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Weight loss after the first year of stavudine-containing antiretroviral therapy and its association with lipoatrophy, virological failure, adherence and CD4 counts at primary health care level in Kigali, Rwanda

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ABSTRACT

This study was conducted among 609 adults on stavudine-based antiretroviral treatment (ART) for at least one year at health center level in Kigali, Rwanda to (a) determine the proportion who manifest weight loss after one year of ART (b) examine the association between such weight loss and a number of variables, namely: lipoatrophy, virological failure, adherence and on-treatment CD4 count and (c) assess the validity and predictive values of weight loss to identify patients with lipoatrophy. Weight loss after the first year of ART was seen in 62% of all patients (median weight loss 3.1 kg/year). In multivariate analysis, weight loss was significantly associated with treatment-limiting lipoatrophy (adjusted effect/kg/year –2.0 kg, 95% confidence interval –0.6;-3.4 kg; $P < 0.01$). No significant association was found with virological failure or adherence. Higher on-treatment CD4 cell counts were protective against weight loss. Weight loss that was persistent, progressive and/or chronic was predictive of lipoatrophy, with a sensitivity and specificity of 72% and 77%, and positive and negative predictive values of 30% and 95%. In low-income countries, measuring weight is a routine clinical procedure that could be used to filter out individuals with lipoatrophy on stavudine-based ART, after alternative causes of weight loss have been ruled out.

1. Introduction

Successful decentralization of antiretroviral treatment (ART) delivery is one of the key strategies required to achieve universal access to HIV care and treatment in low income countries (LIC).[1] Consequently, ART is increasingly being provided at lower levels of the health care system by less sophisticated and skilled medical staff. This requires easy-to-use, point-of-care, monitoring tools.[2,3] Unfortunately, such tools are not available as yet and care providers have to rely on the evolution of clinical markers to assess patients. Measurement of body weight is an easy-to-implement, routinely measured parameter used for the follow-up of patients on ART in LIC. A number of studies have reported on low baseline body weight or body mass index and its association with early mortality.[4–9]

However, the determinants of weight evolution at later stages, particularly after the first year of ART, and its clinical significance remain poorly understood and there is

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limited published literature on this subject. With regards to ART, weight loss after the first year of stavudine-containing ART could occur due to poor adherence, treatment failure[10,11–13] and lipoatrophy,[14–16] the latter having been shown to occur frequently in several African countries.[14–16] Although never specifically addressed, several studies suggest a potential association of lipoatrophy with weight loss.[15,17,18]

We conducted a study on patients on stavudine-containing ART to (a) determine the proportion who manifest weight loss after one year of ART, (b) examine the association between such weight loss and a number of variables namely: lipoatrophy, virological failure, adherence and on-treatment CD4 count and (c) assess the validity and predictive values of weight loss to identify patients with lipoatrophy.

2. Methods

2.1. Design

Retrospective cohort study using routine programme data.

2.2. Study setting and population

The study was conducted between October 2003 and July 2007 in two public health centres, both supported by Médecins Sans Frontières (MSF) in Kigali, Rwanda. One was an urban health center with a catchment area of about 75 000 people while the other was semi-rural, being located at the outskirts of Kigali, with an estimated population of 17 000. Both mainly cared for poor patient populations. Comprehensive HIV care and ART has been provided in these health facilities from 2003.

Patients were included in the analysis if they met the following criteria: (1) adult ($\geq$ 18 years) ART-naïve individuals initiating stavudine-based ART with a non-nucleoside reverse transcriptase inhibitor, (2) a minimal uninterrupted follow-up on stavudine treatment of >1 year, (3) a minimum of three weight measurements during the second year of ART, (4) a viral load result available at the time of analysis and (5) no recorded pregnancy during the study period.

Patients missing baseline CD4 cell count or baseline weight measurements were excluded. Patients with stavudine-related lactic acidosis were excluded as well, since these patients generally required treatment interruption.

2.3. ART eligibility, regimens and treatment monitoring

All HIV-infected individuals presenting with World Health Organization (WHO) clinical stage 4, stage 3 with a CD4 count < 350 cells/mm3 or stage 1 and 2 with CD4 cells <200 were eligible for antiretroviral treatment.

