Symptomatic Lactic Acidosis in Hospitalized Antiretroviral-Treated Patients with Human Immunodeficiency Virus Infection: A Report of 12 Cases


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We retrospectively investigated the clinical and histopathologic features of hospitalized patients infected with human immunodeficiency virus who had symptomatic lactic acidosis syndrome at a university teaching hospital during 1995–2000. Twelve patients were identified, 11 during 1998–2000; of these, 5 died with rapid progression to otherwise unexplained multiple-organ failure. All had extensive prior exposure to nucleoside analog reverse-transcriptase inhibitors (NRTIs). At presentation, the most commonly identified NRTI component of antiretroviral regimens was stavudine plus didanosine. Eleven patients presented with abdominal pain, nausea, and/or emesis. Eight patients had prior acute weight loss (mean [±SD], 12 ± 5.3 kg). Median venous plasma lactate levels were 2-fold greater than the upper limit of normal (2.1 mmol/L). Serum transaminase levels were near normal limits at presentation. Histopathologic studies confirmed hepatic macrovesicular and microvesicular steatosis in 6 patients. Concurrent chemical pancreatitis was identified in 6 patients. The increasing number of cases identified during the study period suggests that physicians better recognize symptomatic lactic acidosis and/or that cumulative NRTI exposure may increase the risk for this syndrome.

Nucleoside analog reverse-transcriptase inhibitor (NRTI) therapy for chronic HIV infection has been associated with drug-induced toxicities. A clinical syndrome designated “type B lactic acidosis” (i.e., without hypoxemia), which is associated with mitochondrial myopathy, hepatic macrovesicular and microvesicular steatosis (hereafter, macrosteatosis and microsteatosis, respectively), lipoatrophy, liver dysfunction and/or fulminant liver failure, and occasional concomitant pancreatitis, has been associated with HIV NRTI therapy [1–9]. A standardized case definition for this syndrome has not yet been defined. The exact mechanism or mechanisms are unclear, but the syndrome appears to reflect mito-
PATIENTS AND METHODS

Study population. From January 1995 through February 2000, 12 cases of symptomatic lactic acidosis in hospitalized patients infected with HIV who had been treated with antiretrovirals were identified clinically by physicians and referral physicians at the University of Alabama at Birmingham (UAB) School of Medicine. Eleven patients were routinely followed at the UAB HIV outpatient clinics, Jefferson County Cooper Green Hospital, UAB Montgomery Internal Medicine Residency Program Infectious Disease Subspecialty Clinic, or the Medical Center East Infectious Diseases Clinic. One subject was followed at the UAB-affiliated general medical clinic in Selma, Alabama. Inpatient and outpatient medical records were reviewed retrospectively.

Study assessments. The following parameters were assessed: treatment history, clinical symptomatology, physical examination findings, CD4+ T lymphocyte counts, plasma HIV RNA levels, history of opportunistic infections, hematologic tests, biochemical tests, venous plasma lactic acid levels, and arterial pH.

Four liver specimens obtained at autopsy and 2 liver biopsy specimens obtained from patients who survived were available for histopathologic examination. All tissues were fixed in formalin, embedded in paraffin, and examined by light microscopy by use of hematoxylin-eosin staining. Tissues were also stained with periodic acid–Schiff to accentuate the appearance of macrosteatosis and microsteatosis (i.e., a clear round space in processed liver samples, reflecting dissolved fat). Macrosteatosis was defined as the presence of fat vacuoles greater than or equal to the size of hepatocyte nuclei; microsteatosis was defined as the presence of smaller fat vacuoles [12].

Statistical analyses. For comparison of categorical variables, a 2-tailed Fisher’s exact test was used. For comparison of continuous variables, the Wilcoxon–rank sum test was used. For all tests, P < .05 was considered to be statistically significant.

RESULTS

Study population. We identified 12 hospitalized HIV-infected patients who were receiving antiretroviral therapy and had symptoms and signs of lactic acidosis: 1 patient in 1995, 3 in 1998, and 8 during 1999–2000 (see table 1). Five patients died during hospitalization, which corresponds to a mortality rate of 42%. The median time from admission to the hospital to death was 3 days (range, 1–18 days). For 1 patient, this included a stay at another hospital prior to transfer to our institution. Four of 5 nonsurvivors were African American, compared with 3 of 7 survivors (P = .29). HIV risk factors were reported as homosexuality (4 patients) or heterosexual/unknown risk (8 patients). Four patients (2 survivors and 2 nonsurvivors) had prior AIDS-defining diagnoses.

