academicJournals

Vol. 5(12), pp. 448-454, December, 2012
DOI: 10.5897/JAHR12.017
ISSN 1996-0816 © 2013 Academic Journals
http://www.academicjournals.org/JAHR

Journal of AIDS and HIV Research

Full Length Research Paper

Factors associated with the development of HIV associated lipodystrophy in patients on long-term HAART

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

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

Accepted 13 October, 2012

Highly active antiretroviral therapy is effective in reducing viral load and increasing survival in HIV-1-infected patients. It consists of two nucleoside reverse transcriptase inhibitors and a protease inhibitor or two nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor. The efficacy of Highly active anti-retroviral therapy (HAART) is however compromised by adverse events such as lipodystrophy in patients on long-term HAART. This study was carried out in 265 HIV-1 seropositive patients treated with HAART for 6 months and longer, in order to correlate patients' age, gender, CD4 counts, WHO stage at initiation of HAART, duration and type of anti-retroviral therapy with development of 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 to 3.51, p value 0.004) and 39 patients (67.2%) (OR 2.34; CI 1.21 to 1.46, p value 0.006) having lipodystrophy at 6 to 18, 18 to 36 and 36 to 72 months of treatment, respectively. The odds of lipodystrophy after HAART for 18 to 36 months and 36 to 72 months was 4.14 (p < 0.0001) and 6.179 (p < 0.0001) times, respectively, higher than after HAART for 6 to 18 months. There was no association between age, gender, CD4 counts, WHO stage and the development of lipodystrophy.

Key words: Lipodystrophy, immune reconstitution, protease inhibitors, WHO clinical stage, duration of highly active anti-retroviral therapy (HAART).

INTRODUCTION

Lipodystrophy, sometimes referred to as fat redistribution is common in HIV infected adults on antiretroviral therapy for prolonged duration (Saint-Marc et al., 1999). This can lead to both short and long-term suboptimal adherence to antiretroviral regimens due to social stigmatization and low self esteem leading to virological and even clinical failure (Reynolds et al., 2006). The risk of developing lipoatrophy has been linked repeatedly to the use of nucleoside reverse transcriptase inhibitors (NRTIs), especially Stavudine. In the fat re-distribution evaluated by by computed tomography and metabolic abnormalities in patients on antiretroviral therapy (LIPOCO) study, the use of Stavudine significantly correlated with wasting when compared with the use of Zidovudine (Saint-Marc et al., 2000). In the Fat redistribution and metabolic change (FRAM) analysis, use of the antiretroviral drugs Stavudine or Indinavir was associated with less leg subcutaneous adipose tissue but did not appear to be associated with more visceral adipose tissue accumulation (Bacchetti, 2005).

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

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 (Nolan et al., 2003). Newer NRTI agents Abacavir and Tenofovir have not been associated with lipoatrophy. In fact, 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 (McComsey, 2005).

Protease inhibitor use appears to accelerate the rate of development of NRTI-associated lipoatrophy (Van der Valk et al., 2001). *In vitro*, protease inhibitors have been shown to impair adipose cell differentiation by interfering with the transcription factor sterol regulatory element-binding protein-1 (SREBP-1). Another hypothesis 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 (Carr et al., 1998). The total period of exposure to HAART appears to be relevant to the onset of lipodystrophy. The majority of cases occur after 3 to 18 months of exposure.

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 (Mallal, 2000). However, combined PI and dual NRTI therapy leads to peripheral lipoatrophy dramatically faster than does dual NRTI therapy alone (Van der Valk et al., 2001; Mallal, 2000).

