
</tr>
<tr>
<td>Normal</td>
<td>74 (54.1%)</td>
<td>136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>89 (65.9%)</td>
<td>136</td>
<td>3.8 (2.3-6.4)</td>
<td>0.000</td>
</tr>
<tr>
<td>Normal</td>
<td>47 (34.1%)</td>
<td>136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low HDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>61 (45.2%)</td>
<td>136</td>
<td>1.3 (0.8-2.2)</td>
<td>0.257</td>
</tr>
<tr>
<td>Normal</td>
<td>75 (54.8%)</td>
<td>136</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hypertriglyceridemia was the most common type of dyslipidemia associated with lipodystrophy occurring in 89 (65.9%) of the patients. The association was found to be statistically significant (OR 3.8 CI 2.3-6.4 p=0.000).

Hypercholesterolemia was found in 77 (57%) of the patients with lipodystrophy and this also achieved statistical significance (OR 1.94 CI 1.2-3.2 p=0.008).

Neither elevated LDL-C nor low HDL was significantly associated with lipodystrophy.

38
Dysglycemia

Out of the total study population, 64 (24.4%) had dysglycemia.

Category

Diabetes was detected in 9 (3.5%) of the study participants.
Impaired fasting glucose was found in 55 (20.8%) of the study participants.

Dysglycemia and lipodystrophy

Table 12: Association between fasting blood glucose and lipodystrophy

<table>
<thead>
<tr>
<th>FBS</th>
<th>Prevalence of lipodystrophy</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>95 (69.8%)</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>IFG</td>
<td>34 (25.1%)</td>
<td>136</td>
<td>0.124</td>
</tr>
<tr>
<td>DM</td>
<td>7 (5.1%)</td>
<td>136</td>
<td></td>
</tr>
</tbody>
</table>

Abnormality in blood glucose was not found to be significantly associated with the presence of lipodystrophy. Among patients with lipodystrophy, 93 (69.8%) had normal fasting blood sugar, 34 (25.1%) had impaired fasting glucose and 7 (5.1%) were diabetic.
LOGISTIC REGRESSION ANALYSIS

A logistic regression model was constructed to find which of the associated factors independently predicted lipodystrophy while controlling for the other factors and to quantify this association.

Table 13: Logistic regression model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal Triglycerides</td>
<td>2.913</td>
<td>&lt;.0001</td>
<td>1.635 5.191</td>
</tr>
<tr>
<td>Abnormal total Cholesterol</td>
<td>1.288</td>
<td>0.388</td>
<td>0.725 2.286</td>
</tr>
<tr>
<td>HAART dur of 18-36</td>
<td>4.14</td>
<td>&lt;.0001</td>
<td>2.14 8.009</td>
</tr>
<tr>
<td>HAART dur of &gt;36</td>
<td>6.179</td>
<td>&lt;.0001</td>
<td>2.828 13.5</td>
</tr>
</tbody>
</table>

From logistic regression analysis model above, we estimated that for patients with abnormal triglycerides (i.e. triglycerides levels>1.69) who have same levels of total cholesterol and HAART duration, the odds of Lipodystrophy was 2.913 times higher compared to those with normal triglycerides. This estimate was statistically significant (p<0.0001). From the same model we estimated that for patients with abnormal total cholesterol levels (i.e. total cholesterol levels>5.17) who had same levels of triglycerides and HAART duration, the odds of Lipodystrophy is 1.288 times higher compared to those with normal total cholesterol, though this estimate was not statistically significant (p=0.388). In addition, it was estimated that for patients who had been on HAART for 18-36 months and who had same levels of triglycerides and same levels of total cholesterol, the odds of Lipodystrophy is 4.14 times higher compared to those who had been on HAART for 6-18 months. This estimate was statistically significant ((p<0.0001). Similarly, the odds of Lipodystrophy are 6.179 times in those who had been on HAART for longer than 36 months compared to those who have been on HAART for 6-18 months. This estimate was statistically significant ((p<0.0001).

