Hyperlactatemia and Hepatic Abnormalities in 10 Human Immunodeficiency Virus–Infected Patients Receiving Nucleoside Analogue Combination Regimens

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During a 6-and-a-half month period, we identified 10 human immunodeficiency virus (HIV)–infected men who were receiving antiretroviral regimens, including nucleoside analogues, and who developed unexplained reproducible hyperlactatemia in association with either abdominal symptoms or an unaccounted-for elevated alanine aminotransferase level, or both. After careful consideration of the possible etiologies, antiretrovirals were discontinued; lactate levels normalized in all patients. The estimated incidence of this phenomenon in our clinic was 20.9 cases per 1000 person-years of nucleoside analogue treatment. These observations extend the spectrum of the nucleoside analogue–induced lactic acidosis/hepatic steatosis syndrome by the identification of a subtle and perhaps earlier form, which has characteristic symptoms and laboratory abnormalities, and a favorable prognosis on discontinuation of antiretroviral therapy.

An often fatal syndrome of lactic acidosis and hepatic steatosis is a recognized but rare complication of nucleoside analogue reverse transcriptase inhibitor (NRTI) therapy for HIV infection [1]. Mitochondrial toxicity is the proposed mechanism of hepatic injury [1]. Nucleoside analogues can also inhibit DNA polymerase-γ, the enzyme responsible for mitochondrial DNA synthesis [2]. The ensuing mitochondrial dysfunction may result in lactic acidosis, hepatic steatosis, and other adverse events (i.e., myopathy, pancreatitis, and peripheral neuropathy) that are observed in patients treated with this class of antiretrovirals [2, 3].


From mid-July 1998 through January 1999, we identified 10 adult HIV-infected patients who attended an urban, university-based HIV clinic and had a milder and possibly earlier form of the lactic acidosis/hepatic steatosis syndrome. These patients were receiving antiretroviral therapy, including ≥2 nucleoside analogues, and had unexplained reproducible hyperlactatemia associated with either abdominal symptoms or an unaccounted-for elevated alanine aminotransferase (ALT) level, or both. The first case will be described in detail, and features of the remaining cases will be summarized.

Case Report

A 36-year-old homosexual man with HIV infection since 1991 (CD4+ cell count, 652 cells/mm³; HIV-1 RNA viral load, 23,758 copies/mL; by use of the Amplicor PCR assay [Roche, Nutley, NJ]) presented for evaluation of a 1-week history of worsening abdominal pain and distention, nausea, and diarrhea. Nine months before presentation, the patient had initiated a salvage antiretroviral regimen that included ritonavir 400 mg twice daily, soft-gel saquinavir 400 mg twice daily, stavudine 40 mg twice daily, and didanosine 300 mg once daily. He had previously been treated with the antiretrovirals indinavir, nelfinavir, zidovudine, and lamivudine. His only other medication was trimethoprim-sulfamethoxazole (TMP-SMZ), which was prescribed because of a CD4+ cell count nadir of 41 cells/mm³.

Upon examination, the patient was overweight and in mild distress with a temperature of 36.4°C and a blood pressure of 136/74 mm Hg. The remainder of the examination findings were notable only for abdominal distention and right upper quadrant tenderness.

Abnormal laboratory findings included the following: aspartate aminotransferase (AST) level, 139 U/L (normal range, 10–45 U/L); ALT level, 211 U/L (normal range, 10–45 U/L); bicarbonate level, 17 mmol/L (normal range, 24–31 mmol/L); anion gap, 22 (normal range, 10–12 mmol/L); venous plasma lactate level, 5.3 mmol/L (normal range, 0.7–2.1 mmol/L); and an arterial pH of 7.43, a pO2 level of 87 mm Hg, and a pCO2 level of 30 mm Hg. Results of stool studies, pancreatic enzyme, bilirubin, and alkaline phosphatase levels, complete blood count, and viral hepatitis serologies were unremarkable.

