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Weight evolution in HIV-1 infected women in Rwanda after stavudine substitution due to lipoatrophy: comparison of zidovudine with tenofovir/abacavir

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Summary This cohort study was conducted amongst female patients manifesting lipoatrophy while receiving stavudine-containing first-line antiretroviral treatment regimens at two urban health centres in Rwanda. The objectives were to assess weight evolution after stavudine substitution and to describe any significant difference in weight evolution when zidovudine or tenofovir/abacavir was used for substitution. All adult patients on stavudine-containing first-line regimens who developed lipoatrophy (diagnosed using a lipodystrophy case definition study-based questionnaire) and whose treatment regimen was changed were included ($n = 114$). In the most severe cases stavudine was replaced with tenofovir or abacavir ($n = 39$), and in the remainder with zidovudine ($n = 75$). For patients changed to zidovudine a progressive weight loss was seen, while those on tenofovir/abacavir showed a progressive weight increase from six months. The between-group difference in weight evolution was significant from nine months (difference at 12 months: 2.3 kg, $P = 0.02$). These differences were confirmed by follow-up lipoatrophy scores. In multivariate analysis, substitution with tenofovir/abacavir remained significantly associated with weight gain. This is the first study in Africa assessing weight gain as a proxy for recovery after stavudine substitution due to lipoatrophy, providing supporting evidence that tenofovir/abacavir is superior to zidovudine. The weight loss with zidovudine might justify earlier substitution and access to better alternatives like tenofovir/abacavir.

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1. Introduction

Body fat changes, commonly referred to as lipodystrophy, occur frequently in HIV-1 infected patients on highly active antiretroviral treatment (HAART). Lipodystrophy can present as subcutaneous fat loss, including hollowing of the cheeks, wasting of extremities or flattening of the buttocks (lipoatrophy), or relative/absolute accumulation of central/visceral fat in the abdomen, neck or breasts (lipohypertrophy).[1] Whereas lipohypertrophy can present independently of HIV and HAART,[2,3] lipoatrophy is clearly linked with HAART, especially stavudine, and is more likely to improve upon treatment change.[4]

Due to the frequent occurrence of side-effects, including lipoatrophy, stavudine is no longer a first-choice drug in high-income countries.[1,4] Although several papers have reported on the relatively high prevalence of lipoatrophy and other complications, such as symptomatic hyperlactataemia/lactic acidosis (SH/LA) linked to the use of stavudine in Africa,[4–6] its use in Africa is likely to continue for some years to come for various reasons.[7] The WHO has recently recommended a dose-reduction strategy for stavudine in the hope that this will significantly reduce the occurrence of these long-term side-effects without compromising treatment efficacy. However, the effectiveness of this plan is yet to be determined.[8]

Based on studies from high-income countries, current WHO guidelines recommend substitution with abacavir (ABV) or tenofovir (TDF) when lipoatrophy occurs while on stavudine-containing regimens.[8] In low-income countries, the high cost and limited availability of TDF and ABV preclude their being widely used, and in these contexts patients will often be changed to zidovudine (ZDV). Although cumulative toxicity is less pronounced with ZDV, it still exists, rendering such a strategy a temporary measure. What is not known is how, once lipoatrophy has developed, substitution with ZDV compares to TDF/ABV. This is important when considering how long resource-poor contexts can rely on ZDV.[6]

One of the challenges of performing studies addressing lipoatrophy in Africa is the lack of technical measurements to confirm the findings. Instead, we rely on questionnaires and clinical assessments that, despite being simple, have performed well in comparative studies.[4] We note that lipoatrophy has been shown to be associated with (recent) weight loss.[9–14]

Medecins Sans Frontières (MSF) has been supporting two health centres in Rwanda since 2003. Due to the fact that this support programme has had access to TDF and ABV we have been in the unique position of being able to follow patients who were switched to either ZDV or TDF/ABV. There has been only one study in the literature that used both ZDV and ABV for stavudine replacement,[15] but it did not directly compare the efficacy of the drugs and we would like to report on our experience.