There was marked heterogeneity in CD4+ T lymphocyte counts at presentation (range, 60–805 cells/mm3; median, 284 cells/mm3). The median historical CD4+ T lymphocyte count nadir was 111 cells/mm3 (range, 15–517 cells/mm3). Ten patients had nadir counts of <200 cells/mm3, meeting the AIDS case definition. Nonsurvivors had a historical median nadir count of 86 cells/mm3, compared with a median of 122 cells/mm3 among survivors (P = 1.00). The median plasma HIV RNA level at presentation was 714 copies/mL, which reflects recent receipt of highly active antiretroviral therapy.

Median aspartate aminotransferase (AST) levels prior to hospitalization were 36 U/L for survivors and 34 U/L for nonsurvivors (normal range for serum values, 0–37 U/L; P = .75). None had a history of significant liver disease or concurrent hepatitis B or C virus infection. The history of alcohol consumption, a known cause of limited hepatic reserve and steatosis, was known for all patients. For 10 patients, there was no history of alcohol consumption. One nonsurvivor had a remote history of modest alcohol consumption, and 1 survivor had a history of intermittent alcohol intake. One nonsurvivor and 1 survivor had diabetes mellitus, a risk factor for hepatic steatosis.

Eight patients had experienced rapid weight loss (mean ± SD, 12 ± 5.3 kg) prior to presentation. One survivor lost ~20 kg in the 6 weeks preceding hospitalization. In 10 patients with available data, the median body mass index at presentation was 29 (range, 22–47; median, 27 for 7 survivors, versus 34 for 3 nonsurvivors; P = .07).

Lifetime NRTI experience in these patients was considerable, as shown in table 2. At presentation, 1 patient was receiving monotherapy with zidovudine, and 11 patients were receiving dual NRTI-containing highly active antiretroviral therapy regimens. Four were receiving concomitant hydroxyurea therapy. The most commonly identified 2-drug combined NRTI regimen was stavudine plus didanosine (9 patients, 4 of whom were on concomitant hydroxyurea and survived). The median lifetime number of antiretroviral regimens was 3 (range, 1–10). The median total duration of lifetime antiretroviral exposure was 21 months (20 months for survivors vs. 22 for nonsurvivors; P = .68; range, 6–70 months). The median total duration of lifetime antiretroviral treatment was 21 months (20 months for survivors vs. 22 for nonsurvivors; P = .68). Eleven patients
Table 1. Summary of findings for 12 hospitalized antiretroviral-treated HIV-infected patients with symptomatic lactic acidosis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>CD4+ T lymphocyte count, cells/mm³ at nadir; at presentation</th>
<th>Plasma HIV-1 RNA level, copies/mL</th>
<th>Duration of NRTI therapy, months</th>
<th>Laboratory test results, key value or rangea</th>
<th>Findings of abdominal US and/or CT</th>
<th>Histologic findingsb</th>
<th>Outcome of hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>139; 139</td>
<td>2000</td>
<td>70</td>
<td>7.26 13-14.3 15-21 175-200 107 99 108</td>
<td>Unremarkable</td>
<td>NA</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>122; 286</td>
<td>862</td>
<td>22</td>
<td>7.36 4.6-9.6 20-26 73 588 83-229 93-775</td>
<td>Fatty liver; normal pancreas</td>
<td>NA</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>168; 168</td>
<td>&lt;400</td>
<td>20</td>
<td>7.22 19.6-23.9 18-28 75-173 63 609-1209 2387-6805</td>
<td>Fatty liver; mild to moderate pancreatitis without necrosis</td>
<td>NA</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>70; 222</td>
<td>&lt;50</td>
<td>17</td>
<td>7.37 14.5-16 23 85-116 50 43 NA</td>
<td>1st CT: normal liver and pancreas; 2d CT: minimal focal fatty change</td>
<td>NA</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>517; 801</td>
<td>&lt;25</td>
<td>14</td>
<td>7.39 7.1-9.9 28 235-446 147 74-79 699-1002</td>
<td>Hepatomegaly, echogenic and fatty liver, normal pancreas</td>
<td>50% microsteatosis, 50% macrosteatosis, moderate steatosis, very mild portal inflammation</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>100; 442</td>
<td>714</td>
<td>46</td>
<td>7.2 17.3-18.4 25-27 117 415 348 1312</td>
<td>Hepatomegaly, fatty liver, mildly inflamed pancreas without necrosis</td>
<td>NA</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>16; 351</td>
<td>1303</td>
<td>16</td>
<td>7.4 5.5-9.7 21-32 56-90 148 40-153 48-56</td>
<td>CT: small focal area, fatty liver; US: mildly echogenic liver</td>
<td>Mild diffuse steatosis, moderate portal inflammation, 50% macrosteatosis, &gt;30% microsteatosis</td>
<td>Survived</td>
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<tr>
<td>8</td>
<td>38; 60</td>
<td>12,000</td>
<td>29</td>
<td>7.36 6.6-14.2 22-27 41 285 100 261</td>
<td>NA</td>
<td>NA</td>
<td>Died</td>
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<tr>
<td>9</td>
<td>86; 389</td>
<td>459</td>
<td>13</td>
<td>7.31 5.9-12 18-34 51-111 308-2834 51 NA</td>
<td>Hepatomegaly and fatty liver</td>
<td>85%-90% macrosteatosis, minimal portal inflammation, mild steatohepatitis</td>
<td>Died</td>
</tr>
<tr>
<td>10</td>
<td>83; 181</td>
<td>8300</td>
<td>22</td>
<td>6.7 22.9 26-34 52 45-183 86 242</td>
<td>NA</td>
<td>NA</td>
<td>Died</td>
</tr>
<tr>
<td>11</td>
<td>191; 282</td>
<td>NA</td>
<td>6</td>
<td>7.36 4.7-21.2 23-67 39-1455 113-6294 57-229 57-3272</td>
<td>1st CT: fatty liver; 2d CT: fatty liver and acute pancreatitis without necrosis</td>
<td>NA</td>
<td>Died</td>
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<tr>
<td>12</td>
<td>364; 805</td>
<td>&lt;50</td>
<td>38</td>
<td>6.9 25.7-39.6 19-34 76-163 4766 224-1971 2149-19,824</td>
<td>Normal liver, enlarged pancreatic head without inflammation</td>
<td>Microsteatosis and macrosteatosis</td>
<td>Died</td>
</tr>
</tbody>
</table>