Abdominal ultrasound showed mild hepatomegaly (16.7 cm in length, normal 15 cm) with normal echogenicity. Evaluation of a liver biopsy specimen revealed mild macrovesicular steatosis and severe diffuse microvesicular steatosis. Oil-red-O staining of frozen biopsy tissue confirmed the steatosis. There was no significant inflammation, fibrosis, or hepatocyte necrosis. Electron microscopic examination demonstrated increased density in the inner mitochondrial compartment without swelling or disintegration of the mitochondria.
Antiretroviral medications were suspended 2 days after presentation. Twelve days later the patient’s condition had improved markedly; his lactate level was 4.0 mmol/L and his ALT levels was 106 U/L. Within 34 days the patient’s symptoms resolved and his laboratory values normalized.

Results

During a 6-and-a-half month period, 10 patients who were receiving nucleoside analogues were identified with hyperlactatemia and either abdominal symptoms or an abnormal ALT level, or both. Table 1 summarizes the pertinent characteristics of these patients. All patients were adult men (median age, 35 years; range, 25–48 years), and the majority were overweight (median body mass index [BMI], 28.5 kg/m²; range, 20.1–37.5 kg/m²). Their median CD4⁺ cell count was 375 cells/mm³ (range, 217–1397 cells/mm³), and their median plasma HIV-1 RNA viral load was 780 copies/mL (range, 40–27,941 copies/mL). All patients were taking stavudine and ≥1 other nucleoside analogue, and 8 were also receiving either a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor, or both, with median treatment duration of 10 months (range, 4–20 months).

Three patients had concomitant chronic hepatitis B or C. No patient had concurrent clinical disorders that would either predispose to or result in lactic acidosis. In addition, none of the patients reported excessive alcohol ingestion or strenuous physical activity during the previous 6 months.

Gastrointestinal complaints prompted evaluation in 8 patients (including all 3 patients with chronic viral hepatitis), whereas ALT level elevations not attributable to another cause led to the identification of hyperlactatemia in 2 asymptomatic patients. The most common symptoms were abdominal pain (n = 8), nausea (7), and distention (6). Before the onset of these symptoms, the patients had been tolerating their medications well for several months.

All patients had reproducible elevated venous lactate levels (median peak, 4.4 mmol/L; range, 2.9–6.2 mmol/L) while receiving antiretroviral therapy. To minimize false lactate elevations, blood was collected by venipuncture into a tube containing sodium fluoride (an inhibitor of lactate dehydrogenase) and immediately placed on ice. The icd specimen was then centrifuged, and the plasma lactate level was measured by using a Beckman Synchron CX7Δ (Beckman Instruments, Brea, CA) instrument. If the lactate level was elevated, it was confirmed by having the patient return to the clinic and repeating the measurement using the same technique. Seven of 10 patients with hyperlactatemia had evidence of metabolic acidosis—either decreased bicarbonate or increased unmeasured anions—but only 2 of these patients had both simultaneously.

Median peak ALT level was 3 times the upper limit of normal (range, 2.1–10.7 times normal). All the patients, with the exception of the 3 who had chronic viral hepatitis, had normal ALT levels prior to starting their current antiretroviral regimen. CT and/or ultrasonographic imaging of the liver was performed for 7 patients. Hepatomegaly, determined by use of ultrasound (>15 cm in length) was evident in 4 of 5 patients (median, 18.5 cm; range, 12.4–19.0 cm), and imaging by either technique was consistent with fatty infiltration in 5 patients.

To rule out other causes of liver disease and to provide supporting evidence, liver biopsies were performed for 6 patients. One patient’s specimen showed changes consistent with moderately active hepatitis B. For the remaining 5 patients, biopsy specimens revealed a spectrum of similar findings including normal liver architecture and minimal portal inflammation. Bile ducts, arteries, and portal veins were normal. The hepatocytes showed variable degrees of micro- and macrovesicular steatosis (figure 1). The microvesicular fat involved 0–100% of liver cells, and the macrovesicular fat appeared in <2%–100% of liver cells. The biopsy specimen from a patient with 100% macrovesicular fat had features of steatohepatitis. In all of the biopsy specimens, the uninvolved liver cells had abundant eosinophilic granular cytoplasm. There were Kupffer cell aggregates containing brown-gray pigment and small fat vacuoles. With the exception of the biopsy specimen that resembling steatohepatitis, there was little hepatocyte necrosis. There was no iron in any of the specimens. Two specimens demonstrated glassy hepatocyte cytoplasm and hepatocyte rosettes. The patient without hepatic steatosis had been off antiretrovirals for 3 weeks before the biopsy. The other 5 patients’ biopsies were performed within 13 days of drug discontinuation.