We previously reported a high level of lipoatrophy amongst patients on stavudine-containing first-line regimens within our antiretroviral treatment (ART) programme in Rwanda, using a standardized questionnaire.[14] Based on this population, the objectives of this study were to assess weight evolution after stavudine substitution and to describe the differences in weight evolution following stavudine replacement by ZDV and TDF/ABV in patients manifesting lipoatrophy while receiving first-line ART regimens.

2. Methods

2.1. Design and setting

This was an observational cohort study using routinely collected data from a programmatic setting. The study was conducted between October 2003 and July 2007 in two urban public health centres (Kimironko and Kinyinya health centres) in Kigali, Rwanda that were supported by MSF.[16] The two centres have over 3000 patients on ART, which is offered according to WHO eligibility criteria and using WHO-recommended first-line regimens.[8] Approximately 90% of this cohort was started on generic fixed-dose combination regimens containing stavudine, lamivudine and nevirapine.

General measures were provided in the ART facility to ensure patient confidentiality, consent for HIV testing, and counselling and support for those who received a positive HIV test result. All patients were counselled on the potential side-effects of ART and were managed for these by experienced clinicians. Confidentiality was maintained with no patient identifiers used.

2.2. Inclusion criteria

Patients were routinely screened for stavudine-related lipoatrophy using a lipodystrophy case definition study-based questionnaire (see below). At the same time, patients were evaluated for symptoms suggestive of SH/LA. All adult patients on stavudine-containing first-line regimens for a minimum uninterrupted duration of six months and for whom stavudine had been substituted due to lipoatrophy were included in this study.

2.3. Exclusion criteria

Patients diagnosed with severe SH/LA (serum lactate level of $\geq$5 mmol/l [Accutrend Lactate; Roche, Basel, Switzerland] or a serum lactate level of $\geq$2.5 mmol/l with profuse vomiting or with a respiratory rate >20/min) with associated features of lipoatrophy were excluded, since they generally required different clinical management including treatment interruption. Since weight can be affected by various conditions, strict exclusion criteria were applied to reduce misclassification and improve the specificity of our assessment. Particular attention was given to ruling out opportunistic infections, especially tuberculosis. Every case of suspected lipoatrophy was carefully examined by an experienced physician and underwent appropriate testing. If necessary, patients were referred to the university hospital (Centre Hospitalière Universitaire de Kigali, Rwanda) for further investigation (bronchoscopy, ultrasound, X-ray, etc). All cases with concurrent infections were excluded. During each follow-up visit patients were re-assessed for subclinical infections and, if confirmed, they were excluded from the analysis.

All patients in the programme had a viral load test done after one year of therapy. In addition, patients with

immunological or clinical signs suggestive of treatment failure[8] had a viral load test performed; those with a viral load >1000 copies/ml were excluded.

For every patient with a clinical suspicion of lipoatrophy, poor nutritional intake was explored as an alternative explanation for the body changes.[17,18] The dietary intake over the last 3—6 months was assessed and the social situation was evaluated by the social assistant or nurse. If nutrition-related fat loss seemed plausible, nutritional support was provided for 1—2 months. Those with clinical improvement upon nutritional support were excluded from the analysis. None of the patients included in this study received or required further nutritional support after stavudine substitution. The study excluded the only two eligible male patients so as to obtain a homogeneous population of female patients.

2.4. Assessment and management of lipoatrophy

Lipoatrophy was assessed using a lipodystrophy case definition study-based questionnaire as described previously.[14,19] In brief, this method combines self-reporting along with a formal clinical assessment by the healthcare provider, and was routinely performed on all adult patients who had been on stable first-line ART for over one year. This method has been shown to correlate well with dual energy X-ray absorptiometry (DEXA) measurements.[20] Fat loss occurring in any of seven body regions (face, neck, arms, breasts, abdomen, buttocks and legs) was systematically assessed. The degree of lipoatrophy at each region was rated using the HIV Outpatient Study (HOPS) scale 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 on the fit of patients' clothing was also noted. A total lipoatrophy score was obtained by adding the scores for each body region. A clinical protocol reflecting the consensus on the management of lipoatrophy among treating physicians within the programme was developed to decide on whether to substitute with TDF or AZT, with the aim of reserving TDF for the more severe cases. Stavudine substitution was indicated for those with a total lipoatrophy score >5, which we considered to be clinically significant. TDF (or ABV when TDF was not available) was given to all patients with a high total lipoatrophy score (>10) or with a rapid clinical evolution and associated (non-severe) SH/LA. The remainder were given AZT. Although this assignment was arbitrary, the criteria had face value and addressed our clinical context. Plus, they were applied consistently to all eligible patients.

