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High prevalence of lipoatrophy among patients on stavudine-containing first-line antiretroviral therapy regimens in Rwanda

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Summary This study was conducted among individuals placed on WHO-recommended first-line antiretroviral therapy (ART) at two urban health centres in Kigali, Rwanda, in order to determine (a) the overall prevalence of lipodystrophy and (b) the risk factors for lipoatropy. Consecutive individuals on ART for >1 year were systematically subjected to a standardised case definition-based questionnaire and clinical assessment. Of a total of 409 individuals, 370 (90%) were on an ART regimen containing stavudine (d4T), whilst the rest were receiving a zidovudine (AZT)-containing regimen. Lipodystrophy was apparent in 140 individuals (34%), of whom 40 (9.8%) had isolated lipoatrophy, 20 (4.9%) had isolated lipohypertrophy and 80 (19.6%) had mixed patterns. Fifty-six percent of patients reported the effects as disturbing. The prevalence of lipoatrophy was more than three times higher when taking d4T compared with AZT-containing regimens (31.4% vs. 10.3%). Being female, d4T-based ART, baseline body mass index $\geq$25 kg/m^2 or baseline CD4 count $\geq$150 cells/μl and increasing duration of ART were all significantly associated with lipoatrophy. Lipoatrophy appears to be an important long-term complication of WHO-recommended first-line ART regimens. These data highlight the urgent need for access to more affordable and less toxic ART regimens in resource-limited settings.

1. Introduction

In industrialised countries, body fat changes, commonly referred to as lipodystrophy, are known to occur in 20—80% of HIV-infected patients receiving antiretroviral therapy

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(ART) (Grinspoon and Carr, 2005). Lipodystrophy can present as peripheral fat loss, including hollowing of the cheeks, wasting of extremities or flattening of the buttocks (lipoatrophy), or relative/absolute accumulation of central fat in the abdomen, neck or breasts (lipohypertrophy). Although lipoatrophy and lipohypertrophy can occur together (mixed pattern), both presentations are thought to occur independently from each other and to have different risk factors (Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM), 2006). Whereas lipohypertrophy can present independently of HIV infection and ART (Palella et al., 2004; Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM), 2006), lipoatrophy is clearly linked with ART, especially stavudine (d4T), and is more likely to improve upon treatment change (Grinspoon and Carr, 2005). Although current WHO guidelines recommend regimens containing d4T as first-line ART regimens in resource-limited settings (WHO, 2006), information on the prevalence of associated complications such as lipoatrophy is limited. Lipoatrophy affects cosmetic appearance, which may contribute to stigma and influence long-term adherence. The condition is also often associated with other metabolic complications such as dyslipidaemias, insulin resistance and hyperlactataemia, osteopenia and osteonecrosis, which might all contribute to ART-related morbidity and mortality (Grinspoon and Carr, 2005). In an African setting, severely affected by the HIV pandemic, we conducted an assessment of patients placed on WHO-recommended first-line ART regimens in order (a) to determine the overall prevalence of lipodystrophy (isolated lipoatrophy, isolated lipohypertrophy and mixed patterns) and (b) to identify characteristics and risk factors associated with lipoatropy.

2. Methods

This assessment was conducted between October 2005 and May 2006 in two government health centres (Kimironko and Kinyinya Health Centres) in Kigali, Rwanda. The ART programme was launched in Kimironko and Kinyinya Health Centres in October 2003 and January 2004, respectively. Patients were started on ART according to WHO eligibility criteria and using WHO-recommended first-line regimens. Patients are educated on the implications of ART, and adherence to treatment is monitored by self-report, regular clinical attendance and pill count. HIV/AIDS care, including ART, is provided free of charge. All adult patients who have been on stable first-line ART for >1 year are routinely assessed for lipodystrophy using a Lipodystrophy Case Definition Study-based questionnaire (Carr et al., 2003). This method combines self-reporting with clinical assessment by the healthcare provider. The same personnel performed the assessments throughout the study period.

Lipoatrophy (hollowing of the cheeks, wasting of extremities or flattening of the buttocks) or fat accumulation (in the face, neck, dorsocervical spine, arms, breasts, abdomen, buttocks and legs) were recorded. The combination of both lipoatrophy and lipohypertrophy was recorded as a mixed pattern. The degree of lipoatrophy and fat accumulation at each region was rated using the HIV Outpatient Study (HOPS) scale, which was categorised as follows: absent (score of 0); mild (noticeable on close inspection; score of 1); moderate (readily noticeable by patient or physician; score of 2); or severe (readily noticeable to a casual observer; score of 3). The impact of body habitus changes on the manner in which the patient's clothes fit was also noted. Patients with lipodystrophy were routinely screened (by clinical, laboratory and radiological assessment) for associated complications such as hyperglycaemia, cardiovascular complications and lactic acidosis, and management was provided free of charge. For the time being, diagnosis and treatment of hyperlipidaemia is not routinely available in our programme.