Older age has consistently been shown to be associated with increased lipodystrophy risk. In the FRAM analysis, age was associated with less leg fat, but more visceral fat, in HIV-infected subjects (Bacchetti, 2005). However body changes occur naturally with ageing. Furthermore, body fat distribution abnormalities have also been reported in HIV-1–infected children. Males appear more likely to develop peripheral lipoatrophy, whereas females have greater central fat accumulation (Saint-Marc, 2000). The clinical 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 less than 100 cells/µL (Lichtenstein et al., 2001). Viral load, duration of HIV infection, prior AIDS diagnosis, immune reconstitution, genetic predisposition and cytokine mediated response (Mynarcik, 2000) have also been cited as important in some studies.

There are increasing numbers of patients on HAART in Kenya. Stavudine and Zidovudine are the predominantly used first line anti-retroviral therapy, used by over 90% of patients on anti-retroviral therapy. This study aims to document the role of these drugs and their duration of use, patient age, weight, nadir CD4, immune reconstitution and WHO stage at HAART initiation of HAART in the development of lipodystrophy.

MATERIALS AND METHODS

Ethical considerations

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

Study site

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

Study population

The participants were HIV-1 positive adult patients on combination HAART as recommended by the National HIV program and defined as either dual NRTI (d4T or zidovudine (AZT) or tenofovir disoproxil fumarate (TDF) with 3TC) with a non-nucleoside reverse transcriptase inhibitors (NNRTI) [Nevirapine (NVP) or Efavirenz (EFV)] or the dual NRTIs with a PI (LPV/r) for 6 to 72 months who attended the HIV clinic between August 2007 and 2008.

Study design

This was a cross-sectional descriptive study. Random sampling was done daily during routine visits until the desired sample size was reached. The minimum sample size required to determine the prevalence of lipodystrophy was determined at 265 patients. The criteria for statistical significance was p value < 0.05.

Inclusion criteria

HIV-1 positive male and female patients aged 15 years and older on HAART regularly reviewed and compliant with treatment for six months or more were deemed eligible for this study.

Exclusion criteria

Patients on HAART for less than 6 months, patients on anabolic steroids or immuno-modulatory therapy, patients known to have Cushing's disease or other endocrine disorders, pregnancy, moribund patients such as patients with malignancy or HIV wasting syndrome were excludedfor this study.

Patient assessment

The Comprehensive Care Centre operates five days in a week. All

Table 1. Demographic characteristics of the study population.

Variable		Number of patients	Mean/%
Age		265	40.69±23.41
Gender	Female	158	59.6%
WHO stage	I	24	8.9%
	II	47	17.3%
	III	99	37.3%
	IV	95	36%
CD4 counts	Nadir	256	119±49
	Most recent	265	335±76.50
Duration of HAART	6-18 months	83	31.2%
	19-36 months	123	46.4%
	>36 months	59	22.4%
HAART combinations	d4T based	188	70.9%
	AZT based	41	15.5%
	TDF based	36	13.6%

marital status, occupation, level of education, WHO clinical staging, current and prior anti-retroviral therapy, physical examination findings and baseline and subsequent laboratory investigations including full blood count, liver and renal function tests, CD4 and CD8 counts are recorded in the patients' charts. Patients deemed eligible for antiretroviral therapy 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 anti-retroviral therapy for more than six months. The patients were informed about the study and their eligibility assessed. Those who met the inclusion criteria and gave signed informed consent were recruited. A study questionnaire was used to collect baseline and clinical data. Lipodystrophy was assessed by patient report and physician examination using a modified version of the lipodystrophy case definition questionnaire (Carr, 2003). Anthropometric measurements (height, weight, mid upper arm circumference, waist circumference and hip circumference) were obtained using a standardized protocol based on the Third National Health and Nutrition Examination Survey.

Outcomes

The outcomes studied for association with development of lipodystrophy included the following: age and gender; WHO clinical stage at diagnosis of HIV with stage I being asymptomatic disease, stage II being minor mucocutaneous infections, stage III being moderate to severe opportunistic infections and stage IV being AIDS defining illnesses; type of HAART used by the patients defined as any combination of at least three drugs from the three classes of anti-retroviral drugs, that is, two Nucleoside analogue reverse-transcriptase inhibitors (NRTIs) and one Non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitors (PI); duration of treatment defined as the cumulative duration of treatment of an individual until the recruitment day; baseline/nadir CD4 defined as the lowest level of CD4 counts that has ever been measured; current CD4 defined as the CD4 done at the time of the study.

