A High Incidence of Lactic Acidosis and Symptomatic Hyperlactatemia in Women Receiving Highly Active Antiretroviral Therapy in Soweto, South Africa

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Background. Lactic acidosis and symptomatic hyperlactatemia may complicate nucleoside reverse-transcriptase inhibitor use. Females may be at increased risk for such complications. Our study evaluated the incidence of lactic acidosis and symptomatic hyperlactatemia by sex, analyzed clinical features, and described the safety of reintroducing highly active antiretroviral therapy (HAART) with zidovudine replacing stavudine.

Methods. A retrospective cohort analysis was performed for 1735 adults (63% of whom were female) who initiated HAART from April 2004 through August 2005 in Soweto, South Africa, with follow-up until February 2006. Patients with lactate levels ≥4.5 mmol/L and no potential cause of elevated lactic acidosis other than receipt of HAART were included in the study.

Results. A total of 23 patients (22 of whom were female) experienced lactic acidosis. The overall incidence was 10.6 cases per 1000 patient-years; the incidence was 16.1 cases per 1000 patient-years in female patients and 1.2 cases per 1000 patient-years in male patients. Seven (30.4%) of the patients died. Eight (34.8%) of the patients were obese (body mass index [calculated as weight in kilograms divided by the square of height in meters], >30) at HAART initiation. Forty-four patients (37 of whom were female) had symptomatic hyperlactatemia. The overall incidence was 20.2 cases per 1000 patient-years, with an incidence of 27.0 cases per 1000 patient-years in female patients and 8.7 cases per 1000 patient-years in male patients. None of the patients died. Nine (20.4%) of the patients were obese at HAART initiation. Sixty-six of 67 patients were receiving stavudine, and 5 patients were receiving didanosine. Among 56 patients who restarted HAART with zidovudine for a cumulative nucleoside reverse-transcriptase inhibitor reexposure of 44.6 patient-years—including 41 patients who received treatment for ≥9 months—there were no relapses.

Conclusion. Women in Soweto, South Africa, have a higher frequency of symptomatic hyperlactatemia and lactic acidosis than has been reported for patients in other study groups. In cases associated with stavudine use, restarting HAART with zidovudine seemed to be safe and effective for patients with limited nucleoside reverse-transcriptase inhibitor alternatives.

Although HAART has been shown to be of great value in reducing morbidity and mortality in patients infected with HIV, long-term treatment has been associated with serious drug-related toxicities [1]. Mitochondrial toxicity is associated with hyperlactatemia, lactic acidosis, hepatic steatosis, pancreatitis, lipodystrophy, and peripheral neuropathy [2]. The proposed mechanism of mitochondrial toxicity is nucleoside reverse-transcriptase inhibitor (NRTI)–induced inhibition of mtDNA polymerase leading to derangements in oxidative phosphorylation and lactate homeostasis [3, 4].

Symptomatic hyperlactatemia and lactic acidosis have been observed as class-specific toxic adverse effects of treatment with NRTIs. Lactic acidosis was first described in 1990 in patients using didanosine [5]. A mortality rate as high as 30%–100% has been reported.
[6]. Females appear to be at greater risk of developing lactic acidosis [7]. Symptomatic hyperlactatemia as a separate entity was first described in 2000 [8]. Both syndromes have been most frequently described in association with prolonged stavudine treatment, especially when stavudine is combined with didanosine [9]. It has been demonstrated that it is safe and efficacious to reintroduce therapy with NRTIs, including zidovudine, that are less potent inhibitors of mitochondria after episodes of lactic acidosis and symptomatic hyperlactatemia [10].

Although stavudine is no longer recommended as first-line treatment in developed countries, the recommended first-line regimen in the public sector in South Africa is stavudine in combination with lamivudine and a nonnucleoside reverse transcriptase inhibitor (either efavirenz or nevirapine) [11]. Zidovudine, didanosine, and a protease inhibitor are available as a second-line regimen or for individual drug substitutions.

This study aimed to evaluate the incidence of lactic acidosis and symptomatic hyperlactatemia in total and by sex, analyze patient characteristics and outcome, and describe the safety and efficacy of reintroducing HAART with zidovudine (NRTI) following symptomatic hyperlactatemia and lactic acidosis caused by stavudine use.