Data analysis was performed using STATA software version 9 (Stata Corp., College Station, TX, USA). Unpaired Student's *t*-test and the χ^2 test were used to determine differences in means and proportions. The presence of lipoatropy (be it in an 'isolated' or 'mixed form') was designated as the dependent variable for identifying potential risk associations. A focus was placed on lipoatrophy instead of lipodystrophy for two main reasons. First, HIV-induced lipoatrophy is less prevalent than lipohypertrophy both in HIV-positive individuals before starting ART and in control groups (Palella et al., 2004; Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM), 2006). This limits the likelihood of overestimating the risk of lipodystrophy related to ART. Second, lipoatrophy is more frequently associated with d4T-linked cumulative toxicity and, as this drug forms the pillar of our current ART regimen in Rwanda, we were particularly interested in examining the possible association between d4T and lipoatropy. Measures of risk were determined by crude odds ratios (OR) and adjusted odds ratios (AOR). ORs were adjusted using multivariate logistic regression, and all related *P*-values were based on the Wald test. The level of significance was set at $P \leq 0.05$ and 95% CI were used throughout.

3. Results

A total of 409 individuals on first-line ART were included in the assessment after a median follow-up time of 16 months. Table 1 shows the characteristics of these individuals. The most frequent ART regimen was d4T/lamivudine/nevirapine, with 80.9% of patients on this regimen, followed by 9.5% on a d4T/lamivudine/efavirenz regimen. Lipodystrophy was apparent in 140 individuals, resulting in an overall prevalence of 34.2%. Of these, 40 individuals (9.8%) had isolated lipoatrophy, 20 (4.9%) had isolated lipohypertrophy and 80 (19.6%) had mixed patterns (Table 2). Changes were reported as being disturbing to 78 patients (56%) with lipodystrophy (data not shown). Whereas fat accumulation was mostly mild, fat loss was usually severe and/or diffuse, with a total lipoatrophy score of >6 in 42.5% of cases. Patients with lipoatrophy had a higher baseline and maximum body mass index (BMI). Lipoatrophy occurred more frequently in those with recent onset weight loss (BMI decrease of 1.7 kg/m^2 vs. 0.3 kg/m^2) and those with a faster rate of weight loss (0.51 kg/week vs. 0.20 kg/week) (Table 3). The prevalence of lipoatrophy was more than three times higher for d4T-based ART compared with zidovudine (AZT)-containing regimens, with an AOR of 4.7 (Tables 2 and 4). In addition, being female, a baseline BMI $\geq$ 25 kg/m^2, a baseline CD4 count $\geq$150 cells/μl and

Table 1 Patient characteristics ($N = 409$)

Characteristic	
Age (years)[a]	38 (34–44)
Sex (male/female)[b]	88/321 (21.5/78.5)
WHO clinical stage at baseline[b]	
I	3 (0.7)
II	47 (11.5)
III	293 (71.6)
IV	66 (16.1)
Baseline BMI (kg/m^2)[a]	21 (19–23)
Baseline CD4 count (cells/μl)[a]	128 (74–189)
Time on ART (months)[a]	16 (13–21)
ART regimen[b]	
d4T/3TC/NVP	331 (80.9)
d4T/3TC/EFV	39 (9.5)
AZT/3TC/NVP	24 (5.9)
AZT/3TC/EFV	15 (3.7)

BMI: body mass index; ART: antiretroviral therapy; d4T: stavudine; 3TC: lamivudine; NVP: nevirapine; EFV: efavirenz; AZT: zidovudine.
[a] Values expressed as median (interquartile range).
[b] Values expressed as *n* (%).

increasing duration of ART were all significantly associated with lipoatrophy (Table 4). Since patients with subtle fat loss might be misclassified as lipoatrophy and bias differences with the control group, we repeated the analysis considering only patients with moderate to severe lipoatrophy. The risk factor analysis remained essentially unchanged (data not shown).

4. Discussion

This is one of the first studies reporting the issue of lipoatrophy in Africa, revealing it as a frequent complication of WHO-recommended first-line regimens containing d4T. Our findings are consistent with data from India, where lipodystrophy was reported in 46.1% and lipoatrophy in 26.7% of individuals on WHO first-line regimens for >1 year, and this figure is comparable with prevalence rates in our study (Pujari et al., 2005).

