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Stavudine- and nevirapine-related drug toxicity while on generic fixed-dose antiretroviral treatment: incidence, timing and risk factors in a three-year cohort in Kigali, Rwanda

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ABSTRACT

This cohort study was conducted to report on the incidence, timing and risk factors for stavudine (d4T)- and nevirapine (NVP)-related severe drug toxicity (requiring substitution) with a generic fixed-dose combination under program conditions in Kigali, Rwanda. Probability of 'time to first toxicity-related drug substitution' was estimated using the Kaplan-Meier method and Cox-proportional hazards modeling was used to identify risk factors. Out of 2190 adults (median follow-up: 1.5 years), d4T was replaced in 175 patients (8.0%) for neuropathy, 69 (3.1%) for lactic acidosis and 157 (7.2%) for lipoatrophy, which was the most frequent toxicity by 3 years of antiretroviral treatment (ART). NVP was substituted in 4.9 and 1.3% of patients for skin rash and hepatotoxicity, respectively. Use of d4T 40 mg was associated with increased risk of lipoatrophy and early (<6 months) neuropathy. Significant risk factors associated with lactic acidosis and late neuropathy included higher baseline body weight. Older age and advanced HIV disease increased the risk of neuropathy. Elevated baseline liver tests and older age were identified as risk factors for NVP-related hepatotoxicity. d4T is associated with significant long-term toxicity. d4T-dose reduction, increased access to safer ART in low-income countries and close monitoring for those at risk are all relevant strategies.

1. Introduction

Over the last few years, significant progress has been made in the scale-up of antiretroviral treatment (ART) in low-income countries, with over three million people placed on therapy in low- and middle-income countries by the end of 2007.[1] The availability of a cheap, generic fixed-dose combination (FDC) containing stavudine (d4T), lamivudine and nevirapine (NVP) has played an important role in the scale-up of ART in these countries and still remains the pillar of many national ART programs in sub-Saharan Africa.

Considering the high incidence of d4T-related toxicities in Africa,[2] WHO currently recommends either using alternative drugs to d4T or, when this is not possible, reducing the dose of d4T to 30 mg in all patients, irrespective of body weight.[3,4] For various reasons, including the high cost and limited availability (as FDC) of alternatives, d4T will most likely remain frequently used within this continent over the coming years.[5]

Similarly, NVP has been shown to be associated with significant toxicity in high-income countries. Women with

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higher baseline CD4 counts, above 250 cells/μl in particular, are at higher risk of toxicity, with a documented 12-fold increase in risk of severe hepatotoxicity.[6] With ART treatment guidelines tending toward therapy initiation at higher CD4 thresholds (<350 cells/μl), an increasing number of patients, particularly women, will initiate NVP-based ART with higher baseline CD4 counts with concerns regarding safety.[7,8]

Although d4T- and NVP-related toxicity will remain important clinical challenges in Africa over the next few years, only limited long-term follow-up data on these toxicities from field settings are available. Such information could help design preventive strategies and contribute to improving patient care. In this study, we report on the incidence, timing and risk factors for d4T- and NVP-related toxicity requiring drug substitution after 3 years of ART in a large cohort followed up under program conditions in Kigali, Rwanda.

2. Materials and methods

2.1. Study setting and population

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 centers (Kimironko and Kinyinya health centers) in Kigali, Rwanda that were supported by Médecins Sans Frontières (MSF). The analysis included all ART-naive adult patients initiated on a generic FDC containing d4T, lamivudine and NVP up to January 2007.

2.2. Antiretroviral treatment and related toxicity

All HIV-positive adult patients presenting with WHO clinical stage IV, WHO clinical stage III with CD4 cell count <350 cells/μl or any patient with a CD4 cell count <200 cells/μl were considered eligible for ART.[3] Before ART initiation, patients were educated about the implications of the treatment, including recognition of drug side effects. In line with WHO recommendations, first-line ART consisted of an FDC of d4T, lamivudine and NVP.[3] d4T was given as 40 mg twice daily for patients with a body weight >60 kg at treatment initiation, and 30 mg for the remainder. In case of contraindications to d4T or NVP, zidovudine or efavirenz was prescribed. Once started on ART, patients were reviewed after 2 and 4 weeks and then monthly. Adherence to treatment was evaluated by self-report, regular clinical attendance and pill counts. Patients missing appointments were actively traced through community-based support groups. Those not coming to their last scheduled visit for more than 2 months without alternative explanations were defined as lost to follow-up. HIV care, including ART, consultations, lab tests and opportunistic infection medications, were provided free of charge.