The first line regimen consisted of a fixed dose combination of stavudine, lamivudine and nevirapine. Stavudine was given at a dose of 40 mg twice daily for patients with a body weight >60 kg at treatment initiation, and 30 mg for the remainder. Zidovudine was used in case of stavudine-related toxicity. Tenofovir and abacavir were reserved for the more severe stavudine-related toxicities. In the event of contraindication or toxicity of nevirapine, efavirenz was prescribed. All patients were educated on the implications of ART, including the recognition of side effects and the importance of adherence.

Following visits at two and four weeks after treatment initiation, patients were seen every month. After the first year of ART, medical visits were scheduled every two months unless the patients' clinical condition indicated otherwise. Patients who had not presented at the facility for more than two months after the last scheduled appointment were defined as 'lost to follow-up' and were traced through community support groups.

During the study period, nutritional support (standard package, corn soya blend (CSB)-based) was routinely provided during the first three months of ART. All HIV-related treatment and care was provided free of charge. Viral load testing was performed systematically for all patients after the first year of treatment.[2] Virological failure was defined as a viral load >1000 copies/ml after >1 year of ART.

We used pharmacy refills as a measure of adherence to therapy, which has been associated with virological failure.[22–24] We defined excellent, good and poor adherence as being punctual for >95%, 90–95% or <90% of the visits respectively. CD4 cell counts were measured at baseline and every six months after ART initiation.

At each follow-up visit, side effects were evaluated in line with WHO guidelines, with treatment changed for grade III/IV toxicities.[19] Lipoatrophy was assessed using a Lipodystrophy Case Definition Study-based questionnaire, which combines self-reporting along with a formal clinical assessment by the health care provider, and has been described previously.[15,20] This assessment was routinely performed on all adult patients who had been on stable first-line ART for over one year, or on clinical indication. The degree of lipoatrophy at each of seven regions 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).[21] The impact of body habitus changes on the manner in which the patient's clothes fit was also noted. Patients with suspected lipoatrophy were carefully examined by an experienced physician, with further investigations if needed to rule out mimicking conditions such as treatment failure or new opportunistic infections. Poor nutritional intake was also explored as an alternative explanation for the body changes. A diagnosis of lipoatrophy was retained only after alternative explanations for the fat changes were ruled out.[17] Stavudine was replaced for those with a total lipoatrophy score >5 ('treatment-limiting lipoatrophy'), which was considered to be clinically significant among treating physicians within the program.

Patients were weighed early in the morning before the consultations without shoes and with minimal clothing. Both centres used weigh balances (Seca, Hamburg, Germany), provided and maintained by MSF, throughout the study period.

2.4. Statistical analysis

On a daily basis, routine clinical information was prospectively gathered using Microsoft Access® software (Microsoft Corp., Redmond, WA, USA). Data were censured at the two year follow-up visit or at the latest visit if the total follow-up was shorter. To describe the overall pattern of weight evolution after ART initiation, a non-parametric method was used called LOWESS smoothing (for locally weighted scatterplot smoothing; 'lowess' command in STATA [StataCorp LP, College Station, Texas, USA]). This provides a representative smooth curve through data using robust local regression.

For each patient, we calculated the slope of weight (expressed as kg/year) during the second year of ART by linear regression. To identify determinants of weight change during the second year of ART, we performed multivariate linear regression analysis with the estimated slope of weight over time as dependent variable.

For the identification of patterns of weight loss predictive of lipoatrophy, sensitivity, specificity, negative and positive predictive values and area under the curve were calculated at different cut-offs of weight changes. Based on the receiver operating characteristic (ROC) curve, the cut-off with the optimal diagnostic performance was calculated taking into account the prevalence ('pre-test probability') of lipoatrophy. Given the higher prevalence of lipoatrophy in female patients, different cut-offs were calculated for men and women. Data analysis was done using the STATA software, version 10. The level of significance was set at $P < 0.05$.

3. results

3.1. Characteristics of the study population

There were 705 patients who met the inclusion criteria. Of these, 96 were excluded due to missing baseline data or a diagnosis of lactic acidosis leaving 609 patients in the analysis. Besides more advanced WHO clinical stage at baseline and lesser treatment adherence, excluded patients were generally comparable with the 609 retained for analysis.