Electron microscopy available for 3 biopsy specimens showed lipid inclusions and prominent endoplasmic reticulum. One specimen had increased density of the inner mitochondrial membrane, whereas another had enlarged mitochondria containing paracrystalline inclusions and dense bodies.

All patients had favorable outcomes: only 1 required hospitalization, and none died. Clinical symptoms abated more rapidly than did biochemical markers. Within a few days of discontinuing their medications, most patients noticed significant symptomatic improvement. Lactate levels, in contrast, often increased initially after ceasing NRTI therapy, but in all cases were declining by 4 weeks. Median time to normalization of the lactate level was 62 days (range, 16–111 days).

Of 1245 patients seen in our clinic from mid-July 1998 through the end of January 1999, the overall incidence was 14.8/1000 person-years, and among those receiving nucleoside analogue therapy (n = 883), 20.9/1000 person-years.

Discussion

Our observations extend the spectrum of the lactic acidosis/hepatic steatosis syndrome by the discovery of a milder and possibly earlier presentation. This variant has characteristic symptoms of abdominal pain, nausea, and distention, and laboratory abnormalities of slightly elevated lactate and ALT lev-
Table 1. Characteristics of 10 HIV-infected patients with nucleoside-analogue induced hyperlactatemia (HL) and hepatic abnormalities.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age, y</th>
<th>BMI, kg/m²</th>
<th>CD4 count, cells/µL</th>
<th>HIV RNA, copies/mL</th>
<th>Antiretroviral treatment</th>
<th>Duration, mo</th>
<th>Hepatic disease</th>
<th>Symptoms</th>
<th>Peak laboratory levels</th>
<th>Liver biopsy or imaging results (liver length)</th>
<th>Time to resolution of HL, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>31.6</td>
<td>652</td>
<td>23,758</td>
<td>Rtv, Sqv, d4T, ddI</td>
<td>9</td>
<td>None</td>
<td>Abdominal pain, nausea, distention, diarrhea</td>
<td>Lactate, mmol/L: 5.3, Bicarbonate, mmol/L: 17, Anion gap: 22, ALT, U/L: 211</td>
<td>Microvesicular steatosis</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>20.1</td>
<td>377</td>
<td>&lt;40</td>
<td>Nlf, d4T, ddI</td>
<td>10</td>
<td>HCV RNA+</td>
<td>Abdominal pain, nausea, distention, dyspnea</td>
<td>Lactate, mmol/L: 4.2, Bicarbonate, mmol/L: 22, Anion gap: 10, ALT, U/L: 95</td>