NOTE. AST, aspartate aminotransferase; CPK, creatine phosphokinase; lactate, plasma venous lactate; NA, not available; NRTI, nucleoside analog reverse-transcriptase inhibitor; US, ultrasonography.

a Key values or ranges of values observed during the course of illness. Normal serum values are as follows: amylase, 14-151 U/L; AST, 0-37 U/L; CPK, 32-250 U/L; lactate (venous plasma lactate), 0.7-2.1 mmol/L; and lipase, 0-61 U/L.

b Findings are reported for standard light microscopy of liver biopsy specimens.

c The normal ranges at this time were amylase, 30-110 U/L; and lipase, 23-203 U/L.

d The normal ranges at this time were amylase, 25-125 U/L; and lipase, 114-286 U/L.

e The normal ranges at this time were amylase, 34-122 U/L; and lipase, 114-286 U/L.

f The normal ranges at this time were amylase, 30-110 U/L; and lipase, 23-203 U/L.

g The normal ranges at this time were amylase, 25-125 U/L; and lipase, 114-286 U/L.
Table 2. Current and cumulative (i.e., lifetime) history of nucleoside analog reverse-transcriptase inhibitor (NRTI) or adjuvant therapy for 12 HIV-infected patients hospitalized with symptomatic lactic acidosis syndrome.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Zidovudine</th>
<th>Lamivudine</th>
<th>Stavudine</th>
<th>Didanosine</th>
<th>Dideoxycytidine</th>
<th>Abacavir</th>
<th>Hydroxyurea</th>
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<tbody>
<tr>
<td>Survivors</td>
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<td>Nonsurvivors</td>
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NOTE. C, current therapy at time of presentation; H, any history of therapy.

had prior stavudine exposure. The median total duration of lifetime stavudine treatment was 16 months (17 months for survivors vs. 8 for nonsurvivors; \( P = 1.00 \)). The median total duration of lifetime treatment with nonnucleoside analog reverse-transcriptase inhibitors was 0 months (range, 0–15 months). The median total duration of lifetime hydroxyurea therapy was 1 month for survivors (range, 0–11 months); none of the nonsurvivors had received hydroxyurea therapy. The median total duration of lifetime protease inhibitor (PI) therapy was 12 months (range, 0–46 months; 13 months for survivors vs. 0 for nonsurvivors; \( P = .21 \)). Three of 7 survivors were receiving PI therapy; in contrast, only 1 of 5 nonsurvivors was receiving concurrent PI therapy (\( P = .58 \)).

