Symptomatic Hyperlactatemia Associated with Nucleoside Analogue Reverse-Transcriptase Inhibitor Use in HIV-Infected Patients: A Report of 24 Cases in a Resource-Limited Setting (Uganda)

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We describe 24 Ugandan patients with human immunodeficiency virus infection who developed symptomatic hyperlactatemia associated with the use of nucleoside analogues. All patients were receiving combination therapy that contained stavudine. The median serum lactate level was 6.6 mmol/L. All patients had their antiretroviral treatment regimen discontinued. Hospital admission was required for 5 patients. Five patients died.

The prognosis of Ugandan patients with HIV infection has improved dramatically with increased access to free antiretroviral therapy from programs such as the Multicountry AIDS Program and the President's Emergency Plan for AIDS Relief. The first-line combination therapy recommended by Ugandan guidelines that is provided by the free antiretroviral therapy programs includes zidovudine or stavudine plus lamivudine, in combination with either nevirapine or efavirenz [1].

A clinical syndrome described as type B lactic acidosis, without hypoxemia, has been associated with the use of nucleoside reverse-transcriptase inhibitors (NRTIs), especially didanosine and stavudine [2–4] and, to a lesser extent, zidovudine [5]. The exact mechanism of this syndrome is not clearly understood, but it appears to result from mitochondrial damage [6, 7].

Although symptomatic hyperlactatemia is a well-known and well-documented complication of nucleoside analogue use in the western world [8, 9], there are few data from Africa. One report documented an incidence of symptomatic hyperlactatemia of up to 19% per 1000 person-years among South African patients who were receiving antiretroviral therapy [10]. Unfortunately, the fixed-dose, generic combination of stavudine, lamivudine, and nevirapine is the most widely used antiretroviral therapy regimen in Uganda and other African countries.

In this article, we describe 24 HIV-infected African patients who received first-line antiretroviral treatment and developed symptomatic hyperlactatemia. We also describe the challenges associated with diagnosis and management of this syndrome in resource-limited settings.

Methods. The study was performed at the Adult Infectious Diseases Clinic (AIDC) at Mulago Hospital (Kampala, Uganda). The AIDC is part of the Makerere University Infectious Diseases Institute and provides HIV care, including free antiretroviral therapy, to HIV-infected patients with a $CD4^+$ cell count <200 cells/μL or with World Health Organization stage IV disease. Patients commenced treatment with first-line combinations of lamivudine, zidovudine or stavudine, and nevirapine or efavirenz, as recommended by Ugandan guidelines [1].

Cases of confirmed symptomatic hyperlactatemia were reported by clinicians to the study team during the period from October 2005 through October 2006. A retrospective chart review of identified cases was performed, and data were collected using a standard data abstraction form. Data included demographic characteristics, antiretroviral therapy history, symptoms, laboratory analysis findings (i.e., $CD4^+$ count, liver enzyme level, and venous plasma lactic acid level), information on other mitochondrial toxicity–associated conditions (including lipodystrophy, peripheral neuropathy, and liver steatosis), treatment, and follow-up.

Symptomatic lactic acidosis was defined as follows: (1) the presence of at least 2 of the following symptoms: vomiting, fatigue, myalgia, nausea, diarrhea, abdominal distension, weight loss, or dyspnea; (2) confirmed hyperlactatemia, defined as a serum lactate level >2 mmol/L determined using the Cobas Integra 400 Plus (Roche; blood specimens were obtained without a tourniquet, and samples were stored in ice and processed within 4 h); and (3) absence of other causes of metabolic acidosis (e.g., opportunistic infection, malaria, sepsis, and diabetes).

Results. As of October 2006, >17,000 clients with HIV infection had been registered at AIDC; 8860 were undergoing

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active follow-up, and 3745 were receiving antiretroviral therapy. Of the antiretroviral therapy recipients, 64% were female. A total of 38% of patients started receiving regimens that contained zidovudine, and 62% started receiving regimens that contained stavudine.

We identified 24 patients who were receiving antiretroviral therapy and who had documented lactic acidosis; their characteristics are shown in table 1. All of these patients were receiving a fixed-dose, generic combination regimen that contained stavudine, lamivudine, and nevirapine (Triomune; Cipla). The median duration of antiretroviral therapy was 12.5 months (mean, 13.3 months; range, 7–36 months). Twenty patients (83%) were female. The median age was 36 years (mean, 37.4 years; range, 28–50 years), and the median baseline $CD4^+$ cell count was 104 cells/μL (mean, 101.9 cells/μL; range, 1–149 cells/μL).