The weight evolution at 3, 6, 9 and 12 months after stavudine substitution was recorded. Weight, not body mass index (BMI), was chosen as the main outcome for the following reasons: first, this study involved only adults whose height did not change, i.e. was a constant variable, and was only measured at baseline. In addition, the data analysis was restricted to female patients and thus BMI variation between genders was not an issue. Finally, in practice in busy ART clinics, the parameter that is routinely measured on follow-up visits to judge clinical evolution is weight and not BMI. However, we did measure BMI at the beginning of treatment and report on its evolution in the results.

Weighing scales (Seca, Hamburg, Germany) were provided and regularly checked/calibrated by the MSF logistics department. Training on the use and maintenance of the scales was integrated into the HIV care training sessions. Patients were weighed early in the morning before the consultations, without shoes and with minimal clothing. The same weighing scale was used for all patients. Height was measured on admission with the patient standing upright and looking straight ahead.

2.5. Statistics

Data analysis used Stata 9 (Stata Corp., College Station, TX, USA). Differences between groups were compared using the Wilcoxon rank-sum test for continuous variables, the X^2 test for categorical variables and Fisher's exact test if numbers were small. The Wilcoxon signed-rank test was used to assess within-group differences. Multivariate linear regression was used to determine the independent association of drug for substitution with change in weight after stavudine substitution. The weight at nine months after substitution was used as the dependent variable, since this was the longest duration of weight data that was available for all patients (given the differences in follow-up time after substitution). Due to collinearity with the main exposure, the lipoatrophy score was not added in the multivariate model (type of drug for substitution based on score). The level of significance was set at $P < 0.05$.

3. Results

A total of 164 patients had a substitution for stavudine; 48 were excluded as they had other concurrent conditions along with lipoatrophy, e.g. treatment failure, malnutrition, opportunistic infections or severe SH/LA, and two male patients were excluded to ensure a cohort of females only. A total of 114 women were thus included in the study and were followed up for a median period of 342 days. The characteristics of patients in whom stavudine was substituted by ZDV ($n = 75$) or TDF/ABV ($n = 39$) are shown in Table 1. Most patients had a relatively high BMI, had been on stavudine-containing regimens for over 16 months and experienced a median body weight loss of 3 kg. The median CD4 count prior to lipoatrophy-related stavudine replacement was 293 cells/μl, reflecting good immunological recovery. For a minority, SH/LA was a secondary diagnosis. Seventy-five patients were switched to ZDV, and 39 to TDF ($n = 27$) or ABV ($n = 12$). Patients who had been changed to ZDV had lower lipoatrophy scores, had a shorter follow-up period after substitution and were less likely to have a secondary diagnosis of SH/LA.

Weight evolution after stavudine substitution is shown in Table 2. For patients changed to ZDV, a progressive weight loss was seen that became statistically significant three months after substitution, with a mean loss by 12 months of 1.62 kg ($P < 0.01$). By contrast, those on TDF/ABV maintained a stable body weight, with a trend towards a progressive increase in weight after an initial period of three months.