In conclusion, we observe from the logistic model that abnormal levels of triglycerides and the duration on HAART were significantly associated with a higher likelihood of developing lipodystrophy for patients in this study.
Lipodystrophy is a well recognised problem in western world but with very little data in the African population. This study was conducted between August and December 2007 at Kenyatta National Hospital, a referral and teaching hospital in Kenya. It comprised 59.6% females (female to male ratio 1.5:1). This is similar to findings reported by Manuthu et al (74) in a study of the prevalence of dyslipidemia and dysglycemia in HIV patients at the Kenyatta National Hospital where 58% of the study participants were female. 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 compared to 44% of males. These findings reflect the National AIDS and STI control programme (NASCOP) estimates (75) that at least two-thirds of all HIV infected individuals in Kenya are women. Also, according to NASCOP, young women aged 25-29 years are more vulnerable to HIV infection whereas males are infected later at 40-45 years (75). Therefore the age and gender distribution of this study population is fairly representative of the sample of AIDS patients in Kenya.

The mean body mass index (BMI) was 23.1 kg/m². This was within the normal range of 18-25 kg/m². The median mid-upper arm circumference was 27 cm, the median waist circumference was 84 cm and the median waist to hip ratio (WHR) of this population was 0.96. These were similar in both male and female patients and within normal (Table 5). 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 dietary advice given to patients attending our clinics regularly.

In comparison, a study among the MACS cohort (19) using standardized NHANES III protocol as we did, in patients on HAART, reported a mean BMI of 25 ±3, mean waist to hip ratio of 0.95 ±0.07, MUAC of 32 ± 4, waist circumference of 90±9 and mean weight of 69.6±10.8. These higher values could be explained by the fact that these measures were done in caucasian patients who probably start 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 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 45.6-57.6) discerned on physical examination (Figure 5). This high prevalence was expected because stavudine and zidovudine which are components of our country's first line regimens are the strongest culprits implicated in aetiology of lipodystrophy from majority of studies (12, 13, 31).

In Rwanda, a multicenter study in 571 patients reported a prevalence of 48.5% in urban population and 17.3% in rural groups (76). This study was comparable to ours in terms of duration of HAART use, type of HAART combination and clinical methods for diagnosing lipodystrophy. Our study was done in an urban set-up and the higher prevalence than in the rural area may have been due to influence of diet, lifestyle and behavioural choices on the development of lipodystrophy.

A cross-sectional analysis done on 1077 patients belonging to the HIV Outpatient Study (HOPS) cohort (29) found a prevalence of 49%. This study was similar to ours in using patient report and physician examination to diagnose lipodystrophy. These patients had also been on HAART for a median duration of 3 years. However majority of the participants were older and had been on treatment with indinavir.

Peripheral lipoatrophy was the most common phenotype described in 44% of our patients (Figure 6). With reference to commonly affected body sites, facial atrophy was reported in 75.7% of our patients, arm atrophy in 48.5%, leg and buttock atrophy in 36.8% each (Table 6). Most of the patients described the wasting as severe (Figure 7). 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 that patients associated with these very obvious changes.

The Rwanda study (76) reported facial, arm, leg and gluteal atrophy in 67%, 66%, 70%, and 46% respectively. The prevalence may be higher than ours due to other probable environmental and genetic factors which were not specified.
Figure 10: A 30 year old patient who had been on stavudine-based regimen for two years and developed facial atrophy

Figure 11: Lipoatrophy of the leg in a female patient who had been on HAART for three years. She had used both stavudine-based and ziduvudine-based regimens
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 (76) 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 analysed alongside those with several signs.

**Figure 12:** A 42 year old man who had been on stavudine-based regimen for five years. He developed severe gynecomastia and facial atrophy.
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 multicenter AIDS cohort study (MACS) in the USA (19) which used anthropometric assessment in a case control study of HIV positive and negative 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 (76), 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 waist to hip ratio. Waist circumference is known to be a more sensitive and specific measure of visceral adiposity than waist to hip ratio (67).

