

REVIEW

Lactic acidosis in HIV infected patients: a systematic review of published cases

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Objective: To describe the clinical, epidemiological, and biochemical characteristics of published cases of lactic acidosis (LA) and to generate hypotheses concerning risk factors associated with this complication.

Methods: Systematic review of cases reported in the medical literature.

Results: 217 published cases were identified, 90 of which fulfilled the study definition and had sufficient individual data on potential risk factors to be included. The 90 patients had a mean age of 40.1 years (range 16–69) and 53% were female. All 90 patients were taking nucleoside reverse transcriptase inhibitors (NRTI) at the time of the episode. Among the 83 patients with details of their antiretroviral therapy (ART) regimen 51 patients were taking stavudine, 29 zidovudine, 27 didanosine, and 25 lamivudine. Around 50% of the patients had abdominal pain, nausea, or vomiting. Hepatic steatosis was consistently reported (53/90) and in 36 (68%) there was histological evidence. The case fatality rate was 48%. Six cases were rechallenged with NRTI and three developed a further LA episode. Using data on the numbers of HIV infected individuals receiving care in the United States, we estimate that the risk of LA could be 2.5 times higher for women than men.

Conclusions: NRTI use and female sex appear to be risk factors for the development of LA. What other factors are involved is still not clear but might include duration of NRTI therapy, specific drug use, and genetic predisposition. A case-control study is needed to better define risk factors for severe LA.

Lactic acidosis (LA) is an uncommon but serious complication of antiretroviral therapy (ART). The reported incidence rates vary from 1.3 to 10 per 1000 person years on ART^{1–4}; one explanation for this may be differences in case definition. Asymptomatic hyperlactataemia is a common finding. The prevalence of hyperlactataemia in outpatients on ART is around 9–16%.^{5,6} Among untreated patients it is about 2%.⁷ However, only 1% of those with raised lactate levels have severe hyperlactataemia (lactate >5 mmol/l).^{5,7} Between asymptomatic hyperlactataemia and severe lactic acidosis there is a group of patients with moderately raised lactate (2.5–5 mmol/l) and non-specific symptoms referred to as symptomatic hyperlactataemia with an incidence rate estimated to be between 8 to 20.9 cases per 1000 person years at risk.^{3,8,9}

Studies to date suggest that LA is caused by mitochondrial toxicity through the inhibition of mitochondrial DNA polymerase γ (mtDNA polymerase γ) by nucleotide reverse transcriptase inhibitors (NRTI). In vitro studies have shown that NRTI vary in their ability to inhibit mtDNA polymerase γ with a hierarchy of effect. Drugs such as stavudine (d4T), didanosine (ddI), and zalcitabine (ddC) induce more mtDNA inhibition than others.^{10–12} There is evidence of variable tissue specificity, determined by differences in cellular penetration and phosphorylation, different mitochondrial uptake of NRTI and their metabolites, and the tissue dependence on mitochondrial metabolism.¹⁰

METHODS

Published cases of severe LA in HIV infected adults were reviewed: Medline (1982–2000), Aidsline (1982–2001), Web of Science, the Cochrane Database of Systematic Reviews (Issue 2, 2001), and the CAB Abstract Database. The key terms used for the search were lactic acid*, metabolic acid*, and HIV infection for Medline and lactic acidosis, lactic acidemia, metabolic acidosis, metabolic acidemia, and hepatic steatosis

for Aidsline. Abstracts of relevant conferences were reviewed as indexed references on Aidsline and in available abstract books of relevant scientific events such as international AIDS conferences and workshops. All references cited in included papers were checked and included if pertinent. Reports from clinical trials, which recorded drug adverse events, were not searched.

Cases were included if the patient was over 16 and was hospitalised with biochemical evidence of LA (one or more of the following: pH <7.34, serum bicarbonate <20 mmol/l, anion gap > 12 mEq/l). If biochemical data were not available, the patient was included when the author(s) stated the case had lactic acidosis. Patients who had other underlying potential causes for LA were excluded.

Date, author, city, and hospital of the report were checked for duplication of reporting. History of HIV related complications, previous medical history, clinical symptoms and signs, laboratory results, and evidence for mitochondrial toxicity were also collected onto a standardised proforma.

Continuous variables were summarised using the mean and standard deviation if normally distributed or median and range if not. For categorical data, variables were presented as proportions.

RESULTS

The review identified 217 cases of LA; 87 were presented as part of case series with aggregated data without sufficient individual data on potential risk factors to be included; 40 were reported as part of cohort studies examining outcomes other than LA without individual descriptions. The remaining 90 fulfilled our definition and were included in this study.

