Original article

Severe hyperlactataemia complicating stavudine first-line antiretroviral therapy in South Africa

David Stead[1,2], Meg Osler[3,4], Andrew Boulle[3], Kevin Rebe[1,5] and Graeme Meintjes[1,5,6]*

[1]GF Jooste Hospital, Cape Town, South Africa
[2]Médicins Sans Frontières, Cape Town, South Africa
[3]Infectious Disease Epidemiology Unit, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa
[4]Department of Health, Provincial Government of the Western Cape, Cape Town, South Africa
[5]Department of Medicine, University of Cape Town, Cape Town, South Africa
[6]Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa

*Corresponding author: E-mail: davestead@mweb.co.za

Background: In the public sector antiretroviral therapy (ART) programme in South Africa the standardized first-line regimen includes stavudine (d4T). Severe symptomatic hyperlactataemia (SHL) is a potentially life-threatening complication of d4T.

Methods: GF Jooste Hospital is a referral centre for six ART clinics. We retrospectively reviewed cases referred with lactate levels ≥5 mmol/l that were attributed to nucleoside reverse transcriptase inhibitors from August 2003 to November 2005. We calculated cumulative ART exposure in patients attending these clinics to derive a referral rate.

Results: In total, 75 patients were referred with severe SHL (71 female). All had been on d4T and on ART for a median of 10 months. The referral rate for severe SHL was 17.5 cases per 1,000 patient-years. In 53 patients (71%), lactic acidosis (standard bicarbonate [$SHCO_3$]<20 mmol/l) was confirmed, resulting in a referral rate of 12.3 cases per 1,000 patient-years. Twelve patients (16%) died during acute admission (≤30 days). $SHCO_3$<15 mmol/l and pH<7.2 were the only factors associated with acute mortality (odds ratio [OR] 22.5, 95% confidence interval [CI] 2.8–1,045.7 and OR 13.9, 95% CI 2.7–86.9, respectively). A total of 30 less severe cases were rechallenged with zidovudine without recurrence of SHL.

Conclusions: This study confirms a high incidence of severe SHL in Africa, which has been shown in previous studies. Rechallenge with zidovudine in less severe cases was found to be safe.

Introduction

Symptomatic hyperlactataemia (SHL) is an infrequent, but potentially life-threatening, complication of nucleoside reverse transcriptase inhibitors (NRTIs). It results from the inhibition of human mitochondrial DNA polymerase-γ by these agents and, in severe cases, could lead to metabolic acidosis (termed lactic acidosis [LA]), which is associated with a mortality risk of up to 60% [1,2]. The NRTIs stavudine (d4T) and didanosine (ddI) have been most consistently associated with the occurrence of SHA and LA (SHL/LA) [2–6]. In cohorts from the developed world, the incidence of LA has ranged from 1.3 to 3.9 cases per 1,000 patient-years on treatment [7]. Other manifestations of mitochondrial toxicity (such as peripheral neuropathy, pancreatitis, lipodystrophy and hepatic steatosis) may present in association with SHL/LA. Recent reports have raised concerns regarding the problems posed by SHL/LA for antiretroviral therapy (ART) programmes in the developing world [6,8,9,11]. In these settings SHL/LA present significant diagnostic and management challenges because of staff and resource shortages that limit clinical and laboratory monitoring.

The South African public sector ART programme was initiated in April 2004 following successful outcomes demonstrated by pilot treatment programmes that were run by non-governmental organizations and the provincial government since 2001 [12]. It is estimated that >400,000 people are now receiving ART via the government programme. First-line ART is standardized, comprising d4T, lamivudine (3TC) and either efavirenz or nevirapine. Second-line therapy consists of zidovudine (AZT), ddI and lopinavir/ritonavir [13]. Tenofovir (TDF) and abacavir were not available during the study period because of cost and registration issues. Given the routine use of d4T in first-line therapy, as is the case

for most sub-Saharan African countries, a high rate of mitochondrial toxicity was anticipated [6,8,9].

We undertook this study to document the referral rate and outcomes of severe SHL (defined as serum lactate ≥5 mmol/l) related to ART in a South African setting and to investigate risk factors for developing SHL. We also assessed the safety of rechallenge with AZT (an NRTI that carries a lower risk for mitochondrial toxicity) in a subset of patients with less severe presentations, with close lactate monitoring.