Age had no influence on the development of lipodystrophy in our study (Table 7). This is in contrast to findings in other studies. In the HOPS cohort (29), increase in age above 40 years was found to be associated with the development of both lipoatrophy and lipohypertrophy. Similarly increase in age was found to be a predictor of lipodystrophy in a prospective French cohort study by Chene et al (57).

The reason for lack of association in our study could be because majority of the participants were younger (>50% aged less than 40 years) and might not have been subject to the physiological changes in body fat distribution such as a decrease in limb fat and increased central adiposity that occur normally with aging. Most of the patients in the HOPS cohort were over 40 years old while the group studied by chene et al had a mean age of 36 but males comprised 80% of the population.

Gender had no influence on the development of lipodystrophy in this study (Table 7). This lack of sex influence was also reported by Chene et al (57) in the French cohort study. We had more females in this study than males. However, most of our patients had lipoatrophy which other studies have shown to be more common in males whereas females are more prone to central obesity.
Baseline (nadir) CD4 count of the study population was low at a mean of 119 cell/mm³ and a median of 97.5. This can be explained by the fact that majority of our patients are commenced on HAART late. This finding is supported by the fact that 73.2% of our patients started HAART at WHO stage III and IV.

The study participants achieved immune reconstitution with a median follow-up CD4 of 313 cells/mm³. Adherence levels to, and good immunological response to HAART have been reported to be high in patients on HAART at Kenyatta National Hospital and this can explain the rise in follow-up CD4 counts. These findings are similar to those reported by Wong A et al (77) who reported a mean rise in CD4 from 95 ± 73 to 245 ± 121 in a South African study after a mean follow-up duration of 1.49 years in patients on HAART with stavudine toxicity.

The level of baseline CD4 count as well as presence or absence of immune reconstitution was not significantly associated with lipodystrophy in our study (Table 7). This is in contrast to the HOPS cohort (29) that reported significant association of both baseline and recent CD4 count and the development of lipodystrophy. However, in this study, lipodystrophy was noted at a baseline and recent CD4 counts less than 100 cells/mm³. Our study on the other hand analysed for the association with lipodystrophy at CD4 counts less than or greater than 200/mm³. Heath et al (29) in prospective population-based study found, like in our study, that neither CD4 levels at entry to study nor change in CD4 count over the follow up period was associated with lipodystrophy development. The patients in this study group had high baseline median CD4 counts of 370/mm³. Our study shows that the development of lipodystrophy is relatively independent of changes in immune function.

Duration of therapy was found to be a predictor of lipodystrophy. Patients who had been on HAART for longer than 18 months were twice as likely to have lipodystrophy than those who had been on therapy for less than 18 months (OR 2.1; CI 1.2-3.5 p=0.004) (Table 7). Similarly, the Rwanda study (76) also showed lipodystrophy prevalence of 69.6% in patients who had been on HAART for longer than 72 weeks. Chene et al (57) followed up HAART naïve patients started on nucleoside analogues and reported that lipoatrophy was frequent among patients after 30 months of exposure. Other studies
have reported that lipodystrophy develops 3-18 months after initiating HAART (27). Our study showed, on multivariate analysis that prolonged HAART use was an independent predictor of lipodystrophy. Patients who had used HAART for 18-36 months were four times more likely to develop lipodystrophy while those who had been on HAART for longer than 36 months were six times more likely to develop lipodystrophy. This is in comparison to those who had been on HAART for 6-18 months. Long follow-up period may be therefore needed in order to identify such patients.

Eighty six percent (86%) of the patients on HAART were on regimens containing nucleoside reverse transcriptase inhibitor (NRTI) mainly stavudine-based and zidovudine-based regimens at the time of enrolment (Figure 4). This is as dictated by the national guidelines on the initiation of antiretroviral medications (1). A Rwanda study on lipotoxity (76) reported that 81.6% of their patients were on stavudine-based regimen. This is in keeping with the current WHO recommended first line treatment of HIV disease in resource-poor countries. However, over 20% of our patients had undergone switch therapy at the time of enrolment due to either drug toxicity or treatment failure. This high rate of switch from first line agents to safer alternatives is an indication that newer antiretroviral agents may be needed in our set-up.