METHODS

Study site. Chris Hani Baragwanath Hospital (Soweto, South Africa) is a public sector university hospital with 2700 beds. The Adult HIV Clinic at Chris Hani Baragwanath Hospital was one of the initiating sites of the public sector antiretroviral drug program, which started in April 2004. A retrospective cohort analysis was performed.

Study population. The patient cohort included all adults (both HAART-naive and HAART-experienced patients) who initiated HAART at the Adult HIV Clinic from 1 April 2004 through 31 August 2005; they were followed up until 28 February 2006. Patients were included in the study if they had lactate levels ≥4.5 mmol/L determined using 2 separate specimens. The second specimen was obtained within 24 h for lactic acidosis and within 7 days for symptomatic hyperlactatemia. A list of all patients with lactate levels ≥4.5 mmol/L recorded at the National Health Laboratory Service at Chris Hani Baragwanath Hospital from April 2004 through February 2006 was cross-referenced with a list of patients receiving HAART at the Adult HIV Clinic. Patients were excluded from the study if they had any other documented cause of a high lactate level. Lactate levels were not routinely determined for all patients but were determined only when a clinician suspected lactic acidosis or symptomatic hyperlactatemia on the basis of compatible symptoms. The calculation of patient-years receiving HAART was based on the 1735 patients (1093 [63%] of whom were female and 642 [37%] of whom were male) who completed at least 3 months of therapy at this facility during the study period. Patients restarting HAART were followed up until November 2006.

Definitions. Lactic acidosis was defined as present in patients with a lactate level >5 mmol/L and a pH <7.34 and/or a serum bicarbonate level <18 mmol/L. All such patients had blood chemistry results that revealed low CO2 levels. Patients with symptomatic hyperlactatemia had compatible symptoms and lactate levels ≥4.5 mmol/L but normal CO2 levels, normal pH, and normal serum bicarbonate levels (if measured) [6]. Lactate levels were considered to be normal if venous lactate levels were 0.60–2.45 mmol/L and arterial lactate levels were 0.5–1.6 mmol/L. Compatible symptoms included nonspecific gastrointestinal symptoms (nausea, vomiting, abdominal pain, and abdominal distension), anorexia and weight loss, peripheral neuropathy, tiredness, and dyspnea [6, 12].

Procedures. For each patient, the following data were captured on a standard form: age, sex, duration of HAART, antiretroviral drugs used, weight gain or loss, symptoms and signs on clinical assessment, baseline CD4+ cell count and viral load, lactate levels (first and peak readings), liver function test results, arterial blood gas or CO2 levels in blood, time to normalize lactate levels following diagnosis, outcome, duration of interruption of HAART (as well as time to stabilization of weight), duration of an additional course of HAART, and subsequent CD4+ cell count and viral load. The phlebotomists at the Adult HIV Clinic were instructed to ensure that patients had rested for at least 20 min before venous blood samples were obtained. These samples were taken without tourniquet or fist clenching. Samples were immediately transported to the laboratory during the study and processed without delay. A Roche/Hitachi analyzer (Roche) was used to measure the lactate levels.

Ethics. Consent for the study was obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand (Johannesburg, South Africa).

Statistical analysis. Exact confidence intervals around incidence rates were calculated using Stata software, version 9.0 (Stata). For categorical variables, the χ² contingency table test was used.

RESULTS

The overall incidence of lactic acidosis and symptomatic hyperlactatemia was 30.8 cases per 1000 patient-years receiving HAART. The denominator over the study period was 2174 patient-years receiving HAART, 1370 (63%) of which were in female subjects and 804 (37%) of which were in male subjects. One of these syndromes was found in 1 of every 18 women (5%) and 1 of every 80 men (1.2%) during the study period.

Lactic acidosis. During the 23-month period of observation, 23 patients experienced lactic acidosis (table 1). Twenty-two of these patients were female, including 1 pregnant woman. The incidence of lactic acidosis was 10.6 cases per 1000 patient-
Table 1. The incidence of symptomatic hyperlactatemia and lactic acidosis among patients who initiated HAART at the Adult HIV Clinic at Chris Hani Baragwanath Hospital (Soweto, South Africa) from 1 April 2004 through 31 August 2005.