Methods

Study site and population

GF Jooste Hospital is a public sector secondary hospital in Cape Town, South Africa. It is the referral centre for ART complications for six surrounding primary level ART clinics. The majority of patients enrolled at these clinics are of Black ethnicity. Local clinical guidelines for the management of SHL/LA during the study period recommended that all suspected cases were referred to GF Jooste Hospital. All patients referred in whom there was a clinical suspicion of SHL or LA had serum lactate measured, together with a clinical assessment and other relevant investigations. There was a high index of suspicion among the attending doctors at GF Jooste Hospital, because of doctor education on this toxicity. Those patients with laboratory-confirmed severe SHL were managed by withdrawing ART in most cases, by supportive therapy (intravenous fluids, intravenous vitamin B supplementation and empiric antibiotics in severely ill patients) and by management of complications [2,14].

Procedure

A retrospective cohort analysis was performed. The hospital laboratory database was reviewed from 1 August 2003 to 30 November 2005 to retrieve all cases with a serum lactate measurement ≥5 mmol/l. The case notes of these patients were reviewed, and where the hyperlactataemia was not NRTI-related, patients were excluded. For each case we collected data from the primary ART clinic and hospital case notes relating to demographics, HIV and ART history, weight trends, clinical features, laboratory results, management and outcome. Follow-up continued until 31 July 2006.

At presentation all venous blood samples for lactate were taken without a tourniquet, in a tube containing fluoride, and rapidly transported to the laboratory for processing. Lactate was measured on a Beckman–Coulter Synchron CX® system (Brea, CA, USA). Blood gas for pH and $SHCO_3$ was done for venous or arterial blood samples. Patients reinitiated on AZT regimens had clinical assessments and lactate measurements done at 1, 2, 4, 8, 12 and 24 weeks. Many of these follow-up lactate measurements were on point-of-care Roche Accutrend® lactate devices (Mannheim, Germany) used at the primary clinics.

Definitions

Severe SHL was defined as a serum lactate (arterial or venous) measurement ≥5 mmol/l, together with compatible symptoms of NRTI-related hyperlactataemia. LA was defined as a subgroup of severe SHL, with a standard bicarbonate ($SHCO_3$)<20 mmol/l. Compatible symptoms included non-specific gastrointestinal symptoms (anorexia, nausea, vomiting and abdominal cramps), fatigue, weight loss and dyspnoea [2,7]. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Acute mortality was defined as death ≤30 days from the time of admission to hospital.

Ethics

Ethical approval was given by the University of Cape Town Research Ethics Committee.

Statistical analyses

We calculated the cumulative patient-years of ART exposure among patients attending the six ART clinics for the same period during which the cases were referred. This was based on the provincial monthly reporting from the facility-based aggregate record keeping [15] and formed the denominator for calculating a referral rate for SHL/LA. Poisson 95% confidence intervals (CIs) were calculated for rates. The percentage of females on ART at the six facilities was calculated using the same provincial data source.

Associations with acute mortality were explored using exact logistic regression. Factors found to be associated with mortality were initially identified in univariate analyses and subsequently tested in bivariate models that included the major association with acute mortality, which was low $SHCO_3$ at presentation. $SHCO_3$ was chosen over pH in multivariate models as it was felt to be a more reliable marker of metabolic acid-base status than pH, which is affected by respiratory compensation. Further multivariate model building was not possible because of the limited sample size. Median durations on d4T were compared using the Kruskal–Wallis rank test. All tests of significance were two-tailed. All analyses were performed using Stata™ version 9 (Stata Corporation, College Station, TX, USA).

Results

A total of 89 patients had laboratory lactates recorded at ≥5 mmol/l during the study period. Of these patients, 14 were excluded because of hyperlactataemia that was attributed to reasons other than NRTI toxicity. Reasons

for exclusion were ART-naive (*n*=4), a normal repeat lactate level suggesting spurious increase (*n*=5) and severe hypoxia, hepatitis or dehydration as the cause rather than NRTIs (*n*=5). Overall, 75 patients were included in the analysis; their characteristics are shown in Table 1 and all were of Black or mixed ethnicity.