The majority (73.2%) of patients were female and the median age was 35 years (interquartile range (IQR) 31–41). Most presented with advanced clinical disease as reflected in the median baseline CD4 cell count of 143 cells/μL (IQR 81–206). In total, 44 patients (7.2%) developed virological failure during the second year of ART, 74 (12.2%) were diagnosed with treatment-limiting lipoatrophy (Table 1). Lipoatrophy occurred more frequently in women (15.7%) than in men (2.4%).

3.2. Proportion of patients with weight loss after the first year on ART

As shown in Figure 1, after a rapid increase of weight during the first 6–12 months of treatment, an overall progressive decline in body weight was seen in patients at all baseline WHO stages, with a calculated median change of weight during the second year of ART of -1.1 kg/year (IQR -3.9;1.5; $P < 0.01$) for the entire study population. We estimated that 61.9% of patients had a progressive decline in body weight (a negative slope) during the second year of treatment, with a calculated median change of -3.1 kg/year (IQR -1.6;-5.6; $P < 0.01$). For those with stable or increasing weight, a median change of +2.3 kg/year (IQR 0.8; 5.2; $P < 0.01$) was observed.

Table 1
Baseline and on treatment characteristics of adult ART naïve patients on stavudine-based treatment regimens ($n = 609$).

Characteristic	Total ($n = 609$)
Age (years)[b]	35 (31–41)
Female sex[a]	446 (73.2)
Baseline WHO clinical stage III/IV (vs I/II)[a]	467 (76.7)
Use of nevirapine (vs efavirenz)[a]	587 (96.4)
Stavudine dose 40 mg (vs 30 mg)[a]	138 (22.7)
Baseline body weight (kg)	
Female[b]	54 (54–59)
Male[b]	56 (52–62)
Baseline CD4 count (cells/μL) [b]	143 (81–206)
Weight increase over the 1st year of ART (kg) [b]	2.0 (-0.3;5.4)
CD4 cell count during 2nd year of ART(cells/μL) [b]	279 (188–398)
Lipoatrophy during 2nd year of ART [a]	74 (12.2)
Virological failure during 2nd year of ART [a]	44 (7.2)
Adherence to ART[a,c]	
95–100%	273 (44.8)
90–95%	172 (28.4)
<90%	164 (26.9)

[a] n (%); [b] median (interquartile range); [c] based on pharmacy refill data. ART: antiretroviral treatment.

3.3. Association between weight loss and lipoatrophy, virological failure, ART adherence, and on-treatment CD4 count

In univariate analysis, the development of treatment-limiting lipoatrophy was positively associated with weight loss after the first year of ART (Table 2). This association remained significant in multivariate analysis, with an average decrease in weight of 2 kg/year associated with the development of lipoatrophy. No significant associations were found between weight loss and the development of virological failure or treatment adherence. Higher on-treatment CD4 cell count during the second year was found to be associated with a more favorable weight evo-

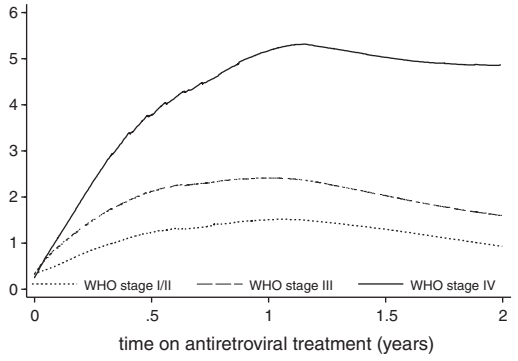

Figure 1. Weight evolution after initiation of stavudine-based antiretroviral treatment, stratified by baseline WHO clinical stage. Mean values are given.

Table 2
Multivariate analysis to identify on-treatment determinants of weight change during the second year of treatment (kg) ($n = 609$)[a].