<table>
<thead>
<tr>
<th>Toxicity, patient group</th>
<th>No. of patients</th>
<th>Duration of HAART, total patient-years</th>
<th>Incidence, no. of cases per 1000 patient-years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic hyperlactatemia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>44</td>
<td>2174</td>
<td>20.2 (14.7–27.2)</td>
</tr>
<tr>
<td>Female patients</td>
<td>37</td>
<td>1370</td>
<td>27.0(^a) (19.0–37.2)</td>
</tr>
<tr>
<td>Male patients</td>
<td>7</td>
<td>804</td>
<td>8.7(^a) (3.5–17.9)</td>
</tr>
<tr>
<td><strong>Lactic acidosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>23</td>
<td>2174</td>
<td>10.6 (6.7–15.9)</td>
</tr>
<tr>
<td>Female patients</td>
<td>22</td>
<td>1370</td>
<td>16.1(^a) (10.1–24.3)</td>
</tr>
<tr>
<td>Male patients</td>
<td>1</td>
<td>804</td>
<td>1.2(^a) (0.03–6.9)</td>
</tr>
<tr>
<td><strong>Both toxicities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>67</td>
<td>2174</td>
<td>30.8 (23.9–39.1)</td>
</tr>
<tr>
<td>Female patients</td>
<td>59</td>
<td>1370</td>
<td>43.1(^a) (31.0–62.6)</td>
</tr>
<tr>
<td>Male patients</td>
<td>8</td>
<td>804</td>
<td>9.9(^a) (4.8–21.8)</td>
</tr>
</tbody>
</table>

\(^a\) \(P < .001\).

years receiving HAART; it was 16.1 cases per 1000 patient-years in female subjects and 1.2 cases per 1000 patient-years in male subjects (\(P < .001\)). One of every 75 patients (female patients, 1:50; male patients, 1:642) who received HAART developed lactic acidosis.

Twenty-two patients received a stavudine-containing regimen, 1 of whom received stavudine combined with didanosine (table 2). Stavudine was given at the standard dosage. One patient received didanosine and zidovudine.

The patients presented predominantly with gastrointestinal symptoms (87% of patients), loss of weight (73.9%), and dyspnea (56.6%) (figure 1). Ten patients (43.5%) had an associated painful peripheral neuropathy.

Body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) data were available for 19 of the 23 patients; 4 patients who died had no height measurement (table 2). Eight treatment-naive patients (34.8%) were obese (defined as a BMI >30) at the start of HAART; 1 other patient was already receiving HAART when starting this program. Five patients (22%) were overweight (defined as a BMI of 25–30). None were underweight (defined as a BMI <18.5) at baseline. The median duration for ongoing weight loss after interruption of HAART was 14 weeks (range, 4–45 weeks).

**Mortality.** The mortality rate for lactic acidosis was 30.4%, despite treatment interruption and supportive therapy. The incidence of fatal lactic acidosis was 3.2 deaths per 1000 patient-years of HAART. Four patients died within 5 days after hospital admission, and an additional 3 patients died within 14 days after hospital admission. Of the 7 patients who died, 6 had peak lactate levels >11 mmol/L, and 5 patients had a pH <7.17 mmol/L. Only 2 patients with a pH <7.2 mmol/L survived. Six (50%) of the 12 patients with peak lactate levels >11 mmol/L survived. All 3 patients with lactate levels >15 mmol/L died. An additional 3 patients (13%) died of severe acute lower respiratory tract infection before restarting HAART. Two of these patients showed marked decreases in CD4\(^+\) count of 217 cells/mm\(^3\) and 159 cells/mm\(^3\) during the period of treatment interruption. All 3 of these patients had ongoing weight loss.

The 13 surviving patients, who had all experienced virologic suppression before treatment interruption, were rechallenged with zidovudine (substituted for stavudine), together with lamivudine and efavirenz, after normalization of lactate levels (table 2); the patient who received therapy with didanosine and zidovudine died. The total duration of the additional course of HAART was 10.7 patient-years. Six patients received >9 months of the additional course of HAART, and an additional 4 patients received >12 months. To date, none of the patients has experienced a relapse. Two patients have experienced virologic failure (HIV load, >400 copies/mL) after restarting HAART.