Viral load counts were performed routinely after the first year of treatment from 2005.[9] CD4 cell counts were measured at baseline and every 6 months after ART initiation. A full blood count was done at baseline and at 12 weeks, and then every 6 months and on clinical grounds. Patients were weighed early in the morning before the consultations without shoes and with minimal clothing. Side effects were evaluated at each follow-up visit in line with WHO guidelines.[3] Liver-function tests were performed at baseline, 2, 4 and 8 weeks, and then every 6 months and on clinical grounds. Hepatotoxicity was identified on the basis of alanine aminotransferase levels. Neuropathy was assessed clinically.[3]

Lipoatrophy was assessed using a lipodystrophy case definition study-based questionnaire, as has been described previously.[10,11] This method combines self-reporting along with a formal clinical assessment by the health-care provider. This assessment was routinely performed on all adult patients who had been on stable first-line ART for over 1 year, or on clinical indication. For each of seven body regions, the degree of lipoatrophy was rated using the HIV outpatient study scale.[12] d4T substitution was indicated for those with a total lipoatrophy score >5, which was considered to be clinically significant among treating physicians within the program.[13]

Patients on ART were routinely screened for symptoms suggestive of symptomatic hyperlactatemia/lactic acidosis (SH/LA). In 2006, a point-of-care device for determination of the lactic acid levels (Accutrend Lactate, Roche, Basel, Switzerland) was introduced for patients with clinically suspected SH/LA. A case was defined as a patient on ART, presenting with compatible symptoms with other conditions associated with the symptoms ruled out, and a lactic acid level ≥2.5 mmol/l (uncuffed venous sample taken at rest). Gradual clinical improvement after ART interruption provided additional evidence of the correct diagnosis.[14] Before 2006, a standardized clinical protocol was used to diagnose and manage SH/LA, which was subsequently shown to perform well relative to the strategy using lactic acid levels.[15]

2.3. Data collection and statistical analysis

On a daily basis, routine clinical information was prospectively gathered using Microsoft Access software (Microsoft Corp., Redmond, WA, USA). The reasons for drug substitutions documented by the clinicians were subsequently coded during data extraction. Symptomatic hyperlactatemia and lactic acidosis were grouped together as SH/LA, as no pH measurements were performed. Patient time on a specific drug was calculated from initiation of ART until the date of drug substitution, with right-censoring done at the last clinical visit for the remainder. The outcome in the analysis was severe toxicity, defined as toxicity requiring drug substitution, due to NVP and d4T. Probabilities of 'time to first toxicity-related drug substitution' related to NVP and d4T were estimated using the Kaplan-Meier methodology. Risk-factor analysis was performed using multivariate Cox regression. For NVP-related toxicity, owing to the lower number of events, the number of covariates included in the multivariate model was restricted, besides sex and baseline CD4 count, to those with a *P*-value <0.1 in univariate analysis; for d4T-related toxicity, all covariates assessed in univariate analysis were included in the multivariate analysis. For the analysis of d4T-related toxicity, the occurrence of neuropathy was defined as early (<6 months on ART) or late (>6 months on ART) for the

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following reasons: (1) in our clinical experience, neuropathy occurring late is often associated with features of lipoatrophy and/or SH/LA, in contrast with early neuropathy; (2) the overlapping clinical presentation of lipoatrophy, SH/LA and late neuropathy has been reported before;[16] (3) consequently, early and late neuropathy might be expressions of different underlying processes and grouping these together might bias the risk-factor analysis. The level of significance was set at $P < 0.05$. Data analysis was done using STATA version 9 (Stata Corp., College Station, TX, USA).

3. Results

3.1. Characteristics of the study population

By January 2007, 2654 adult patients had been started on ART, of whom 2190 ART-naive adults had started a generic FDC containing d4T, lamivudine and NVP (Table 1). The majority of these were female, and the median age at the start of treatment was 36 years. Sixty percent were in WHO stage III at treatment initiation, and the median baseline CD4 count was 158 cells/μl. Treatment outcomes censored on July 1 2007 included 100 (4.6%) deaths, 107 (4.9%) lost to follow-up and 127 (5.8%) transferred to another ART site. Over 74% were initiated with d4T dosed at 30 mg twice daily. The median time of follow-up with exposure to d4T was 1.5 years, and slightly higher for NVP (Table 1).