All 24 patients had nonspecific symptoms, such as abdominal discomfort, anorexia, vomiting, or fatigue. Twenty patients (83%) had $\geqslant$1 other symptom related to mitochondrial toxicity; 20 patients reported having peripheral neuropathy, and 4 reported having severe lipoatrophy of the face and lower extremities. Eighteen patients had a weight loss >5 kg (median weight loss, 8.5 kg; mean, 9.4 kg; range, 1–15 kg). The median weight at the time of diagnosis was 65 kg (range, 37–115 kg). The median serum lactate level at the time of diagnosis of symptomatic hyperlactatemia was 6.61 mmol/L (mean, 7.5 mmol/L; range, 3.33–21.74 mmol/L). Of 9 patients who underwent abdominal sonography, 7 (78%) had features of hepatic steatosis with fatty liver infiltration.

Antiretroviral therapy regimens were discontinued for all patients, who were administered vitamin B supplements (most frequently vitamin B complex). Five (21%) of 24 patients were admitted to the hospital for supportive care that included intravenous hydration; the remaining patients were observed on an outpatient basis. Five of the 24 patients died; 2 died during hospitalization, and 3 died at home. Of the remaining 19 patients, 3 switched their regimen from stavudine to lopinavir/ritonavir (Kaletra; Abbot Laboratories), 1 switched to abacavir, 1 switched to tenofovir, and 6 switched to zidovudine. To date, 8 patients are still not receiving antiretroviral drugs, while they await normalization of lactate levels and the availability of alternative drugs.

Discussion. In resource-limited settings, symptomatic hyperlactatemia may occur relatively frequently, as shown by cases

Table 1. Characteristics of 24 HIV-infected patients who had symptomatic hyperlactatemia while receiving a fixed-dose combination of stavudine, lamivudine (3TC), and nevirapine (NVP).

Patient	Sex	Age, years	Duration of NRTI therapy, months	Symptoms	Weight loss, kg	LA	PN	$CD4^+$ cell count before ART, cells/μL	Serum lactate level, mmol/L	AST level, U/L	ALT level, U/L	Abdominal sonography	Outcome and new ART
1	F	32	8	AD, palpitation	7	No	Yes	22	7.7	55	41	ND	LPV/r, 3TC, and EFV
2	F	38	36	Fatigue, ANX	10	Yes	Yes	ND	5.74	ND	ND	ND	Died
3	F	49	14	AD, VMT	12	Yes	Yes	149	7.7	62	79	HS	LPV/r, 3TC, and EFV
4	F	39	7	Palpitations, VMT	6	No	Yes	3	8.11	ND	ND	ND	LPV/r, 3TC, and EFV
5	F	50	15	Nausea, VMT	6	Yes	Yes	90	6.67	40	40	HS	Died
6	M	28	12	AD, fatigue, VMT	15	No	Yes	1	4.12	ND	ND	HS	ABC, 3TC, and EFV
7	F	36	17	ANX, fatigue, VMT	15	Yes	Yes	122	3.33	ND	ND	HS	Died
8	F	34	20	AD, ANX, VMT	18	No	Yes	21	12.4	319	184	HS	TFV, 3TC, and EFV
9	F	34	8	AD, VMT	12	No	Yes	65	10.97	48	50	ND	AZT, FTC, and EFV
10	M	48	10	AD, fatigue	9	No	Yes	148	11	29	39	HS	Not receiving treatment
11	F	42	10	AD, ANX	12	No	Yes	37	8.37	ND	ND	Normal	Not receiving treatment
12	F	36	8	ANX, VMT	3	No	Yes	71	21.74	ND	ND	ND	Died
13	F	34	13	AD, VMT	4	No	No	58	5.23	ND	ND	ND	AZT, 3TC, and NVP
14	F	36	8	VMT, ANX	1	No	Yes	141	4.52	ND	ND	ND	AZT, 3TC, and NVP
15	F	35	14	ANX, VMT	25	No	Yes	3	7.99	83	58	Normal	Not receiving treatment
16	M	41	13	AD, nausea	4	No	No	104	6.55	52	ND	ND	Not receiving treatment
17	F	33	8	VMT, dyspnea	8	No	Yes	78	12.28	ND	ND	ND	Died
18	F	32	7	VMT, ANX	2	Yes	Yes	171	4.51	ND	ND	ND	Not receiving treatment
19	F	30	13	AD, VMT	9	No	No	162	4.34	ND	ND	ND	Not receiving treatment
20	F	45	18	AD, ANX	7	No	Yes	208	4.32	ND	ND	ND	AZT, 3TC, and NVP
21	F	42	21	AD, fatigue	13	No	Yes	185	7.91	ND	ND	ND	AZT, 3TC, and EFV
22	F	36	12	AD, fatigue	8	No	No	266	4.20	ND	ND	ND	Not receiving treatment
23	F	28	16	ANX, VMT	15	No	Yes	2	4,95	ND	ND	ND	AZT, 3TC, and EFV
24	M	41	11	ANX, VMT	4	No	Yes	104	6.55	ND	ND	HS	Not receiving treatment