Whereas several publications (Calmy et al., 2006; Spacek et al., 2006; Wester et al., 2005) and recent presentations from large cohorts in Uganda, Kenya and South Africa (Boulle et al., 2006; Forna et al., 2006; Kim et al., 2006) reported on toxicities such as neuropathy and lactic acidosis, lipoatrophy has not been stated as an important problem and this is in clear contrast to our data (van Griensven et al., 2006). There might be a number of possible reasons for this difference. First, all patients on ART for >1 year in our setting were systematically assessed for lipoatrophy, and health providers were well trained to be vigilant and to look out for this condition. This might not necessarily have been the case in the other settings and thus cases of lipoatrophy might either have been missed or underreported. Second, other study cohorts might have been younger (on ART) with a limited manifestation of this condition. Third, in the context of dramatic HIV-related mortality figures in Africa, morphological changes especially in the early stages might not be considered a priority by patients and care providers.

There are a number of important operational implications linked to a high prevalence of lipoatrophy. First, although lipoatrophy may be considered a cosmetic problem, the condition is often associated with other metabolic abnormalities such as dyslipidaemias, hyperlactataemia and diabetes, which may all contribute to morbidity and mortality (Grinspoon and Carr, 2005). In resource-limited settings where facilities for measurement of abnormalities of blood glucose, lactic acid and lipid metabolism can be challenging, clinical assessment for lipoatrophy might be a 'red flag' indication of the overall syndrome, although this hypothesis needs to be assessed in further studies. Second, lipoatrophy affects the overall appearance of individuals and in certain cultures this might be considered unacceptable and may contribute to stigma. Finally, if the prevalence in our setting is anything to go by as a

Table 2 Pattern and severity of lipodystrophy[a]

	d4T regimen ($n = 370$)	AZT regimen ($n = 39$)	Total ($n = 409$)
Lipodystrophy	134 (36.2%)	6 (15.4%)	140 (34.2%)
Isolated lipoatrophy	39 (10.5%)	1 (2.6%)	40 (9.8%)
Mixed pattern	77 (20.8%)	3 (7.7%)	80 (19.6%)
Isolated lipohypertrophy	18 (4.9%)	2 (5.1%)	20 (4.9%)
Lipoatrophy[b]	116 (31.4%)	4 (10.3%)	120 (29.3%)
Mild	39 (10.5%)	2 (5.1%)	41 (10.0%)
Moderate	26 (7.0%)	2 (5.1%)	28 (6.8%)
Severe	51 (13.8%)	0 (0%)	51 (12.5%)
Lipohypertrophy[b]	95 (25.7%)	5 (12.8%)	100 (24.4%)
Mild	50 (13.5%)	3 (7.7%)	53 (13.0%)
Moderate	34 (9.2%)	1 (2.6%)	35 (8.6%)
Severe	11 (3.0%)	1 (2.6%)	12 (2.9%)

d4T: stavudine; AZT: zidovudine.
[a] Values are expressed as *n* (%).
[b] A total score was obtained by adding the scores for each body region. A total score of 1–3 was (arbitrarily) defined as mild and a score >6 was considered severe.

Table 3 Characteristics of patients with and without lipoatrophy

	Lipoatrophy ($n=120$)	No lipoatrophy ($n=289$)	*P*-value
ART regimen[a]			<0.001
AZT-containing	4 (3.3)	35 (12.1)	
d4T-containing	116 (96.7)	254 (87.9)	
Age[b]	38.8 ± 7.0	39.0 ± 8.2	0.771
Sex (male/female)[a]	9/111 (7.5/92.5)	79/210 (27.3/72.7)	<0.001
WHO clinical stage at baseline[a]			0.592
I	1 (0.8)	2 (0.7)	
II	17 (14.2)	30 (10.4)	
III	86 (71.7)	207 (71.6)	
IV	16 (13.3)	50 (17.3)	
BMI baseline (kg/m^2)[b]	22.5 ± 3.8	20.8 ± 3.3	<0.001
Maximum BMI (max.) (kg/m^2)[b]	24.4 ± 3.6	22.5 ± 3.3	<0.001
Current BMI (kg/m^2)[b]	22.6 ± 3.4	22.1 ± 3.4	0.247
BMI increase (max. − baseline) (kg/m^2)[b]	1.7 ± 1.5	1.6 ± 2	0.933
BMI decrease (current − max.) (kg/m^2)[b]	1.7 ± 1.6	0.3 ± 0.6	<0.001
Weight loss rate (kg/week)[b]	0.51 ± 0.36	0.20 ± 0.15	<0.001
CD4 count baseline (cells/μl)[b]	146 ± 83	130 ± 73	0.045
Maximum CD4 count (cells/μl)[b]	336 ± 156	294 ± 154	0.011
CD4 count increase (6 months)[b]	110 ± 91	112 ± 96	0.864
Current CD4 count[b]	309 ± 154	279 ± 153	0.083
Time on ART (months)[b]	18.6 ± 5.3	17.2 ± 5.2	<0.001

ART: antiretroviral therapy; AZT: zidovudine; d4T: stavudine; BMI: body mass index.
[a] Values are expressed as *n* (%).
[b] Values are expressed as mean ± SD.

