Breast hypertrophy and Gynaecomastia in HIV-associated Lipodystrophy, a problematic side-effect of life-saving antiretroviral therapy

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DECLARATION

I, Richard Zinn, declare that the content of the paper is my own work. It is being submitted for the degree of Master of Medicine, in the division of Plastic and Reconstructive Surgery, at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

Signature

Day_____of_____2014

Dedicated to my supportive family. Even though you are far, you are always close to my heart. And to Tiffany.

LIST OF OUTCOMES FROM THIS WORK

Papers:

Part of this research report has been published in The Journal of Plastic Reconstructive and Aesthetic Surgery (JPRAS).

- Zinn RJ, Serrurier C, Takuva S, Sanne I, Menezes CN.
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Congress presentations arising from this study:

- Presented at the Burt Myburgh Research Forum, 2010, Johannesburg, South Africa.
- Presented at the congress of Association of Plastic Reconstructive and Aesthetic Surgeons of South Africa (APRSSA), 2011, Johannesburg, South Africa

SUMMARY

With 67% of the world's human immunodeficiency virus (HIV) infected population existing in Sub-Saharan Africa and recent access to highly active antiretroviral therapy (HAART); demand for plastic surgical intervention in addressing HIV-associated lipodystrophy has expanded dramatically. This study assessed the prevalence of lipodystrophy in a random clinic cohort, the demand for surgical correction, and risk of treatment non-compliance

A questionnaire and database cross-sectional review of 554 patients was performed over a three-month period at the Themba Lethu Clinic, Johannesburg, South Africa.

A total of 479 patients completed the questionnaire, 83% were female. Nearly 90% of patients were currently being treated, or had been treated with stavudine (d4T). The prevalence of lipodystrophy was 11.7%. Nearly 5.9% of patients had considered stopping treatment due to changes in body morphology following the onset of HAART, 47% of patients interviewed would consider surgery to correct unwanted physical changes following treatment with HAART. Male patients were satisfied by physical changes in their body habitus following treatment (pre-treatment satisfaction 38% vs. post-treatment satisfaction of 94%). Female patients had 6.5 times more breast hypertrophy related symptoms than in their pretreatment state.

This study identified a prevalence of 11.7% of patients with HIV-associated lipodystrophy. A total of 3.8% of all patients would consider non-compliance on the basis

of this side effect alone. The demand for surgical correction is significant, extends beyond patients diagnosed with HIV-associated lipodystrophy, and needs to be addressed.

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Abbreviations

AD: Autosomal dominant

APROCO: Antiproteases Cohorte

APRSSA: Association of Plastic and Reconstructive Surgeons of South Africa

APS: Australian Lipodystrophy Prevelance Survey

AR: Autosomal recessive

AZT: Zidovudine

BMI: Body mass index

CD4: Cluster of differentiation

CT: Computer tomography

DEXA: Dual-energy X-ray absorptiometry

d4T: Stavudine

EFV: Efavirenz

HAART: Highly active antiretroviral therapy

HDL: High-density lipoprotein

HIV: Human Immunodeficiency Virus

HOPS: HIV Outpatients Study

HR: Hazard ration

IQR: Interquartile ranges

JPRAS: Journal of Plastic Reconstructive and Aesthetic Surgery

LIPOCO: Lipodystrophie Cohorte

NVP: Nevirapine

NRTI: Nucleoside reverse transcriptase inhibitors

PEPFAR: President's plan for AIDS relief

PI: Protease inhibitor

STATA: Stata Corporation, College Station, Texas, USA

SALSA: Self Ascertained Lipodystrophy Syndrome Assessment

SLE: Systemic lupus erythematosus

TE: Therapy Edge- HIV^{TM} (Associated Biological Systems, South Africa)

TNF-α: Tumour necrosis factor-α

TDF: Tenofavir

USAID: United States Agency for International Development

WHO: World Health Organisation

3TC: Lamivudine

Definitions

Highly active antiretroviral therapy (HAART): initiated in accordance with the 2004 South African National Antiretroviral Treatment Guidelines, which include initiation criteria of a cluster of differentiation (CD4) count ≤ 200 cells/mm^3 or World Health Organisation (WHO) stage 4 and Acquired Immunodeficiency Syndrome (AIDS) defining illness irrespective of CD4 count. First line therapy consisted of stavudine (d4T), lamivudine (3TC) and efavirenz (EFV) or nevirapine (NVP); however kaletra (ritonavir/lopinavir) was used as part of the first line therapy regimen if there were contra-indications to other first line drugs. Single drug substitutions were permitted depending on the underlying clinical presentation of the patient.[1]

Lipodystrophy: defined as lipoaccumulation or lipoatrophy, was based on the development of peripheral fat wasting (face, arms, buttocks or thighs) and/or central abdominal fat accumulation and may include enlarged breasts.[2]

Stigmatization: is defined as the action of branding, marking, scarring or blemishing or to mark with stigmata[3].

Compliance: is the action of complying with a regimen. In terms of HAART, compliance is considered 100% intake of one's prescribed daily pills for each drug[4].

Gynaecomastia: ("women's breast") is defined as the physiological or pathological development of breast tissue in men.[5]

Chapter 1. Introduction and Literature review

1.1 Overview of lipodystrophy

Lipodystrophy is a term used to describe a heterogeneous group of disorders characterized by fat accumulation or atrophy, which may be classified as generalized, partial (extensive but not generalized) or localized (limited to a specific area). They may be congenital or acquired disorders. The function of adipose tissue is for padding and cushioning, but it also has an endocrine and metabolic role, secreting leptin, tumour necrosis factor-α (TNF-α), adiponectin and interleukins. Consequently, lipodystrophies are associated with metabolic derangements including hypertension, insulin-resistance, dyslipidemia and coronary artery disease, commonly termed metabolic syndrome.[6]

1.2 Familial lipodystrophies

Familial lipodystrophies are conditions that demonstrate Mendelian inheritance patterns and may be inherited as a dominant or recessive trait. Clinical presentation is a direct result of adipocyte apoptosis or dysfunctional lipid storage resulting from specific gene mutations. They may present from birth to puberty and may be either generalized or partial.

1.2.1 Familial generalized lipodystrophy – Berardinelli Seip syndrome

An autosomal recessive (AR) condition that affects males and females equally. Onset is at birth. There are 3 types. Types 1 and 3 have generalized lipoatrophy but retain palmar and periorbital fat (mechanically active fat), while type 2 has lipoatrophy not sparing any region. Metabolic derangements include insulin resistance, diabetes and hypertriglyceridemia. An increased metabolic rate is noted. Systemic manifestations

include cardiomyopathy, liver cirrhosis and liver failure, proteinuric nephropathy and acute pancreatitis.[6]

1.2.2 Familial partial lipodystrophy - Kobberling-Dunnigan syndrome

An autosomal dominant (AD) condition affecting females more commonly that males. Onset is at puberty. Patients manifest with lipoatrophy of limbs and trunk, and lipohypertrophy of faces and neck. Associated metabolic derangements include insulin resistance, diabetes mellitus, hypertriglyceridemia and reduced high density lipoprotein (HDL). Patients may develop acute pancreatitis, steatohepatitis, liver cirrhosis and menstrual abnormalities.[6]

1.2.3 Familial partial lipodystrophy with mandibulacral dysplasia

A condition with childhood onset and AR inheritance. Males are more commonly affected than females. There may be partial lipoatrophy involving the extremities but in some cases lipoatrophy may be generalized. There is associated insulin resistance, diabetes mellitus, hypertriglyceridemia and reduced HDL. There is also premature ageing, mandibular, clavicular and terminal phalangeal hypoplasia and short stature. Skin acquires a scleroderma like appearance with mottled pigmentation.[6]

1.3 Acquired lipodystrophy

The acquired lipodystrophies have varying aetiologies, including iatrogenic, traumatic, infective and autoimmune causes. Patients are affected at any age. Clinical presentation is directly related to the underlying cause, and underlying medical conditions and therapeutic modalities should be sought in order for a diagnosis to be made.

1.3.1 Acquired generalized lipodystrophy - Lawrence syndrome

This condition affects patients at adolescents and childhood. Females are affected three times more commonly than males. There is atrophy of face, trunk and limb fat with sparing of bone marrow fat. Around 33% of patients have a preceding autoimmune disorder (Sjögrens, dermatomyositis), which suggests there may be an underlying autoimmune aetiology to this condition.[6]

1.3.2 Acquired partial lipodystrophy - Barraquer-Simons syndrome

Affects females more commonly than males (3:1). This condition commonly occurs in childhood and adolescence, although it can rarely develop in adulthood. There is often an initial febrile illness, followed by progressive lipoatrophy in a cephalocaudal distribution, with lipohypertrophy in a caudal – cephalic direction. There are also hemi-lipodystrophy forms. Insulin resistance, diabetes mellitus, and hypertriglyceridemia are associated with the disease. There may also be co-existent autoimmune disorders such as Sjögrens, systemic lupus erythematosis (SLE) and dermatomyositis as well as mesangiocapilliary glomerulonephritis.[6]

1.3.3 Acquired localized lipodystrophy

This is a heterogeneous group of disorders. Infective causes include pyogenic abscesses and localized panniculitis. Systemic autoimmune disorders may manifest with localized lipoatrophy, such as SLE and dermatomyositis. Trauma and pressure may result in localized lipoatrophy. Various injections may cause localized lipodystrophy including

hormones (insulin, corticosteroid and growth hormone), methotrexate, heparin, iron and vaccinations (Diphtheria-pertussis-tetanus).[6]

1.4 HAART-associated lipodystrophy

This is an acquired, partial form of lipodystrophy. It is a consequence of the standard of care for HIV-positive patients, namely highly active antiretroviral therapy (HAART). The use of HAART has significantly reduced the morbidity and mortality associated with HIV infections. The morbidity of HIV-associated lipodystrophy is now becoming apparent with implications on social, sexual and psychological functioning, all of which may result in decreased treatment compliance.