Slightly over 50% of patients on stavudine-based and zidovudine-based regimens developed lipodystrophy (Table 8). This finding is similar to that reported in the HOPS cohort (29) where prolonged use of stavudine was associated with lipodystrophy. This cohort had been on HAART for a duration exceeding 3 years. In the LPOCO study, the use of Stavudine significantly correlated with wasting in the nucleoside reverse transcriptase inhibitor and protease inhibitor groups when compared with the use of zidovudine containing combinations (31).

The patients who were on a non stavudine, non zidovudine based regimen were also noted to have significant lipodystrophy. This is expected because most of them had been on stavudine and zidovudine and switched to second-line treatment on developing lipodystrophy. This may be a reflection on non-reversibility or delayed reversibility of lipodystrophy.
Dyslipidemia was found in 79.6% of our study participants. All four types of lipid abnormalities (high total cholesterol, high LDL cholesterol, high triglycerides and low HDL cholesterol) were encountered (Figure 9) in our patients and were more prevalent in patients with lipodystrophy. In this study population, the aetiology of dyslipidemia is probably multifactorial and the high prevalence was expected. This is because HIV itself, use of antiretroviral therapy and lipodystrophy have been shown to be associated with abnormalities in lipid levels. This is mainly due to increased apolipoprotein B levels, increased dense LDL 2 levels and a shift towards hepatic secretion of VLDL-triglycerides. Circulating cytokines and acute phase reactants may also play a role (34). Studies have shown that HIV infection and HAART use are both associated with dyslipidemia. Manuthu et al (74) found an overall prevalence of 63.1% in patients at KNH. This was in a study population similar to ours in age and gender but included both HAART experienced and HAART naïve patients. In addition, our study population had been on HAART for longer and over 50% of them had lipodystrophy.

The commonest type of dyslipidemia in this study was hypertriglyceridemia. This finding is not surprising in this population who had multiple risk factors for development of hypertriglyceridemia. These include HIV infection, where the pathophysiology is thought to be due to cytokine mediated (especially IFN-α) suppression of lipases with decreased clearance of triglycerides from blood (34). In addition, use of HAART, especially protease inhibitors as well as having lipodystrophy are cited as risk factors for elevated triglycerides.

The prevalence of elevated total cholesterol in our study (>5.17 mmol/l) was 48.6%, high LDL-cholesterol was found in 41.5%. Majority of the patients who had elevated total and LDL- cholesterol had borderline elevation. LDL cholesterol is atherogenic and this is therefore of concern in this young population on long term HAART and who probably have other cardiovascular disease risk factors. It may be important to institute therapeutic lifestyle modification and lipid lowering agents in these patients.

Low HDL- cholesterol was found in 40.3% of patients. This is also expected as HIV infection has been shown to suppress HDL- cholesterol (34). This finding however is in contrast to those reported by Manuthu et al (74) who found HDL not to be reduced in patients on HAART.
Figure 13: 50 year old patient with buffalo hump. She also had central obesity and focal fat deposits in the neck, epigastrium and axilla; was diabetic and hypertensive with elevated total and LDL cholesterol. She had used d4T based regimen for 3 years.

Patients with lipodystrophy were more likely to have dyslipidemia than normal lipids, and dyslipidemia was found in 55.4% of patients with lipodystrophy (Table 10). Similar findings were reported by the Data collection on adverse events from anti-HIV drugs (D:A:D) study group who found dyslipidemia in 57% of patients with lipodystrophy. The D:A:D study also reported on a follow up study that after the initial 7 years of HAART, the risk of myocardial infarction was 27% per year (39). In our study, triglycerides were 3.8 likely to be elevated and total cholesterol 1.94 likely to be elevated in patients with lipodystrophy (Table 11).