Table 4 Risk factors associated with lipoatrophy[a]

Risk factor	Lipoatrophy[b]	Crude OR[c]	Adjusted OR[c]	*P*-value
NRTI use				
AZT	4/35 (10.3)	1	1	0.019
d4T	116/254 (31.4)	4.0 (1.4–11.6)	4.7 (1.3–17.1)	
Sex				
Male	9/79 (10.2)	1	1	
Female	111/210 (34.6)	4.6 (2.2–9.8)	4.2 (1.8–9.9)	0.001
Baseline BMI (kg/m^2)				
<25	72/230 (23.8)	1	1	
≥25	24/29 (45.3)	2.6 (1.4–4.9)	2.3 (1.2–4.3)	0.010
Baseline CD4 count (cells/μl)				
<150	60/179 (25.1)	1	1	
≥150	60/103 (36.8)	1.7 (1.1–2.7)	1.9 (1.1–3.2)	0.014
Time on ART (months)				
<18	64/191 (25.1)	1	1	
≥18	56/98 (36.4)	1.7 (1.1–2.6)	1.9 (1.1–3.2)	0.020
Age (years)				
<40	74/164 (31.1)	1	1	
≥40	46/125 (26.9)	0.8 (0.5–1.3)	1.3 (0.8–2.2)	0.328

OR: odds ratio; NRTI: nucleoside reverse transcriptase inhibitor; AZT: zidovudine; d4T: stavudine; BMI: body mass index; ART: antiretroviral therapy.
[a] Patients with lipoatrophy ($n=120$) were compared with patients without lipoatrophy ($n=289$).
[b] Values are expressed as *n* with lipoatrophy/*n* with no lipoatrophy; the prevalence of lipoatrophy (%) is given in parentheses.
[c] 95% CI in parentheses.

'forecast' for other programmes, then this problem might have a negative influence on ART adherence and the overall acceptability of ART as cohorts become more mature. One of the main culprits associated with lipoatrophy in our setting, similar to India (Pujari et al., 2005), is the use of a d4T-containing ART regimen. Although reducing the dose of d4T from 40 mg to 30 mg and shifting to AZT are possible options for the clinician, since toxicity is thought to be cumulative, these can only be but temporary measures.

There are a number of limitations of this study. First, the study has all the intrinsic limitations of a cross-sectional design. Second, body fat changes were not associated with technical investigations. However, a recent study found a strong correlation of this type of assessment with dual energy X-ray absorptiometry (DEXA) (McComsey et al., 2006). Finally, since we did not make any laboratory measurements of blood glucose, lipid and lactate levels, we are unable to assess the prevalence of other metabolic complications that may comprise the lipodystrophy syndrome (Lichtenstein, 2005).

Our data show a high prevalence of lipoatrophy. One of the ways forward for avoiding this problem and particularly for our older cohorts is urgently to replace d4T in ART regimens by less toxic drugs such as tenofovir and abacavir (WHO, 2006). Unfortunately, both these drugs are faced with the challenges of registration in the developing world and remain extremely expensive for large-scale ART roll out. These barriers will have to be addressed if we are to cope with the toxic complications of current first-line ART regimens, which will inevitably manifest in maturing ART cohorts. The clock is ticking, what is now needed is the political impetus for action!

Ethical considerations

General measures are provided in the ART facility to ensure patient confidentiality, consent for HIV testing, and counselling and support for those who receive a positive HIV test result. All patients are counselled on the possibility of side effects to ART and are managed for the same by experienced clinicians. The data included in this analysis and paper constituted part of routine programmatic data for monitoring and evaluation purposes and were collected in collaboration with the Ministry of Health of Rwanda.

Authors' contributions: JVG, LDN, TM and SU carried out the clinical assessment; JVG, DG, CG and RZ carried out analysis and interpretation of the data; JVG and RZ drafted the manuscript. All authors read and approved the final manuscript. JVG is guarantor of the paper.

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