3.2. ART-related toxicity

d4T was replaced because of severe toxicity for 411 patients (18.8%). In total, 175 patients (8.0%) developed a severe neuropathy, 69 (3.1%) were diagnosed with severe SH/LA, 157 (7.2%) changed d4T owing to lipoatrophy and 10 substituted d4T because of other d4T-related toxicity. This corresponded to an incidence rate of 52, 20 and 47/1000 patient-years for neuropathy, SH/LA and lipoatrophy, respectively. The time of occurrence of the different side effects is summarized in the Kaplan-Meier graph in Figure 1. Within the first 6 months of ART, the main side effect was peripheral neuropathy. After 6 months of treatment, cases of SH/LA became more apparent, and after 1 year of ART a growing incidence of lipoatrophy was reported. By 3 years of treatment, it was the most frequent complication, requiring drug substitution for 20.8% (Table 2).

Table 1
Baseline characteristics of adult patients initiating stavudine- and nevirapine-containing antiretroviral treatment ($N = 2190$)

Age (years)[a]	36 (31–42)
Female[b]	1567 (71.5)
Baseline WHO clinical stage[b]	
Stage I	103 (4.7)
Stage II	620 (28.4)
Stage III	1306 (59.7)
Stage IV	157 (7.2)
Baseline body weight (kg) ($n = 2102$)[a]	56 (50–62)
Female	55 (49–61)
Male	57 (52–62)
Baseline CD4 count (cells/μl) ($n = 2064$)[a]	158 (94–220)
>250 cells/μl[b]	311 (15.1)
Follow-up time on d4T-based ART (years)[a]	1.5 (0.8–2.1)
Follow-up time on NVP-based ART (years)[a]	1.7 (0.9–2.3)
Stavudine dose at ART start[b]	
30 mg	1637 (74.7)
40 mg	553 (25.3)

ART: antiretroviral treatment; d4T: stavudine; NVP: nevirapine.
[a] Data represent *n* (%).
[b] Data represent median (interquartile range).

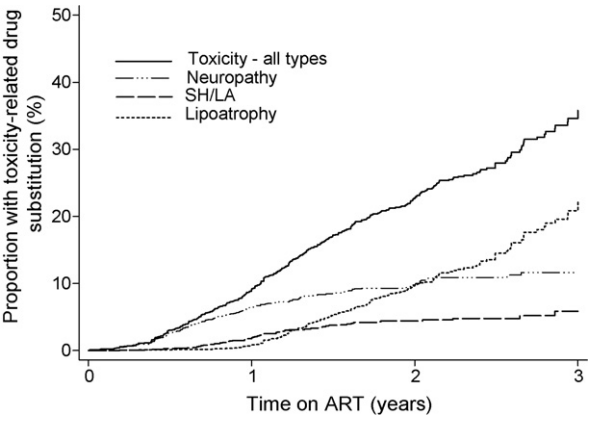

Figure 1. Kaplan-Meier curve depicting the proportion of patients substituting stavudine because of drug toxicity.

In univariate analysis, the use of d4T 40 mg increased the risk of all toxicities. Similarly, higher body weight was associated with increased risk, except for early neuropathy, and most pronounced for SH/LA. However, as patients with higher body weight were also more likely to receive d4T at a higher dose, the association was further explored in multivariate analysis (Table 3). In multivariate analysis, after adjusting for body weight, the use of d4T 40 mg was associated with increased risk of lipoatrophy and early neuropathy. Irrespective of the d4T dose, higher baseline body weight increased the risk of SH/LA and late neuropathy. In an alternative manner, to take into account the weight-adjusted dosing of d4T, we repeated the analysis using d4T dose/body weight in the model instead of d4T 40 vs. 30 mg, which yielded essentially the same findings, except that increased body weight was associated with increased risk of lipoatrophy (HR 6.2; 95% CI 3.2–12.2 for body weight >70 kg). Equally, when patients that had their d4T dose changed during follow-up were excluded, the same risk factors were identified. Being female was a strong risk factor for lipoatrophy and SH/LA. Age and advanced clinical HIV disease were identified as additional risk factors for neuropathy. Finally, we restricted the analysis to the 1677 patients with body mass index (BMI) data available. Relative to patients with a BMI of <20 kg/m^2, a significant increased risk of SH/LA was seen for those with a BMI of >30 kg/m^2 (adjusted HR 5.7; 95% CI 1.8–18.2) and with a BMI of 25–30 kg/m^2 (adjusted HR 2.5; 95% CI 1.0–6.6). Patients with a BMI >30 kg/m^2 were more likely to change d4T due to lipoatrophy, but this difference was not statistically significant (adjusted HR 2.3; 95% CI 0.9–5.9). A positive association of BMI 25–30 kg/m^2 (adjusted HR 2.1; 95% CI 1.0–4.2) and BMI >30 kg/m^2 (adjusted HR 2.8; 95% CI 1.0–7.9) with

