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Short Communication: Severe Symptomatic Hyperlactatemia Among HIV Type 1-Infected Adults on Antiretroviral Therapy in Côte d'Ivoire

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Abstract

Stavudine is no longer recommended for use in first-line antiretroviral therapy (ART), but it remains in high demand worldwide because it is affordable. We report the clinical presentation and incidence of severe hyperlactatemia (SL) in HIV-infected adults who initiated ART between April 2005 and May 2009 in Côte d'Ivoire, West Africa. In a prospective cohort study at the HIV care center affiliated with the National Centre for Blood Transfusion, we used standardized forms to record baseline and follow-up data. We measured serum lactate levels for all adults on ART who showed signs of hyperlactatemia. SL was defined as serum lactate >2.5 mmol/liter. Overall, 806 adults initiated ART. Among the 591 patients (73%) on stavudine-containing regimens, 394 were women (67%); the median pre-ART CD4 count was 150 /mm^3 and the median body mass index was 20.9 kg/m^2. These patients were followed for a median of 28 months. We detected SL only among patients taking stavudine. The incidence of SL was 0.55/100 person-years (PY) (95% CI 0.47–0.63) overall and 0.85/100 PY among women (95% CI 0.75–0.95). Among the eight patients with SL, 100% lost >9% of body weight before diagnosis, 100% had serum lactate >4 mmol/liter (range 4.2–12.1), 50% had pre-ART BMI >25 kg/m^2, and three patients died (38%), accounting for 6.4% of deaths among patients taking stavudine. As long as HIV clinicians continue to use stavudine in sub-Saharan Africa, they should watch out for acute unexplained weight loss in patients taking ART, particularly among women and patients with high pre-ART BMI.

Introduction

In 2006, the World Health Organization (WHO) removed stavudine, a nucleoside reverse transcriptase inhibitor (NRTI), from its list of recommended first-line antiretroviral drugs for HIV-infected patients in resource-limited settings.[1] There was sufficient evidence in high-income countries[2–6] as well as in sub-Saharan Africa and Asia[7,8] that stavudine was associated with significant adverse effects, including hyperlactatemia, lactic acidosis, lipoatrophy, and peripheral neuropathy. Although the clinical diagnosis and management of neuropathies are reasonably straightforward in resource-limited settings,[9–11] hyperlactatemia and lactic acidosis are greater challenges because clear diagnoses require laboratory tests and prognoses are often poor. Even today, however, stavudine is often the first option for first-line antiretroviral therapy (ART) in resource-limited settings, because it is affordable and available in fixed-dose combinations.[12–14]

We report the clinical presentation and incidence of symptomatic hyperlactatemia (SL) in a prospective cohort consisting of all HIV-infected adults who initiated ART between April 2005 and May 2009 in a West African HIV care center. As a secondary objective, we aim to compare the initial characteristics of patients on stavudine with those who were not on stavudine. Among patients on stavudine-based ART we aim to compare patients who developed SL with those who did not develop SL.

Materials and Methods

We conducted a prospective cohort study at the HIV care center affiliated with the National Centre for Blood Transfusion (CNTS) in Abidjan, Côte d'Ivoire. In this cohort, pre-ART

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CD4 counts and proportion of first-line regimens comprising stavudine were similar to that observed in other large ART programs in Abidjan.[12] Our study included all patients who initiated ART at the CNTS between April 2005 and May 2009.

We obtained verbal informed consent to perform HIV, syphilis, hepatitis B, and hepatitis C tests before each blood donation.[15] Donors were informed that they could return for their test results after a posttest counselling session at the CNTS, which also provides voluntary HIV tests and HIV care to nonblood donors. Routine follow-up laboratory tests for patients on ART included hemoglobin, white blood cell, and CD4 cell counts; glycemia; and blood creatinine, as recommended in the national guidelines. Before August 2008, patients paid $1 to $2 monthly for antiretroviral drugs and routine monitoring tests. After August 2008, the Ivoirian government provided ART and routine tests to all patients in the country at no charge.