Demographic data

The mean age of the 90 patients was 40 years (range 16–69 years), 47 (53%) were female. Three of the female patients were pregnant, all at 32 weeks or more of gestation at presentation. Reports from three countries account for the 83% of the

Table 1 Antiretroviral therapy (ART) at the time of the lactic acidosis event (n=83)

ART	Cases	%
Monotherapy	30	
Zidovudine	26	87
Didanosine	2	7
Stavudine	2	7
2 drugs	16	
Zidovudine + didanosine	2	13
Zidovudine + stavudine	1	6
Stavudine + didanosine	6	38
Stavudine + lamivudine	7	44
3 or more drugs	37	
Stavudine + didanosine + lamivudine	1	3
Stavudine + didanosine + PI	12	32
Stavudine + lamivudine + PI	12	32
Stavudine + didanosine + nevirapine	4	11
Stavudine + lamivudine + nevirapine	3	8
Stavudine + lamivudine + delavirdine	1	3
Stavudine + didanosine + efavirenz	1	3
Stavudine + didanosine + delavirdine + PI	1	3
Stavudine + lamivudine + nevirapine + PI	1	3
Stavudine + 2 PI	1	3

PI = protease inhibitors.

included cases; 56 (62%) from the United States, 14 (16%) from France, and five (6%) from the Netherlands.

ART at the time of the LA event

ART at the time of the event was recorded in 83 of the 90 patients (table 1). Information about past ART history before the LA episode was sparse. All cases were taking at least one NRTI at the time of the LA episode. Thirty cases (36%) were on monotherapy regimens when LA was diagnosed, 26 were on zidovudine (ZDV), 16 (19%) were taking two ART drugs (a combination of NRTI), and 37 (43%) were on combinations of three or more drugs, including either a protease inhibitor (PI) or NNRTI, at the time of the LA event. One additional patient was taking three NRTI.

Fifty one of 83 (61%) patients were taking d4T, 49 of them with at least one other antiretroviral drug. The median duration of d4T treatment was 8 (range 1–36) months (data available for 45/51 patients); 29/83 (35%) cases were on ZDV for a median of 8 (range 1–24) months (data from 25/29 cases).

Twenty seven of 83 cases (33%) were on ddI for a median of 8.5 (range 3–48) months (data from 23/27 patients); 25/83 patients (30%) were on lamivudine (3TC) for a median of 8 (range 1–18) months (23/25 cases). No patient was on abacavir (ABC) or zalcitabine (ddC) at the time LA was diagnosed. In 17 patients with previous ART regimens reported, seven had received ddC; 13 of these 17 cases were on d4T at the time of the LA event, but all of them had received ZDV therapy in the past.

Patients on ZDV at the LA event had more advanced disease than those exposed to other NRTI. The median CD4 cell count among patients on ZDV was $79 \times 10^6/l$ (range 18–406) (data from 10/29 cases) compared to $282.5 \times 10^6/l$ (range 35–1321) (data from 36/61 cases) in those not on ZDV.

Previous adverse effects related to ART were described in 16 patients, and the majority could have been attributed to NRTI toxicity (six cases of myelosuppression, four cases of myopathy, four cases of peripheral neuropathy, and one case of pancreatitis). One patient had lipotrophy.

Past medical history and previous ART related adverse effects

In 17 cases previous hepatic diseases were mentioned and 11 of these were viral hepatitis; two had chronic hepatitis B

Table 2 Symptoms reported at the time of the lactic acidosis event

Symptom	Number of cases (n=85)	Proportion (%)
Nausea	45	53
Vomiting	44	52
Abdominal pain	38	45
Weight loss	19	22
Weakness	19	22
Dyspnoea	19	22
Anorexia	16	19
Tachypnoea	13	15
Diarrhoea	8	9
Fatigue	7	8
Abdominal distension	5	6
Impairment of consciousness	2	2
Other	8	9

(HBsAg positive), two hepatitis C (HCV RNA positive), four previous acute hepatitis B, one past hepatitis A. There was no specific information on the two other patients with a history of hepatitis.

Among only 24 patients with information about concurrent drug therapy other than ART, nine were on concurrent treatment with potentially hepatotoxic drugs such as fluconazole, ketoconazole, or isoniazid.

Symptoms and laboratory findings at the time of LA event

Non-specific gastrointestinal symptoms; nausea, vomiting, and abdominal pain were the most frequently reported, in over 50% of the 85 patients with available information (table 2). Dyspnoea and tachypnoea classically associated with metabolic acidosis were reported in 35 (41%).