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Table 2
Occurrence of toxicity-related drug substitutions for adult patients on stavudine- and nevirapine-based antiretroviral treatment regimens ($N = 2190$)

Drug-related toxicity	Events (%)	Rate/1000 py	Proportion with toxicity-related drug substitution (%)[a]			
			6 m	12 m	24 m	36 m
Stavudine						
Toxicity – all types	411 (18.8)	122	3.0	9.2	22.7	34.6
Neuropathy	175 (8.0)	52	2.6	6.5	9.8	11.6
SH/LA	69 (3.1)	20	0.2	1.9	4.4	5.8
Lipoatrophy	157 (7.2)	47	0.1	0.8	9.7	20.8
Nevirapine						
Toxicity – all types	138 (6.3)	39	5.8	6.0	6.9	7.1
Skin toxicity	108 (4.9)	30	4.8	4.9	5.3	5.4
Liver toxicity	29 (1.3)	8	1.0	1.1	1.5	1.6

Py: patient-years; SH/LA: symptomatic hyperlactatemia/lactic acidosis.
[a] Kaplan-Meier estimates, time to first severe toxicity (i.e. requiring treatment change) at specified months on ART.

Table 3
Risk factors associated with stavudine-related neuropathy, lipoatrophy and SH/LA[a]

	Early neuropathy[b]		Late neuropathy[b]		Lipoatrophy		SH/LA	
	HR (95% CI)	aHR (95% CI)	HR (95% CI)	aHR (95% CI)	HR (95% CI)	aHR (95% CI)	HR (95% CI)	aHR (95% CI)
Sex								
Male	1	1	1	1	1	1	1	1
Female	0.7 (0.4–1.3)	0.9 (0.5–1.9)	1.1 (0.7–1.7)	1.4 (0.9–2.2)	8.3 (3.9–17.8)	9.7 (4.5–21.0)	4.5 (1.8–11.4)	5.2 (2.1–13.1)
Age (years)								
≤35	1	1	1	1	1	1	1	1
>35	1.9 (1.0–3.7)	1.8 (1.0–3.6)	2.7 (1.8–4.3)	2.7 (1.7–4.3)	0.9 (0.7–1.3)	1.2 (0.8–1.6)	1.2 (0.7–2.0)	1.3 (0.8–2.2)
Baseline body weight (kg)								
<50	1	1	1	1	1	1	1	1
50–60	1.0 (0.4–2.2)	0.9 (0.4–2.0)	0.8 (0.5–1.4)	0.8 (0.5–1.5)	1.3 (0.8–2.0)	1.5 (0.9–2.4)	1.6 (0.7–3.8)	1.8 (0.8–4.3)
60–70	1.4 (0.6–3.3)	0.8 (0.3–2.2)	1.7 (1.0–3.0)	2.5 (1.3–4.9)	1.6 (1.0–2.7)	1.3 (0.6–2.6)	3.2 (1.3–7.6)	3.9 (1.3–11.5)
>70	0.8 (0.2–2.7)	0.4 (0.1–1.9)	3.0 (1.7–5.5)	4.4 (2.0–9.5)	3.2 (1.8–5.6)	1.9 (0.9–4.3)	7.0 (2.9–17.1)	7.4 (2.3–23.9)
Stavudine starting dose								
30 mg	1	1	1	1	1	1	1	1
40 mg	2.0 (1.1–3.8)	2.6 (1.1–6.0)	1.7 (1.2–2.6)	0.6 (0.3–1.1)	2.0 (1.4–2.8)	2.1 (1.1–3.9)	2.6 (1.6–4.3)	1.0 (0.4–2.3)
Baseline CD4 count (cells/μl)								
<100	1	1	1	1	1	1	1	1
100–200	1.0 (0.4–2.2)	1.3 (0.5–3.0)	1.3 (0.8–2.1)	1.3 (0.8–2.1)	1.2 (0.8–1.8)	1.0 (0.7–1.6)	1.8 (0.9–3.6)	1.4 (0.7–2.9)
>200	1.2 (0.5–2.6)	1.8 (0.8–4.1)	1.3 (0.8–2.1)	1.2 (0.7–2.1)	1.4 (0.9–2.2)	1.1 (0.7–1.7)	1.8 (0.9–3.8)	1.3 (0.6–2.8)
Baseline WHO clinical stage								
I/II	1	1	1	1	1	1	1	1
III/IV	2.6 (1.1–6.2)	2.6 (1.1–6.3)	1.9 (1.2–3.1)	2.0 (1.2–3.2)	1.4 (0.9–2.1)	1.6 (1.0–2.4)	1.5 (0.9–2.8)	1.8 (1.0–3.2)