The HIV center's electronic data management system was approved by the Côte d'Ivoire National Ethics Committee. We used standardized forms to record baseline and follow-up data, including drug prescriptions and reasons for regimen modifications.[12] Patients initiated ART when they met the WHO starting criteria.[1,9] First-line ART consisted of two NRTIs, combined with one nonnucleoside reverse transcriptase inhibitor (NNRTI) for HIV-1-infected adults or one protease inhibitor (PI) for HIV-2-infected adults.[9] National guidelines recommended using one of two NRTI combinations for first-line ART during the study period: stavudine plus lamivudine or zidovudine plus lamivudine. Stavudine dosages (30 or 40 mg twice a day) were according to patient weight (less than or more than 60 kg). When patients presented with unexplained nausea, vomiting, fatigue, myalgia, weight loss, or dyspnea, we collected blood samples without using a tourniquet in order to measure serum lactate (Beckman-Coulter Synchron CX System, Brea, CA). Samples were stored in fluoride-containing tubes, stored in ice, and processed within 4 h of collection.

SL was defined as the observation of at least three signs associated with SL (dyspnea, weight loss, fatigue, nausea, and vomiting) and serum lactate >2.5 mmol/liter. The study began in April 2005 and follow-up was censored on 31 May 2009 for patients who were still alive and receiving care. Among patients who died or were lost to follow-up before 31 May 2009, follow-up was censored on the date of death or last contact with the clinic. Rates of SL were calculated per 100 person-year (PY), with 95% confidence intervals (CI).

We compared the initial characteristics of patients on stavudine with those of patients on other antiretroviral drugs using the chi square test for categorical variables and the Student's test for continuous variables. We used Fishers' exact test to compare patients who developed SL with those who did not develop SL among patients on stavudine-based ART.

Results

Cohort characteristics

Overall, 1513 HIV-infected patients were included in the study and 806 patients initiated ART. Of these, 527 (65%) were female, 215 (27%) received non-stavudine-containing regimens (zidovudine plus lamivudine, $n = 173$; other NRTI combinations, $n = 42$), and 591 (73%) received regimens containing stavudine plus lamivudine. As a third drug, patients on stavudine-containing regimens could receive nevirapine ($n = 518$; 88%), efavirenz ($n = 53$; 9%), indinavir/ritonavir ($n = 14$; 2%), or other drugs ($n = 6$; 1%). Among the 591 patients (73%) on stavudine-containing regimens, 394 were women (67%); the median pre-ART CD4 count was 150 cells/mm^3 and the median body mass index was 20.9 kg/m^2. These patients were followed for a median of 28 months. Other pre-ART characteristics for patients on regimens with or without stavudine can be found in Table 1.

Clinical presentation and incidence of symptomatic hyperlactatemia

Eight patients were diagnosed with SL during the study period. All events occurred among patients on ART regimens containing stavudine and lamivudine, plus either nevirapine ($n = 5$), efavirenz ($n = 2$), or a PI ($n = 1$). The incidence of SL was 0.55/100 PY (95% CI: 0.47–0.63) overall and 0.85/100 PY (95% CI: 0.75–0.95) among women. Of the eight patients who developed SL, eight had serum lactate >4 mmol/liter (range 4.2–12.1), eight lost >9% body weight in the month preceding diagnosis, and four had pre-ART body mass indices (BMI) >25 kg/m^2 (Table 2). The incidence of SL was 4.76/100 PY (95% CI, 0.21; 9.32) among patients with pre-ART BMI >25 kg/m^2 and 0.79/100 PY (95% CI, 0.02; 1.56) ($p = 0.002$) among patients with pre-ART BMI <25 kg/m^2.

At the onset of SL, the median time on stavudine-containing ART was 12 months and all patients had achieved immunologic success. Three patients developed peripheral neuropathy in addition to SL. None of these patients had any conditions that cause metabolic acidosis.

The most common clinical signs of SL were nausea (8/8), vomiting (8/8), anorexia (8/8), fatigue (8/8), weight loss ≥10% in less than 1 month (6/8), and dyspnea (5/8). Four women presented with painful peripheral neuropathy and three patients (38%) died. Two patients died after being admitted to the intensive care unit and discontinuing all medications including ART. A third patient died before the diagnosis was complete. All three patients had serum lactate levels >8 mmol/liter. These patients represented 6.4% of all deaths among patients taking stavudine during the study period. The five patients who survived switched to a non-NRTI-based ART regimen that included efavirenz and lopinavir/ritonavir for four patients and nevirapine plus lopinavir/ritonavir for one patient.

The mean age among patients who developed SL was 43 years; among patients who did not develop SL it was 35 years ($p = 0.03$). Patients who developed SL had higher median pre-ART BMIs (24 vs. 20 kg/m^2; $p = 0.0001$) and 50% had BMI >25 kg/m^2, compared to only 14% of patients who did not develop SL ($p = 0.006$). Gender did not differ significantly between these two groups.