1.4.1 Prevalence

The prevalence of lipodystrophy in various population groups being treated with combination therapy, protease inhibitor (PI) and nucleoside reverse transcriptase inhibitor (NRTI), has been quoted in a number of studies and varies widely (see Table 1). One of the earliest reports of d4T-related lipodystrophy compared the prevalence of lipodystrophy among patients on d4T-based regimens (63%), to patients on zidovudine (AZT) -based regimens (18,75%). The study looked at a cohort of 43 patients.[7] A Korean study found the prevalence of lipodystrophy to be 3.5% among a clinic population of 156 patients, and questioned whether the Asian racial group were somehow protected from developing HIV-associated lipodystrophy.[8] Other studies performed in Africa reported prevalence of 34% in Rwanda and 30% in Benin.[9,10]

Table 1. Prevalence of lipodystrophy in previously published studies.[9,10,11,12]

Study name	Number of patients	Definition	Study type	Prevelance
HOPS	1077 (87% male)	Moderate to severe lipoatrophy or lipohypertrophy	Cross-sectional: - Clinical examination - Questionaire - Database	49%
APS	1348 (97% male)	Lipoatrophy and lipohypertrophy	Cross-sectional: - Clinical examination - Questionaire - DEXA scan - CT scan	53%
SALSA	526 (84% male)	Lipoatrophy and lipohypertrophy	Cross-sectional: - Questionaire	67%
APROCO	614 (80% male)	Lipoatrophy and lipohypertrophy	Cross-sectional: - Clinical examination - Laboratory	24%
LIPOCO	154 (100%male)	Lipoatrophy and lipohypertrophy	Cross-sectional: - Clinical examination - Laboratory - CT scan	53.2%
Benin	88 (40.5% male)	Lipoatrophy Lipohypertrophy Metabolic syndrome	Prospective cohort (24 months): - Clinical examination -Questionaire	30%
Rwanda	409	Lipoatrophy Lipohypertrophy Neuropathy Lactic acidosis	Cross-sectional (18 months): - Clinical examination -Questionaire	34%

APROCO Antiproteases Cohorte. APS Australian Lipodystrophy Prevelance Survey. HOPS HIV Outpatients Study. LIPOCO Lipodystrophie Cohorte. SALSA Self Ascertained Lipodystrophy Syndrome Assessment

1.4.2 Risk factors

Risk factors for the development of lipodystrophy can be divided into host and treatment factors. Host factors include advanced age, female sex, greater nadir of CD4+ count (<350), higher viral load (>100,000 copies/ml) at the onset of HAART, higher baseline triglyceride levels and coinfection with hepatitis C. Treatment factors include the agent used, a longer duration of therapy (>2 years) and greater compliance on therapy. The different groups of antiretroviral drugs are associated with specific lipodystrophy presentations. NRTIs are associated with lipoatrophy, peripheral fat wasting, as well as myopathies, peripheral neuropathies, steatosis, hyperlactataemia, pancreatitis and bone marrow toxicity. PIs are associated with lipoaccumulation, lipid metabolic disorder and insulin resistence. Causative factors may be additive.[11]

1.4.3 Pathophysiology

The pathophysiology of lipodystrophy is a complex multifactorial process that includes the effect of the drugs on mitochondrial function and adipocyte metabolism, as well as the direct effect of the HIV virus's R-protien. Furthermore, these factors are modified by the age, sex, genetics and inflammatory state of the hoste. This ultimately results in:

-Impaired preadipocyte differentiation

-Increased adipocyte apoptosis

-Impaired lipogenesis and increased lipolysis

-Mitochondrial toxicity

Both NRTIs (particularly d4T, AZT and didanosine), as well as PIs are common offending agents. Different combinations of drugs are thought to result in characteristic clinical manifestations.

1.4.4 Clinical presentation

As in congenital lipodystrophy syndromes, HIV-associated lipodystrophy commonly presents with fat redistribution prior to metabolic complications. Clinical presentation includes lipoatrophy of the face, limbs and buttocks. In the face, wasting of subcutaneous fat, buccal, parotid, temporal and Bichat (preauricular) fat pads results in prominent zygoma, sunken eyes, exaggerated nasolabial and marionette lines, yielding a cachexic appearance. Lipohypertrophy results in fat deposition in the breasts (in males resulting in gynaecomastia), dorsocervical hump (buffalo hump), submental and submandibular areas. Abdominal girth increases secondary to increased subcutaneous fat, mesenteric, omental and visceral fat deposition. Clinical presentation may be purely lipoatrophy or lipohypertrophy or a combination. These changes are progressive, non-reversible and potentially stigmatizing. There are accompanying metabolic derangements including insulin resistance, type 2 diabetes, reduced HDL cholesterol, hypertriglyceridemia, hyperlactataemia and elevated hepatic transaminases.[13,14] There may also be boney abnormalities such as osteopenia, osteoporosis and avascular necrosis.

1.4.5 Classification

Only recently has a case definition been developed.[13, 15] This consists of 10 parameters (clinical, metabolic and radiological) and aims to guide the diagnosis of lipodystrophy. It has been shown to be accurate in 80% of cases when compared to patient and clinician

assessments.[13, 15] Since this requires access to dual energy x-ray absorptiometry (DEXA) and computer tomography (CT) scans, it may be less useful in the resource-limited environment.[2] Patient self-reporting combined with physical examination remains the earliest, cheapest and best method of diagnosing this condition.

1.4.6 Social Implications

HIV-associated lipodystrophy is related to poor body image, impacts social and sexual functioning and other activities of daily living. Reports suggest patients fear that changes in their body habitus jeopardize the confidentiality of their HIV status and this may even lead to treatment non-compliance.[11, 16-21]

1.4.7 Management

Management of HIV-associated lipodystrophy incorporates prevention and treatment. Prevention is facilitated by the choice of a drug regimen less likely to cause lipodystrophic side effects. The treatment modalities for lipodystrophy are medical and surgical in nature.

1.4.7.1 Management – Medical

Patients on HAART should be screened for metabolic derangements. Smoking cessation and lifestyle changes such as exercise and diet may assist in reducing their cardiovascular risk.[6] Statins and fibrates are beneficial in improving unfavourable lipid profile. Metformin and glitazones are recommended for treating type 2 diabetes.[6] Once lipodystrophy has been diagnosed, regimen change is commonly instituted. Interrupting or changing treatment will not reverse the morphological changes of lipodystrophy, but

will merely reduce its progression.[19, 22] Diet and exercise may reduce manifestations of lipohypertrophy, but adherence to these lifestyle changes remains difficult and the result may only be a partial correction.[11] The use of systemic therapies to reduce and treat the symptoms of lipodystrophy have been investigated, but have yielded disappointing results. The use of glitazones, such as rosiglitazones, have shown improved insulin sensitivity and adiponectin levels, but worsened lipid profiles.[6] Daily subcutaneous growth hormone injections improved truncal and visceral adiposity, but also yielded a loss of peripheral limb fat, and increased insulin resistance.[6, 20]

1.4.7.2 Management – Surgical

Facial lipoatrophy may be managed with the use of autologous fat injection if adipose-rich donor sites exist. Some patients, specifically those with a mixed lipoatrophy and lipohypertrophy presentation may have abdominal and flank donor sites that are harvested with small liposuction cannulae. This is prepared and injected into areas of lipoatrophy such as temporal wasting, malar fat pads, zygomatic and buccal regions. This is a cheap and effective way of addressing stigmatizing facial lipoatrophy, but may need to be repeated in order to attain long term, durable improvement. Dermal fat grafting has also been described. In this case, de-epithelialised grafts of fat and dermis are tunneled through small punch incisions into areas of facial atrophy to improve and camouflage contour deformities.[24] When there are no donor sites available due to severe generalized lipoatrophy, synthetic poly-L-lactic acid and hyaluronic acid facial fillers can be used.[11,22] These are much more expensive in the large volumes that are necessary to yield a benefit to the patient. They may be temporary or permanent. Permanent fillers have greater risk of infection and complications including foreign body reactions. Temporary fillers are

designed to reabsorb over 3 to 24 months.[22] Repeat injections will therefore be required. Due to their cost, synthetic fillers are not used in state practice but are freely available in private practice. Alloplastic facial implants are available and have been used to improve contour deformities with good effect and equal complication rates as compared to immunocompetent patients.[20]

Lipohypertrophy affecting the breasts and chest, dorsal hump and abdomen are treated with traditionally cosmetic body-contouring techniques. These include breast reduction, gynaecomastia resection, liposuction, abdominolipectomy and dorsal hump lipectomy.[20, 23,25] These services are offered in state practice to patients affected by lipodystrophy as treatment for the side-effects of HAART. Cosmetic and functional outcome are good, with complication rates equal to that of immunocompetent patients. Recurrence has been noted in some cases.[18-20, 22-25] Expectations should be correctly addressed, especially in patients with significant intra-abdominal, visceral, and omental fat deposits which cannot safely be accessed using current surgical technique.

1.5 Aims of Study

The aims of this study were to:

1) Determine the prevalence of lipodystrophy in a random sample of a clinic population in South Africa, looking particularly at the side effect of breast hypertrophy in females and gynaecomastia in males.

2) Explore awareness of lipodystrophy as a side effect of HAART.

3) Assess whether the occurrence of lipodystrophy posed a threat to compliance on HAART

4) Assess the demand that exists for surgical correction of HIV-associated lipodystrophy among study participants.

Chapter 2. Methodology

2.1 Study population

A total of 554 patients were interviewed between October and December 2009 at Themba Lethu Clinic, Helen Joseph. This is a public-sector hospital affiliated to the University of the Witwatersrand in Johannesburg, South Africa. It is one of the largest HIV clinics in South Africa. The programme is funded by the South African National and Gauteng Departments of Health, with support from Right to Care funded by United States Agency for International Development (USAID) and President's plan for AIDS relief (PEPFAR). Inclusion criteria included both genders, a minimum age of 18 years, HAART for longer than 6 months and, in females, not having been pregnant in the previous 12 months. Patients were approached in the waiting area of the pharmacy and offered the opportunity to be enrolled in a study that would take a few minutes of their time. They were under no obligation, were not informed about the study content until they had opted into the study, but would be able to withdraw from the study at any time. Once a patient volunteered to enroll in the study, they were taken to an interview room where the study was explained and full informed consent taken. Interviews took an average of 10 minutes to perform. Following the interview, the clinic database was used to complete a patient's history, which included demographic profile, medical history, HAART-regimen history, diagnosis of lipodystrophy and their most recent CD4+ count, as well as their CD4+ at onset of therapy (appendix 2).

2.2 Data collection

Data was collected during the interview using a questionnaire devised for the study, as well as from the clinic electronic database via a medical management software system,

Therapy Edge-HIV™ (TE) (Associated Biological Systems, South Africa). Knowledge, attitudes and perceptions of lipodystrophy were assessed. Male and female chest and breast symptoms were assessed using the Gynaecomastia Evaluation Questionnaire and the Breast-related Symptoms Questionnaire respectively (both are disease-specific for breast/chest enlargement) [26,27]. Patient's experiences of stigmatization, compliance and their demands for surgical correction were examined. TE was used to collate patient demographic data, their past and present HAART regimens and any previous lipodystrophy diagnosis made in the clinic setting by one of the clinic's physicians.

2.3 Data analysis and Statistics

Patient characteristics at initiation of HAART were summarized using medians and interquartile ranges (IQR) for continuous variables and frequencies and proportions for categorical variables. Frequencies and proportions were also used to describe responses to the questionnaire. For the analysis of time to lipodystrophy, person-time accrued from time of HAART initiation until the earliest of: 1) lipodystrophy; 2) close of the data set; 3) transfer out; or 4) lost to follow-up (4 months late for last clinic visit). Kaplan-Meier curves were used to compare progression to lipodystrophy by exposure group. An estimation of crude and adjusted hazard ratios of progression to lipodystrophy using Cox proportional hazards models was made. Data were analyzed using STATA version 11 (Stata Corp., College Station, TX, USA).

2.4 Ethical approval

This study and use of Themba Lethu Clinic data was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand and the medical superintendent of Helen Joseph Hospital.

Chapter 3. Results

3.1 Baseline Characteristics of the Study Population

The baseline characteristics of the study group are summarized in Table 2. A total of 554 patients were interviewed between October and December 2009. Of those interviewed, 479 patients fulfilled the inclusion criteria and were included in the final data set for analysis. Females comprised 83% (n=395) of the study group while 95% (456) of the participants were black Africans. The median age of participation was 35 (IQR 29.8-40.2) years and the median CD4 at onset of therapy was 114 cells/mm^3 (IQR 48-176). Nearly 89% (n=425) of participants had received a d4T-based regimen.