**Symptomatic hyperlactatemia.** Forty-four patients, including 37 female patients, experienced symptomatic hyperlactatemia (table 1). The overall incidence of symptomatic hyperlactatemia was 20.2 cases per 1000 patient-years of HAART; the incidence was 27.0 cases per 1000 patient-years in female patients and 8.7 cases per 1000 patient-years in male patients (\(P < .001\)). One of every 39 patients (female patients, 1:30; male patients, 1:92) who received HAART developed symptomatic hyperlactatemia.
Table 2. Demographic and clinical characteristics of patients with lactic acidosis and symptomatic hyperlactatemia who initiated HAART at the Adult HIV Clinic at Chris Hani Baragwanath Hospital (Soweto, South Africa) from 1 April 2004 through 31 August 2005.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lactic acidosis (n = 23)</th>
<th>Symptomatic hyperlactatemia (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, no. (%) of patients</td>
<td>22 (95.6)</td>
<td>37 (84.1)</td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>32 (24–52)</td>
<td>37 (22–64)</td>
</tr>
<tr>
<td>Obese at baseline, no. (%) of patients</td>
<td>8 (34.8)</td>
<td>9 (20.4)</td>
</tr>
<tr>
<td>CD4+ cell count at baseline, median cells/mm³ (range)</td>
<td>114 (8–273)</td>
<td>67 (5–319)</td>
</tr>
<tr>
<td>NRTI regimen, no. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d4T and 3TC</td>
<td>21</td>
<td>41</td>
</tr>
<tr>
<td>ddl and d4T</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>AZT and ddl</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Duration of HAART prior to toxicity diagnosis, median weeks (range)</td>
<td>34 (17–76)</td>
<td>47 (41–61)</td>
</tr>
<tr>
<td>CD4+ cell count at toxicity diagnosis, median cells/mm³ (range)</td>
<td>244 (47–472)</td>
<td>190 (56–661)</td>
</tr>
<tr>
<td>Range of lactate levels at toxicity diagnosis, mmol/L</td>
<td>5.6–15.4</td>
<td>4.5–11.3</td>
</tr>
<tr>
<td>CO₂ level, mean mmol/L</td>
<td>13.5</td>
<td>20</td>
</tr>
<tr>
<td>Elevated aminotransferase levels, a no. (%) of patients</td>
<td>8 (34.8)</td>
<td>4 (9.1)</td>
</tr>
<tr>
<td>Previous exposure to hepatitis B, no. (%) of patients</td>
<td>2 (8.7)</td>
<td>7 (15.9)</td>
</tr>
<tr>
<td>Coinfection with hepatitis C, no. (%) of patients</td>
<td>0</td>
<td>3 (6.8)</td>
</tr>
<tr>
<td>Mortality rate, no. (%) of patients</td>
<td>7 (30.4)</td>
<td>0</td>
</tr>
<tr>
<td>Duration of HAART interruption, median weeks (range)</td>
<td>8.5 (3–20)</td>
<td>8 (2–15)</td>
</tr>
<tr>
<td>Duration of second course of HAART, median weeks (range)</td>
<td>43 (22–67)</td>
<td>40 (13–91)</td>
</tr>
</tbody>
</table>

NOTE. AZT, zidovudine; ddl, didanosine; d4T, stavudine; NRTI, nucleoside reverse transcriptase inhibitor; 3TC, lamivudine.

* Two times the upper limit of normal.

All 44 patients were receiving a stavudine-containing regimen, with 3 patients also receiving didanosine (table 2). One patient had a peak lactate level >10 mmol/L.

The main adverse effects were weight loss (occurring in 75% of patients) and anorexia (61.4%) (figure 1). Sixteen patients (36.4%) had an associated painful peripheral neuropathy.

BMI data were available for 42 patients (table 2). Nine (20.4%) of the treatment-naive patients were obese at the start of HAART; 1 other patient was already receiving HAART. Thirteen patients (30%) were overweight (BMI, 25–30). Five patients (11%) were underweight (BMI, <18.5) at baseline. The median duration of ongoing weight loss after interruption of HAART was 8.5 weeks (range, 1–28 weeks).