Other ART modifications

Patients on ART were followed for a median of 25 months. During this time, 57 patients (7.1%) died, 91 (11.3%) were lost to follow-up, and 124 (15%) switched first-line drugs. Among the 591 patients on regimens containing stavudine and lamivudine, 102 (17%) switched drugs. Of these, 62 switched drugs because of adverse effects, including peripheral neuropathy ($n = 45$), SL ($n = 8$), rash or Stevens–Johnson syndrome ($n = 6$), and liver toxicity ($n = 3$). The remaining 40 patients switched regimens due to one or more factors, which included tuber-

Table 1. Baseline and Follow-up Characteristics of Patients Initiating ART[a,b]

	Stavudine-containing regimen (n = 591)	*Other regimens (n = 215)*	*Overall (n = 806)*	p[c]
Pre-ART characteristics				
Female, *n* (%)	394 (67)	133 (62)	527 (65)	0.10
Median age, years (IQR)	36 (31–43)	36 (30–42)	36 (30–43)	0.07
HIV serostatus				
HIV-1, *n* (%)	581 (98.3)	186 (86.5)	767 (95.2)	$<10^{-3}$
HIV-2, *n* (%)	3 (0.5)	15 (7)	18 (2.2)	—
HIV-1 + 2, *n* (%)	7 (1.2)	14 (6.5)	21 (2.6)	—
Median BMI, kg/m^2 (IQR)	20.9 (18.6–23.3)	21.2 (19.0–23.9)	21.0 (18.7–23.5)	0.15
Median CD4 $count/mm^3$ (IQR)	150 (73–220)	205 (107–286)	166 (81–238)	0.07
Median hemoglobin, g/liter (IQR)				
Male	120 (100–130)	124 (106–135)	120 (105–132)	0.22
Female	101 (88–12)	103 (93–114)	101 (90–112)	0.16
Median creatininemia, μM (IQR)	70.8 (62.0–88.5)	66 (53.1–79.6)	70.8 (62.0–88.5)	0.74
Median glycemia, mM (IQR)	4.4 (4.1–5.0)	4.4 (4.0–4.7)	4.4 (4.2–5.0)	—
Serum transaminases >1.25 ULN	56 (9%)	32 (15%)	88 (11%)	0.01
BMI $>25\,kg/m^2$ (%)	84 (14.21)	37 (17.21)	121 (15.01)	0.15
Follow-up characteristics				
Follow-up, person-years	1377	377	1749	
Median follow-up, months (IQR)	28 (17–38)	16 (12–27)	25 (15–36)	10^{-3}
ART modifications,[d] *n* (%)	102 (17)	22 (10)	124 (15)	0.007
Status at study termination, *n* (%)				
Dead	47 (8.0)	10 (4.7)	57 (7.1)	0.05
Lost to follow-up	70 (11.8)	21 (9.8)	91 (11.3)	0.05

[a]ART was initiated at the HIV care center affiliated with the National Centre for Blood Transfusion in Abidjan, Côte d'Ivoire: 8 April 2005–31 May 2009.
[b]BMI, body mass index; IQR, interquartile range; ULN, upper limit of normal value; ART, antiretroviral therapy.
[c]Chi square test for categorical variables or Student's test for continuous variables.
[d]Among the 88 patients who had abnormal serum transaminase values, 69 (78%) had 1.25×ULN < transaminase < 2.5×ULN; 14 (16%) had 2.5×ULN < transaminase < 5×ULN; 3 (3%) had 5×ULN < transaminases < 10×ULN; and 2 (2%) had transaminase > 10×ULN.

culosis ($n = 15$), drug stock-outs ($n = 14$), pregnancy ($n = 11$), and ART failure ($n = 2$). Of the 215 patients on regimens containing zidovudine and lamivudine, 22 (10%) switched drugs due to severe anemia ($n = 6$), ART failure ($n = 4$), and tuberculosis ($n = 2$). None of these patients developed SL.

Discussion

Unlike previous retrospective studies,[6–8,16] the results of our prospective cohort study allowed us to better estimate the incidence rate of SL. We found the incidence of SL in female patients to be 0.85/100 PY, consistent with rates reported in South Africa.[14]

SL is a well-known adverse effect that has a well-documented association with nucleoside analogues, particularly stavudine, but also other drugs including didanosine, zidovudine, and lamivudine.[11,12] At the CNTS, clinicians systematically measured serum lactate when patients on ART presented with unexplained symptoms that were consistent with hyperlactatemia. All of the patients who were diagnosed with SL were on stavudine-containing regimens. The incidence of SL in female patients was estimated to be 0.85/100 PY, consistent with rates reported in South Africa.[16] This value is likely to underestimate the rate of SL, because some patients who were lost to follow-up or who died outside of the CNTS during the study period may have had SL.

