Hyperlactatemia and Antiretroviral Therapy: The Swiss HIV Cohort Study

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The prevalence, clinical presentation, and risk factors for hyperlactatemia among patients receiving antiretroviral therapy was determined during a 1-month period for patients in the Swiss HIV Cohort Study. Overall, 73 (8.3%) of 880 patients presented an increase in serum lactate of >1.1 times the upper normal limit (UNL). For 9 patients (1%), lactate elevation was moderate or severe (>2.2 times the UNL). Patients who presented with hyperlactatemia were more likely to be receiving stavudine with or without didanosine (odds ratio, 2.7; 95% confidence interval, 1.5–4.8), as compared with patients who received zidovudine-based regimens. The risk increased with increasing time receiving stavudine with or without didanosine. The association between hyperlactatemia and stavudine with or without didanosine was not biased by these medications being more recently available and, therefore, being given preferentially to patients who had prolonged use of nucleoside analog reverse-transcriptase inhibitors. Hyperlactatemia was associated with lipoatrophy, hyperlipidemia, and hyperglycemia. Age, sex, or stage of infection with human immunodeficiency virus were not predictive of hyperlactatemia. Determination of lactate levels may prove useful in the screening for mitochondrial toxicity.

Identification and characterization of novel forms of toxicity—clinical presentation, spectrum of severity, and risk factors—has become a priority, because prolonged use of antiretrovirals makes long-term toxicity a critical issue for the treatment of HIV-infected patients. Hyperlactatemia is an increasingly recognized adverse effect of antiretroviral therapy (ART) for which only few data exist.

HIV-associated disorders of lactic acid metabolism were first described in the early 1990s. Originally reported as rare instances of lactic acidosis and hepatic failure associated with the use of didanosine [1], they were later described in association with use of most of the available nucleoside analog reverse-transcriptase inhibitors (NRTIs) [2–7]. More recently, disorders such as myopathy, neuropathy, and pancreatitis have been proposed as part of a common spectrum of toxicity [2, 8–11]. Carr et al. [3] described the association of lactic acidemia and hepatic dysfunction with a fat redistribution syndrome dominated by lipoatrophy and weight loss. NRTIs are thought to induce mitochondrial toxicity by inhibiting the nuclear polymerase γ, resulting in depletion of mitochondrial DNA and damage of the respiratory chain [8, 12–15].

In the present study, we aimed to do the following: (1) estimate the prevalence of hyperlactatemia in a large observational cohort of HIV-infected patients receiving ART; (2) identify the severity and the spectrum of lab-

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oratory and clinical abnormalities associated with increased lactate levels; and (3) assess factors associated with the presence of this metabolic abnormality.

PATIENTS AND METHODS

Swiss HIV Cohort Study. The Swiss HIV Cohort Study (SHCS; see http://www.shcs.ch) enrolls HIV-infected people aged ⩾16 years. Patients are followed up in 1 of 7 study centers (Basel, Bern, Geneva, Lausanne, Lugano, St. Gall, and Zurich). Data are collected according to a common protocol at registration and at follow-up visits scheduled at 6-month intervals. CD4 cell count is measured by means of flow cytometry, and virus load is determined using the Roche Amplicor Monitor assay (Roche Diagnostic; level of detection, <20 or 400 copies/mL).

Study design. To determine the period prevalence of adverse events among SHCS participants receiving ART, a cross-sectional study was conducted during a 4-week period in August and September 1999; it included all SHCS participants receiving potent ART, with the exception of patients who started or switched a regimen within the previous 30 days. A questionnaire based on the classification of adverse events used by the AIDS Clinical Trials Group was completed by the doctor during the outpatient visit. Patients were explicitly asked by their doctors if symptoms itemized in the questionnaire occurred within the 30 days preceding the visit. Potential adverse events were scored according to a severity score (grades 1–4, or mild, moderate, severe, and serious, respectively), and the likelihood of adverse events being related to ART ("definitely not attributed," "possible," "probable," and "definitive"), following the definition of causality of the World Health Organization (http://www.who-umc.org/defs.html), was assessed. Definition of lipodystrophy (lipoatrophy and fat accumulation) was based on doctors' examinations, as indicated in the study protocol.

"Contemporary treatment" was defined as the treatment that the patient was receiving at the time of the study visit. "Contemporary treatment exposure" referred to the length of continuous exposure to the contemporary drug regimen. "Total NRTI exposure" was defined as the cumulative exposure time to each single agent.