In total, 73 patients were on first-line ART. The NRTI component of the ART regimen was d4T and 3TC in 65 patients, d4T and ddI in two patients (who were on second-line ART) and AZT and 3TC in eight patients. All of these eight patients had been switched from d4T-containing regimens within the preceding 3 weeks because of neuropathy or symptomatic lactate elevations of 2.5–5 mmol/l. Patients had been on ART for a median of 10 months (interquartile range [IQR] 8–12; Figure 1). The most frequently reported symptoms were nausea and vomiting (65%), abdominal pain (44%), dyspnoea (19%) and fatigue (16%). The median serum lactate at presentation was 7.6 mmol/l (IQR 5.9–9.8), with the highest level at 24.9 mmol/l.

LA was confirmed in 53 patients (71%). In seven patients, no $SHCO_3$ measurement was performed. During the study period there was a cumulative exposure to ART of 4,295 patient-years at all six ART clinics, resulting in a referral rate for severe SHL of 17.5 cases per 1,000 patient-years (95% CI 13.7–21.9) and for LA of 12.3 cases per 1,000 patient-years (95% CI 9.2–16.1) on ART. Among the patients on ART during the study period, 68% were female. This represented a referral rate for severe SHL of 24.3 cases per 1,000 patient-years (95% CI 19.0–30.7) for females and 2.9 cases per 1,000 patient-years (95% CI 0.8–7.5) for males.

Most patients gained weight on ART to a peak weight and then lost weight prior to presentation with severe SHL (Figure 2). The median weight at initiation of ART was 71 kg (IQR 64–82). BMI was calculated on 47 patients for whom heights were obtainable: 26 patients (55% of calculated BMIs) were obese (BMI≥30) at ART initiation. The median duration on ART at which peak weight was attained was 7 months (IQR 5–9). The median peak weight was 82 kg (IQR 71–95), representing a median 11 kg weight gain on ART (*P*<0.001). The median weight at diagnosis of severe SHL was 74 kg (IQR 65–85), representing a median 8 kg loss from peak weight (*P*<0.001).

There was a high frequency of comorbid conditions identified during the presentation with severe SHL (Table 2). Sixty-one patients (81%) had one or more additional manifestations of mitochondrial toxicity identified. The most frequent was peripheral neuropathy in 38 patients (51%), followed by hepatic steatosis in 20 (27%), lipodystrophy in 15 (20%), acute pancreatitis in 12 (16%), idiopathic oedema in 7 (9%) and 3 (4%) cases of HIV-associated neuromuscular weakness syndrome. Eleven patients (15%) had concurrent infections diagnosed, including bacterial pneumonias, tuberculosis, urinary tract infections and septicaemia. The median duration on d4T in the 11 patients presenting with an infection was 30 weeks, compared with 43 weeks in the 64 patients who did not have an acute infection at presentation (*P*=0.002).

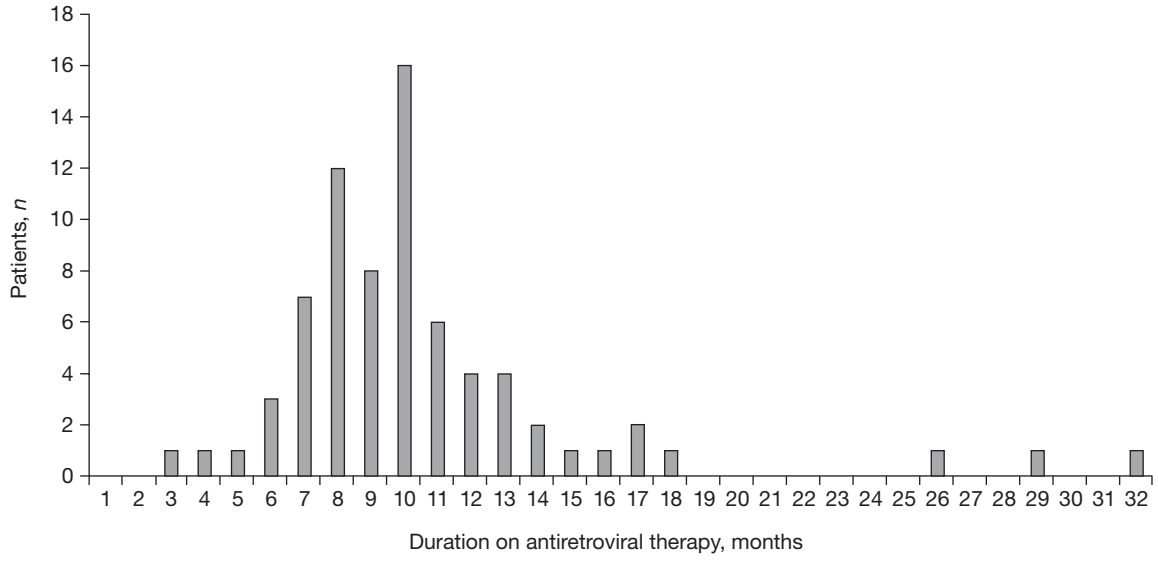
Twelve patients (16% of the severe SHL patients and 21% of LA patients) died during acute admission. The median time to death was 2.5 days (IQR 1.0–9.3). Factors found to be strongly associated with acute mortality in univariate analyses were a pH<7.2 (odds ratio [OR] 13.9, 95% CI 2.7–86.9) and $SHCO_3$<15 mmol/l (OR 22.5, 95% CI 2.8–1,045.7). Although lactate levels, renal failure, shortness of breath and pancreatitis at presentation were associated with mortality in univariate analysis, these associations no longer persisted when combined with $SHCO_3$ in bivariate models (Table 3).