Clinical symptomatology. The most common symptoms were nausea and emesis (9 patients), which usually occurred 1–14 days prior to hospitalization. Four patients had these symptoms for \(~1\) day. Eleven patients had these symptoms and/or poorly localized abdominal pain. Other symptoms and signs included weight loss (8 patients), tachypnea (\( \geq 24 \) breaths/min; 7 patients), abdominal distension (6 patients), motor or generalized weakness (6 patients), dyspnea (3 patients), and dis-equilibrium/neuropathy (1 patient). Dyspnea and/or tachypnea became more prominent as the lactic acidosis syndrome progressed to multiple-organ failure within days of hospitalization in nonsurvivors. For 3 survivors, nerve conduction velocity/electromyography studies were performed to evaluate proximal muscular weakness and/or neuropathic pain. Two of these 3 patients had demyelinating polyneuropathy that suggested Guillain-Barré syndrome with profound weakness; they had to use wheelchairs temporarily and gradually recovered during the 6 months after discontinuation of drug therapy. One of these 3 patients had electromyographic evidence of proximal muscle myopathy despite a normal creatinine phosphokinase level.

Therapeutic interventions after drug discontinuation were limited to supportive measures. Interventions included administration of total parenteral nutrition, iv hydration with glucose supplementation, oral and iv bicarbonate, and mechanical ventilation as necessary for control of acidemia. Sepsis and other usual causes of multiple-organ failure were excluded. Antibiotics were administered to 4 of 5 nonsurvivors as multiple-organ failure progressed; however, significant pathogens were not isolated from blood cultures; 1 blood culture yielded coagulase-negative \textit{Staphylococcus} species, but this result was discounted. In 1 patient with a normal serum creatinine level, correction of lactic acidemia with continuous venovenous hemodialysis allowed lactic acidemia to be controlled. Four patients, 3 of whom survived, received vitamin-fortified total parenteral nutrition, including riboflavin, which has been proposed as a possible therapy for lactic acidosis [13].

Laboratory findings. The ranges of laboratory values at admission and during hospitalization overlapped widely in survivors and nonsurvivors. For the group of all patients, the median initial venous plasma lactic acid level was \( \geq 2\) fold greater than the upper limit of normal (ULN; 2.1 mmol/L), at 10.1 mmol/L (range, 4.6–25.7 mmol/L; median, 13 mmol/L for survivors vs. 6.6 for nonsurvivors; \( P = .87 \)). The median peak venous plasma lactic acid level was 15.2 mmol/L (range, 9.6–39.6 mmol/L; median, 14.3 mmol/L for survivors vs. 21.2 for nonsurvivors; \( P = .26 \)). The median initial serum anion gap was 21.5 mEq/L (range, 15–28 mEq/L; median, 21 mEq/L
for survivors vs. 22 for nonsurvivors; \(P = 1.00\)). The median peak serum anion gap was 28 mEq/L (range, 21–67 mEq/L; median, 27 mEq/L for survivors vs. 34 for nonsurvivors; \(P = .03\)). The median initial serum bicarbonate level was 14.0 mEq/L (range, 5–20 mEq/L; median, 13 mEq/L for survivors vs. 14 for nonsurvivors; \(P = .75\)). The median nadir serum bicarbonate level was 7 mEq/L (range, 3–15 mEq/L; median, 11 mEq/L for survivors vs. 4 for nonsurvivors; \(P = .12\)). Creatine phosphokinase levels were elevated (1.2-fold to 25-fold above normal) in 6 patients during hospitalization, 4 of whom died. Initial mean arterial pH was lower in nonsurvivors (7.13) than normal in 6 patients during hospitalization, 4 of whom died. Initial mean arterial pH was lower in nonsurvivors (7.13) than in survivors (7.31; \(P = .25\)).