Table 2: Baseline characteristics of study participants at initiation of HAART

	Overall	Female	Male
Total, n (%)	479	395(82.5%)	84 (17.5%)
Employed, n (%)	197 (41.1%)	161 (40.8%)	36 (42.9%)
Alchohol, n (%)	54 (11.3%)	33 (8.4%)	21 (25%)
Smoking, n (%)	43 (9%)	25 (6.3%)	18(21.4%)
Black, n (%)	456 (95.2%)	377 (95.4%)	79 (94%)
Age (years)	34.7 (29.8-40.2)	33.4 (29.1-39.4)	39.2 (34.5-42.8)
Baseline CD4;	114 (48-176)	119 (55-181)	95 (23-158)
< 50, n (%)	114 (23.8%)	84 (73.7%)	30 (26.3%)
50 – 200	255 (53.2%)	214 (83.9%)	41 (16.1%)
≥ 200	110 (23%)	97 (88.2%)	13 (11.8%)
Baseline BMI(kg/m^2);	22.6 (19.6-26.8)	23 (20.2-27.8)	19.7 (18.4-23.4)
< 18.5, n (%)	58 (15.1%)	40 (69%)	18 (31%)
≥ 18.5	325 (84.9%)	277 (85.2%)	48 (14.8%)
W.H.O stage I/II, n (%)	317 (66.2%)	269 (68.1%)	48 (57.1%)
W.H.O stage III/IV, n (%)	162 (34%)	126 (31.9%)	36 (42.9%)
d4T-based regimen, n (%)	425 (89%)	351 (90%)	74 (88%)
non-d4T-based regimen, n (%)	50 (11%)	40 (11%)	10 (12%)

Data is expressed as N (%) except for age, baseline CD4 and baseline BMI which are expressed as median (IQR)

W.H.O World Health Organisation clinical staging of HIV/AIDS. BMI Body mass index

d4T is a nucleoside analogue reverse transcriptase inhibitor (NRTI) also known as stavudine

3.2 Knowledge, Stigma and Compliance

The majority (78%) of respondents were aware that lipodystrophy is a side effect of HAART. Amongst the 479 patients on therapy, 303 patients (63%) had encountered a gain or loss of body mass since commencing HAART. Of these, 27% (n=72) felt the change in mass 'gave away' their diagnosis of being HIV positive. Nearly 47% (n=129) would be willing to undergo surgery to reverse these body changes, while 5.9% (n=18) were currently considering, or had previously considered stopping HAART to limit further impact on their body form. Therefore, 3.8% of the total cohort of patients on HAART are at risk of treatment non-compliance on the basis of this side effect alone.

3.3 Male respondents

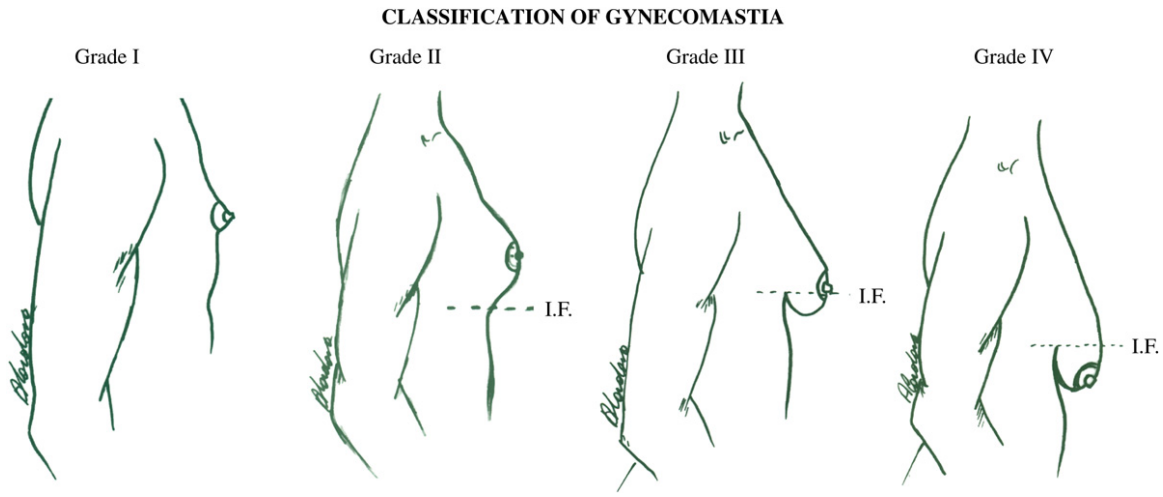
In this cohort, a total of 84 (17.5%) of the patients were male. When asked about the effect that recent changes breast fat composition had on them since starting HAART; 4 patients (4.7%) admitted to pain/discomfort, reduced self confidence and emotional distress, 17 (20.2%) admitted to pain/discomfort, reduced self confidence, emotional distress and inability to play sports, 1 patient (1.2%) had both pain/discomfort, reduced self confidence, emotional distress, inability to play sports and other psychological issues, whereas 53 patients (63.1%) denied any of these mentioned issues. A pictorial guide was used to represent the classification of gynaecomastia as described by Rorhich (see figure 1).

Around 60.7 % of patients (n=51) described themselves as grade I, 23.8 % (n=20) described themselves as grade II, 4.8 % (n=4) described themselves as grade III, none thought they were grade IV and 6 % (n=5) felt they had normal chest size and

morphology. A total of four of the patients did not respond. Therefore, when asked to describe their chest shape following treatment, 34.5% of male patients chose at least a grade 2 gynaecomastia[28,29]. Even in the light of these findings, 38% of male patients described themselves as happy with their pre-treatment body habitus ($p = 0.05$) while 94% of male subjects described themselves as satisfied with their body morphology following six months of treatment. These findings are demonstrated in table 6.

Figure 1. Pictorial description of gynaecomastia for patient's self assessment [28,29]

Which of the following pictures best depicts your chest / breasts wall:



A ☐ B ☐ C ☐ D ☐

E ☐ None of the above, my chest / breast is normal

3.4 Female respondents

Complaints of symptomatic breast hypertrophy were 6.5 times more common in females following six months of HAART. This is demonstrated in table 3. These complaints included difficulty in finding an adequate bra size, lower back pain, painful bra straps, difficulty participating in sporting activity due to their breast size and shoulder pain.

Table 3: Female patients' symptomatic macromastia pre and post HAART

	Prior to HAART			Post HAART		
Symptom	All the time	Some of the time	Never	All the time	Some of the time	Never
Upper back pain	1	25	318	11	115	246
Bras, clothes don't fit	7	7	329	32	40	296
Headaches	3	43	298	15	165	194
Breast pain	1	16	326	9	103	249
Lower back pain	6	22	314	15	141	214
Rashes or itching	0	11	331	8	40	319
Painful bra-strap grooves	7	9	327	33	61	271
Difficulty in sport activity	8	9	326	83	38	247
Neck pain	0	10	331	8	91	263
Shoulder pain	1	13	327	6	91	262
Difficulty running	10	4	328	86	39	244
Hands feel pain / numb	2	6	334	8	72	288
Arm pain	2	9	331	6	77	284

HAART: Highly active antiretroviral therapy

3.5 Regional body weight changes

Patients with and without a formal clinician's diagnosis of lipodystrophy indicated weight gain and weight loss in specific regions of their bodies. Weight gain was mainly identified in the abdomen (n = 212), breast (n = 190) and dorsal cervical hump (n=135). Weight loss was seen in the buttocks (n = 150), lower limbs (n=150), and to a lesser extent, the upper limbs (n=44). (figures 2,3)

Figure 2. Male and female participant's regional weight loss since initiating HAART

HAART Highly active antiretroviral therapy. L/Limb Lower limb. U/Limb Upper limb.

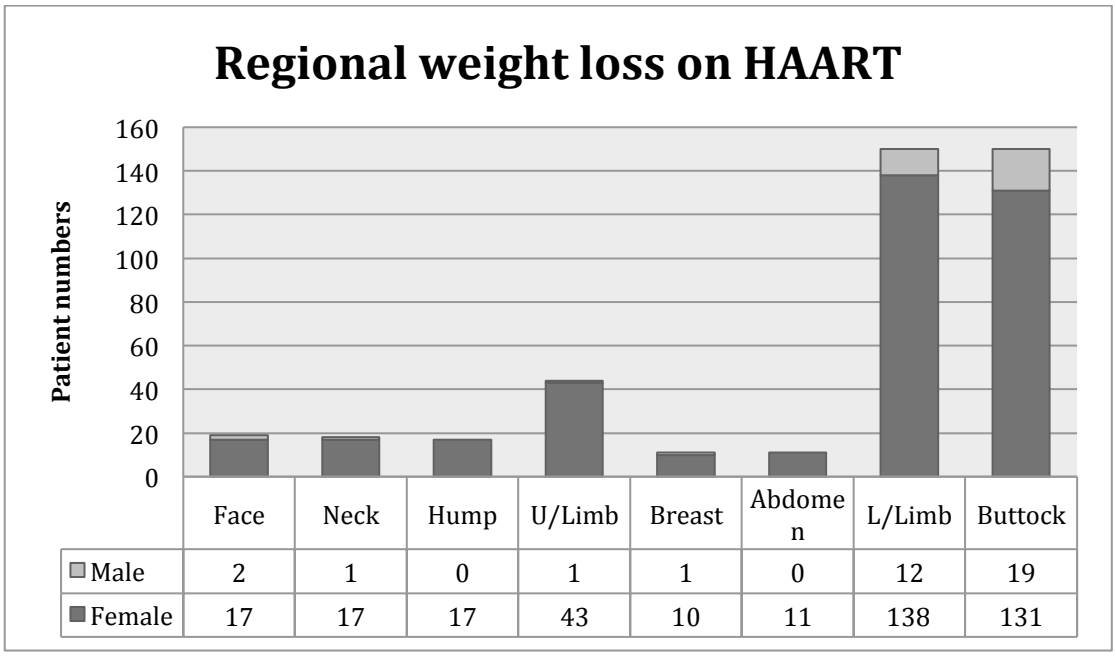
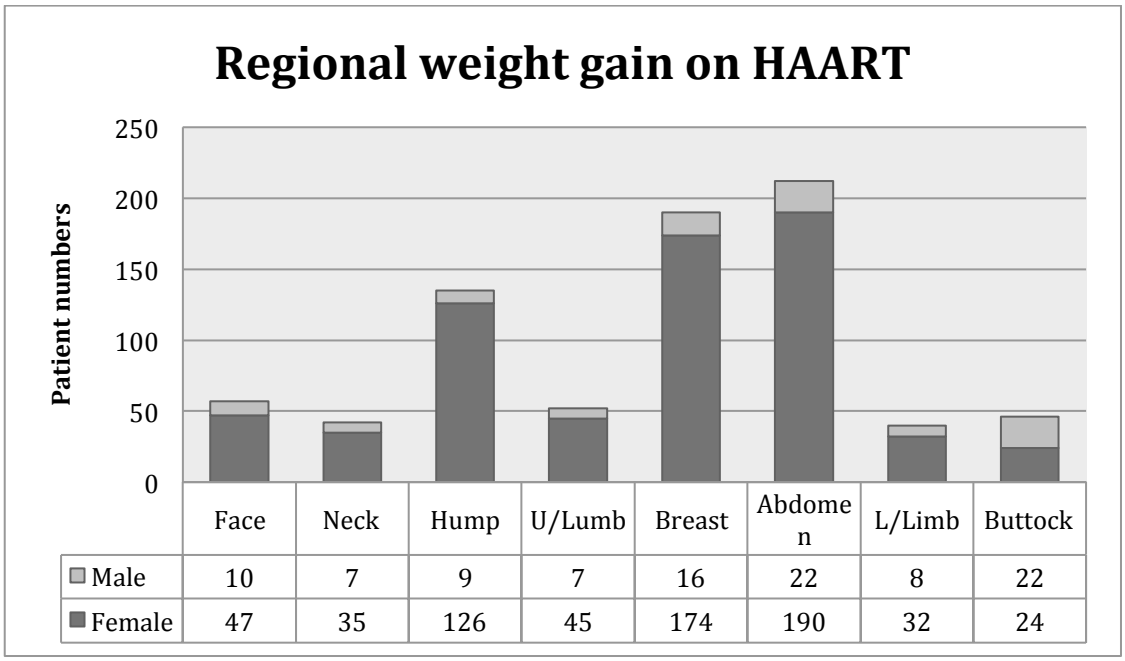


Figure 3. Male and female participant's regional weight gain since initiating HAART

HAART Highly active antiretroviral therapy. L/Limb Lower limb. U/Limb Upper limb



3.6 Prevalence and predictors of lipodystrophy

The prevalence of lipodystrophy in the cohort was found to be 11.7%. These patients had been diagnosed with lipodystrophy by a physician on previous consultation and this diagnosis had been documented on the clinic database. The prevalence was 13.7% in females and 2.4% in males (p= 0.004). The median time to development and diagnosis of symptomatic lipodystrophy from the onset of treatment with HAART was 12.7 months (IQR 5.8-24.1). (See figure 3). In our cohort of 479 patients, only 50 had not been treated with a d4T-based regimen. A total of three of these patients developed lipodystrophy on treatment. The prevelance of lipodystrophy among patients exposed to a d4T-based regimens was 12.4% (n=53). The prevelance of lipodystrophy among patients who had not been exposed to d4T was 5.8% (n=3).