Statistical analysis

All data was entered into data base using Microsoft excel. Qualitative variables were described in frequencies or percentages and compared between groups using Chi square (χ^2) test. Quantitative variables were described with medians or means and compared between groups using Wilcoxon rank sum test. Cox proportion hazard regression modeling was used to determine variables that predicted the outcomes. Statistical analysis was performed using Statistical Package for Social Sciences, version 15.0. Results were presented in form of tables. The criteria for statistical significance was p value < 0.05

RESULTS

We screened 318 HIV-seropositive patients on chronic HAART and excluded 53 (16.6%) patients; 40 had been on HAART for less than 6 months, five had opportunistic infections, three were moribund, two had HIV wasting syndrome, two declined consent and one had a malignancy. Two hundred and sixty five patients were thus enrolled into the study.

Patients' baseline characteristics

As depicted in Table 1, the mean age of the study population was 40.69 years with 59.6% of the study population being female. Among the study participants, the mean baseline CD4 count was 119/mm^3 with a median of 97.5. The study participants achieved immune reconstitution with a median follow-up CD4 of 313 cells/mm^3 and a mean of 335/mm^3. Majority of the patients, that is 194 (73.3%) were in WHO stage III and IV at initiation of HAART, with only 71 (26.2 %) patients being

Table 2. Factors associated with lipodystrophy in the 265 study participants.

Variable	Prevalence of lipodystrophy (%)	Total	Odds ratio (OR) (95% CI)	p value
Female	88 (55.6)	158		0.083
Male	48 (44.9)	107		
Age (year)				
21-30	10 (37)	27		0.415
31-40	59 (50.9)	116		
41-50	48 (55.2)	87		
>50	16 (45.7)	35		
WHO stage				
I	12 (50)	24		0.059
II	23 (48.9)	47		
III	50 (50.5)	99		
IV	48 (50.5)	95		
HAART duration (months)				
6-18	19 (22.9)	83	0.34 (0.1-0.6)	0.000
18-36	73 (59.3)	123	2.1 (1.2-3.5)	0.004
36-72	39 (66.1)	59	2.3 (1.2-4.6)	0.006
CD4 nadir < 200 (Cell/µL)	108 (52.4)	206		0.285
> 200	22 (44)	50		
CD4 Current < 200 (Cell/µL)	25 (43)	58		0.150
> 200	104 (53.8)	193		

patients being in stage I and II. The mean duration of treatment of the study participants was 29.7 months with a median of 28 months. One hundred and eighty two patients (68.8%) had been on HAART for longer than 18 months. Only 83 (31.2%) had used HAART for 6 to 18 months. Stavudine based regimens were the most commonly used, with 188 (70.9%) patients being on this combination and 41 (15.5%) patients being on AZT-based regimen. Twenty six of the patients on AZT had switched from a d4T based regimen prior to enrolment into the study. It was also noted that of 36 (13.6%) patients who were on TDF based regimen, 30 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 regimens during their follow-up in the clinic. The switches were mainly due to drug toxicity (lipodystrophy and peripheral neuropathy) and treatment failure and occurred after 2 to 4 years of treatment.

Gender and lipodystrophy

Approximately fifty-five percent (55.6%) of females and 44.9% of males involved in the study developed lipodystrophy as shown in Table 2. 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 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 2. There was no significant association between age and lipodystrophy.

WHO clinical stage and lipodystrophy

Lipodystrophy developed in 50.0 % of study participants in WHO stage I, 48.9% of those in stage II, 50.5% of participants in stage III and 50.5% of those in WHO IV as shown in Table 2. There was no significant association between lipodystrophy and WHO stage at initiation of HAART.