	Univariate analysis		Multivariate analysis	
Variables	Effect (kg/year)	*P*	Effect (kg/year)	*P*
Lipoatrophy	−2.2 (−3.6;−0.8)	<0.01	−2.0 (−3.4;−0.6)	<0.01
Virological failure	0.9 (−0.9-2.7)	0.32	0.9 (−0.8-2.7)	0.29
Adherence to ART				
90–95% vs 95–100%	0.3 (−0.8;1.4)	0.58	0.0 (−1.0;1.1)	0.93
<90% vs 95–100%	0.7 (−0.4;1.9)	0.21	0.6 (−0.5;1.7)	0.41
CD4 cell count during 2nd year of ART(/100 cells/μL increase)	0.2 (−0.1;0.5)	0.18	0.4 (0.1;0.7)	0.01

[a] change (95% CI) in weight during second year of ART (kg/year); adjusted for age, sex, baseline WHO clinical stage and CD4 cell count, baseline weight, stavudine dose, non-nucleoside reverse transcriptase inhibitor used, weight change over the first year of treatment.
ART: antiretroviral treatment.

lution. Figure 2 shows the relation between weight loss and lipoatrophy (Figure 2A), virological failure (Figure 2B), adherence (Figure 2C) and on-treatment CD4 counts (Figure 2D) for up to two years of ART.

3.4. Validity and predictive values of weight loss for identifying patients with lipoatrophy

We reasoned that, compared to transient weight changes, weight loss associated with the occurrence of treatment-limiting lipoatrophy would be persistent, progressive and/or chronic (Figure 1). Consequently, the association between the following indicators and lipoatrophy were explored: (1) weight loss occurring on at least two consecutive occasions relative to the 'set-point' at 6–12 months after ART initiation, the period when weight appeared to stabilise in most patients (Figure 1), (2) progressive weight loss on at least two consecutive occasions with a minimal interval of one month and (3) weight loss occurring over a period of at least six months (Table 3). Overall, the diagnostic performance of the individual criteria was relatively limited. Sensitivity ranged from 29–100%; specificity varied between 58% and 93%. The criteria performed better for men than women, but higher positive predictive values were seen for women due to their increased prevalence of lipoatrophy. By combining different criteria, specificity could be improved. If only those meeting two out of the three criteria were considered to have a positive 'test', we obtained a sensitivity and specificity of 75% and 93% for men, and 71% and 70% for women. Positive and negative predictive values of 21% and 99% were found for men, and 32% and 92% for women. Overall, 177 patients (163 women and 14 men) or 29% of the study population would score 'positive' on these combined crite-

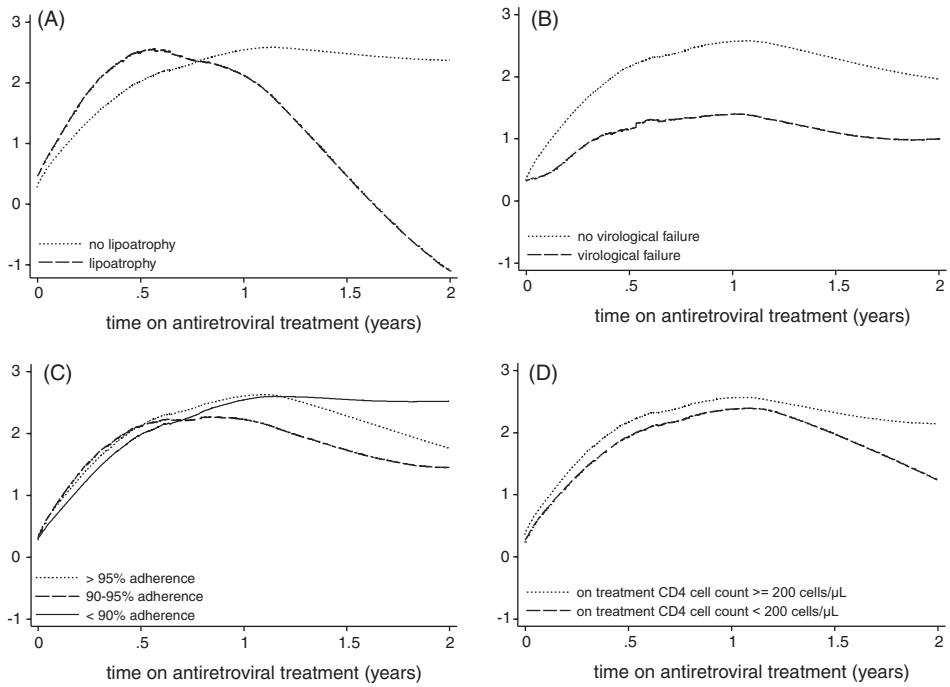

Figure 2. Weight evolution after initiation of stavudine-based antiretroviral treatment. The influence on weight evolution of the following on-treatment parameters is shown A. the development of treatment-limiting lipoatrophy during the 2nd year of treatment; B. the development of virological failure during the 2nd year of treatment; C. different treatment adherence levels; D. the mean CD4 cell count levels during the 2nd year of treatment. Mean values are given.