<td>Mixed steatosis, glassy hepatocyte cytoplasm</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>37.5</td>
<td>217</td>
<td>&lt;40</td>
<td>Ind, Nvp, d4T, 3TC</td>
<td>9</td>
<td>HCV RNA+</td>
<td>Abdominal pain, nausea, distention, dyspnea</td>
<td>Lactate, mmol/L: 3.5, Bicarbonate, mmol/L: 23, Anion gap: 12, ALT, U/L: 207</td>
<td>Mixed diffuse steatosis</td>
<td>111</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>21.2</td>
<td>479</td>
<td>39.9</td>
<td>Rtv, Sqv, d4T, 3TC</td>
<td>20</td>
<td>None</td>
<td>Abdominal pain, distention, dyspnea, anorexia</td>
<td>Lactate, mmol/L: 4.4, Bicarbonate, mmol/L: 27, Anion gap: 11, ALT, U/L: 135</td>
<td>Microvesicular steatosis, glassy hepatocyte cytoplasm</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>26.4</td>
<td>224</td>
<td>&lt;40</td>
<td>Nlf, d4T, 3TC</td>
<td>12</td>
<td>None</td>
<td>None</td>
<td>Lactate, mmol/L: 6.2, Bicarbonate, mmol/L: 22, Anion gap: 19, ALT, U/L: 133</td>
<td>Mixed diffuse steatosis</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>28.4</td>
<td>260</td>
<td>3811</td>
<td>Nlf, d4T, ddI, 3TC</td>
<td>10</td>
<td>HBsAg+</td>
<td>Abdominal pain, nausea, distention, dyspnea</td>
<td>Lactate, mmol/L: 5.7, Bicarbonate, mmol/L: 26, Anion gap: 16, ALT, U/L: 107</td>
<td>Chronic hepatitis B</td>
<td>47</td>
</tr>
<tr>
<td>7</td>
<td>42</td>
<td>28.6</td>
<td>364</td>
<td>27,941</td>
<td>Nlf, MKC, d4T, ddI</td>
<td>4</td>
<td>None</td>
<td>None</td>
<td>Lactate, mmol/L: 2.9, Bicarbonate, mmol/L: 21, Anion gap: 12, ALT, U/L: 483</td>
<td>Fatty infiltration on US (19 cm)</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>30</td>
<td>1397</td>
<td>&lt;40</td>
<td>Nlf, d4T, 3TC</td>
<td>9</td>
<td>None</td>
<td>None</td>
<td>Lactate, mmol/L: 5.5, Bicarbonate, mmol/L: 26, Anion gap: 12, ALT, U/L: 175</td>
<td>Fatty infiltration on CT</td>
<td>67</td>
</tr>
<tr>
<td>9</td>
<td>48</td>
<td>25.4</td>
<td>373</td>
<td>489</td>
<td>d4T, ddI, 3TC, HU</td>
<td>11</td>
<td>None</td>
<td>None</td>
<td>Lactate, mmol/L: 3.4, Bicarbonate, mmol/L: 26, Anion gap: 9, ALT, U/L: 152</td>
<td>Fatty infiltration on US (18.5 cm)</td>
<td>63</td>
</tr>
<tr>
<td>10</td>
<td>33</td>
<td>35.4</td>
<td>849</td>
<td>1070</td>
<td>Nvp, d4T, 3TC</td>
<td>7</td>
<td>None</td>
<td>Abdominal pain, nausea</td>
<td>Lactate, mmol/L: 4.4, Bicarbonate, mmol/L: 25, Anion gap: 16, ALT, U/L: 109</td>
<td>Fatty infiltration on US (18.5 cm)</td>
<td>60</td>
</tr>
</tbody>
</table>