Table 1. Demographic and clinical characteristics of patients referred with severe symptomatic hyperlactataemia

Characteristic	Value
Median age, years (range)	33 (21–57)
Female gender, *n* (%)	71 (95)
WHO clinical stage	
1 and 2, *n* (%)	10 (13)
3, *n* (%)	32 (43)
4, *n* (%)	30 (40)
Unknown, *n* (%)	3 (4)
Median $CD4^+$ T-cell count	
Nadir, cells/mm^3 (IQR)	84 (42–145)
Before presentation, cells/mm^3 (IQR)*	222 (160–295)
Most recent HIV viral load†	
<400 copies/ml, *n* (%)	67 (89)
400–5,000 copies/ml, *n* (%)	3 (4)
>5,000 copies/ml, *n* (%)	2 (3)
Unknown, *n* (%)	3 (4)
NRTI regimen	
d4T+3TC, *n* (%)	65 (87)
AZT+3TC, *n* (%)‡	8 (11)
d4T+ddI, *n* (%)	2 (3)
d4T dose§	
80 mg daily, *n* (%)	68 (91)
60 mg daily, *n* (%)	7 (9)
NNRTI or PI in regimen	
Efavirenz, *n* (%)	55 (73)
Nevirapine, *n* (%)	18 (24)
Lopinavir/ritonavir, *n* (%)	2 (3)
Median lactate level, mmol/l (IQR)	7.6 (5.9–9.8)

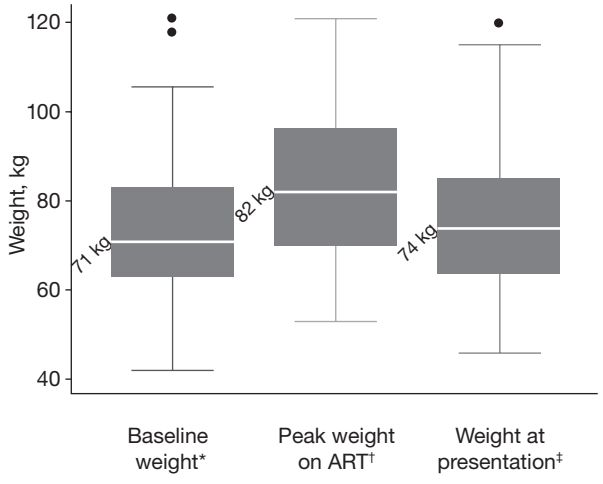
Overall, 75 patients were included in the study. *These are the most recent routine $CD4^+$ T-cell counts, tested every 6 months, before patients presented with severe symptomatic hyperlactataemia. †Viral loads were routinely tested every 6 months. ‡All eight patients on zidovudine (AZT) had been switched from stavudine (d4T) to AZT within the preceding 3 weeks because of symptomatic hyperlactataemia (lactate level 2.5–5 mmol/l) or neuropathy. §Includes the eight patients recently switched to AZT. ddI, didanosine; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; WHO, World Health Organization; 3TC, lamivudine.