All 44 patients with symptomatic hyperlactatemia survived (table 2). Initially, 40 patients were rechallenged with zidovudine, substituted for stavudine, in combination therapy after normalization of lactate levels. Of the other 4 patients, 1 was lost to follow-up, and 3 were inadvertently rechallenged with stavudine at the standard dosage. One of these 3 patients continued to receive stavudine for 7 months without any symptoms. One was receiving stavudine for 2 weeks and experienced worsening of symptoms, with normal lactate levels. The third patient was receiving stavudine for 2.5 months with increasing lactate levels but no symptoms. All 3 of these patients were switched to zidovudine therapy. The total duration of therapy for the 43 patients receiving an additional course of HAART was 33.9 patient-years. Twenty-three patients received an additional course of HAART for >6 months but ≤12 months, 6 patients received an additional course of HAART for >12 months but ≤18 months, and 2 patients received an additional course of HAART for >18 months. To date, none of the patients has had a relapse of symptomatic hyperlactatemia. Three patients have experienced virologic failure since resuming HAART.

**DISCUSSION**

In cohort studies, the incidence of lactic acidosis has been reported to be 1.3–3.9 cases per 1000 person-years, and the incidence of symptomatic hyperlactatemia has been reported to be 8–14.5 cases per 1000 person-years [6]. In this study, the total incidence of lactic acidosis was 10.6 cases per 1000 person-years, which is 2.7 times the highest rate previously reported. This was because of the extremely high rate in women (16.1 cases per 1000 person-years), which was 13 times the rate in men, which was, in turn, at the low end of previously published rates. The higher rate of symptomatic hyperlactatemia in our study (20.2 cases per 1000 person-years) was attributable to the high rate in women (27 cases per 1000 person-years), which was 3.2 times the rate in men. Female sex has been implicated...
as a risk factor for lactic acidosis. Women appeared to be overrepresented in a report of 12 cases from Spain (50% of which occurred in women) and in the 60 published cases reviewed (42% of which occurred in women) [13]. The incidence of lactic acidosis in a cohort from Montreal, Canada, was significantly higher in women (5.2%) than in men (2.2%). The definition of lactic acidosis in the study was broad and appeared to include patients with lactic acidosis and patients with symptomatic hyperlactatemia [14]. A review, based on published literature, has estimated that the risk of developing lactic acidosis could be 2.5 times higher in women than in men [7]. In contrast, the Swiss HIV Cohort Study found no difference by sex [15]. The reasons for the observed sex differences in rates of toxicity are uncertain. Differences in BMI, fat composition, hormonal secretion, and drug metabolism may play a role individually or in concert [16, 17]. The high rates in this study may also be at least partly explained by the use of stavudine as first-line therapy. Stavudine use is the most frequently identified risk factor [6–8, 13, 18, 19].

The onset of mitochondrial toxicity requires prolonged time. In this study, the median duration of HAART before diagnosis of lactic acidosis was 34 weeks (range, 17–76 weeks), and for symptomatic hyperlactatemia, it was 47 weeks (range, 41–61 weeks). In published studies, the median duration of exposure to NRTIs in the most recent course of combination therapy was 9 months (range, 3–20 months) for patients with lactic acidosis [6] and 11 months for patients with symptomatic hyperlactatemia [8], both very similar to the findings of this study. The duration can vary from as little as 1 month to as much as 8 years [13, 19, 20].

Elevated lactate levels can produce a variety of symptoms that range from mild to severe. In this study, patients with lactic acidosis reported gastrointestinal symptoms, dyspnea, and tiredness more frequently than did patients with symptomatic hyperlactatemia. A comparable presentation has been described in the literature [7, 8, 13, 19]. Painful peripheral neuropathy was a common complication of mitochondrial toxicity.

The prognosis associated with symptomatic hyperlactatemia is good [6, 8, 15, 18, 21], as was found in this study, in which all patients survived. Patients with lactic acidosis had a mortality rate of 30.4%, which is at the low end of mortality rates reported in published studies [6, 7, 19]. Strong correlations between lactate levels >10 mmol/L and death have been recognized [13]. Awareness of the syndrome among clinicians and the education of patients may account, at least partly, for the reduction in mortality in more recent reports [7]. Once the exact mechanism of mitochondrial toxicity is elucidated, new specific therapies to add to treatment interruption and supportive therapy may be developed. There was a 13% increase in the mortality rate during the period of treatment interruption, because patients with low CD4+ cell counts developed serious opportunistic infections. This may be an underrecognized hazard of treatment interruption and one that causes anxiety in patients who require treatment interruption.