Despite the recognized association between lactic acidosis syndrome and hepatic failure, serum AST levels were near normal limits at presentation in all patients. The median initial AST level at presentation for nonsurvivors was \(\leq 2\)-fold greater than the ULN (52 U/L), which was modestly lower than the median level for survivors (85 U/L; \(P = .02\)). The median serum AST levels increased during hospitalization, to 4-fold to 5-fold greater than the ULN. Alkaline phosphatase levels were generally normal. There was minimal hyperbilirubinemia (median peak total bilirubin was \(\leq 2.1\)-fold greater than the ULN).

Five patients died within days of presentation at the hospital, with rapid and precipitous progression to hepatic and multiple-organ failure. Two patients presented with high venous plasma lactic acid levels: 1 had a level of 22.9 mmol/L and died within 24 h of admission; the other had a level of 25.7 mmol/L (with a peak of 39.6 mmol/L prior to death). Three other nonsurvivors had at least a doubling of initial plasma venous lactate levels, from a median initial value of 6.6 mmol/L to a median peak level of 14.3 mmol/L. In contrast, none of the survivors had changes to this degree during hospitalization. Because there were significant associations between peak anion gap and mortality, as well as between initial AST and mortality, the changes in these parameters were evaluated as predictive factors. A change in anion gap (i.e., the peak minus the initial values for each subject) was positively related to mortality (\(P = .07\)), although change in AST over time was not related significantly to mortality (\(P = .66\)). Changes in venous plasma lactic acid levels were also positively related to mortality (\(P = .10\)).

Concurrent chemical pancreatitis, defined as serum lipase levels \(\geq 3\)-fold greater than the ULN, was present in 6 patients, 4 of whom survived. Four survivors and 1 nonsurvivor were on combined stavudine plus didanosine. Three of 4 survivors, but none of the nonsurvivors, also had recently received hydroxyurea adjuvant therapy. During hospitalization, there was a broad range of initial serum lipase values (0.3-fold to 39-fold greater than the ULN) and maximum serum lipase values (4.9-fold to 112-fold greater than the ULN). Two nonsurvivors had serum lipase levels that were \(\geq 16\)-fold greater than the ULN, despite having no evidence of pancreatic necrosis on initial abdominal imaging. Two of 12 patients had normal amylase levels, but no lipase levels were drawn; we may have missed identifying concurrent pancreatitis in these patients because of our definition. Four of 12 patients had normal amylase and lipase levels. Median triglyceride levels were 398 mg/dL for nonsurvivors (normal range, 40–200 mg/dL).

**Radiographic findings.** Ten patients had abdominal CT and/or ultrasound studies performed (5 had both); 2 patients died before imaging studies were obtained. Initial radiographic imaging had limited success for identification of fatty liver infiltration (i.e., hepatic steatosis) and/or pancreatitis. Nine patients had radiographic density changes consistent with some fatty liver infiltration (determined by use of CT for 7 patients and by use of ultrasound for 2). Only 6 patients had evidence of definite diffuse steatosis. For 1 patient, the CT scan was reported as indicating “probable diffuse hepatic steatosis.” Radiographic changes consistent with hepatic steatosis were evident even in patients with initial venous plasma lactic acid levels as low as 4.6 mmol/L; nevertheless, 1 patient with an initial venous plasma lactic acid level of \(\geq 25\) mmol/L and autopsy-proven hepatic steatosis had a reportedly “normal” CT scan. Radiographic pancreatitis was also seen on CT in 3 patients. None had radiographic evidence of pancreatic necrosis or choledochitis. Three patients without evidence of pancreatic inflammation on initial ultrasound studies developed abnormal lipase levels (4.9-fold to 69-fold greater than the ULN).

**Histopathologic studies.** Histopathologic studies of liver tissue samples obtained from 6 patients demonstrated macrosteatosis and microsteatosis by light microscopy; photomicrographs from 2 specimens are depicted in figure 1. Four autopsy liver specimens had 25%–90% macrosteatosis and \(\approx 70\%\) microsteatosis. Two liver biopsy specimens had \(\approx 50\%\) macrosteatosis and 30%–50% microsteatosis. Macrosteatosis was predominantly perivenular, whereas microsteatosis was more diffuse. Bile ducts were well preserved. One autopsy sample showed mild steatohepatitis, which suggested a possible preexisting liver dysfunction. There was minimal neutrophilic and lymphocytic inflammation, which was usually portal in location. Only 1 specimen showed focal areas of confluent necrosis. Special staining revealed no evidence of concurrent infections in any of the tissue samples examined.