Laboratory tests. For all participants, we proposed measurement of the following values: hemoglobin, neutrophil and platelet count, creatinine, urate, serum transaminases, alkaline phosphatase, bilirubin, pancreatic amylase, creatinine phosphokinase, glucose, triglycerides, cholesterol, and proteinuria. Abnormal findings of laboratory evaluations were reported as "mild," "moderate," and "severe" in relation to the normal limit of each variable. Normal limits are defined as the central interval of 95% (between 2.5 and 97.5 percentiles) of the values of healthy people. Blood sampling for lactate determination was performed after removal of the tourniquet in tubes containing sodium fluoride [16]. A "mild augmentation of blood lactate" was defined as 1.1–2 times the upper normal limit (UNL); "moderate" was defined as 2.1–3 times the UNL; "severe," as 3.1–4 times the UNL; and "serious," as >4 times the UNL. For glucose, triglyceride, and cholesterol determinations, actual values in the fasting or nonfasting state were used for analysis.

Statistical analysis. Univariate assessment of risk factors for hyperlactatemia, including previous or concurrent treatment with specific drugs, was conducted using the χ^2 test, for categorical variables, and t test, for continuous variables. To further measure the independent association between these variables and hyperlactatemia, we used multiple logistic regression. Variables significantly associated with the outcome in the univariate analysis as well as variables that were clinically relevant were included in the initial models. Two specific models were developed to assess the role of individual drugs and the role of drug combinations in hyperlactatemia. Models were then simplified by means of a backward stepwise approach. Variables considered in the final model were age, sex, most recent CD4 cell count and virus RNA load value, duration of total NRTI exposure, and relevant antiretroviral combinations.

RESULTS

Subjects. Data from 1359 patients receiving ART were obtained; 880 of these patients had a valid blood lactate measurement. Patients included in the study represented 33% of the 4151 actively followed-up patients in the SHCS at the time of the study. Patients included were more advanced in the course of illness than were patients who were not seen at the time of the study (data not shown). A lactate determination was not available for 479 patients because laboratory testing had been performed before the study visit, because of the doctor's decision, because of patient refusal, or because of poor compliance with the specifications for blood sampling for lactate determination with sodium fluoride tubes. There were no significant differences between participants with or without lactate measurement in terms of demographic characteristics, HIV disease-specific parameters, or type of ART.

Overall, 73 (8.3%) of 880 patients had an elevated lactate level (mild in 64 patients and moderate in 9). One patient's condition evolved to severe lactic acidosis and multiorgan failure. There were no demographic, virologic, or immunologic differences between participants who had increased or normal lactate values (table 1).

Antiretroviral agents and hyperlactatemia. Analysis of the antiretroviral agents used at the time of lactate determination (contemporary treatment) identified stavudine and didanosine to be associated with an increased risk of hyperlactatemia, whereas zidovudine and lamivudine were associated

Table 1. Characteristics of patients with and without hyperlactatemia.

Characteristic	Patient lactate level		
	Increased (n = 73)	Normal (n = 807)	P[a]
Male sex	54 (74)	587 (73)	.820
CDC group			.581
A	24 (33)	310 (38)	
B	24 (33)	260 (32)	
C	25 (34)	237 (29)	
Risk group			.052
Men who have sex with men	30 (41)	337 (42)	
Heterosexual transmission	28 (38)	232 (29)	
Injection drug use	9 (12)	205 (25)	
Other	3 (4)	19 (2)	
Age, mean years ± SD	42.8 ± 1.2	40.7 ± 0.3	.056
Body mass index, mean ± SD	22.3 ± 0.4	22.8 ± 0.1	.220
Most recent CD4 cell count, mean cells/mm^3 ± SD	428 ± 38.2	414 ± 9.3	.848
CD4 nadir, mean cells/mm^3 ± SD	359 ± 39.3	339 ± 10.0	.694
Most recent RNA measurement, mean copies/mL ± SD	8771 ± 3857	18697 ± 3499	.352

NOTE. Data are no. (%) of patients, unless otherwise indicated. CDC, Centers for Disease Control and Prevention.

[a] P values were determined using Pearson χ^2, for categorical variables, and t test, for continuous variables.

with a lower risk (table 2). To study the impact of specific drug combinations, 7 groups of ART were determined a priori. Three were regimens that contained zidovudine, and 4 were regimens with combinations of stavudine with or without didanosine. Overall, hyperlactatemia was determined in 54 (11.1%) of 485 patients who received regimens that included stavudine with or without didanosine and in 15 (4.2%) of 361 patients who received regimens that contained zidovudine. Figure 1 summarizes the results and identifies hyperlactatemia associated with use of regimens that contain stavudine with or without didanosine (OR, 2.7; 95% CI, 1.5–4.8), as compared with regimens that contain zidovudine. Hyperlactemia was not associated with stavudine regimens without concomitant didanosine administration (OR, 1.6; 95% CI, 0.8–3.2). Only 28 patients were receiving didanosine without concomitant administration of stavudine, and no increased risk for hyperlactatemia could be demonstrated for this small group of patients (OR, 2.6; 95% CI, 0.5–13.1).