Diagnosing and treating SL can be difficult in resource-limited settings, because its symptoms are nonspecific. Anion gaps were not performed in our study.

The high rate of SL-related mortality in our study can be explained in part by the absence of mild cases, since at least three signs of SL were required to fulfill the case definition. Moreover, SL diagnoses are difficult and often delayed because the symptoms are nonspecific and lactic acid measurements are frequently unavailable. Finally, the resources for treating severe cases of SL in Côte d'Ivoire are limited. The SL-related mortality rate reported in our study is similar to rates reported elsewhere[6,17] and supports the 2006 and 2009 WHO recommendations to discontinue stavudine use in first-line ART.[9]

To our knowledge, no antiretroviral drug except for stavudine has adverse effects associated with a close to 1% mortality rate. This drug remains an enticing option, however, because it is affordable and widely available in fixed-dose combinations. These attributes have allowed for a rapid scaling up of ART in Côte d'Ivoire over the past 4 years. As resource-limited countries continue to increase access to ART, stavudine will gradually be replaced with other NRTIs. During this transitional period and until the use of stavudine is completely discontinued, however, health workers must be trained to detect the early signs of severe stavudine-related toxicities and discontinue the drug in time. If patients develop severe lactic acidosis, clinicians should replace NRTI-based regimens with a PI plus efavirenz once the symptoms have dissipated. Our study points out some key characteristics associated with SL that are consistent with previous studies: 100% of patients were female, 50% had pre-ART BMI $>25\,kg/m^2$, 40% had pre-ART BMI $>30\,kg/m^2$,[6] 100% lost >9% body

Table 2. Symptomatic Hyperlactatemia (SL) at the HIV Care Center[a]

	Patient 1	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*	*Patient 6*	*Patient 7*	*Patient 8*
Pre-ART characteristic								
Gender	Female	Female	Female	Female	Female	Female	Female	Female
Age, years	36	31	42	53	45	50	52	38
Weight, kg	75	85	51	99	111	47	60	51
BMI, kg/m^2	26.6	33.6	18.7	37.8	42.4	18.4	22.9	16.3
WHO clinical stage	IV	I	IV	I	I	III	II	II
CD4 count, /mm^3	30	187	3	196	173	66	225	5
Hemoglobin, g/liter	115	103	94	110	99	92	78	72
Glycemia, mmol/liter	115	103	94	110	99	92	78	72
Creatininemia, μmol/liter	4.4	NA	4.8	4.6	5. 1	3.7	4.7	5.7
Initial ART regimen[c]								
Stavudine dosage, mg	30	30	30	30	30	40	30	30
Third drug	Efavirenz	Nevirapine	Nevirapine	Nevirapine	Nevirapine	Efavirenz	Nevirapine	IDV/r[b]
Event characteristics								
Time since ART start, months	12	9	14	7	10	16	16	13
Most recent CD4 count, /mm^3	411	375	201	285	243	605	302	84
Weight 1 month before, kg	95	92	64	105	110	58	62	68
Weight at diagnosis, kg	81	82	57	95	100	53	56	57
Weight loss in month preceding SL, kg	14	10	7	10	10	5	6	11
Serum lactate level, mmol/liter	5.58	4.82	4.16	9.54	12.11	8.41	7.71	5.17
Outcome	Survived	Survived	Survived	Died	Died	Died	Survived	Survived
New ART regimen	Efavirenz LPV/r	Efavirenz LPV/r	Efavirenz LPV/r	—	—	—	Efavirenz LPV/r	Nevirapine LPV/r

[a]Affiliated with the National Centre for Blood Transfusions in Abidjan, Côte d'Ivoire: 8 April 2005–31 May 2009.
[b]IDV/r, 400 mg indinavir + 100 mg ritonavir twice a day.
[c]Lamivudine was the second drug for all patients.

weight in the month preceding diagnosis, and 100% had achieved immunologic success. As long as HIV clinicians continue to use stavudine in sub-Saharan Africa, they should watch out for acute unexplained weight loss in patients taking ART, particularly among women and patients with high pre-ART BMI.

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Author Disclosure Statement

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