Treatment-naive patients with a BMI >30 at baseline accounted for at least 24% of the cases in this study. Several studies have reported that a high BMI might be a risk factor, although it has never been quantified. [6, 13, 20] It would be speculative to suggest that avoiding the use of stavudine in patients who are obese at baseline might significantly reduce the number of people who develop these syndromes. In this study, stabilization of ongoing weight loss took longer than did

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Figure 1. Clinical features of patients with symptomatic hyperlactatemia (SHL) and lactic acidosis (LA) who initiated HAART at the Adult HIV Clinic at Chris Hani Baragwanath Hospital (Soweto, South Africa) from 1 April 2004 through 31 August 2005.
the normalization of lactate levels, as has been described in another report [20]. The delay in stabilizing ongoing weight loss is more likely to be attributable to mitochondrial toxicity than to HIV disease progression.

All of the patients who resumed HAART were prescribed zidovudine to replace stavudine as part of combination therapy. We adopted this policy on the basis of published studies, in which only 1 patient experienced relapse [10, 22], and because of the imperative of retaining a protease inhibitor for use in a salvage regimen. Five of 56 patients restarting HAART have experienced virologic failure to date and, as a consequence of our policy, have an alternative regimen available. After 44.6 patient-years of follow-up after restarting HAART, including both patients with symptomatic hyperlactatemia and patients with lactic acidosis, and with 41 patients having completed at least 9 months of treatment, no relapses have developed. Neither tenofovir nor abacavir are available as alternatives to zidovudine in the public sector program.

It is unclear whether and to what extent symptomatic hyperlactatemia might progress to lactic acidosis or whether they are 2 completely separate disorders [18, 23]. The lack of a standard biochemical definition for lactic acidosis and symptomatic hyperlactatemia causes confusion and may affect incidence rates. All patients in this study had symptoms, as well as markedly elevated lactate levels. Not all patients with symptomatic hyperlactatemia had their arterial blood gas measured, and in these patients, we relied on blood chemistry results showing normal CO2 levels. Therefore, errors in labelling patients as having symptomatic hyperlactatemia, rather than lactic acidosis, were possible. None of the patients with symptomatic hyperlactatemia who were temporarily rechallenged with stavudine therapy experienced progression to lactic acidosis.

The incidence rates found in our study may be underestimated. First, patients who enrolled in the latter stages of the study period were followed up for <9 months and may have developed a syndrome after the end of the study period. Second, some patients with symptoms may not have had lactate levels measured, may have attended other hospitals, or may have died of lactic acidosis without the cause being recognized or communicated to us.

Sampling variability of lactate measurement was taken into account by requiring >1 elevated lactate level per patient to exclude errors. The denominator of obese patients was not available, because not all patients had their height measured. Having the denominator would have enabled computation of relative risk of obesity and would have helped to clarify whether such patients should avoid stavudine therapy.

A longer follow-up period after restarting HAART with zidovudine was needed to observe for relapses and to confirm the long-term safety of HAART with zidovudine in our patients. The high incidence of symptomatic hyperlactatemia and lactic acidosis in patients receiving HAART in Soweto, South Africa, was attributable to the predominance of women (in whom the high incidence occurred), as well as to the use of stavudine as initial therapy. The high incidence of often-fatal lactic acidosis in women would seem to demand only limited use of stavudine for women in the developing world if these findings are confirmed in other studies and once sufficient stocks of alternative NRTIs that are safe and cheap are available. An alternative approach would be to investigate the use of lower doses of stavudine as part of HAART as a way to delay the development and lower the incidence of this toxicity. Additional evidence is required to definitively decide whether women who are obese at baseline should avoid stavudine therapy. The future availability of tenofovir or abacavir may provide choices in therapy. Reintroducing HAART with the substitution of zidovudine for stavudine seemed to be a safe option in a setting with limited alternatives, although a longer observation period is needed.

Acknowledgments


References