Table 4 illustrates risk factors identified for the development of lipodystrophy. In this cohort, protective factors included male sex (Hazard ratio ((HR)) 0.12 ((0.03-0.48)) p=0.004), with a trend for reduced lipodystrophy in patients who consumed alchohol (HR 0.45 (0.14-1.46), p = 0.18), smoked tobacco (HR 0.47 (0.15-1.50), p = 0.20), were of older age at the onset of HAART as well patients who had a baseline BMI of less than 18.5 at the onset of treatment (HR 0.71 (0.28-1.79), p= 0.46). Risk factors for the development of lipodystrophy included the use of d4T (HR 1.78 (0.55-5.70), p = 0.33) and a baseline CD4+ count of less than 50 at the onset of therapy (HR 1.68 (0.76-3.71) p = 0.20).

Figure 4. Kaplan-Meier curve comparing the development of lipodystrophy in patients exposed to d4T versus those never exposed to d4T

HAART Highly active antiretroviral therapy. d4T Stavudine

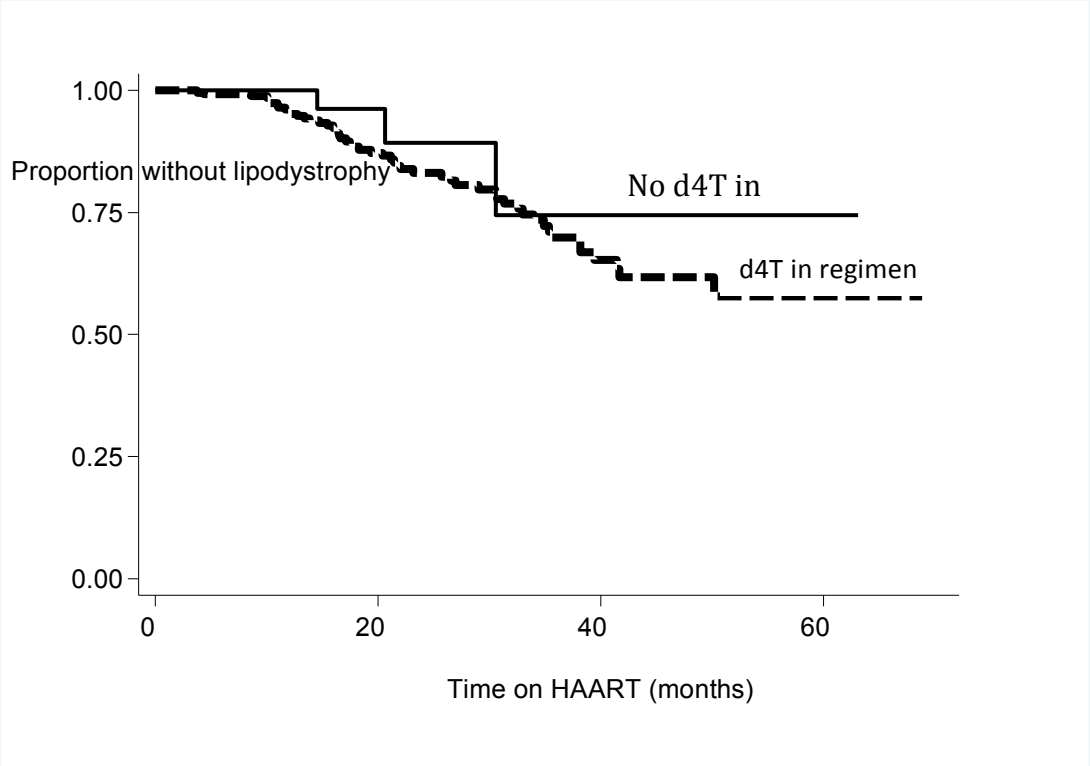


Table 4. Risk factors for the development of lipodystrophy

	crude HR (95% CI)	adjusted HR(95% CI)
Male	0.12 (0.03-0.48) 0.003	0.12(0.03-0.48)0.003
Employed	1.08 (0.63-1.86) 0.78	-
Alchohol	0.45 (0.14-1.46) 0.18	-
Smoking	0.47 (0.15-1.50) 0.20	-
Age 18-35	1	
35-55	0.87 (0.51-1.48) 0.61	
>55	0.53 (0.07-3.90) 0.53	-
Baseline CD4		
<50 cells/mm^3	1.68 (0.76-3.71) 0.20	-
50-200	1.18 (0.56-2.51) 0.66	
>200	1 (ref)	
Baseline BMI		
<18.5 kg/m^2	0.71 (0.28-1.79) 0.46	-
≥18 .5	1 (ref)	
d4T in regimen	1.87 (0.59-6.01) 0.29	1.78(0.55-5.70) 0.33
No d4T in regimen	1 (ref)	1 (ref)

HR Hazard ratio. CD4 Cluster of differentiation. BMI Body mass index.

d4T Stavudine

The effect of d4T on lipodystrophy was adjusted for gender.
The effect of gender on lipodystrophy is adjusted for d4T use.

Chapter 4. Discussion

4.1 Prevalence

The prevalence of lipodystrophy at one year of HAART has been quoted as ranging from 6% to as high as 67% in international literature.[9-12] Literature pertaining to lipodystrophy in African patients has show a prevalence of 34% in a Rwandan study at 18 months and 30% in Benin at 2 years of treatment.[9, 10] The Rwandan study was a cross-sectional review using both a questionnaire and clinical assessment to diagnose lipodystrophy. They do not specify their diagnostic criteria. They looked at 409 patients, of whom, 90% were on a d4T-based regimen. Most patients were on both a PI and a NRTI's. The study out of Benin was a prospective study, undertaken over 24 months. They looked at 88 patients, all of whom were HAART-naïve at the onset of therapy. Again, most patients (94%) were on a d4T-based regimen, but in this study, no patients received a PI. They agree that the lack of a standardized clinical definition of lipodystrophy results in different findings across studies. Other limitations of this study included its small sample size, lack of PI's in the treatment regimen, and the fact that most patients in the study commenced HAART at a very advanced stage of their disease. Their median time to onset of lipodystrophy was 11 months.

I have assessed a random group at a large South African HIV clinic, and found the prevalence of lipodystrophy to be 11.7%. The mean duration of therapy prior to diagnosis was 12.7 months. In this cohort, patients were diagnosed with lipodystrophy by physicians on routine patient follow up. The diagnosis was completely independent of this study. This diagnosis was based on clinical examination, with or without laboratory confirmation in the form of lipogram, lactic

acid and diabetic profile and was then captured on the TE system, the clinic database. Both the Rwandan and Benin studies used investigators who looked specifically to diagnose lipodystrophy. The large discrepancy in the prevalence may in part be an over-diagnosis in these studies, combined with an under-diagnosis in this study. The prevalence at the Themba Lethu clinic has been identified through the record review of clinicians performing clinical duties, and not tasked with specifically looking for lipodystrophy in their patients. On direct questioning, 27% of the 479 patients would consider surgery if it was offered to address changes in their body following treatment with HAART, and 17% felt stigmatized by their body habitus following HAART. This may represent a higher prevalence of lipodystrophy than had been diagnosed and documented.

4.2 Compliance

Antiretroviral treatment programs aim for compliance as close to 100% as possible. The population assessed indicated a high risk of non-compliance (3.8% of the total cohort and 5.9% of patients who had noted weight gain or loss on treatment) as a direct effect of symptomatic lipodystrophy. A study of an Italian outpatient cohort at 45 weeks of treatment identified 21% (n=182) of their cohort defaulting treatment on the basis of systemic toxicity. Within this group of treatment failure, only 1 patient (0.1% of the cohort) had stopped their therapy due to developing lipodystrophy[30]. In a French cohort, 30% of patients who were compliant at four months were non-compliant at 20 months of treatment. There was a trend (p=0.16) for more non-compliant patients having been diagnosed with lipodystrophy (71.4%) as compared to the compliant group (61.2%)[18]. In the Themba Lethu setting, patients may have already defaulted therapy on the basis of lipodystrophic symptoms. These patients

would have been excluded from the cohort, as I used a group of patients awaiting medication in the pharmacy queue to conduct this study.

4.3 Gender of participants

Baril et al, and *Miller et al*. present studies of European, Australian and American cohorts that examine the prevalence of lipodystrophy in these population groups. They utilise cohorts that were predominantly male. African cohorts such as the study performed in Benin, and the Themba Lethu cohort have predominantly female participants. There may be various reasons for these findings. HIV-Aids remains a disease commonly encountered in homosexual groups in Europe, America and Australia. In Africa, there is equal prevalence among the heterosexual population. Furthermore, females are more likely to be screened and referred from the antenatal clinic setting. Females may seek healthcare more often than males, which could account for the bias to more female patients in this cohort [9,10,11,12].

4.4 Knowledge of lipodystrophy

Patients should be well counseled prior to commencing HAART as they should prior to undertaking any potentially hazardous medical treatment or procedure. Only 78% of this cohort was aware of lipodystrophy as a side effect of HAART and HIV. This figure suggests more needs to be done to educate patients about this problem. This could include patient-doctor counseling, group counseling and support groups, posters and information packages.

4.5 Diagnosing lipodystrophy using a questionnaire

When body mass was assessed, 63% of patients (303 of 479) noted weight gain or weight loss once they commenced HAART. As many as 17% of patients (82 of the 479) felt this change in body mass was stigmatizing or indicated their HIV status, while 27% of participants indicated they would consider surgery to address some of the changes in their body habitus resulting after treatment. This is a greater number of patients than the 11.7% who had received a formal diagnosis of lipodystrophy from a doctor and had it documented on the TE system. This highlights a number of issues. Weight change on HAART is not only a symptom of lipodystrophy, but of recovery from the wasting effect of advanced HIV infection. As a patient's immune status improves, they are less likely to suffer from opportunistic infections, and will gain weight previously lost. Therefore, simply using weight gain and loss as an indicator of lipodystrophy is inaccurate and leads to false positive findings. As many as 150 (31%) patients indicated weight loss of their limbs and buttocks, while 190 (39.7%) indicated increased fat distribution of their breast and chest. Furthermore, 212 (44.3%) indicated increased fat distribution within their abdomen. Fewer patients experienced regional changes in body fat distribution than general weight gain and weight loss but this is also higher than the 11.7% who had been diagnosed with lipodystrophy. Again, using regional weight gain and weight loss to try determine a diagnosis of lipodystrophy is likely to yield false positives and false negatives. This was demonstrated by this study's attempt to produce a questionnaire that would be able to diagnoses HIV-associated lipodystrophy.