Table 1 Baseline characteristics of patients with lipoatrophy prior to substitution for stavudine

Baseline characteristic	Total ($n=114$)	TDF/ABV ($n=39$)	ZDV ($n=75$)	*P*-value
Age (years)[a]	35.7 (32.3–38.4)	37.0 (34.0–39.9)	34.6 (31.9–38.1)	0.06
WHO clinical stage at baseline (*n*) (%)				
Stage 1	1 (0.9)	0	1 (1.3)	0.47
Stage 2	13 (11.4)	3 (7.7)	10 (13.3)	0.37
Stage 3	83 (72.8)	31 (79.5)	52 (69.4)	0.25
Stage 4	17 (14.9)	5 (12.8)	12 (16.0)	0.65
CD4 count before substitution (cells/μl)[a,b]	293 (196–370)	286 (222–367)	293 (191–375)	0.82
Time on ART (days)[a]	492 (404–632)	513 (392–597)	489 (404–672)	0.89
NNRTI (*n*) (%)				
NVP	94 (82.5)	35 (89.7)	59 (78.7)	0.51
EFV	20 (17.5)	4 (10.3)	16 (21.3)	0.19
Body weight at time of substitution (kg)[a]	60 (53–67)	61 (53–72)	60 (52–65)	0.57
Body mass index at time of substitution (kg/m^2)[a]	23.0 (20.9–25.5)	23.4 (21.2–26.0)	23.0 (20.7–25.4)	0.47
Total lipoatrophy score[a,c]	8 (7–11)	12 (11–13)	7 (6–8)	<0.01
Body weight loss prior to substitution (kg)[a]	3.0 (2.0–5.3)	3.3 (2.1–6.0)	3.0 (1.1–5.3)	0.39
Rate of weight loss (g/week)[a]	171 (93–261)	158 (101–304)	181 (80–250)	0.33
Secondary diagnosis of SH/LA (*n*) (%)				
No	100 (87.7)	30 (76.9)	70 (93.3)	0.40
Yes	14 (12.3)	9 (23.1)	5 (6.7)	0.02
Length of follow-up after substitution (days)[a]	342 (252–436)	398 (261–507)	337 (241–400)	0.03

TDF: tenofovir; ABV: abacavir; ZDV: zidovudine; ART: antiretroviral treatment; NNRTI: non-nucleoside reverse transcriptase inhibitors; NVP: nevirapine; EFV: efavirenz; SH/LA: symptomatic hyperlactataemia/lactic acidosis.
[a] Median (interquartile range).
[b] In the 6 months prior to substitution; missing for five individuals.
[c] Obtained by adding the HIV Outpatient Study lipoatrophy scores for each region of the body: lipoatrophy absent = 0; mild = 1; moderate = 2; severe = 3.

A significant difference in weight evolution between the two treatment groups was seen from nine months (Table 2). The corresponding difference in BMI between both groups was 0.65 kg/m^2 (95% CI 0.09–1.20) and 0.89 kg/m^2 (95% CI 0.13–1.64) at 9 and 12 months, respectively.

Since allocation to ZDV or TDF/ABV was based on clinical parameters, we performed a multivariate analysis to assess whether the observed differences in weight remained valid after adjusting for various clinical parameters (Table 3). After adjustment for potential confounders, the association of TDF/ABV with weight recovery remained significant. The findings did not change substantially when BMI evolution was included as the outcome variable (between-group difference in BMI evolution of 0.95 kg/m^2 by nine months after substitution).

To assess the extent to which the difference in weight evolution correlated with differences in the clinical evolution, we compared follow-up lipoatrophy scores in both groups at 6–9 months after substitution. Results were available for 63 (84%) of those changed to ZDV and for 34 (87%) of those changed to TDF/ABV. For those on ZDV, the median lipoatrophy score decreased significantly (−2 [IQR −3 to −1], $P<0.01$), while the increase seen with TDF/ABV was not statistically significant (+1 [0 to +2], $P=0.06$). However, the between-group difference in scores at 6–9 months after substitution was highly significant ($P<0.01$). For the 92 individuals with complete data, TDF/ABV was associated with a more favourable score evolution in the multivariate analysis (mean between-group difference in score of 2.4).