**DISCUSSION**

This retrospective case series presents clinical, radiographic, and histopathologic manifestations of symptomatic lactic acidosis in 12 hospitalized patients infected with HIV who had been treated with antiretrovirals. An increasing number of cases were identified during 1995–2000, which suggests enhanced physician recognition and/or evidence that cumulative NRTI exposure may increase risk for the syndrome. Symptoms and signs
Figure 1. Photomicrographs showing hepatic macrovesicular and microvesicular steatosis (hereafter, macrosteatosis and microsteatosis, respectively) in liver specimens obtained at autopsy from 2 patients. A, Hematoxylin-eosin stain showing marked macrosteatosis in a liver biopsy specimen obtained from an HIV-infected patient with symptomatic lactic acidosis (original magnification, low power, ×10). B, Macrosteatosis around central veins in a liver specimen obtained from a different HIV-infected patient with symptomatic lactic acidosis. The central vein is highlighted by periodic acid–Schiff stain (original magnification, high power, ×40). C, Periodic acid–Schiff stain highlighting microsteatosis (arrow) in a liver specimen obtained from the same patient as the specimen shown in B (original magnification, high power, ×40).

were similar to those reported previously: nausea, emesis, abdominal pain, and distension associated with elevated venous plasma lactic acid levels, elevated liver function tests, and hepatic steatosis. Tachypnea and dyspnea were not as helpful diagnostic signs as has been reported elsewhere [1–3, 5, 8], because these symptoms did not identify high-risk patients early but rather signaled worsening preterminal lactic acidosis. Elevated venous plasma lactic acid levels and serum anion gaps were critical for making the clinical diagnosis. Indeed, there was a trend toward mortality for the group of patients who experienced greater changes in each of these laboratory parameters during hospitalization. However, other laboratory and radiographic parameters were not very helpful in discerning the clinical course. Serum transaminase levels were nearly normal at presentation and were not as predictive of the lactic acidosis syndrome as has been reported elsewhere [9]. The minimal inflammation histopathologically mirrored the relatively normal serum transaminase levels seen at presentation and the modest elevations observed during hospitalization; this finding is analogous to that described for cases of fialuridine-associated hepatic failure and lactic acidosis [4]. Interestingly, higher body mass indices were evident in our nonsurvivors. Although the exact significance of this finding is unknown, it is possible that preexisting steatosis related to comorbid obesity may increase the risk of drug-induced hepatic dysfunction and development of lactic acidosis. Concurrent chemical pancreatitis was identified in 6 patients.

It has been hypothesized that mitochondrial damage is a cause of the NRTI-associated lactic acidosis syndrome and that mitochondrial changes within adipocytes may result in a recently described NRTI-associated lipodystrophy syndrome [8, 14]. Carr et al. [8] reported a syndrome of lipoatrophy, fatigue, nausea, weight loss, and hepatomegaly associated with lactic acidemia. Chariot et al. [6] also described a single subject who had a progressive 20% weight loss before the onset of fatal zidovudine-associated lactic acidosis. In our cohort, 66% of patients also experienced a syndrome that suggested acute lipoatrophy immediately prior to hospitalization, with evidence of weight loss and poorly defined malaise preceding the diagnosis of lactic acidosis. This weight loss may indicate bioenergetic mitochondrial dysfunction that appears before the expression of more-commonly recognized lactic acidosis symptoms. Susceptible patients with cumulative NRTI exposure may accumulate subclinical mitochondrial DNA mutations over time to a threshold level of mitochondrial dysfunction at which clinical symptoms develop. This may be analogous to the “threshold expression phenomenon” seen in congenital mitochondrial mutation disorders, whereby symptoms are expressed only after a critical percentage of mitochondria become dysfunctional [15]. Furthermore, patients who died despite discontinuation of antiretroviral therapy may have reached a “physiologic point
of no return,” possibly because of irreversible mitochondrial damage and poor reserve function.