Table 5: Performance of the questionaire as a lipodystrophy prediction tool

Test (Tool)		**Disease (lipodystrophy)**		**Total**
		+ ve	**- ve**	
	+ ve	161	237	398
	- ve	63	18	81
	TOTAL	**224**	**255**	**479**

Table 5 depicts the performance of the questionaire as a tool to diagnose lipodystrophy. The questionnaire was shown to have a 72% sensitivity for identifying lipodystrophy, but only an 8% specificity. Using the questionaire, the prevalence of lipodystrophy was found to be 46.8%. The positive predictive value of the test questionaire was 41% while the negative predicitive value was 22%. Accuracy of the test was found to be 37%. The development of lipodystrophy is along a continuum from normal to frank lipodystrophic morphology. In the clinical context of a busy clinic, where the managing physicians may not have been focused on making a diagnosis of lipodystrophy, a prevelance of 11,7% may be too conservative a value. Nearly 17% of patients stated they felt their body morphology was stigmatising and indicative of their status. This subjective measure may be closer to the real prevalence of lipodystrophy within the cohort, or it may represent the category of patient with self-percieved stigmatising disease.

4.6 Demand for surgery

The Themba Lethu cohort indicated a high demand for surgical correction of the morphological changes that developed following HAART. A total of 129 of 479 patients interviewed (27%) were willing to undergo surgery to improve some of the physical changes following HAART. This included patients who had not been diagnosed with lipodystrophy. Currently, there are no reliable medical treatments to reverse lipodystrophy. Diet and exercise, regimen change and surgery offers the best chance at improving this side effect once it has developed. At the time of writing, no other published studies have quantified the demand that exists for surgical correction of lipodystrophy.

4.7 Stigmatisation

Stigmatization of HIV+ patients has existed since the early history of the disease and continues to this day. The physical manifestation of lipodystrophy is recognized by laymen within communities. It also serves as a constant reminder to the patient that they are infected with, and are on treatment for HIV[31]. In our study, 17% of patients on HAART felt their associated weight change could alert others to their diagnosis of HIV, regardless of whether they had been diagnosed with lipodystrophy. Preau *et al* (2008) investigated the high rate of suicide attempts among patients living with HIV in France. They identified a higher rate of suicide attempts among HIV+ patients who had lipodystrophy (26%) versus those who did not (18%). They attributed this to two factors: negative body image and the stigmatization within society[32].

4.8 Gynaecomastia and breast hypertrophy

It has been documented that females are more likely to develop lipodystrophy than males.[2] This study shows the prevalence of lipodystrophy in males to be 2.4% and in females to be 13.7% ($p=0.004$). Interestingly, males were more satisfied with their body image and habitus following at least 6 months of treatment, even though 29% of male respondents described their own chest/breast morphology as at least a grade 2 gynaecomastia. Women on the other hand, had a 6.5 times higher rate of symptomatic breast hypertrophy complaints following at least 6 months of HAART.

Table 6: Male psychological experiences pre- and post- HAART

	Pre HAART			Post HAART		
	Dissatisfied	Neutral	Satisfied	Dissatisfied	Neutral	Satisfied
1. **During social activities:**	42 (50%)	9 (10.7%)	32 (38.1%)	3 (3.6%)	1 (1.2%)	79(94.1%)
2. A**mong certain people when dressed:**	42 (50%)	11 (13.1%)	34 (40.5%)	3 (3.6%)	1 (1.2%)	79 (94.1%)
3. **Among certain people when undressed:**	40 (47.6%)	12 (14.3%)	30 (35.7%)	3 (3.6%)	1 (1.2%)	76 (94.1%)

HAART: Highly active antiretroviral therapy

4.9 Risk factors for developing lipodystrophy

The distribution of weight gain and weight loss in this population was similar to that seen in previous studies (Figure 1, 2). [13-15] Since 1999, d4T has been identified as a major cause of lipodystrophy[33]. In the Themba Lethu cohort, almost all patients had received d4T-based treatment regimens (89%). As a result of the non-d4T group being of small numbers, this study is only able to show a trend toward d4T as a risk factor (adjusted HR 3.49 range 0.44 – 27.6(p=0.29)). Patients on non-d4T based regimens still develop lipodystrophy (n = 3, 5.8%) but with a lower prevalence than patients who had been on d4T-based regimens (n = 53, 12.4%). This finding is demonstrated in table 7 and corresponds with another study from the same unit[4]. Tenofovir (TDF) has replaced d4T in the South African context since 2010. Physicians and surgeons can still expect to be confronted with the side effects of lipodystrophy from non-d4T based regimens.

Host risk factors for the development of lipodystrophy include advanced age, female sex, longer duration of therapy and patients commencing treatment at a later stage in their illness. This study found that patients commencing treatment when their BMI was less than 18.5, as well as those commencing therapy at an older age, were less likely to develop lipodystrophy. This data concurs with other studies in that the lower the CD4 count at onset of therapy, the higher the risk of developing lipodystrophy on recovery[19, 34-37]. There was also a non-significant trend towards tobacco and alchohol use being protective against the development of lipodystrophy. This may represent a real relationship or a population less compliant on therapy. While the protective effect of tobacco use is supported by a previous study of Hispanic HIV+ patients, the

finding of a protective effect of alchohol contradicts another study that suggests heavy alchohol users may be more likely to develop lipodystrophy while on HAART[38,39]

Table 7: Effect of d4T on development of lipodystrophy

	Total, n (%)	Lipodystrophy, n (%)	crude HR	adjusted HR
d4T in regimen	426 (89.1%)	53 (12.4%)	1.87 (0.59-6.01) 0.29	3.49 (0.44-27.6)
No d4T	52 (10.9%)	3 (5.8%)	1 (ref)	1 (ref)

Adjusted for gender. Median time to lipodystrophy = 12.7 months (IQR 5.8-24.1 months)

d4T Stavudine. HR Hazard ratio. IQR Interquartile ratio

Chapter 5. Study limitations

The study was limited to 3 months of data collection. I had initially hoped to interview 1000 patients and this was calculated according to an initial 3-day pilot study. Unfortunately, I had not factored into my calculations that the clinic closed early on Fridays and closed in mid-December for year-end holidays. This resulted in a loss of 24 out of a possible 66 days of data collection. Furthermore, of the 554 patients interviewed, only 479 fulfilled inclusion criteria or had filled in consent forms and questionnaires correctly, resulting in 75 participants being excluded from the study

Of a total of 479 participants, 83% of were female (395 patients). The reason as to why more females were recruited relative to males is a reflection of different attendance at the clinic between the genders. The reason for this is complexed.

There exists a selection bias among the study sample. Generally patients commence their treatment at the Themba Lethu clinic, and are often 'stepped down' to peripheral clinics once their treatment regimen has been well tolerated at 18 months. This means that the patients seen at the clinic were more likely to be at an early stage of their therapy and may not yet have manifested their symptoms of lipodystrophy. Furthermore, patients may have withdrawn from the study if they were not affected by the condition that was being discussed, and other affected patients may have been drawn to the study once they heard by 'word-of-mouth' what the study was addressing. Certainly some patients anticipated they may be candidates for surgery, and used the interview as a time to address these requests.

There is also a potential for a reporting bias in this study. I used diagnosis of lipodystrophy as that having been made by a physician on a previous consultation and noted on the TE system. There is likely to have been an under-diagnosing or under-reporting of lipodystrophy in a busy clinic setting. Certainly, as has been shown, there were more patients complaining about unsightly body morphology than the number diagnosed with lipodystrophy.

Finally, there may have been an exclusion bias in that patients suffering from severe symptoms of lipodystrophy may either have died from metabolic manifestations (such as myocardial infarctions), or may have already become non-compliant on treatment and no longer be attending clinic.

Chapter 6. Conclusion and recommendations

6.1 Conclusion

Breast Hypertrophy and Gynaecomastia in HIV associated lipodystrophy, a problematic side-effect of life-saving antiretroviral therapy showed the following:

- Female patients comprised 82.5% of our study cohort suggesting more female patients are treated at the clinic as compared to males.
- The majority (78%) of respondents were aware that lipodystrophy is a side effect of HAART.
- The incidence of lipodystrophy was found to be 11.7%.
- A large proportion of patients on HAART (3.8%) considered stopping therapy due to the morphological changes resulting from lipodystrophy.
- Male patients were more satisfied with their body habitus following at least 6 months of therapy, even though 34.5% indicated at least a grade 2 gynaecomastia.
- Female patients complained of symptomatic macromastia 6.5X more often following 6 months of HAART.
- In a busy clinic setting, lipodystrophy may be difficult to diagnose and clinically significant cases may be missed by physicians not looking for this side-effect.
- Surgical demand was calculated at 27% of the cohort, these patients were willing to undergo surgery to reverse changes in their body habitus following HAART.
- Regional weight gain and weight loss, as well as risk factors and protective factors for the development of lipodystrophy were consistent with previously published literature.

- Most patients have been treated with a d4T-based regimen. Although this is a major offending agent, patients on non-d4T-based regimens still develop HIV-associated lipodystrophy, albeit at a lower incidence. Therefore, although d4T is no longer offered in HAART regimens in South Africa, we can still expect to see cases of lipodystrophy from newer HAART regimens.

6.2 Recommendations:

- Awareness needs to be raised in the male population to know their HIV-status and to seek treatment for their disease.
- Patients embarking on HAART should be well informed about the side-effects of these medications, especially lipodystrophy, which has metabolic and morphological implications, and may be stigmatizing and life-threatening.
- Highly sensitive and specific, non-invasive screening methods for diagnosing lipodystrophy in a busy clinic setting need to be developed so that early diagnosis and management of these patients can be instituted.
- Increased awareness of the available treatment options for lipodystrophy is necessary. Non-compliance due to this side-effect would not be considered if patients were aware of the treatments available, and felt therapy were easily accessible.
- Due to the large numbers of patients who have and will develop HIV-associated lipodystrophy, specialised clinics should be set up to manage these complexed cases. Multidisciplinary teams including infectious disease specialists, endocrinologists, dieticians, biokineticists, psychologists and plastic surgeons should work together to prevent progression, conservatively

reduce symptoms, and finally resort to surgical measures to treat these side effects.

- Access to surgery needs to increase if we are to offer meaningful treatment of this side effect. Protocols that determine who qualifies for surgery should be established. Simple weight gain or loss may not be enough reason to operate on patients. Stigmatizing morphology and functionally disabling side effects such as massive breast hypertrophy and gynaecomastia warrant surgical management. Dedicated theatre time, specialised body contouring equipment and adequate manpower will also need to be provided to address the pending epidemic of cases that we are likely to see.

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Chapter 8. Appendices

8.1 Appendix 1. Questionnaire

Participant Information sheet

Good day sir / madam

My name is Dr Richard Zinn and I would like to give you some information on a study I am conducting. The study will take a few minutes of your time but the findings may help you, and patients like yourself in the near future.

I am looking at side-effects of antiretroviral treatment, particularly, how your body's fat changes when you are on this treatment. We will be looking at how much of a problem this is, and if there is anything we can do about this problem to make your treatment a little more comfortable.

If you do decide to participate in the study, you will remain completely anonymous and none of your details will be open to anyone outside of the study. If you refuse to take part in the study there will be no loss of benefits or penalties to you. You may decide to refuse further involvement in the study at any time, even after having answered the questionnaire. There is no risk to you or your health in answering the questionnaire.