Figure 1. Duration from the initiation of antiretroviral therapy to presentation with severe symptomatic hyperlactataemia



The median duration on antiretroviral therapy was 10 months (interquartile range 8–12). The two late cases at 29 and 32 months had been switched from zidovudine- and lamivudine-containing first-line regimens to stavudine- and didanosine-containing second-line regimens because of virological failure at 13 and 24 months, respectively. The maximum time exposed to stavudine was 26 months.

Figure 2. Weight changes from antiretroviral therapy initiation to presentation with severe symptomatic hyperlactataemia



Box and whisker plot depicting the distribution, medians and interquartile ranges (IQRs) of patient weights at different time points. The upper edge of the box indicates the 75th percentile and the lower edge represents the 25th percentile. The horizontal line dividing the box indicates the median point of the data and the ends of the lines (whiskers) represent the minimum and maximum data points. Black circles represent outlier values. *Represents weight at the time of antiretroviral therapy (ART) initiation. †Represents the maximum weight attained on ART before developing severe symptomatic hyperlactataemia (SHL). This occurred at a median of 7 months on ART (IQR 5–9). ‡Represents weight at the time of diagnosis of severe SHL.

The association with $SHCO_3$ was not attenuated in these bivariate models. The number of deaths was not enough to model the association between presentation weight and acute mortality. However, both patients who presented with a weight <50 kg died and 8 patients out of 27 (30%) presenting with weights >75 kg died during the admission compared with only 1 patient of the 33 who presented with weights in between.

Admission to hospital was required by 49 patients for a mean of 10 days, with 24 requiring admission to the intensive care unit. Sixty-eight patients had their ART stopped immediately, whereas seven were switched to AZT-containing regimens. For five of these seven patients, ART was subsequently interrupted (after 7–18 days) because of rising lactates and/or progressive symptoms. Three patients who recovered initially were lost to follow-up and one of these was found to have died 4 months later. ART was reinitiated for 58 patients, after interrupting for a median of 87 days; hence, a total of 60 patients were re-established on ART, including the two patients who switched without interrupton. Thirty patients with less severe presentations were started on AZT-containing regimens, including two patients who switched without requiring interruption. The lowest $SHCO_3$ in this group was 14.1 mmol/l, the highest lactate was 10.4 mmol/l and there was no severe or complicated clinical course, for example pancreatitis. An additional 25 severe cases were restarted on lopinavir/ritonavir and non-NRTI (NNRTI) regimens and five

patients were restarted on TDF, 3TC and an NNRTI or lopinavir/ritonavir, accessed through private funding.

The AZT group was followed for a median of 10 months with regular point-of-care lactate monitoring. One patient in this group was lost to follow-up after 24 weeks. The others were all clinically well with no recurrence of SHL symptoms at the time of censoring, representing 22.5 patient-years on AZT. There were no lactates raised >3 mmol/l, monitored to a median of 17 weeks. Two patients had virological failure (viral load >400 copies/ml) during follow-up.

There was one death in the lopinavir/ritonavir and NNRTI group that was related to post-surgical complications. There were no recurrences of hyperlactataemia in this or the TDF group and each group had one patient developing virological failure during follow-up.

Discussion

This is the largest cohort of severe SHL to be reported from a single centre to date. The referral rate for severe SHL was 17.5 cases per 1,000 patient-years on ART and for LA was 12.3 cases per 1,000 patient-years. This is higher than the rate reported from developed-world cohorts of 1.3–3.9 cases of LA per 1,000 patient-years [7], but similar to that reported from other South African

Table 2. Comorbid conditions identified during acute presentation with severe symptomatic hyperlactataemia

Comorbidity	Value, *n* (%)
Peripheral neuropathy*	38 (51)
Hepatic steatosis*†	20 (27)
Lipodystrophy*‡	15 (20)
Acute pancreatitis*§	12 (16)
Infection	11 (15)
Bacterial pneumonia	5 (7)
Tuberculosis	3 (4)
Urinary tract infection	2 (3)
Septicaemia	1 (1)
Acute renal failure	8 (11)
Idiopathic oedema¶	7 (9)
Hyperglycaemia	5 (7)
New onset diabetes	3 (4)
Pre-existing diabetes	2 (3)
HANWS*	3 (4)
Upper gastrointestinal haemorrhage	2 (3)
Pregnant	1 (1)

*Denotes conditions ascribed to be the result of mitochondrial toxicity [2,23]. †Defined by clinical hepatomegaly, suggestive ultrasonography, serum transaminases and/or alkaline phosphatase >2× upper limit of normal (ULN). ‡Defined by clinically apparent lipoatrophy or lipohypertrophy. §Defined by serum lipase >4×ULN. ¶All had normal renal function; cardiac failure was excluded clinically and nephrotic syndrome excluded with urine dipsticks. HANWS, HIV-associated neuromuscular weakness syndrome.