NOTE. AD, abdominal discomfort; ANX, anorexia; ART, antiretroviral treatment; AZT, zidovudine; EFV, efavirenz; FTC, emtricitabine; HS, hepatic steatosis; LA, lipoatrophy; LPV/r, lopinavir/ritonavir; ND, not done; NRTI, nucloeside reverse-transcriptase inhibitor; PN, peripheral discomfort; VMT, vomiting.

reported from South Africa [10] and our case series. It also seems to be more common among women.

There are many challenges in the diagnosis and management of symptomatic hyperlactatemia in resource-constrained settings. Diagnosis of this syndrome is problematic, because estimation of the serum lactate concentration requires highly specialized laboratory facilities and technicians, and these are not widely available in Uganda. At the time of this chart review, the AIDC did not have laboratory facilities that could perform this test. Patients with suspected symptomatic hyperlactatemia were sent to a private laboratory, where the test cost $7, and some of the patients could not afford to pay for the test.

The clinical diagnosis of lactic acidosis is challenging because the symptoms are nonspecific. Moreover, in tropical countries, common symptoms of symptomatic hyperlactatemia, such as anorexia, nausea, vomiting, abdominal pain, fatigue, weight loss, and shortness of breath [8], can be misleading and mistaken for symptoms of malaria or gastroenteritis.

It is important that the new point-of-care tests, which provide simple, accurate measurements of lactic acid levels at relatively low cost, are field tested in Africa. Use of these tests in an HIV treatment program in rural Haiti greatly assisted clinical decision-making with regard to patients who had symptoms suggestive of lactic acidosis [11].

Regarding the management of symptomatic hyperlactatemia syndrome, it is recommended that use of the presumed causative agents is discontinued, and that the agents are switched to an NRTI that is less likely to cause symptomatic hyperlactatemia. Antiretroviral drugs should be withheld until the serum lactate concentration is back to normal levels. However, recovery is protracted (4–28 weeks after discontinuation of NRTI treatment [2]), thus posing a clinical risk to patients whose $CD4^+$ cell counts are low.

The treatment for symptomatic hyperlactatemia is mainly supportive and may include, for severely ill patients, intravenous fluids, mechanical ventilation, and dialysis [8, 9]. In resource-limited settings, even intensive care units may lack some of these facilities. The mortality rate was high in our case study (5 [21%] of 24 patients died). Few case studies have suggested that cofactors, such as use of thiamine, riboflavin, vitamin C, and antioxidants, may induce faster recovery from lactic acidosis [2, 12, 13]. However, agents such as riboflavin, which appears to be the most studied and effective, are generally not available in resource-limited settings.

Switching therapy in patients with stable disease poses a dilemma, because abacavir and tenofovir, which are less toxic to the mitochondria, are both expensive and not readily available via the free antiretroviral therapy programs. Another option is for patients to recommence treatment with NRTI-sparing regimens, including non-NRTIs and protease inhibitors. This strategy, however, poses challenges related to adherence because of the high pill burden and dietary and/or dosing implications, and it narrows the choices of subsequent second-line regimens. At present, many patients in our study are still not receiving any antiretroviral drugs, as they await the normalization of serum lactate concentration and because the only alternative drug is zidovudine.

Because of difficulties in recognizing symptomatic hyperlactatemia and in accessing diagnostic facilities, the true number of cases of symptomatic hyperlactatemia in our study period may certainly be underestimated. Cases were reported only when there was a clinical suspicion, and the level of suspicion was likely to be relatively low, because physicians were not very familiar with the syndrome. A low level of clinical suspicion and lack of diagnostic capacity may also explain the low number of cases reported in Asian cohort studies [14]. More studies are certainly needed to determine the incidence, prevalence, risk factors, prevention, and management of this syndrome in African populations.

In conclusion, symptomatic hyperlactatemia is an important and potentially fatal complication of antiretroviral therapy in African patients, and it is associated with a high mortality in otherwise stable patients who are receiving long-term antiretroviral therapy. To improve the patient outcomes, all health care workers and patients need to be trained to have a high index of suspicion of this condition, and laboratory facilities need to be accessible and affordable in urban and peripheral health care centers. It is paramount that programs providing free antiretroviral therapy in resource-limited settings have alternative drugs (e.g., abacavir and tenofovir) available for patients who develop symptomatic hyperlactatemia, to spare protease inhibitors for second-line regimens. Free antiretroviral therapy programs should also consider excluding stavudine as a drug of choice in first-line regimens.

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