To participate in the study, you are required simply to complete a questionnaire. I will be available to help you with this. This should take about 30 minutes to complete. I will be doing this from April until September, hoping to recruit 1000 patients in total.

I hope you will be part of the study, and help us collect important information of your experience on antiretroviral treatment.

Yours sincerely,

Dr Richard Zinn
General surgery registrar
Cel: 0834127899
Email: richard.zinn@gmail.com

Questionnaire – Side Effects of Antiretroviral therapy

(Section 1 – data to be collected from the patient)

Patient's TE number……..

Are you aware that the ARV drugs you are taking may change the way your body looks, particularly where the fat in your body is situated?

Yes ☐ No ☐ Maybe ☐

Have you experienced hair loss on ARV treatment?

Yes ☐ No ☐ Maybe ☐

Maximum weight prior to HIV diagnosis ……

Weight at commencing ARV's ……

Weight currently ……

Have you experienced significant weight-gain or weight loss on ARV treatment?

Yes ☐ No ☐ Maybe ☐

IF YES:

How long after commencing ARV treatment did you notice this?

6months ☐ 1 year ☐ 2 year ☐ 3year ☐ other ☐……

Weight gain?		Weight loss?	
Face	☐	Face	☐
Neck	☐	Neck	☐
Dorso-cervical(hump)	☐	Dorso-cervical(hump)	☐
Arm	☐	Arm	☐
Breast	☐	Breast	☐
Abdomen	☐	Abdomen	☐
Leg	☐	Leg	☐
Buttock	☐	Buttock	☐

IF YOU HAVE EXPERIENCED WEIGHT GAIN OR WEIGHT LOSS:

Do you feel this suggests to others that you are HIV+?

Yes ☐ No ☐ Maybe ☐

Has the change in your fat pattern made you consider stopping your ARV's?

Yes ☐ No ☐ Maybe ☐

Would you consider surgery, if it was being offered, for reduction of your breast size?

Yes ☐ No ☐ Maybe ☐

Would you be happy to have fat harvested from areas of excess (perhaps areas of recent fat increase) and be used for areas of deficiency for cosmetic improvement?

Yes ☐ No ☐ Maybe ☐

Females only:

Biggest bra size worn prior to commencing ARV's ……

Bra size at commencement of ARV's ……

Bra size currently ……

Evaluation of breast-related symptoms:

Please indicate the extent to which each statement pertains to you personally. The following symptoms may or may not be related to breast size. Please choose only one response for each statement.

Please check one box (with a cross) for each answer

PRIOR TO ARV's:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
1) My breast caused upper back pain					
2) Because of my breast size, I had difficulty finding bras and clothes to fit					
3) Due to my breast size I had headaches					
4) I had breast pain					
5) My breast size caused lower back pain					
6) Rashes or itching developed under my breast					
7) I had painful bra-strap Grooves					
8) My breast size made it difficult for me to participate in sport					
9) My breast size caused neck pain					
10) My breast size caused shoulder pain					
11) I had a hard time running because of my breast size					
12) Because of my breast size, I had pain in my hands or they felt numb					
13) My breast size caused arm pain					

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
1) My breast causes upper back pain					
2) Because of my breast size, I have difficulty finding bras and clothes to fit					
3) Due to my breast size I have headaches					
4) I have breast pain					
5) My breast size causes lower back pain					
6) Rashes or itching develop under my breast					
7) I have painful bra-strap grooves					
8) My breast size makes it difficult for me to participate in sport					
9) My breast size causes neck pain					
10) My breast size causes shoulder pain					
11) I have a hard time running because of my breast size					
12) Because of my breast size, I have pain in my hands or they feel numb					
13) My breast size causes arm pain					

Males only:

Gynaecomastia Evaluation Questionnaire

1) Do you suffer from any of the below due to recent changes in your chest / breast fat composition since taking ARV's?

Pain / discomfort ☐
Self confidence ☐
Emotional distress ☐
Inability to play sport ☐
Other ☐ Please specify below:

_____
_____
_____

2) How do you feel about your chest / breasts in each of the following situations:

Answer 1 –Very dissatisfied Answer 2 – Dissatisfied Answer 3 – Neutral (not satisfied or dissatisfied) Answer 4 – Satisfied Answer 5 – Very Satisfied

	Before ARV's	After ARV's
During intimate / sexual activity		
During Leisure / social activity		
During your work or job		

3) How comfortable do you feel about your chest / breasts, while fully dressed, in the presence of the following persons:

Answer 1 – Very uncomfortable Answer 2 – Uncomfortable Answer 3 – Neutral (not uncomfortable or comfortable) Answer 4 – Comfortable Answer 5 – Very comfortable

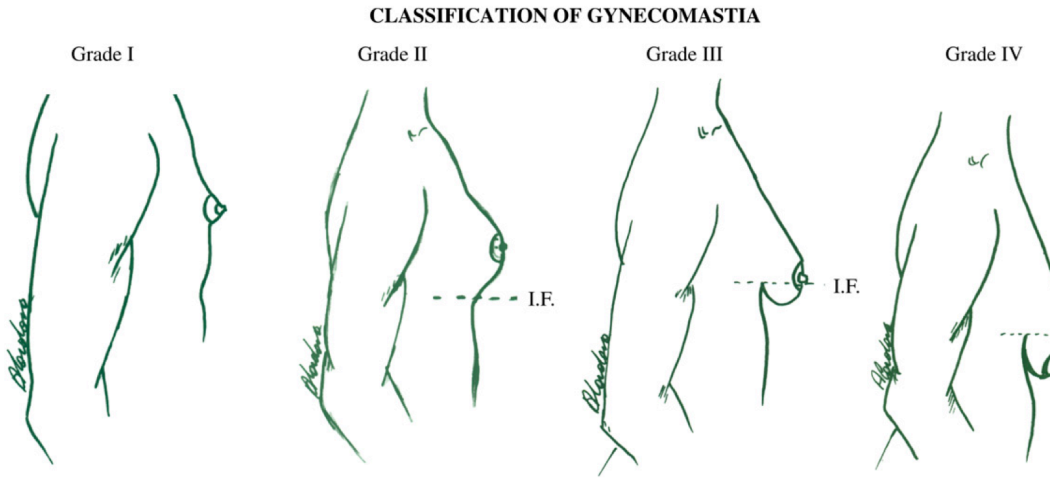
	Before ARV's	After ARV's
Alone		
With Partner		
With other men		
With other women		
With doctor/nurse		

5) How comfortable do you feel about your chest / breasts, when undressed, in the presence of the following persons:

Answer 1 – Very uncomfortable Answer 2 – Uncomfortable Answer 3 – Neutral (not uncomfortable or comfortable) Answer 4 – Comfortable Answer 5 – Very comfortable

	Before ARV's	After ARV's
Alone		
With Partner		
With other men		
With other women		
With doctor/nurse		

6) Which of the following pictures best depicts your chest / breasts wall:



A ☐ B ☐ C ☐ D ☐

E ☐ None of the above, my chest / breast is normal

(Section 2 - Data to be collected from TE database)

Patient's TE number……..

Age ……..
Height ……..
Weight ……..
Date ……..

Sex: Male ☐ Female ☐

Race: White ☐ Black ☐ Coloured ☐ Indian ☐ Other ☐

Other medical problems: Yes☐ No ☐
If Yes, specify ……
……
……

Date commencing ARV's: _ _ / _ _ / _ _ _ _
(dd / mm / yyyy)

Number of ARV regimens used so far 1 ☐ 2 ☐ 3 ☐ more ☐

Current ARV regimen?
☐ Regimen 1A (D4T, 3TC, Stocrin)
☐ Regimen 1B (D4T, 3TC, NVP)
☐ Regimen 2 (AZT, DDI, Lopinavir / Ritonavir)
☐ Modified regimen
……
Reason for modified regimen
……

……

Previously used ARV regimen?
☐ Regimen 1A (D4T, 3TC, Stocrin)
☐ Regimen 1B (D4T, 3TC, NVP)
☐ Regimen 2 (AZT, DDI, Lopinavir / Ritonavir)
☐ Modified regimen
……
Reason for modified regimen
……

……

CD4+ count at onset ARV's …….. (_ _ / _ _ / _ _ _ _)
Viral load at onset ARV's ……..... (dd / mm / yyyy)

Last CD4+ count and date …….. (_ _ / _ _ / _ _ _ _)
Last viral load …….. (dd / mm / yyyy)

8.2 Appendix 2. Informed consent

Informed Consent for Lipodystrophy Questionnaire

Introduction:
Good day, my name is Dr Richard Zinn. I am a surgical registrar at Helen Joseph Hospital and I would like to ***invite*** you to consider **participating in a research study** entitled: Breast hypertrophy and Gynacomastia in HIV-associated lipodystrophy – a problematic side-effect of life-saving anti-retroviral therapy.

1. Before agreeing to participate, it is important that you read and understand the following explanation of the purpose of the study, the study procedures, benefits, risks, discomforts and precautions, and your right to withdraw from the study at any time. This information leaflet is to help you decide if you would like to participate. You should fully understand what is involved before you agree to take part in this study.

2. If you have any questions, do not hesitate to ask me

3. You should not agree to take part unless you are satisfied about the procedure involved

4. In answering health-related questions, please provide as detailed information as possible so that the information attained is accurate and possibly to yours, and others' benefit

5. If you decide to take part in the study, you will be asked to sign this document to confirm that you understand the study. You will be given a copy to keep.

6. We would like to assess you for any physical changes, specifically in your body fat distribution, since the onset of your antiretroviral treatment. **We are looking at changes in your breasts.** The purpose of the study is to assess how many patients are developing breast-size changes on antiretroviral, who is most at risk, and if affected patients would consider surgery as a means to treat this problem?

7. LENGTH OF THE STUDY AND NUMBER OF PARTICIPANTS
The study will be performed at Helen Joseph's Temba Lethu Clinic over 6 months duration.
We aim to include approximately 1000 participants in the study. The participants will be both male and female, of any age, regardless of how long a patient has been on antiretroviral treatment.
The total amount of time required for your participation in the study will be 30 minutes.
Should you be requested in this study on a future visit, please explain that you have already taken part in the study.

8. PROCEDURES

If you agreed to take part in the study, you will be taken to a private room where you can fill in the questionnaire with the investigator. No examination, blood samples or further visits will be needed and we will make every effort to keep your place in the queue, to see your doctor.

9. WILL ANY OF THESE STUDY PROCEDURES RESULT IN DISCOMFORT OR INCONVENIENCE?

We will attempt to keep your place in the queue at the clinic, so that being involved in the study does not make your clinic visit any longer than necessary.

10. There are no risks of the study to your personal well-being

11. BENEFITS?

The study may raise your awareness of this side effect of antiretroviral therapy, and if this problem causes you significant discomfort, embarrassment or difficulty, we will be able to refer you to the appropriate facility for surgical assessment and possibly management.

Also, your participation in this study will yield more information on some of the side-effects of anti-retroviral therapy, and this will help doctors choose **drugs with fewer side effects, helping patients, like yourself, who receive these drugs.**

12. RIGHTS AS A PARTICIPANT IN THIS STUDY

Voluntary: Your participation in this study is entirely voluntary and you can decline to participate or stop at any time, without stating any reason. Your withdrawal will not affect your access to medical care.

New Findings: I will provide you with all findings that become available due to the study, through staff working at the clinic.

Withdrawal:

Your withdrawal will not affect your access to medical care.