Table 3. Univariate and bivariate analyses of factors associated with acute mortality

	Univariate model			Bivariate model with standard bicarbonate		
Variable	OR	95% CI	*P*-value	AOR*†	95% CI	*P*-value
Male gender	1.0	0.0–8.3	0.608	–	–	–
Age (per 10 years)	1.4	0.7–2.7	0.349	–	–	–
Weight loss in preceding months (per 10 kg)	1.1	0.3–3.6	0.117	–	–	–
Standard bicarbonate <15 mmol/l†	22.5	2.8–1,045.7	<0.001	–	–	–
pH<7.2†	13.9	2.7–86.9	<0.001	4.0	0.6–33.8	0.178
Lactate level			0.044			0.790
5–7.4 mmol/l	1.0	–	–	1.0	–	–
7.5–9.9 mmol/l	2.5	0.4–18.8	–	0.8	0.1–9.0	–
≥10 mmol/l	5.0	0.8–37.3	–	0.5	0.0–6.1	–
Presenting comorbidities						
Pancreatitis	5.5	1.1–27.8	0.019	1.2	0.2–7.5	1.000
Hyperglycaemia	1.3	0.0–15.3	1.000	–	–	–
Hepatic steatosis	0.2	0.0–1.7	0.164	–	–	–
Renal failure	7.1	1.1–46.7	0.020	2.8	0.4–22.7	0.423
Acute infection	3.9	0.7–20.1	0.068	1.9	0.3–12.6	0.681
Idiopathic oedema	0.9	0.0–8.3	1.000			
Presenting symptoms						
Abdominal pain	1.3	0.3–5.6	0.755	–	–	–
Peripheral neuropathy	0.4	0.1–1.8	0.222	–	–	–
Shortness of breath	4.2	0.9–19.7	0.041	2.1	0.3–12.8	0.554
Nausea and vomiting	0.5	0.1–2.0	0.321	–	–	–
Weight loss in preceding months	0.5	0.1–2.0	0.321	–	–	–
Lipodystrophy	0.8	0.1–4.3	1.000	–	–	–

*Adjusted for standard bicarbonate <15 mmol/l. †Limited to 68 patients with available data. ‡Limited to 68 observations. All other variables include the full dataset of 75 observations. AOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

cohorts of 10.6 and 19 cases per 1,000 patient-years [6,9]. One explanation for these differences is the common use of d4T in first-line regimens in the South African public sector. A second factor is the female predominance in our ART programme (68% of patients in the cohort from which the cases were referred), compared with initially male-dominated developed-world cohorts. Females have consistently been found to be at increased risk for SHL/LA [2,6,9–11,16]. This was reflected in our calculated referral rate for females, which was 8× more frequent than males. A third probable factor is a Black ethnic vulnerability that was recently reported [16,17]. A total of 91% of patients were on 80 mg of d4T daily, as was previously recommended for weights >60 kg. The World Health Organization has since reduced the recommended dose for all adults to 60 mg daily, which is expected to reduce the high SHL/LA incidence.

The timing of onset of severe SHL shows a clear risk period, ranging from 3–32 months, with a median duration on ART among the cohort of 10 months. This compares closely with other reported median durations on ART of 7.5–12.5 months and ranges of 3–36 months [6,10,11,18].

Among patients whose BMI was measured, 55% were classified as obese at ART initiation. Obesity has been demonstrated as a risk factor for SHL/LA [6,7,10,11]. The pattern of weight changes on ART for this largely overweight group of women is noteworthy. The median peak weight gain on ART was 11 kg at a median of 7 months on ART. The group then lost a median 8 kg over a median of 3 months before being diagnosed with severe SHL. Regular weight monitoring is an essential part of care for patients on ART and a falling weight is often the herald of SHL/LA.