aHR; adjusted hazard ratio; ART: antiretroviral treatment; SH/LA: symptomatic hyperlactatemia/lactic acidosis.
[a] Excluding 193 individuals with missing baseline data ($N = 1997$).
[b] Neuropathy was defined as early if occurring <6 months on ART and later thereafter.

the occurrence of late neuropathy was seen (data not shown).

A total of 138 (6.3%) patients replaced NVP for reasons of toxicity. Of these, 108 (4.9%) were related to skin rash and 29 (1.3%) to hepatotoxicity, which corresponded to incidence rates of 30 and 8/1000 patient-years, respectively (Table 2). Most (93%) of the substitutions due to skin rash occurred within the first 6 months, with a median time of 4 weeks [interquartile range (IQR) 3–6]. For hepatotoxicity, the median time of substitution was 5 weeks (IQR 3–29), with 28% occurring after 6 months of NVP use. No independent risk factors for skin rash were identified. Elevated baseline liver-function tests and older age were identified as risk factors for hepatotoxicity (Table 4). Baseline CD4 count and sex were not associated with NVP-related toxicity. The same findings were seen when analyzing the data stratified by sex, and using different CD4 cell count categories. No single drug substitution was made for lamivudine-related toxicity.

4. Discussion

This study provides long-term estimates of the pattern of toxicity associated with the most commonly used generic FDC combination in sub-Saharan Africa. Significant long-term toxicity was seen with d4T, especially lipoatrophy. Significant risk factors were found for the different d4T-related toxicities. In addition, this is the first report that specifically assesses the impact of weight-dosing of d4T on the occurrence and risk factors for d4T-related toxicity. NVP was mainly associated with early toxicity; no association with sex or baseline CD4 count was found.

With regards to d4T, our findings on incidence and timing are in line with those from an ART program in South Africa.[17] That study identified female sex and high baseline body weight (>60 kg and particularly >75 kg) as risk factors for SH/LA and lipodystrophy. In contrast to that study, we explored the independent effect of d4T dosing to assess whether the association of certain side effects

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Table 4
Risk factors associated with nevirapine-related skin rash and hepatotoxicity

	Skin rash[a]		Hepatotoxicity[b]	
	HR (95% CI)	aHR (95% CI)	HR (95% CI)	aHR (95% CI)
Sex				
Male	1	1	1	1
Female	1.0 (0.7–1.7)	1.1 (0.7–1.7)	0.6 (0.3–1.3)	0.9 (0.4–2.1)
Age (years)				
≤35	1		1	1
>35	0.9 (0.6–1.4)		2.3 (0.9–5.4)	2.6 (1.1–6.4)
Baseline body weight (kg)				
<50	1		1	
50–60	1.3 (0.8–2.2)		1.3 (0.4–2.9)	
60–70	1.1 (0.6–2.1)		1.3 (0.4–2.8)	
>70	1.0 (0.5–2.4)		0.4 (0.1–3.7)	
ALT (IU/l)				
<40	1		1	1
40–100	1.0 (0.5–1.9)		3.8 (1.6–9.0)	4.0 (1.7–9.6)
>100	1.1 (0.2–7.8)		15.6 (4.5–53.6)	18.1 (5.2–63.4)
Baseline CD4 count (cells/μl)				
≤250	1	1	1	1
>250	1.1 (0.7–1.9)	1.1 (0.7–1.9)	0.7 (0.2–2.3)	0.9 (0.3–2.9)
Baseline WHO clinical stage				
I/II	1		1	
III/IV	1.1 (0.7–1.7)		1.3 (0.5–3.1)	