If you do not provide accurate history you will be withdrawn from the study

13. There will be no emergency care, financial reimbursement or **compensation for your involvement in this study.**

14. ETHICAL APPROVAL

This clinical study protocol has been submitted to the University of the Witwatersrand, Human Research Ethics Committee (HREC) and written approval has been granted by that committee.

The study has been structured in accordance with the **Declaration of Helsinki** (last updated 2008), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy should be obtained from me if you wish to review it.

The study has not been sponsored, but is an academic research project of Dr Richard Zinn. I do no have any financial or personal interest with organizations that may bias my actions.

15. My contact details, if required for any study-related information, are as follows:
Cell: 0834127899
Email: Richard.zinn@gmail.com

16. **If you require any information regarding your rights as a research participator, or complaints regarding this research study, you may contact Prof. Cleaton-Jones, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 7172229**

17. CONFIDENTIALITY:
All information obtained during the course of this study, including hospital records, personal data and research data will be kept strictly confidential. Data that may be reported in scientific journals will not include any information that identifies you as a participant in this study.

This information might also be inspected by the University of the Witwatersrand, Human Research Ethics Committee (HREC), the South African Medicines Control Council (MCC) and/or the United States Food and Medicines Administration (FDA), as well as your personal doctor. Therefore, you hereby authorize me to release your medical records to domestic or foreign regulatory health authorities, the South African Medicines Control Council and the University of the Witwatersrand, Human Research Committee.

This information will be used by them only in connection with carrying out their obligations relating to this clinical study.

Any information uncovered regarding your test results or state of health as a result of your participation in this study will be held in strict confidence. You will be informed of any findings of importance to your health or continued participation in this study but this information will not be disclosed to any third party in addition to the ones mentioned above, without your written permission. The only exception to

this rule will be cases of communicable disease where a legal duty of notification of the Department of Health exists. In this case, you will be informed of my intent to disclose such information to the authorized state agency.

18. PERSONAL DOCTOR/SPECIALIST NOTIFICATION OPTION
Please indicate below whether you want me to notify your personal doctor or your specialist of your participation in this study:

☐ YES, I want you to inform my personal doctor/ specialist of my participation in this study.
☐ NO, I do not want you to inform my personal doctor/ specilialist of my participation in this study.
☐ I do not have a personal doctor/ specialist

INFORMED CONSENT:

- I hereby confirm that I have been informed by the study doctor, Dr Richard Zinn, about the nature, conduct, benefits and risks of clinical study: Breast Hypertrophy and Gynacomastia in HIV-associated Lipodystrophy, a problematic side-effect of life-saving Anti-Retroviral therapy.
- I have also received, read and understood the above written information (Participant Information Leaflet and Informed Consent) regarding the clinical study.
- I am aware that the results of the study, including personal details regarding my sex, age , date of birth, initials and diagnosis will be anonymously processed into the study report
- In view of the requirement of research, I agree that the data collected during this study can be processed in a computerized system by Dr Richard Zinn.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in this study.

PARTICIPANT:

Printed Name	Signature/Thumb print	Date & Time

I, Dr Richard Zinn, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study

STUDY DOCTOR:

Printed Name	Signature/Thumb print	Date & Time

TRANSLATOR/ OTHER PERSON EXPLAINING INFORMED CONSENT……...
(DESIGNATION):

Printed Name	Signature	Date & Time

WITNESS:

Printed name	Signature	Date & Time

8.3 Appendix 3. Reprint of article from Journal of Plastic Reconstructive and Aesthetic Surgery (JPRAS)

Journal of Plastic, Reconstructive & Aesthetic Surgery (2013) 66, 839–844

ELSEVIER

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

HIV-associated lipodystrophy in South Africa: The impact on the patient and the impact on the plastic surgeon☆

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KEYWORDS
Lipodystrophy;
Compliance;
Stigma;
Highly-active antiretroviral therapy;
Stavudine

Summary *Background:* With 67% of the world's human immunodeficiency virus (HIV)-infected population existing in sub-Saharan Africa and recent access to highly active antiretroviral therapy (HAART), the demand for plastic surgical intervention in addressing lipodystrophy has expanded dramatically. We assessed the rate of lipodystrophy in a random clinic cohort, the demand for surgical correction and risk of treatment non-compliance.
Method: Questionnaire and database cross-sectional review of 554 patients over a 3-month period at the Themba Lethu Clinic, Johannesburg, South Africa.
Results: A total of 479 patients completed the questionnaire, 83% were female. Nearly 90% of patients were on, or had been on, stavudine (d4T). The prevalence of lipodystrophy was 11.7%. Nearly 5.9% of patients had considered stopping treatment due to the development of lipodystrophy; 47% would consider surgery to correct unwanted physical changes. Male patients were satisfied by the changes they noted in their physical features following treatment (pre-treatment satisfaction 38% vs. post-treatment satisfaction of 94%). Female patients had 6.5 times more breast hypertrophy-related symptoms than in their pre-treatment state.

☆ **Congress presentations arising from this research article:** 1) Presented at the Burt Myburgh Research Forum, November 24, 2010, Johannesburg, South Africa. 2) Presented at the Congress of The Association of Plastic Reconstructive and Aesthetic Surgeons of South Africa (APRSSA), October 15, 2011, Johannesburg, South Africa.

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Conclusion: We identify a prevalence of 11.7% of patients with HIV-associated lipodystrophy, of whom 5.9% would consider non-compliance on the basis of this side effect alone. The demand for surgical correction is significant and needs to be addressed.

Human immunodeficiency virus (HIV)-associated lipodystrophy is a consequence of the standard of care for HIV-positive patients, namely highly-active antiretroviral therapy (HAART). It comprises lipoatrophy, lipoaccumulation and a mixed picture. There are accompanying metabolic derangements including reduced high-density lipoprotein (HDL)-cholesterol, hypertriglyceridaemia, insulin resistance, type 2 diabetes, hyperlactataemia and elevated hepatic transaminases.[1,2] Only recently has a case definition been developed. This consists of 10 parameters (clinical, metabolic and radiological) and aims to guide the diagnosis of lipodystrophy. It has been shown to be accurate in 80% of cases when compared to patient and clinician assessments.[1,3] As this requires access to dual energy X-ray absorptiometry (DEXA) and computed tomography (CT) scans, it may be less useful in the resource-limited environment.[4]

HIV-associated lipodystrophy is related to poor body image and impacts social and sexual functioning and other activities of daily living. Reports suggest patients fear changes in their body habitus jeopardise the confidentiality of their HIV status and may even lead to treatment non-compliance.[5–7,9–12]

The two main treatment modalities are HAART regimen change and surgical correction of the dysmorphology. The demand for traditionally cosmetic techniques such as facial fillers (autologous fat, allogeneic fillers and alloplastic implants), liposuction, abdominolipectomy, dorsal hump lipectomy and breast reduction has expanded dramatically. Cosmetic and functional outcome have been good, with complication rates equal to that of non-immunocompromised patient groups. Recurrence has been noted in some cases.[8,11,13–15]

The aim of this study was to determine the prevalence of lipodystrophy in a random sample of a clinic population in South Africa. We also aimed to explore awareness of this side effect, whether this was affecting compliance to treatment and the demand for surgical correction of this problem among participants.

Methods

Study population

A total of 554 patients were interviewed between October and December 2009 at Themba Lethu Clinic, Helen Joseph, a public-sector hospital affiliated to the University of the Witwatersrand in Johannesburg, South Africa. This is one of the largest HIV clinics in South Africa. The programme is funded by the South African National and Gauteng Departments of Health, with support from Right to Care funded by United States Agency for International Development (USAID) and President's Emergency Plan For AIDS Relief (PEPFAR). Inclusion criteria included both genders, a minimum age of 18 years, HAART for longer than 6 months and, in females, not having been pregnant in the previous 12 months.

Data collection

Data were collected using a questionnaire as well as the clinic electronic database via a medical management software system, Therapy Edge-HIV™ (TE) (Associated Biological Systems, South Africa). Knowledge, attitudes and perceptions of lipodystrophy were assessed. Male and female chest and breast symptoms were assessed using the Gynaecomastia Evaluation Questionnaire and the Breast-related Symptoms Questionnaire, respectively (both are disease-specific for breast/chest enlargement).[16,17] Patient's experiences of stigmatisation, compliance and their demands for surgical correction were explored. TE was used to collate patient demographic data, their past and present HAART regimens and any previous lipodystrophy diagnosis made in the clinic setting.

Definitions

HAART, initiated in accordance with the 2004 South African National Antiretroviral Treatment Guidelines, which include initiation criteria of a CD4 count $\leq$200 cells/mm^3 or World Health Organization (WHO) stage 4 and AIDS defining illness irrespective of CD4 count.[18] The first-line therapy consisted of stavudine (d4T), lamuvidine (3TC) and efavirenz (EFV) or nevirapine (NVP); however, kaletra (ritonavir/lopinavir) was used as part of the first-line therapy regimen if there were contraindications to other first-line drugs. Single drug substitutions were permitted depending on the underlying clinical presentation of the patient.

Lipodystrophy, defined as lipoaccumulation or lipoatrophy, was based on the development of peripheral fat wasting (face, arms, buttocks or thighs) and/or central abdominal fat accumulation and may include enlarged breasts. This was either reported by the patient or diagnosed by the doctor with patient confirmation and had also been documented in the TE system.[4]

Stigmatisation is defined as the action of branding, marking, scarring or blemishing or to mark with stigmata.[19]

Compliance is the action of complying with a regimen. In terms of HAART, compliance is considered 100% intake of one's prescribed daily pills for each drug.[9]

Gynaecomastia ('women's breast') is defined as the physiological or pathological development of breast tissue in men.[20]

Data analysis and statistics

Patient characteristics at initiation of HAART were summarised using medians and interquartile ranges (IQRs) for continuous variables and frequencies and proportions for

categorical variables. Frequencies and proportions were also used to describe responses to the questionnaire. For the analysis of time to lipodystrophy, person-time accrued from time of ART initiation until the earliest of: 1) lipodystrophy; 2) close of the data set; 3) transfer out; or 4) lost to follow-up (4 months late for last clinic visit). Kaplan–Meier curves were used to compare progression to lipodystrophy by exposure group. We estimated crude and adjusted hazard ratios of progression to lipodystrophy using Cox proportional hazards models. Data were analysed using STATA version 11 (Stata Corp., College Station, TX, USA).

This study and use of Themba Lethu Clinic data were approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand and the medical superintendent of Helen Joseph Hospital.

Results

Baseline characteristics of the study population

The baseline characteristics of the study group are summarised in Table 1. A total of 554 patients were interviewed between October and December 2009 of whom 479 fulfilled the inclusion criteria and were included in the final data set for analysis. Females comprised 83% ($n = 395$) of the study group. The median age of participation was 35 (IQR 29.8–40.2) years and the median CD4 at onset of therapy was 114 cells/mm^3 (IQR 48–176). Nearly 89% ($n = 425$) of participants had been on a d4T-based regimen.

Knowledge, stigma and compliance

The majority (78%) of respondents were aware that lipodystrophy is a side effect of HAART. Amongst the 479 patients on therapy, 303 patients (63%) had encountered body mass gain or loss. Of these, 27% ($n = 72$) felt the change in mass "gave away" their diagnosis of HIV-positive status. Nearly 47% ($n = 129$) would be willing to undergo surgery to reverse these body mass changes, while 5.9% ($n = 18$) were considering stopping HAART to limit further impact on their body form. If this is extrapolated, 3.8% of the total cohort of patients on HAART were at risk of treatment non-compliance on the basis of this side effect.