These patients were found to have frequent comorbidities. Indeed, 81% of cases had other manifestations of mitochondrial toxicity, the most common being peripheral neuropathy (51%), hepatic steatosis (27%) and lipodystrophy (20%). The association with SHL/LA is important to be aware of when diagnosing other mitochondrial toxicities [16]. Idiopathic peripheral oedema (present in 9% of patients) is reported as a side effect of d4T, but its mechanism is poorly understood. It has been previously reported to be in association with hyperlactataemia [19]. Concurrent infections have also been shown to be a risk factor for developing LA [16]. In total, 15% of cases had bacterial or tuberculous infections, diagnosed during their admission. Patients might have had compensated, asymptomatic hyperlactataemia that progressed to a decompensated LA because of the metabolic stress of the infection. The finding that patients with these concurrent infections presented with SHL/LA a median of 13 weeks earlier than those without is evidence that infections might be the precipitant for presentation. There is some evidence that lymphocyte mitochondrial toxicity could have an immunosuppressive effect, leaving SHL/LA patients more susceptible to infections [20].

The 21% acute mortality for LA is on the lower end of the 21–57% range reported for LA in African and developed-world studies [2,9,11,18]. This could be partly attributable to efforts to ensure local clinician education and awareness of hyperlactataemia during the study period and might have resulted in earlier referral of cases with less severe acidosis, and hence better outcomes. Previous studies have found the degree of lactate increase to be associated with mortality [10,21]. Interestingly, lactate level was not a statistically significant predictor of mortality in our study. Measures of acidosis (pH<7.2 and $SHCO_3$<15 mmol/l) were shown to be predictors of mortality and are useful for stratifying severity in these patients.

The unsuccessful switching to AZT in five out of seven milder cases of SHL suggests that this strategy cannot be recommended in patients with a lactate level ≥5 mmol/l. The safety of rechallenging SHL/LA patients with AZT after treatment interruption has been assessed in three other studies. This is particularly relevant where other NRTI choices, such as TDF and abacavir, are unavailable. Lonergan *et al.* [17,22] have reported a total of 11 cases of SHL/LA where AZT was successfully reintroduced. Recently Bolhaar and Karstaedt [9] reported 56 SHL/LA patients from South Africa who were restarted on AZT in place of d4T after their lactate levels had normalized. They report no relapses after 44.6 patient-years on AZT. We adopted a more conservative approach by only rechallenging less severe cases with AZT. The lowest $SHCO_3$ in this group was 14.1 mmol/l, the highest lactate was 10.4 mmol/l and there was no severe or complicated clinical course. Of these patients, 30 patients received AZT and 29 were still in care with no recurrence of SHL/LA after 22.5 patient-years of follow-up. This adds to the evidence that rechallenging patients with AZT is safe in drug-limited settings for those with less severe SHL/LA. The TDF and lopinavir/ritonavir-containing regimens were also well tolerated.

Because GF Jooste is a referral hospital, a limitation of our study was that we depended on the primary clinics for suspected case detection. Patients might have died of undiagnosed LA in or out of our institution; thus, the referral rate might underestimate the true incidence and mortality rate. However, the referral rate does compare well to those reported from other South African cohorts, suggesting this is a minor effect, if any [6,9]. Being a retrospective folder review, we were limited to the clinical examination and notes of the attending doctor. Heights were not available for all patients in order to calculate BMI. The weight change trends are limited in their significance by the lack of a comparator group. $SHCO_3$ and pH were not tested in seven patients, hence

probably underestimated our incidence of LA. Lactate monitoring was only performed in 22 of 30 patients rechallenged with AZT because of non-availability of point-of-care lactate machines at some of the primary clinics; none of the other patients had any recurrent symptoms of SHL.

In conclusion, our study confirms other reports of a high incidence of severe SHL and LA in an African context. This adds a significant burden onto already struggling health systems, as well as negatively affecting ART acceptance and long-term adherence by patients. As long as d4T is prescribed in programmes, there needs to be ready availability of point-of-care lactate machines and education among health care providers to monitor for this problem. Furthermore, there needs to be an urgent effort for programmes in the developing world to replace d4T with a more tolerable agent like TDF in the first-line regimen. While we continue to face the problem of limited drug choices, rechallenging less severe SHL/LA cases with AZT after lactate levels have normalized off therapy is a safe alternative.

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Disclosure statement

The authors declare no competing interests.

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