Samaras K et al (33) found significantly elevated total cholesterol and triglycerides in patients with lipodystrophy who did not have other features of metabolic syndrome. Saves et al (28) found the prevalence of hypertriglyceridemia in patients without lipodystrophy and those with lipodystrophy was 20% and 42% respectively, that of hypercholesterolemia was 48% and 62%, respectively.
Hypertriglyceridemia was found to be an independent predictor of lipodystrophy in the multivariate analysis with the odds of lipodystrophy being 2.9 times higher in those with hypertriglyceridemia compared to those with normal lipids (Table 13). These patients may benefit from long-term follow-up with regular cardiovascular risk assessment and institution of intervention strategies to reduce their risk constellation.

Impaired fasting glucose was seen in 24.4% and diabetes mellitus in 3.5% of our study participants.
Insulin resistance and diabetes have been seen with regimens containing Indinavir and stavudine (78). It is thought to be due to inhibition of glucose movement through GLUT 4 transporter (79). Manuthu et al (74) and the Rwanda study (76) also reported the prevalence of dysglycemia as 20.7% and 17.3% respectively.
Abnormalities in fasting blood glucose were not found to be associated with lipodystrophy in this study. IFG was reported in 25.1% and diabetes in 5.1% and normal blood glucose in 68.8% of patients with lipodystrophy. Samaras et al (33) on the other hand found abnormalities in blood glucose to be more common in lipodystrophy than those without (19% vs. 11%) while Saves et al (28) reported that glucose alteration was 16% in patients without lipodystrophy and 28% in patients with lipodystrophy.

It is noteworthy that although metabolic alterations were more common among patients with lipodystrophy, they were also present in patients without lipodystrophy implicating the role of viral and antiretroviral therapy in the aetiology.
The fact that the study was cross-sectional was a limitation because it made understanding of the exposure outcome pathway difficult. We were also not able to perform imaging techniques such as CT and MRI scans for reasons of high costs. These scans are better in quantifying the changes in body fat.

In conclusion, HIVLD is common in our set-up at a prevalence of 51.3%, and the most common phenotype was lipoatrophy. Age, gender, WHO stage and immune reserve were not associated with lipodystrophy. 52.5% of patients on a stavudine based regimen and 51.1% of those on a zidovudine based regimen developed lipodystrophy. Most of these patients had been on HAART for more than 18 months.
Dyslipidemia was common in patients with lipodystrophy and this is likely to increase the risk of cardiovascular disease. However, dysglycemia was not associated with
lipodystrophy. Hypertriglyceridemia and prolonged duration of HAART were found to be independent predictors of lipodystrophy. We recommend that national guidelines be reviewed with the aim of substituting stavudine and zidovudine with 'metabolically friendly' alternatives. In addition, lipid profiles should be performed before HAART initiation and be routinely monitored especially in patients who develop lipodystrophy. Finally regular cardiovascular risk assessment should be done in patients on HAART and institution of intervention strategies done to reduce their risk constellation.
10. LIMITATIONS

1. We were not able to perform imaging techniques such as CT and MRI scans for reasons of high cost. These scans are better in quantifying the changes in body fat.

2. We lacked some data on nadir and most recent CD4 counts on some of our study participants and this may have some effect on our results with reference to the association of CD4 counts with lipodystrophy.
11.0 CONCLUSIONS

1. HIV associated lipodystrophy was common in HIV positive patients on long term HAART at Kenyatta National Hospital with the main phenotype being lipoatrophy.

2. Age, gender, WHO stage and immune reserve were not associated with development of lipodystrophy.

3. More than half of the patients on stavudine-based and zidovudine-based regimens developed lipodystrophy and their effect was found to be time-dependent indicating that long term follow-up is necessary for such patients.