ALT: alanine aminotransferase; ART: antiretroviral treatment; IU: international units.
[a] Excluding 126 individuals with missing baseline CD4 data ($N = 2064$).
[b] Excluding 365 individuals with missing baseline CD4/ALT data ($N = 1825$).

with baseline body weight persisted after adjusting for weight-based dosing. According to our data, the proposed dose reduction would mainly result in a reduction in early neuropathy and lipoatrophy. The risk of SH/LA and late neuropathy appeared to be independent of the use of d4T 40 mg, and as such, patients with a higher body weight (particularly >70 kg) will still need to be monitored closely for these toxicities.

The incidence and timing of NVP-related toxicity are comparable to those from other African countries.[7,8,17] Whereas data from Western countries have not consistently shown specific risk factors for skin rash, it is generally accepted that a high baseline CD4 count and being female are associated with NVP-related liver toxicity.[6] However, African studies have reported different results.[7,8] No single study clearly revealed high CD4 count as a risk factor, and most have not seen an association with sex. Given the trend to initiate lifelong (NVP-based) highly active antiretroviral therapy (HAART) at higher CD4 count levels (<350 cells/μl) and prophylactic HAART at even higher levels, these and our data are reassuring, as for the risk of liver toxicity. However, alternative explanations for these observations have to be considered, as incomplete ascertainment of outcomes (e.g. unreported fatal liver toxicity occurring at home) in some of these studies could easily result in bias. As such, detailed prospective studies are still warranted to corroborate these findings. Equally, more data are needed to define whether this also holds for pregnant women and prophylactic use of HAART within prevention of mother-to-child transmission programs. As reported before, baseline abnormal liver tests were associated with hepatotoxicity.[6,18] Whether this is related to concurrent use of hepatotoxic drugs, alcohol abuse or associated viral hepatitis infection could not be determined from our data, but has been reported before.[7,8,18] Our data would suggest that, if conditions allow, performing a baseline liver-function test might allow identification of patients requiring closer follow-up and/or avoidance of NVP-based HAART. In contrast with another report,[17] we did not find a higher risk of NVP toxicity for those with a baseline body weight <60 kg, although there was a trend toward higher risk with lower BMI (data not shown), as reported previously.[19]

From a programmatic perspective, given the significant overall toxicity related to the FDC ART regimen in this study, especially d4T, these data provide additional evidence for the urgent need for greater accessibility and affordability of safer FDC regimens in low-income countries. Meanwhile, long-term toxicity related to d4T will remain the reality in the field. This underscores the need to provide practical guidance to clinicians in managing these side effects.

There are several strengths to this study, including relatively long follow-up, high retention rates and standardized case definitions and recording of side effects. The study also includes data from a program setting and thus is likely to reflect the operational reality on the ground. However, there are also a number of limitations. This is an observational study performed retrospectively on existing data and, as such, unmeasured confounders might have biased our results. Detailed data on adherence, clinical events and baseline viral load measurements were not available and baseline CD4 counts and liver-function tests were missing for some patients. However, because the only difference in baseline characteristics of the excluded patient population relative to those with complete data was a more recent ART initiation of a month, this potential bias would have been limited. As these data come from routine care settings, we cannot exclude that, over

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time, the team became more 'sensitized' toward certain side effects and that specific toxicities became more readily recognized. However, as our outcome was severe toxicity (i.e. requiring substitution), we do not expect a major impact on our estimates. Equally, in the early stage of the program, no lactic acid determination could be done. However, we have previously observed that the lack of this test had only a minor impact on our management in terms of drug substitution.[15] Still, small biases in the estimates cannot be excluded. Finally, although we tempted to verify all patient records of deceased patients for unreported toxicities, it is still possible that some cases were missed.

One in four patients placed on a d4T-containing FDC in our program setting ended up with significant long-term toxicity. D4T-dose reduction to 30 mg, increased access to safer antiretroviral drugs in low-income countries and close monitoring for those at risk are all relevant strategies that need to be urgently considered.

Authors' contributions

JVG conceived the study and performed the data analysis; JVG and EFA were physicians treating the patients within the ART program and implemented the study; JVG, RZ, FR, JM, EFA and TR contributed to analysis and interpretation of data; JVG, RZ and TR co-drafted the manuscript; EFA, JM and FR 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 the MSF Ethics Review Board has indicated that formal ethics review was not required.

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