We assessed the possibility that previous exposure to other NRTI agents was responsible for the observed rates of hyperlactatemia in patients who were receiving stavudine with or without didanosine. For this, only patients starting a first-ever treatment with a regimen that contained zidovudine (232 patients) or an ART that contained stavudine with or without didanosine (187 patients) were included in the analysis. This confirmed that treatment-naïve patients who developed hyperlactatemia were more likely to have received stavudine with or without didanosine (OR, 5.6; 95% CI, 2.3–13.6) than an ART that contained zidovudine as first treatment.

For patients who were receiving stavudine with or without didanosine, the risk of hyperlactatemia increased from OR 0.9 (95% CI, 0.3–2.9), for patients with <6-month contemporary exposure, to OR 3.7 (95% CI, 12.0–6.9), for patients receiving 6–24 months of therapy, when compared with regimens that contain zidovudine in an analysis adjusted for age, sex, most recent CD4 and viremia values, and total NRTI exposure. Patients with >24 months of consecutive exposure to stavudine did not experience an additional increase in risk. No such association between duration of contemporary treatment and hyperlactatemia was identified for other agents (data not shown).

Association with clinical and laboratory findings. An association was identified between lipoatrophy (fat loss in the face, arm, leg, and buttocks) and hyperlactatemia (table 3). Multivariate analysis (including the variables described in the "Patients and Methods" section) confirmed this association: patients with hyperlactatemia had a greater likelihood of lipoatrophy than did patients without lactate elevation (OR 1.8; 95% CI, 1.1–3.0).

A significant association was also identified between elevated urate levels, a phenomenon described elsewhere in association with use of didanosine [17], plasma glucose, cholesterol and triglycerides, and hyperlactatemia (table 4). The association be-

Table 2. Present therapy, according to substance and hyperlactatemia status.

Substance	No. (%) of patients, by lactate level: Increased (n = 73)	Normal (n = 807)	Crude OR (95% CI)	P
Zidovudine	17 (23)	344 (43)	0.4 (0.2–0.7)	.002
Lamivudine	34 (47)	559 (69)	0.4 (0.2–0.6)	<.001
Stavudine	54 (74)	431 (53)	2.5 (1.4–4.3)	.001
Didanosine	33 (45)	161 (20)	3.3 (2.0–5.4)	<.001
Abacavir	6 (8)	66 (8)	1.0 (0.4–2.4)	.99
Efavirenz	14 (19)	96 (12)	1.8 (0.9–3.3)	.08
Nevirapine	4 (5)	35 (4)	1.3 (0.4–3.7)	.59
Indinavir	10 (14)	158 (20)	0.7 (0.3–1.3)	.17
Ritonavir	10 (14)	163 (20)	0.6 (0.3–1.3)	.20
Saquinavir	7 (10)	118 (15)	0.6 (0.3–1.4)	.29
Nelfinavir	35 (48)	352 (44)	1.2 (0.7–1.9)	.43
Amprenavir	2 (3)	10 (1)	2.3 (0.5–10.5)	.28
Hydroxyurea	4 (5)	18 (2)	2.5 (0.8–7.7)	.10

tween dyslipidemia and hyperlactatemia remained for the subset of patients for whom determinations were performed in the fasting state (data not shown). The association with proteinuria was not retained in a multivariate analysis.

DISCUSSION

Lactate, one of the components of the respiratory chain, is produced during the glycolytic pathway as a product of transformation of pyruvate. When the oxygen supply of tissues is sufficient, the metabolism of pyruvate is primarily oxidative, with no intracellular accumulation of lactate. Impairment of oxygen supply or cytoplasmic accumulation of pyruvate may result in increased lactate formation. Hyperlactatemia is characterized by mild to moderate increases in blood lactate concentration without metabolic acidosis. Lactic acidosis is defined by persistently increased blood lactate levels (usually >5 mmol/L) in association with acidosis (pH <7.35) [18]. Hyperlactatemia is also a marker for altered mitochondrial function [19]. Acquired or congenital abnormalities of mitochondrial oxidative phosphorylation result in a broad spectrum of clinical disorders, including peripheral neuropathy, encephalopathy, sensorineural deafness, myopathy, cardiomyopathy and conduction defects, pancreatitis and diabetes mellitus, liver steatosis, renal tubular dysfunction, pancytopenia, and multiple systemic lipomas [13, 19].