NOTE. ALT, alanine aminotransferase; BMI, body mass index; ddI, didanosine; d4T, stavudine; HBsAg+, hepatitis B surface antigen present; HCV RNA+, hepatitis C RNA present; HU, hydroxyurea; Ind, indinavir; MKC, experimental NNRTI; Nlf, nelﬁnavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; Nvp, nevirapine; Rtv, ritonavir; Sqv, soft-gel saquinavir; 3TC, lamivudine; US, ultrasound.

a All patients were male.
els, as well as clinical and biochemical resolution with discontinuation of antiretroviral therapy. We ascribe the hyperlactatemia and hepatic abnormalities found in our patients to nucleoside analogue toxicity for the following reasons: (1) these were the only medications common to all patients that are known to cause lactic acidosis; (2) the symptoms and laboratory abnormalities abated once antiretrovirals were discontinued; and (3) other possible explanations were excluded. The common biochemical and pathologic findings suggest a relationship to the previously described syndrome. Because most of the patients were also receiving protease inhibitors or nonnucleoside reverse transcriptase inhibitors, neither class of which has been associated with lactic acidosis, we cannot exclude a metabolic interaction among these drug classes.

Similar to other reports describing the lactic acidosis/hepatic steatosis syndrome, our patients had received nucleoside analogue therapy for several months before presentation, and most of them were overweight, had gastrointestinal complaints, hepatomegaly, slightly elevated aminotransaminases, and evidence of hepatic steatosis, either by imaging or biopsy [1, 4–21]. In contrast, our patients had much milder elevations in lactate levels. Only 4 of our 10 patients would have met the usual criterion for lactic acidosis (lactate level, >5 mmol/L) [22]. In accordance with this definition, we describe the abnormalities we observed as hyperlactatemia rather than as lactic acidosis. In addition, the majority of our patients had little evidence of metabolic acidosis, according to bicarbonate and anion gap measurements. Therefore, these markers cannot be solely relied on to screen for the milder syndrome.

Our patients also had better outcomes than did those patients described in previous studies. There were no deaths and only 1 hospitalization among our 10 patients. Previous series have reported a mortality rate >50% [1, 5, 10, 16]. Of 36 cases reported in the literature, the majority required hospitalization, and two-thirds died [4–21]. These higher morbidity and mortality rates may be from spectrum bias resulting in identification of only the most severe cases.

The incidence of this milder syndrome appears to be higher than reported previously. In a patient population similar to our own, Fortgang et al. [8] identified 2 cases, both fatal, over a 5-year period with an overall estimated incidence of 0.9/1000 person-years and 1.3/1000 person-years of nucleoside analogue exposure. The incidence rates in our series were ~16-fold greater than these estimates. Our rates are conservative, because lactate levels were probably not obtained in every patient taking nucleoside analogues who presented to the clinic with either abdominal symptoms or an unexplained abnormal ALT level during this period.

The higher incidence in the present report may be a result of broadened case definition. Fortgang et al. [8] included only severe cases of lactic acidosis in their incidence estimates. Alternatively, these cases may reflect an increasing incidence caused by changes in treatment strategy. Previous rates were estimated on the basis of the use of nucleoside analogue monotherapy. Since the dissemination of clinical trial results documenting improved outcomes with combination antiretroviral therapy, dual nucleoside analogue combinations (in conjunction with protease inhibitors or nonnucleoside reverse transcriptase inhibitors) are increasingly prevalent and may result in greater cumulative exposure to the potential mitochondrial toxicity of this drug class [23, 24].

Another possible basis for the higher incidence is the increased use of stavudine. Previous rate estimates were performed before widespread use of this nucleoside analogue. Stavudine, a regimen component in all our cases, has been shown in vitro to be the most damaging to mitochondria among the frequently prescribed nucleoside analogues [25–27]. Recently, other investigators have implicated nucleoside analogues (especially stavudine) in the pathogenesis of HIV-associated lipoatrophy and have identified hyperlactatemia as a marker of mitochondrial toxicity in that setting [28].

We do not know whether the syndrome we have described would have progressed to the more severe form if treatment had been continued. However, recognition of the milder variant may simplify the diagnostic evaluation of patients receiving nucleoside analogue–containing regimens who present with gastrointestinal complaints and/or unexplained hepatic abnormalities. Many patients in our series underwent several non-diagnostic studies before an association between the nucleoside analogues and the symptoms and laboratory abnormalities was made. We recommend that providers consider obtaining a lactate level for any patient receiving nucleoside analogues who presents with ≥1 of the following: abdominal symptoms, metabolic acidosis, or elevated aminotransaminases. We consider it prudent to discontinue nucleoside analogue therapy for these patients when elevation of the lactate level, not attributable to another cause, is confirmed. The routine measurement of lactate

Figure 1. Masson trichome-stained section of liver shows mixed micro- and macrovesicular steatosis. Arrow, Liver cell containing small cytoplasmic fat droplets (original magnification, ×400).
in all patients receiving nucleoside analogues in an attempt to provide early screening and detection of the syndrome cannot be supported at this time.

Additional research is needed to address several questions raised by these observations. First, in the era of multinucleoside analogue combination regimens, what is the current incidence of hyperlactatemia and hepatic abnormalities, and does it differ by regimen? Second, what is the prognosis for patients with the milder syndrome we have described, both with and without treatment interruption? Third, is rechallenge with the same or other members of the nucleoside analogue class safe if no other treatment options are available for the underlying HIV infection? Lastly, can risk factors and preventive factors for mitochondrial toxicity be identified, so that patients can experience the proven benefit of nucleoside analogue therapy without risk of hepatic damage?

References