Our case series represents an advanced end of the spectrum of NRTI-associated lactic acidosis syndrome, because our patients had symptoms sufficient to require hospitalization. Ten patients had historical nadir CD4+ T lymphocyte counts of <200 cells/mm³. Such patients may be at increased risk for NRTI-associated symptomatic lactic acidosis syndrome, which requires further study. Lonergan et. al. [16] described a cohort of 20 HIV-infected patients with evidence of a milder form of lactic acidosis that did not always require hospitalization. The mean CD4+ T lymphocyte count was 370 cells/mm³ (range, 25–1397 cells/mm³). Only 3 patients required hospitalization, and all survived. Earlier recognition of lactic acidosis with more immediate discontinuation of drug therapy may allow the disorder to be reversed and prevent the need for hospitalization [16, 17].

The most common 2-drug combined NRTI backbone regimen in our patients was stavudine plus didanosine. However, the impact of prior or cumulative NRTI exposure on development of lactic acidosis syndrome was also likely important, given that this exposure was considerable in our patients. Non-survivors may have had a greater net loss of mitochondria after years of antiretroviral use and not-yet identified mitochondrial genetic defects, all of which may lead to inexorable bioenergetic dysfunction. It has been difficult to correlate the results of in vitro NRTI mitochondrial toxicity studies with reports of in vivo effects. Nonetheless, numerous in vitro studies have shown multiple mitochondrial defects after cell exposure to NRTIs, including ultrastructural changes, alterations in oxidative phosphorylation and lactate production, and decreases in total mitochondrial DNA (mtDNA). NRTIs exhibit a range of affinities for human mitochondrial γ DNA polymerase [18–24]. Combined NRTI therapies may have increased mitochondrial effects by inhibiting multiple steps in the complex energy production cascade.

Hydroxyurea boosts intracellular levels of the 5′-triphosphate derivatives of stavudine and didanosine, perhaps exposing mitochondria to enhanced nucleoside-associated toxicities. Recently, several trials that investigated hydroxyurea in combination with other antiretroviral therapies were terminated early because of potentially enhanced NRTI toxicities; in particular, neuropathy, pancreatitis, and liver dysfunction [25, 26]. The precise role of hydroxyurea and of other non-NRTI antiretroviral therapies in the manifestation of antiretroviral toxicities, and in particular NRTI-associated lactic acidosis, remains uncertain.

Our study has numerous limitations related to its design as a retrospective review of clinical and histopathologic data from a small number of patients. The patients described here had symptomatic lactic acidosis syndrome, although there is still no definitive case definition. This series provides insight about clinical, laboratory, and histopathologic features associated with severe cases, but it is recognized that all asymptomatic and milder clinical presentations were likely missed. Venous plasma lactic acid levels were not obtained routinely during the study period; thus, a case-control study design could not be applied retrospectively. Partial data collection and interpretation biases were also probable, as was the possibility of incomplete medical records. Tissue specimens were only available for 6 patients, and they were not well enough preserved for electron microscopy to demonstrate mitochondrial disruption definitively.

In summary, during 1995–2000, we identified an increasing number of cases of the symptomatic lactic acidosis syndrome in patients infected with HIV who had been treated with antiretrovirals, which suggests enhanced physician recognition and/or cumulative toxicities. We found concurrent chemical pancreatitis in 6 patients and identified a clinical syndrome similar to lipodystrophy that occurred as an early component of symptomatic hyperlactatemia. Our study confirms other reported studies that have underscored the likely presence of significant mitochondrial toxicity in susceptible patients, despite normal laboratory parameters. Early recognition and discontinuation of antiretroviral therapies are probably essential to recovery. Earlier clinical diagnosis may require histopathologic correlation and better laboratory tests. Prospective studies are required to delineate the spectrum of NRTI-associated lactic acidosis syndrome, its prevalence, the underlying genetic and biochemical mechanism(s), and possible therapeutic interventions.

Acknowledgments

We are indebted to the patients; to Renee’ Desmond, of the University of Alabama at Birmingham (UAB) Biostatistics Center for AIDS Research Core, for biostatistical support; to William E. Dismukes, for critical manuscript review; to Kristin Fett, for assistance with manuscript preparation; to the Medical Information Departments at UAB Hospital, the UAB HIV Clinic, and the Jefferson County Cooper Green Hospital, for their assistance with medical record review; to Charles M. Soppet and Warren D. Everett, for providing medical records; to Stephen Boudreau, for assistance with autopsies and autopsy materials; to Jennifer L. Koel, for assistance reviewing the patients’ medication histories; and to Jan D. Pauls and Debra K. Horton, for their assistance with preparation of tissue specimens for review by light microscopy.

References