NRTIs are a substrate of the cellular polymerase γ. Inhibition of the polymerase results in decreasing levels of mitochondrial DNA and, thus, a diminished synthesis of mitochondrial enzymes (reviewed in [13]). The relative affinity of the various NRTIs for the polymerase γ, and their capacity for mitochondrial damage remains controversial [20, 21].

Here, we provide an analysis of the prevalence of hyperlactatemia in a large observational study. It underscores the frequency of mild elevations of lactate in blood and confirms the association between lactate elevation and various clinical manifestations. In the SHCS study, the mean lactate value ($\pm$SD) was 1.56 $\pm$ 0.736 mmol/L for patients receiving ART versus 1.24 $\pm$ 0.529 mmol/L for treatment-naïve people. Similar data have been recently described from an Australian cohort [22]. A probable syndrome of NRTI toxicity includes metabolic and lipid disorders. In addition, we confirm reports published elsewhere [23] regarding the association with the atrophic manifestations of lipodystrophy disorders (45% of patients with elevated lactate levels in the present study).

The study allowed the scoring of different antiretrovirals,

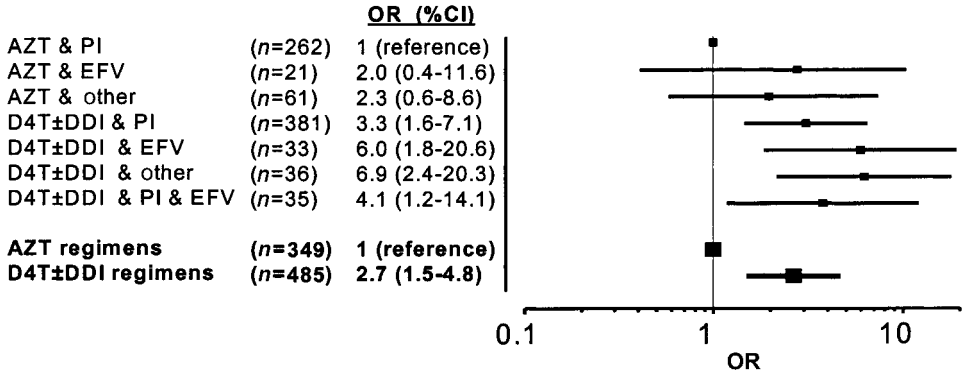

Figure 1. Drug combinations in current therapy and hyperlactatemia. ORs were calculated by means of logistic-regression adjusted for age, sex, most recent CD4 cell count, most recent RNA value, and previous exposure to nucleoside analog reverse-transcriptase inhibitors. Not shown are the combinations zidovudine (AZT), a protease inhibitor (PI), and efavirenz (EFV; n = 12); didanosine (DDI) and AZT combinations (n = 12); or DDI-only combinations (n = 16). Other, use of stavudine (D4T) or AZT in monotherapy or in combination therapy including agents other than a PI or EFV; $\pm$, with or without.

Table 3. Clinical symptoms and hyperlactatemia.

Symptom	No. (%) of patients, by lactate level		Crude OR (95% CI)	*P*
	Increased (*n* = 73)	Normal (*n* = 807)		
Fever	1 (1)	29 (4)	0.4 (0.1–3.0)	.37
Headache	9 (12)	184 (23)	0.5 (0.2–1.0)	.07
Fatigue	24 (33)	282 (35)	0.9 (0.5–1.5)	.64
Lithiasis	2 (3)	6 (1)	3.8 (0.7–19.7)	.11
Rash	4 (6)	54 (7)	0.9 (0.3–2.5)	.78
Myositis	2 (3)	12 (1)	1.8 (0.4–8.5)	.45
Nausea	15 (21)	140 (17)	1.3 (0.7–2.3)	.43
Vomiting	7 (10)	67 (8)	1.3 (0.6–2.9)	.56
Diarrhea	27 (37)	342 (42)	0.8 (0.5–1.3)	.33
Mood disorders	14 (19)	193 (24)	0.7 (0.4–1.4)	.33
Paresthesia	15 (21)	126 (16)	1.3 (0.7–2.4)	.38
Neuromotor disorders	7 (10)	40 (5)	1.9 (0.8–4.5)	.15
Sleep disorders	11 (15)	142 (18)	0.8 (0.4–1.6)	.62
Fat loss				
Facial	28 (38)	153 (19)	2.8 (1.7–4.7)	<.001
Arm	23 (32)	119 (15)	2.6 (1.5–4.5)	.001
Leg	26 (36)	131 (16)	2.9 (1.7–5.0)	<.001
Buttocks	16 (22)	112 (14)	1.6 (0.9–2.9)	.13
Abdomen fat gain	14 (19)	236 (29)	0.5 (0.3–1.0)	.04
Buffalo hump	2 (3)	18 (2)	1.2 (0.3–5.3)	.84
Breast enlargement	6 (8)	55 (7)	1.3 (0.5–3.1)	.60
Parotid enlargement	2 (3)	12 (1)	1.7 (0.4–8.0)	.50
Lipoatrophy, any sign	33 (45)	219 (27)	2.2 (1.3–3.7)	.002
Fat accumulation, any sign	17 (23)	251 (31)	0.6 (0.4–1.1)	.11