Male respondents

Nearly 94% of male subjects described themselves as satisfied with the body morphology after at least 6 months of treatment. Around 38% of these patients were happy with their pre-treatment body habitus ($p = 0.05$). When asked to describe their chest shape following treatment, 29% of male patients chose at least grade 2 gynaecomastia.[21,22]

Female respondents

Complaints of symptomatic breast hypertrophy were 6.5 times more common in females following 6 months of HAART. These complaints included difficulty in finding an adequate bra size, lower back pain, painful bra straps, difficulty participating in sporting activity due to their breast size and shoulder pain.

Regional body-weight changes

Patients, with and without a formal clinician diagnosis of lipodystrophy, indicated weight gain and weight loss in specific regions of their bodies. Weight gain was mainly identified in the abdomen ($n = 212$), breast ($n = 190$) and dorsal cervical hump ($n = 135$). Weight loss was seen in the

Table 1 Baseline characteristics of study participants at initiation of HAART.

Characteristic	Overall	Female	Male
Total, *n* (%)	479	395(82.5%)	84 (17.5%)
Employed, *n* (%)	197 (41.1%)	161 (40.8%)	36 (42.9%)
Alcohol, *n* (%)	54 (11.3%)	33 (8.4%)	21 (25%)
Smoking, *n* (%)	43 (9%)	25 (6.3%)	18(21.4%)
Black, *n* (%)	456 (95.2%)	377 (95.4%)	79 (94%)
Age (years)	34.7 (29.8–40.2)	33.4 (29.1–39.4)	39.2 (34.5–42.8)
Baseline CD4;	114 (48–176)	119 (55–181)	95 (23–158)
<50, *n* (%)	114 (23.8%)	84 (73.7%)	30 (26.3%)
50–200	255 (53.2%)	214 (83.9%)	41 (16.1%)
≥200	110 (23%)	97 (88.2%)	13 (11.8%)
Baseline BMI(kg/m^2);	22.6 (19.6–26.8)	23 (20.2–27.8)	19.7 (18.4–23.4)
<18.5, *n* (%)	58 (15.1%)	40 (69%)	18 (31%)
≥18.5	325 (84.9%)	277 (85.2%)	48 (14.8%)
W.H.O stage I/II, *n* (%)	317 (66.2%)	269 (68.1%)	48 (57.1%)
W.H.O stage III/IV, *n* (%)	162 (34%)	126 (31.9%)	36 (42.9%)
d4T-based regimen, *n* (%)	425 (89%)	351 (90%)	74 (88%)
non-d4T-based regimen, *n* (%)	50 (11%)	40 (11%)	10 (12%)

Data is expressed as *N* (%) except for age, baseline CD4 and baseline BMI which are expressed as median (IQR).
W.H.O: World Health Organisation clinical staging of HIV/AIDS.
d4T is a nucleoside analogue reverse transcriptase inhibitor (NRTI) also known as Stavudine.

buttocks ($n = 150$), lower limbs ($n = 150$) and to a lesser extent, the upper limbs ($n = 44$) (Figures 1 and 2).

Prevalence and predictors of lipodystrophy

The prevalence of lipodystrophy was found to be 11.7% in the study group, as per TE, the clinic database. These patients had been diagnosed with lipodystrophy by a physician. The prevalence was 13.7% in females and 2.4% in males ($p = 0.004$). The median time to development and diagnosis of symptomatic lipodystrophy from the onset of HAART was 12.7 months (IQR 5.8–24.1) (See Figure 3). In our cohort of 479 patients, only 50 had not been on a d4T-based regimen. Three of these patients developed lipodystrophy on treatment. The rate of lipodystrophy among patients on d4T-based regimens was 12.4% ($n = 53$). The rate of lipodystrophy among patients who had not been exposed to d4T was 5.8% ($n = 3$).

In our study group, protective factors in the development of lipodystrophy included male sex (hazard ratio (HR) 0.12 (0.03–0.48), $p = 0.004$), with a trend shown for alcohol consumption (HR 0.45 (0.14–1.46), $p = 0.18$), smoking (HR 0.47 (0.15–1.50), $p = 0.20$), an older age at the onset of HAART as well as a baseline body mass index (BMI) of <18.5 kg m^{-2}at the onset of treatment (HR 0.71 (0.28–1.79), $p = 0.46$). Risk factors included a trend towards a d4T-based-regimen (HR 1.78 (0.55–5.70), $p = 0.33$) and a baseline CD4+ count of <50 at the onset of therapy (HR 1.68 (0.76–3.71), $p = 0.20$).

Discussion

The prevalence of lipodystrophy at 1 year of HAART has been quoted as ranging from 6% to as high as 50% in international literature.[2] The literature pertaining to African patients has found a prevalence ranging from 7.2% in Rwanda to 30% in Benin at 2 years.[23,24] We have assessed the prevalence of lipodystrophy of a random group within a large South African clinic to be 11.7%. The mean duration of therapy prior to diagnosis was 12.7 months. The vast discrepancy in diagnostic criteria among reports is a major factor resulting in these differing rates across different settings.

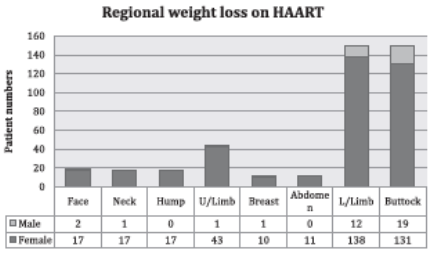

Figure 1 Bar graph showing regional distribution of weight loss in males and females on HAART.

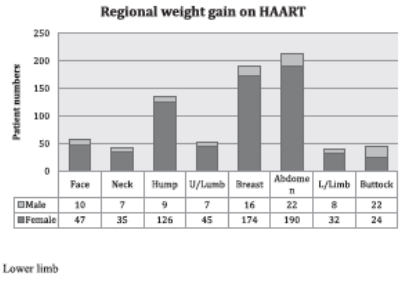

Figure 2 Bar graph showing regional distribution of weight gain in males and females on HAART.

Antiretroviral treatment programmes aim at compliance rates as close to 100% as possible. The population assessed indicated a high risk of non-compliance (5.9%) due to symptomatic lipodystrophy. A study of an Italian outpatient cohort at 45 weeks of treatment identified 21% (182) of their cohort defaulting treatment on the basis of systemic toxicity. Within this group of treatment failure, only one patient (0.1% of the cohort) had stopped their therapy due to developing lipodystrophy.[25] In a French cohort, 30% of patients who were compliant at 4 months were non-compliant at 20 months of treatment. There was a trend ($p = 0.16$) for more non-compliant patients having been diagnosed with lipodystorophy (71.4%) as compared to the compliant group (61.2%).[9]

This cohort indicated a high demand for surgical correction of the morphological changes that developed following HAART. This included patients who had not been diagnosed with lipodystrophy. Currently, there are no reliable medical treatments to reverse lipodystrophy. Surgery, coupled with regimen change, offers some relief. We found 47% ($n = 129$) of patients who developed weight gain or loss on treatment were willing to undergo surgery to reverse these changes. To our knowledge, no other published studies have quantified the demand that exists for surgical correction of lipodystrophy.

Stigmatisation of HIV + patients has existed since the early history of the disease and continues to this day. The physical manifestation of lipodystrophy is recognised within communities. It also serves as a constant reminder to the patient that they are infected with, and are on treatment for, HIV.[26] In our study, 27% of patients who had experienced weight change on HAART felt this alerted others to their diagnosis of HIV. Preau et al. (2008) investigated the high rate of suicide attempts among patients living with HIV in France. They identified a higher rate of suicide attempts among HIV + patients who had lipodystrophy (26%) versus those who did not (18%). They attributed this to two factors: negative body image and the stigmatisation by society.[27]

It has been documented that females are more likely to develop lipodystrophy than males.[4] In our study, the rate of lipodystrophy in males was 2.4% and 13.7% in the female group ($p = 0.004$). Interestingly, males were more satisfied with their body image and habitus following at least 6 months of treatment, even though 29% of male respondents

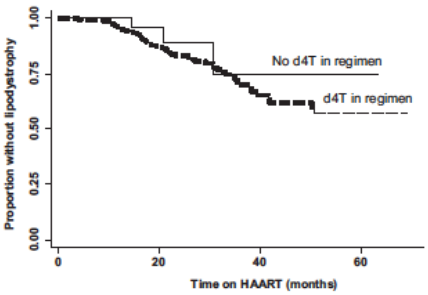

Figure 3 Kaplan–Meier estimates of development of lipodystrophy among the HIV-infected study subjects initiating HAART at the Themba Lethu Clinic.

described their own chest/breast morphology as at least a grade 2 gynaecomastia. Women, on the other hand, had a 6.5 times higher rate of symptomatic breast-hypertrophy complaints following at least 6 months of HAART.

The distribution of weight gain and weight loss in our population was similar to that seen in previous studies[1–3] (Figures 1 and 2). Since 1999, d4T has been identified as a major cause of lipodystrophy.[28] In our cohort, almost all patients had received d4T-based treatment regimens (89%). As a result, we were only able to show a trend towards d4T as a risk factor (adjusted HR 3.49, range 0.44–27.6 ($p = 0.29$)). Patients on non-d4T-based regimens were still shown to develop lipodystrophy ($n = 3$, 5.8%) but at a lower rate than patients who had been on d4T-based regimens ($n = 53$, 12.4%) (Figure 3). This concurs with another study from the same unit.[4] Tenofovir (TDF) has replaced d4T in the South African context since 2010. Physicians and surgeons can still expect to be confronted with the side effects of lipodystrophy from non-d4T-based regimens.

Host risk factors for the development of lipodystrophy include advanced age, female sex, longer duration of therapy and patients commencing treatment at a later stage in their illness. In our study, we found that patients commencing treatment when their BMI was $<18.5\ kg\ m^{-2}$, as well as those commencing therapy at an older age, were less likely to develop lipodystrophy. Our data concur with other studies in that the lower the CD4 count at onset of therapy, the higher the risk of developing lipodystrophy on recovery.[10,29–32] There was also a non-significant trend towards tobacco and alcohol use being protective against the development of lipodystrophy. This may represent either a real relationship or a population less compliant on therapy. While the protective effect of tobacco use is supported by a previous study of Hispanic HIV + patients, this data contradicts another study that suggests heavy alcohol users may be more likely to develop lipodystrophy while on HAART.[33,34]

Conclusion

Patients should be aware of lipodystrophy as a side effect on commencing HAART therapy. We demonstrate that nearly 10% of treated patients developed lipodystrophy, which threatens treatment compliance, impacts quality of life and adds to the stigma surrounding the disease. Significant demand for surgical correction of this side effect exists, making this a massive task ahead.

Authors' contributions

Study concept and design: RJZ, CS, IS and CNM. Acquisition and analysis of data: RJZ, CS, IS, ST and CNM. Interpretation of data: RJZ and ST. Drafting of the manuscript: RJZ and CNM. Critical revisions for important intellectual content: RJZ, CS, ST, IS and CNM. All authors read and approved the final manuscript.

Conflict of interest

None declared.

Acknowledgements

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8.4 Appendix 4. Ethics certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Richard Zinn

CLEARANCE CERTIFICATE	**Protocol M090124**
PROJECT	Plastic Surgery Breast Hypertrophy and Gynacomastia in HIV-Associated Lipodystrophy, a Problematic Side-Effect of Life-Saving Antiretroviral Therapy
INVESTIGATORS	Dr Richard Zinn.
DEPARTMENT	Surgery (General)
DATE CONSIDERED	09.01.30
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 09.04.28 **CHAIRPERSON** .....
(Professor P E Cleaton Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr C Serrurier DR C. MENEZES.

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

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