Table 3
Sensitivity, specificity, positive and negative predictive values and area under the curve of specific patterns of weight evolution to detect lipoatrophy during the second year of stavudine-based antiretroviral treatment ($n = 609$).

	MALE					FEMALE				
	Sensitivity	Specificity	PPV	NPV	AUC	Sensitivity	Specificity	PPV	NPV	AUC
Weight loss relative to the 'set-point' on ≥ 2 consecutive measurements with at least one month interval[a]										
≥ 1 kg	4/4 (100%)	97/159 (61%)	4/66 (6%)	97/97 (100%)	0.80	51/70 (73%)	222/376 (59%)	51/205 (26%)	222/241 (92%)	0.66
≥ 2 kg	2/4 (50%)	130/159 (82%)	2/31 (7%)	130/132 (98%)	0.66	27/70 (39%)	290/376 (77%)	27/114 (25%)	290/232 (86%)	0.58
≥ 3 kg[b]	2/4 (50%)	145/159 (91%)	2/16 (13%)	145/147 (99%)	0.71	22/70 (32%)	327/376 (87%)	22/71 (32%)	327/375 (87%)	0.59
Progressively declining weight on ≥ 2 consecutive occasions with at least one month interval										
≥ 1 kg[b]	3/4 (75%)	130/159 (82%)	3/32 (9%)	130/131 (99%)	0.78	32/70 (46%)	290/376 (77%)	32/119 (28%)	290/327 (88%)	0.61
≥ 2 kg	2/4 (50%)	148/159 (93%)	2/13 (15%)	148/150 (99%)	0.72	20/70 (29%)	346/376 (92%)	20/50 (40%)	346/396 (87%)	0.60
Weight loss occurring over a period of ≥ six months										
≥ 1 kg	3/4 (75%)	110/159 (69%)	3/52 (6%)	110/111 (99%)	0.72	52/70 (74%)	218/376 (58%)	52/210 (26%)	218/236 (92%)	0.66
≥ 2 kg	3/4 (75%)	124/159 (78%)	3/38 (8%)	124/125 (99%)	0.76	39/70 (56%)	271/376 (72%)	39/144 (28%)	271/302 (89%)	0.64
≥ 3 kg[b]	3/4 (75%)	135/159 (85%)	3/27 (11%)	135/136 (99%)	0.80	33/70 (47%)	305/376 (81%)	33/104 (33%)	305/342 (89%)	0.64
Combined criteria: two out of three criteria positive at 'optimal' cut-off										
	3/4 (75%)	148/159 (93%)	11/14 (21%)	148/149 (99%)	0.84	50/70 (71%)	263/376 (70%)	50/163 (32%)	263/284 (92%)	0.71

[a] set-point at six to 12 months after treatment initiation; [b] optimal cut-off;
PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve (receiver operating characteristic (ROC) curve

ria and would require more detailed assessment (Table 4). Inclusion of other clinical information like CD4 cell counts did not substantially improve diagnostic performance but only increased complexity.

4. Discussion

This is the first study reporting on the pattern and determinants of weight evolution after the first year of ART in adults taking stavudine-containing regimens in LIC. Our findings demonstrate that lipoatrophy and on-treatment CD4 cell count levels are the main determinants of weight evolution after the first year of ART.

Our findings are in line with previous observations of weight loss at the time of diagnosis of lipoatrophy.[15,17] The impact of virological failure on weight evolution during the second year of ART was not significant, and this has also been observed by others.[13] This probably reflects the fact that there is a time-lag period until immunological and clinical deterioration occurs following virological failure. However, since the lack of association could merely be due to the low number of patients with virological failure, this should be re-assessed in larger studies. We observed a more favorable weight evolution with higher on-treatment CD4 cell counts. Although the underlying mechanism remains to be explored, weight loss on ART could possibly be related to subclinical illness in those with lower CD4 counts or, alternatively, nutritional factors or treatment adherence might be implicated.