singularly and in combination, in terms of their relative and independent association with hyperlactatemia. There was an increased likelihood of hyperlactatemia in patients who were receiving regimens that contained stavudine with or without didanosine, as compared with regimens that contained zidovudine. Toxicity of didanosine and stavudine combinations may be further aggravated in the presence of hydroxyurea [11].

Analyses were adjusted for duration of exposure to NRTI and confirmed in the subgroup of patients having never received zidovudine before the present treatment with stavudine with or without didanosine. Thus, the observed association between hyperlactatemia and stavudine with or without didanosine should not be biased by these medications being more recently added to the therapeutic armamentarium and, therefore, given preferentially to patients who have had prolonged NRTI use.

Errors in the determination of lactate levels were identified in the course of the present study and led to the exclusion of data from 91 patients from analysis. Although lactate values remain stable for at least 8 h at room temperature in tubes containing sodium fluoride [16], blood lactate levels may be spuriously increased by the ischemia caused by a tourniquet or storage of blood without sodium fluoride.

The present study provides information on the complex issue of lipodystrophy [23], and it reveals associations between hyperlactatemia, fat atrophy, and specific ART regimens. It also suggests that differences in the reporting of lipodystrophy rates between countries and studies may reflect differences in the pattern of antiretroviral drug use. An evaluation at a single time point does not allow analysis of the natural history of the putative mitochondrial disorder. In particular, there was 1 single instance of lactic acidosis and hepatic steatosis; therefore, there is no basis for an analysis of risk factors of these complications. However, a recent report indicates that hyperlactatemia in patients receiving ART usually has a chronic, compensated, and asymptomatic evolution [22].

Future studies should analyze the role of routine lactic acid determination in the management of HIV-infected patients receiving ART, particularly those presenting with hepatic, neurologic, and metabolic disturbances. Randomized intervention

Table 4. Laboratory disorders and values associated with hyperlactatemia.

Characteristic	No. of patients with available data	Patients with		Crude OR (95% CI)	*P*
		Increased lactate level (*n* = 73)	Normal lactate level (*n* = 807)		
Laboratory disorder					
Decreased hemoglobin	868	3 (4)	13 (2)	2.7 (0.8–9.7)	.10
Decreased neutrophil count	874	2 (3)	38 (5)	0.6 (0.1–2.5)	.53
Decreased platelet count	874	0 (0)	45 (6)	—	—
Increased creatinine	833	2 (3)	27 (3)	0.9 (0.2–3.8)	.74
Proteinuria	714	13 (18)	69 (9)	2.3 (1.2–4.4)	.01
Increased urate	862	37 (51)	193 (24)	3.5 (2.1–5.7)	<.001
Increased alanine aminotransferase	864	11 (15)	180 (22)	0.6 (0.3–1.2)	.19
Increased aspartate aminotransferase	440	9 (12)	80 (10)	1.3 (0.6–2.7)	.37
Alkaline phosphatase	874	10 (14)	86 (11)	1.3 (0.7–2.7)	.45
Increased bilirubin	866	7 (10)	65 (8)	1.3 (0.6–2.8)	.65
Increased amylase	867	2 (3)	36 (4)	0.6 (0.2–2.6)	.57
Increased creatine phosphokinase	863	4 (5)	52 (6)	0.9 (0.3–2.5)	.83
Laboratory values, mean ± SEM					
Glucose	870	5.87 ± 0.3	4.99 ± 0.05	—	<.001[a]
Cholesterol	860	5.97 ± 0.2	5.57 ± 0.05	—	.03[a]
Triglyceride	859	2.77 ± 0.09	2.25 ± 0.7	—	<.001[a]

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Determined using the *t* test.

protocols will be required to establish the relative value of treatment interruption; treatment modification from stavudine with or without didanosine to regimens containing zidovudine, lamivudine, or abacavir; or combination therapies excluding NRTIs. The value of riboflavin or other cofactors of the respiratory chain [24–26] in reversing lactate accumulation also needs evaluation.

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