Table 2 Evolution of body weight after substitution for stavudine ($n=114$)

Time since substitution (months)	Mean (SD) change over time (kg)		Mean (95% CI) between-group difference (kg)	*P*-value
	TDF/ABV	ZDV		
3	−0.17 (1.60)	−0.57 (1.75)[a]	0.40 (−0.27; 1.07)	0.24
6	+0.01 (2.49)	−1.24 (3.59)[a]	1.25 (−0.02; 2.52)	0.05
9	+0.25 (2.82)	−1.41 (4.11)[a]	1.66 (0.20; 3.11)	0.03
12	+0.70 (4.18)	−1.62 (4.23)[a]	2.32 (0.36; 4.27)	0.02

TDF: tenofovir; ABV: abacavir; ZDV: zidovudine.
[a] *P*-value <0.05 in signed-rank test (within-group difference).

Table 3 Multivariate analysis to assess the independent association of type of drug substitution with weight change (kg)[a]

Baseline variables	Bivariate analysis		Multivariate analysis	
	Coefficient	*P*-value	Coefficient	*P*-value
NRTI (ZDV vs. TDF/ABV)	−1.787	0.02	−2.413	<0.01
Time on ART (days)	0.003	0.18	0.001	0.51
Age (years)	−0.036	0.53	−0.021	0.70
WHO clinical stage (1/2 vs. 3/4)	−0.257	0.82	−1.500	0.14
CD4 count before substitution (cells/μl)	−0.002	0.42	−0.003	0.18
NNRTI (EFV vs. NVP)	−0.778	0.42	−0.863	0.32
Body weight at time of substitution (kg)	−0.085	0.02	−0.069	0.07
Body weight loss prior to substitution (kg)	0.287	<0.01	0.439	<0.01
Rate of weight loss (g/week)	−0.003	0.18	0.004	0.20
Secondary diagnosis of SH/LA	−2.461	0.02	−2.586	0.02

NRTI: nucleoside reverse transcriptase inhibitor; ZDV: zidovudine; TDF: tenofovir; ABV: abacavir; ART: antiretroviral treatment; NNRTI: non-nucleoside reverse transcriptase inhibitor; EFV: efavirenz; NVP: nevirapine; SH/LA: symptomatic hyperlactataemia/lactic acidosis.
[a] Excluding five individuals with missing CD4 data ($n = 109$).

4. Discussion

This is the first study in Africa assessing weight evolution after the substitution of stavudine due to lipoatrophy. Substituting with TDF/ABV was associated with weight gain, while substituting with ZDV led to a progressive weight loss over time. This difference in weight evolution between the two groups was significant from six months after stavudine substitution. Similar differences in follow-up lipoatrophy scores were found. We note that the two cohorts were not randomly selected, but that the TDF/ABV group had more severe symptoms and hence this difference is clinically more significant.

The positive clinical evolution after substituting TDF or ABV for stavudine was consistent with three studies from high-income countries (including two randomised controlled trials), demonstrating a slow and partial reversal of fat loss.[15,21,22] Only one uncontrolled study addressed the efficacy of substituting stavudine with ZDV or ABV.[15] In that study, some fat recovery was observed with ZDV although less pronounced than with ABV. This was in contrast to the findings in the current study, which we speculate were due to differences in clinical status at presentation, severity/duration of lipoatrophy and the differences in outcome measurements.

One of the possible limitations of this study was that we used self-reporting, clinical assessment and, in particular, 'weight evolution' as an indicator of fat recovery after substitution. However, for health facilities in resource-limited settings that are faced with high patient burdens, shortages of staff (both in terms of numbers and capacity) and lack of sophisticated technical investigations, measurement of body weight is a relevant and easy-to-use parameter for the follow-up of patients on ART, as it can indicate important clinical events such as treatment failure, malnutrition and infections.[23]

Lipoatrophy should also be considered when unexplained weight loss is encountered, in particular for patients on ART for longer periods and/or for those on stavudine-containing regimens. In contrast to the weight loss/wasting syndrome associated with progressive HIV infection, lipoatrophy is distinguished by the preferential loss of fat tissue without substantial loss of lean tissue mass, and has most commonly been documented in patients responding well to therapy.[1] In a prospective evaluation, body weight was shown to increase throughout the first year of successful stavudine- or ZDV-containing ART, resulting from increased central fat, peripheral fat and lean body mass. However, selective peripheral fat loss associated with body weight reduction was observed after longer treatment periods.[11] A number of other studies have confirmed the association of lipoatrophy with (recent) weight loss.[9–14] In any case, unexplained weight loss calls for thorough clinical and laboratory investigations. In settings with limited resources, lipoatrophy is essentially a diagnosis of exclusion, retained as an explanation for (subcutaneous) fat loss after alternative explanations have been ruled out.