Duration of HAART and lipodystrophy

As depicted in Table 2, a longer duration of therapy was

Table 3. Type of HAART used by patients with lipodystrophy.

HAART combination	Prevalence of lipodystrophy (%)	Total	P value
d4T based regimen			
Ever used[1]	128 (52.5)	244	
Never used[2]	8 (38.1)	21	0.144
AZT based regimen			
Ever used[1]	21 (51.1)	41	0.748
Never used[2]	115 (51.3)	224	
TDF based regimen			
Ever used[1]	33 (91.7)	36	0.000
Never used[2]	103 (45)	229	

[1]Ever used: patients who have used the regimen in the course of their treatment.
[2]Never used: patients have never used the regimen in the course of their treatment.

Table 4. Logistic regression model.

HAART duration (months)	Odds ratio	P	95% CI	
18-36	4.14	<0.0001	2.14	8.009
36-72	6.179	<0.0001	2.828	13.5

found to be significantly associated with the development of lipodystrophy with 19 patients (p value 0.000), 73 patients, (OR 2.06; CI 1.21 to 3.51, p value 0.004) and 39 patients (OR 2.34; CI 1.21 to 1.46, p value 0.006) having lipodystrophy at 6 to 18, 18 to 36 and 36 to 72 months of treatment, respectively.

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 failed immune reconstitution was not found to be significantly associated with lipodystrophy. One hundred and four (53.8%) of the patients with current CD4 greater than 200/mm^3 developed lipodystrophy compared to 25 patients (43%) with CD4 less than 200/mm^3 (p value 0.150) as shown in Table 2.

Type of HAART and lipodystrophy

As shown in Table 3, most of our patients were on a Stavudine based regimens. One hundred and twenty eight (52.5%) of our patients who were on a Stavudine based regimen developed lipodystrophy versus 38.1% of those who had never used a Stavudine based regimen (p value 0.144). The association did not reach significant proportions. Similarly, there was no association between the use of Zidovudine and development of lipodystrophy (p value 0.748). Interestingly, more than 90% of patients on TDF based regimens, notably with prior exposure to both AZT and d4T, developed lipodystrophy.

Logistic regression analysis

A logistic regression model was constructed, as shown in Table 4, to find which of the associated factors independently predicted lipodystrophy while controlling for the other factors and to quantify this association. The model estimated that for patients who had been on HAART for 18 to 36 months, the odds of lipodystrophy is 4.14 times in those who had been on HAART for 6 to 18 months (p < 0.0001). Similarly, the odds of lipodystrophy is 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 to 18 months (p < 0.0001).

DISCUSSION

Lipodystrophy is a well recognized problem in the western world but with very little data in the African population. There is currently no published data on its prevalence and factors associated with its development in Kenya. This study was conducted between August 2007 and 2008 at Kenyatta National Hospital, a tertiary referral and teaching hospital in Kenya. It comprised 59.6% females (female to male ratio 1.5:1). Most of the individuals in the study population were young individuals with a median age of 40 years and about 50% were 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, Ministry of Health Kenya estimates, 2010) that at least two-thirds of all HIV infected individuals in Kenya are young women. Therefore the age and gender distribution of this study population is fairly representative of the sample of HIV/ AIDS infected patients in Kenya.

Age and gender had no influence on the development of lipodystrophy in our study. The reason for lack of age association in our study could be because majority of the participants were young and therefore not 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.

The study participants achieved good immune reconstitution with a median follow-up CD4 of HAART of 313 cells/ml after 6 to 72 months of HAART up from a baseline of 119 cells/ml. The level of baseline CD4 count as well as presence or absence of immune reconstitution was not significantly associated with lipodystrophy in our study. This is in contrast to the HOPS cohort (Lichtenstein et al., 2001) that reported significant association of both baseline and recent CD4 count of less than 100 cells/mm^3 with the development of lipodystrophy but similar to findings by Heath et al. (2002) in a prospective population-based study published where neither CD4 levels at entry to study nor change in CD4 count over the follow up period was associated with lipodystrophy development.