4. There was a high prevalence of dyslipidemia in patients with lipodystrophy and hypertriglyceridemia was found to be an independent predictor of lipodystrophy.

5. Dysglycemia was not significantly associated with lipodystrophy.
12.0 RECOMMENDATIONS

1. We recommend review of our country's national guidelines for first line HAART for the public health intervention with the aim of substituting the thymidine analogues with safer alternatives.

2. Long-term follow up of patients on these drugs and a high index of suspicion is necessary for early diagnosis of lipodystrophy. In addition, further studies, especially longitudinal are needed to determine who's at risk of developing HAART related lipodystrophy and the time course because not all people on culprit antiretroviral therapy did develop lipodystrophy.

3. The baseline and thereafter, routine assessment of lipid profiles should be done in all patients on HAART in order to plan for interventions.

4. Regular cardiovascular risk assessment of these patients and institution of intervention strategies such as dietary modification, physical exercise and lipid lowering therapy especially for patients with other traditional cardiovascular


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35. Reynolds NR, Neidig JL. Balancing disfigurement and fear of disease progression: Patient perceptions of HIV body fat redistribution AIDS Care 2006; 18(7): 663-673


42. Nolan D, Hammond E. Mitochondrial DNA depletion and morphologic changes in adipocytes associated with nucleoside reverse transcriptase inhibitor therapy. AIDS. 2003;17:1329-1338.


45. McComsey GA. Improvements in lipoatrophy, mitochondrial DNA levels and fat apoptosis after replacing stavudine with abacavir or zidovudine. AIDS 2005; 19:15-23.


77. 14th conference on retroviruses and opportunistic infections. Los Angeles, California; Feb 25-28


APPENDIX I - SCREENING PROFORMA

Study No: 

Age (Years): 

Hospital No.: 

DOB: 

Contact Details: P.O. Box 
Tel. No.: 
Place of work: 

Presence of HIV disease 1= Yes 2= No

Use of HAART 1= Yes 2= No

ELIGIBILITY
1. Are you willing to consent to the study?

THE PREVALENCE OF LIPODYSTROPHY SYNDROME, ASSOCIATED FACTORS METABOLIC ALTERATIONS IN PATIENTS ON HAART AT THE KENYATTA NATIONAL HOSPITAL?
1 = YES 2 = NO

FOR OFFICIAL USE
Recruited 1 = YES 2 = NO
APPENDIX II - STUDY PROFORMA

Study No. 

Date: 

IP No. 

DOB (month, year) 

Age (years) 

DEMOGRAPHICS

1. Gender
   1 = Male
   2 = Female

2. Marital status
   1 = Single
   2 = Married
   3 = Divorced
   4 = Widowed
   5 = Separated

3. Usual residence

4. Usual occupation
   1 = self employed
   2 = employed
   3 = unemployed
   4 = retired
   5 = training/student

5. Level of education
   1 = None
   2 = Primary school
   3 = Secondary school
   4 = Tertiary

6. WHO clinical stage at initiation of HAART
   1.
   2.
   3.
   4.

7. Exposure to HAART

   CURRENT
   
   PAST

   Lamivudine

   Stavudine
Zidovudine
Didanosine
Abacavir
Zalcitabine
Emtricitabine
Tenofovir
Efavirenz
Nevirapine
Lopinavir/ritonavir
Nelfinavir
Indinavir
Other (specify) ..................................

9. Cumulative duration of HAART use (months)  

10. Patient perception and impact of body fat changes
   
a. Adherent to treatment  
   b. Social interaction changed  
   c. Changed clothing

Not adherent to treatment
No change
not changed clothing
APPENDIX III-PATIENT ASSESSMENT OF BODY SHAPE

For each body part described indicate in the appropriate box whether you currently have body shape changes that have occurred since you started HAART. Severity is to be described as:
Mild (noticeable only when specifically sought)
Moderate (readily obvious to the patient)
Severe (obvious to a casual observer).