The response to treatment can provide additional diagnostic evidence. Weight loss associated with malnutrition tends to resolve readily with nutritional support, something that has been progressively more available within many ART programmes in poor countries.[17] Upon successful virological suppression or treatment of opportunistic infections, body weight generally recovers quickly.[24,25] After stavudine substitution, the peripheral fat loss can gradually be reversed, although this occurs slowly and is probably not fully reversible.[15,21,22] By contrast, associated lipohypertrophy seems to be unaffected by stavudine substitution.[15,21,22] Recent studies have documented the association of lipoatrophy and weight after stavudine substitution.[13,26] Body weight evolution after substitution could thus provide a useful (albeit insensitive) clinical indicator of fat recovery. Although the lipoatrophy follow-up scores were in line with the weight evolution in our study, anthropometric measurements such as waist circumference and skin-fold thickness might have allowed us to correlate the weight changes with regional changes in body fat. Unfortunately, this information was not available in our study as it came from a routinely-collected data set, but this should be considered in further studies.

Another limitation of this assessment was the limited technical investigations available to validate the clinical

diagnosis of lipoatrophy or to rule out mimicking conditions. Although there is a theoretical possibility that some patients might have had sub-clinical infections that would have affected weight, we think this was minimised by screening patients for infections on a routine basis at each follow-up visit; all were given instructions to return in case of feeling unwell. Tuberculosis, in particular, might pass undiagnosed and is a reason for weight loss; however, this is unlikely as all patients were on ART for extended periods, and the resulting restoration in immune function would have facilitated the diagnosis of tuberculosis early in the treatment process. Still, our observations need to be confirmed in other, more controlled settings. Additionally, long-term outcomes remain to be ascertained, and repeated lipoatrophy score assessments, metabolic data and patient self-reporting after substitution might have corroborated our findings. However, our observations indicate the need to explore further this important operational question in low-income countries.

The more favourable response to TDF/ABV than to ZDV adds to the evidence that TDF/ABV is superior to ZDV as an alternative to stavudine. This highlights the need for improved access to TDF/ABV and suggests that pro-active, earlier substitution with TDF/ABV might be justified. This is because, although lipoatrophy is not life-threatening, the potential repercussions of ART-related body changes on adherence to and overall acceptability of ART have to be considered.[27]

There are a number of areas that merit further research. For example, it would be useful to correlate the clinical and weight assessments with more technical investigations such as bioelectrical impedance analysis; assessments could be conducted on larger cohorts in different contexts from ours; and finally, assessments in resource-limited settings still using stavudine in first-line ART regimens could look at when to substitute for stavudine.

Meanwhile, these data provide additional support for the urgent need for increased availability of TDF or ABV for ART programmes in low-income countries. As lipoatrophy is a frequent complication of stavudine-containing regimens and is only partially reversible upon substitution, preventive strategies including earlier detection and substitution for stavudine with drugs such as TDF/ABV need to be explored. Relying on ZDV should only be a stop-gap measure until that time.

Authors' contributions: JVG conceived the study; JVG and EFA were physicians treating the patients within the ART programme and implemented the study; JVG, RZ, FR and TR were involved with the study design and performed the data analysis; JVG and RZ co-drafted the manuscript; EA, FR and TR critically reviewed the manuscript and improved the intellectual content. All authors read and approved the final manuscript. JVG is guarantor of the paper.

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Conflicts of interest: None declared.

Ethical approval: The data included in this analysis constituted part of routine programmatic data collected for monitoring and evaluation purposes carried out in collaboration with the Ministry of Health of Rwanda. The Rwandan National Ethics Committee (RNEC, Kigali, Rwanda) gave exemption from formal ethical review.

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