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 to 3.5 p = 0.004). Multivariate analysis showed that prolonged duration of HAART use was an independent predictor of lipodystrophy. These findings are similar to those reported by Mutimura et al. (2007) in Rwanda where the prevalence of lipodystrophy was 69.6% after HAART use for longer than 72 weeks and by Chene et al. (2002) where lipoatrophy was frequent among patients after 30 months of exposure to nucleoside analogues. A long follow up period may therefore be needed in order to identify affected 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. Slightly over 50% of patients on stavudine-based and zidovudine-based regimens developed lipodystrophy. This suggests that both stavudine and zidovudine are equally associated with the development of lipodystrophy when used for a prolonged duration. In contrast, the LIPOCO study reported that Stavudine significantly correlated with wasting in the Nucleoside Reverse Transcriptase Inhibitor and Protease Inhibitor groups when compared with the use of zidovudine containing combinations (Saint-Marc et al., 2000). The study showed that more than 20% of our patients had undergone switch therapy at the time of enrolment due to either drug toxicity or treatment failure. This is further demonstrated by the occurrence of lipodystrophy in more than 90% of patients with history of single drug switches. 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 and is also a reflection on non-reversibility or delayed reversibility of lipodystrophy.

The limitation in this study is that 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.

Conclusion

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

REFERENCES

Bacchetti P, Gripshover B, Grunfeld C (2005). Fat redistribution in men with HIV infection. J. Acquir. Immune Defic. Syndr. 40:121-13.

Carr A , Emery S, Law M, Puls R (2003) An objective case definition of lipodystrophy in HIV- 1 infected adults: Lancet; 361:726–735.

Carr A, Samaras K (1998). Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. Lancet 351:881-1883.

Cheˆ ne G, Angelini E (2002). Role of Long-Term Nucleoside-Analogue Therapy in Lipodystrophy and Metabolic Disorders in Human Immunodeficiency Virus–Infected Patients. Clin. Infect. Dis. 34:649–657.

Heath KV, Hogg RS, Singer J, Chan KJ (2002). Antiretroviral treatment patterns and incident HIV-associated morphologic and lipid abnormalities in a population-based cohort. J. Acquir. Immune Defic. Syndr. 30:440-447.

Lichtenstein KA, Warda DJ, Moormanb AC (2001). Clinical assessment of HIV-associated lipodystrophy in an ambulatory population AIDS 15:1389-1398

Mallal SA (2000). Contribution of nucleoside analogue reverse transcriptaseinhibitors to subcutaneous fat wasting in patients with HIV infection. AIDS 14:1309–1316.

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

Mutimura E, Stewart A, Rheeder P (2007). Metabolic function andthe prevalence of lipodystrophy in a population of HIV-infected African subjects receiving highly active antiretroviral therapy (HAART). J. Acquir. Immune Defic. Syndr. 46:451–455.

Mynarcik DC (2000). Association of severe insulin resistance with bothloss of limb fat and elevated serum TNF-R levels in HIV lipodystrophy. J. Acquir. Immun. Def. Syndr. 25:312-321

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

Reynolds NR, Neidig JL (2006). Balancing disfigurement and fear of disease progression: Patient perceptions of HIV body fat redistribution

redistribution AIDS Care 18(7):663-673.
Saint-Marc T, Partisani M (1999). A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. AIDS 13:1359–1367.
Saint-Marc T, Partisani M, Poizot-Martin (2000). Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study. AIDS 14:37–49.
Van der Valk M, Gisolf EH, Reiss P (2001). Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. 15:847–855.14th conference on retroviruses and opportunistic infections (2007). Los Angeles, California; Feb 25-28.