<table>
<thead>
<tr>
<th>Body area</th>
<th>If YES indicate</th>
<th>type of change (Increase Or Decrease) and its severity</th>
<th>Current severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
<td>NO</td>
<td>Increase</td>
</tr>
<tr>
<td>Facial fat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Front/side of neck fat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back of neck fat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breasts fat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm fat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal fat</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Buttocks fat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg fat</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other location</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Identify other location     ............................................................................

Identify other location  ............................................................................

66
For each body region described below, indicate in the appropriate box any clinical features apparent at today's visit and note the nature and severity of any abnormality. Severity is to be scored as: Mild (noticeable only when specifically sought) Moderate (readily obvious to the clinician or patient) Severe (obvious to a casual observer).

<table>
<thead>
<tr>
<th>Body area</th>
<th>Is there any fat wasting? If YES, indicate current severity.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>Facial fat</td>
<td></td>
</tr>
<tr>
<td>Front/side of neck fat</td>
<td></td>
</tr>
<tr>
<td>Dorsocervical area</td>
<td></td>
</tr>
<tr>
<td>Breasts fat</td>
<td></td>
</tr>
<tr>
<td>Arm fat</td>
<td></td>
</tr>
<tr>
<td>Abdominal fat</td>
<td></td>
</tr>
<tr>
<td>Buttocks fat</td>
<td></td>
</tr>
<tr>
<td>Leg fat</td>
<td></td>
</tr>
<tr>
<td>Other location (specify)</td>
<td></td>
</tr>
</tbody>
</table>

Identify other location: ........................................................................
<table>
<thead>
<tr>
<th>Body area</th>
<th>Is there any fat accumulation? If YES, indicate current severity.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>Facial fat</td>
<td></td>
</tr>
<tr>
<td>Front/side of neck fat</td>
<td></td>
</tr>
<tr>
<td>Dorsocervical area</td>
<td></td>
</tr>
<tr>
<td>Breasts fat</td>
<td></td>
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<tr>
<td>Arm fat</td>
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<tr>
<td>Abdominal fat</td>
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<td>Buttocks fat</td>
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<tr>
<td>Leg fat</td>
<td></td>
</tr>
<tr>
<td>Other location (specify)</td>
<td></td>
</tr>
</tbody>
</table>

Identify other location...
My name is Dr. Angela Awino, a postgraduate student in Internal Medicine. I am conducting a research study on patients attending the Comprehensive Care Centre, Kenyatta National Hospital.

What is the purpose of the study?
The purpose is to assess the prevalence of lipodystrophy (body fat changes) in patients on Highly Active Anti-retroviral Therapy by self-report and physical examination and to assess the factors associated with its development.

What does the study involve?
A history will be taken from you. You will then undergo a general physical exam including measurement of your blood pressure, weight and height, hip circumference, waist circumference, mid-thigh circumference, and mid-arm circumference followed by a complete physical exam to ascertain the presence or absence of body fat changes. In addition, 10 ml blood taken from you for tests after a period of at least 9 hours without feeding.

Participation in the study is voluntary, and you can decline to participate or withdraw from the study without any penalty.

Are there any risks involved?
You may experience a mild unpleasant sensation during blood withdrawal for the above laboratory tests.

Will I benefit from the above study?
Yes. We will be able to switch you to treatment that does not cause body fat changes and if your laboratory tests are abnormal, you will be informed and treated accordingly.

Thank you for your cooperation.
APPENDIX VI - CONSENT FORM

I ..........................................................................................................., after reading the consent explanation form and having been explained to by Dr. Angela Awino (The Principal Investigator) do voluntarily agree to take part in this research study on THE PREVALENCE OF LIPODYSTROPHY AND ITS ASSOCIATED FACTORS IN PATIENTS ON HAART AT THE KENYATTA NATIONAL HOSPITAL. I am also aware that I can withdraw from this study without losing any benefits or quality of management of my medical problem being affected.

SIGNED: .................................................................

THUMBPRINT....................................................

WITNESS............................................................

DATED .................................................................