We note that even in patients without documented treatment-limiting lipoatrophy, there appeared to be a mild but significant overall weight loss after the first year of ART irrespective of WHO stage. Given the cumulative toxicity of stavudine, it remains to be assessed whether for these patients' weight loss might become clinically important after longer follow up periods. Weight loss associated with the use of stavudine was recently reported in women in the United States, which appeared to be only partly reversible after stavudine substitution.[25] The association of weight loss, body fat changes and stavudine use was also observed in a large randomized trial, comparing stavudine with tenofovir-based ART.[18] This study reported that, after an initial increase, the average body weight of the study population returned to baseline levels by three years of stavudine intake, paralleled by a gradual peripheral fat loss. Although the difference did not reach statistical significance, patients with poor treatment adherence appeared to have less weight loss after the first year of ART in our study. Many factors could be involved in this. It is possible that lesser cumulative exposure to stavudine could 'protect' against or delay weight loss.

Given the associated metabolic disturbance, and the potential detrimental impact on quality of life and adherence to treatment, these body alterations should be taken seriously, and provide another argument for increased access to less toxic drugs like tenofovir in LIC. Since lipoatrophy is only partially reversible upon drug substitution, timely diagnosis at all levels of the health care system will be pivotal. Simple monitoring tools and clinical protocols are required for use at the decentralized level.

Table 4
Proportion of patients with positive and negative test results when using weight evolution as a screening tool to detect lipoatrophy ($n = 609$).

Weight-based screening (combined criteria)	Lipoatrophy	No lipoatrophy	Total
Positive	53 (72%)	125 (23%)	177 (29%)
Negative	21 (28%)	411 (77%)	432 (71%)
Total	74 (100%)	535 (100%)	609 (100%)

In this vein, weight evolution after the first year of ART could be a useful clinical screening tool for lipoatrophy at the primary health care level. Body weight is a routine clinical measure used at all health facilities and it could provide guidance to nurses or non-physician clinicians to decide which patients should be referred for more detailed clinical assessment by the physician. This could help detect lipoatrophy at an early and possibly reversible stage. At the same time, it would be a rational use of the scarce physician time, since only 29% of patients would be referred for clinical assessment, i.e., they would have a positive 'screening' test. However, we note that 28% of the lipoatrophy cases would not have been identified through the assessment of weight evolution, highlighting the need to combine this tool with other strategies for early detection.

There are several limitations to this study. First, the findings have the intrinsic limitations of any observational analysis. Another limitation is the limited technical investigations available to validate the clinical diagnosis of lipoatrophy. However, the method used has been shown to correlate well with dual energy X-ray absorptiometry (DEXA) measurements,[26] patients were routinely screened for lipoatrophy and mimicking conditions were systematically ruled out. In addition, data on intercurrent opportunistic infections (particularly tuberculosis), which equally can cause sustained weight loss, would have been of value. However, since the incidence of tuberculosis is clearly reduced after the first year of ART, we think that the overall impact of new opportunistic infections including tuberculosis on weight evolution after the first year of ART is relatively limited. However, since weight loss was higher among those with CD4 counts <200 cells/ul, the possibility of undiagnosed opportunistic infections including tuberculosis cannot be excluded. Also, we did not integrate data on malnutrition or nutritional support provided in the program during the second year of ART. Since this was only very exceptionally provided for patients on chronic ART, we think this would not have influenced our findings in a significant manner.

At a primary care level in Kigali, Rwanda, lipoatrophy was found to be the principal determinant of weight loss after the first year of ART while on stavudine-based ART. In resource-limited setting, measuring weight is a routine clinical procedure that could be used for early identification of lipoatrophy, after consideration of other causes of weight loss like malnutrition and opportunistic infections.

Authors' contributions: JVG conceived the study and performed the data analysis; JVG, RZ, JM and TR contributed to analysis and interpretation of data; JVG, RZ and TR co-drafted the manuscript; JM 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, and MSF Ethics Review Board has indicated that formal ethics review was not required.

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