Among 79 patients in whom blood lactate levels were reported, the median was 10.5 (range 2.4–168.5) mmol/l. The anion gap was described in 32 patients, median 25.5 (range 10–42) mEq/l (table 3). The values on the day of admission were used even if subsequent values were more abnormal. For this reason some of the ranges include normal values. There was laboratory evidence of mild to moderate hepatic dysfunction in 41 of the 63 cases (65%) in whom information was given, with median transaminase values between 1.5 and 2.5 times over the upper limit of normal (range 1.4–10.7 times over the upper limit of normal).

In 39 premortem or necropsy liver biopsies 36 (92%) had hepatic steatosis; 12/39 (31%) macrovesicular steatosis, 8/39 (21%) microvesicular steatosis, and 16/39 (41%) a mixed pattern. The other three biopsies showed hepatic fibrosis and inflammation.

In 11 patients mitochondrial morphology or function were examined. In nine patients electron microscopy was performed on liver or muscle biopsies or both. In four who had only liver biopsies, enlargement, alteration of shape, or increased mitochondrial density were reported.^{8–13–15} In three patients who had muscle biopsies two showed similar mitochondrial ultrastructural changes^{16–17} and one was reported as normal.¹⁸ In one patient who had both a liver biopsy and muscle biopsy, the liver biopsy was abnormal but the muscle biopsy was normal. The remaining patient had a normal muscle biopsy.¹⁹

Respiratory chain dysfunction was examined in only three cases using spectrophotometric determination of enzymatic complex activity. MtDNA depletion and particularly low levels of activity of complexes 2, 3, and 4 was reported in one case using muscle mitochondria.²⁰ Two other patients with biochemical evidence of mitochondrial dysfunction were tested using hepatic mitochondria and had reduction of complexes 1 and 1, 3, 4, and 5 respectively.^{13–21} Finally, mtDNA

Table 3 Acid base status of the patients at the time of the lactic acidosis event

Test	Normal range	No	Median	Range
Lactate (mmol/l)	0.7–1.2	79	10.5	2.4–168.5
pH	7.35–7.45	52	7.2	6.67–7.42
Bicarbonate (mmol/l)	24–29	51	8	1.2–26
Anion gap (mEq/l)	8.0–12.0	32	25.5	10.0–42.0

Table 4 Estimated relative risk of developing lactic acidosis by sex

	Total HIV infected patients*	Patients with CD4 <500 × 10 ⁶ /l	Lactic acidosis cases observed	Lactic acidosis cases expected†	RR
Female	52 200	44 892	30	12	2.5
Male	179 200	164 864	26	44	
Total	231 400	209 756	56		

*From Bozzette, *et al.*³⁰

†If risk of LA were the same for men and women.

depletion was reported in one other patient on muscle and liver biopsy but enzymatic complexes were not examined.²²

Outcome

Forty three of 90 (48%) patients died in a median period of 7 days (range 2 days to 30 weeks) after diagnosis. Among the 46 survivors, the median time of follow up was 3 months (range 0.25–30 months). In 13/46 (28.3%) cases it was stated that ART was restarted, using NRTI in six of these patients, but the exact duration of follow up was reported only in three of these six. Three of six patients rechallenged with NRTI had further episodes of LA. Two were females. One male and one female were challenged with ZDV as monotherapy; both developed a further episode of LA but no other adverse effect attributable to NRTI.^{23–24} The other female's re-challenge regimen was not specified. An additional female patient was re-treated with a combination of 3TC and nelfinavir and followed for 26 months, with no further LA or other adverse event.¹⁸ One male patient who developed LA on a combination of d4T and ddI did not resume ART. However, 22 months after discontinuation he developed fatal portal hypertension, liver failure, and hepatic mitochondrial dysfunction with normal serum lactate.¹³

DISCUSSION

This is the largest review of published cases of LA to date. Since only 90 cases had sufficient details to be included, robust conclusions about the possible risk factors associated with LA are not possible. However, the results do add some weight to proposed risk factors from the individual case reports, case series, and other smaller reviews. Mégarbane *et al* described 40 cases published during the 1990s accompanied by a literature review of possible causes.²⁵ Falcó *et al* reviewed 60 cases, and performed a multivariate analysis of possible prognostic factors for mortality.²⁶ Neither of these reviews aimed to identify risk factors for LA and their literature review strategies were not described.

Females appear to be at greater risk of developing LA.^{27–28} Our case reports were predominantly from the United States, Western Europe, and Australia, and more cases were female. In all these areas the majority of HIV infected patients (75–90%) are male,²⁹ so this could represent a relatively higher risk of LA among women.

Using data on the numbers of HIV infected individuals receiving care in the United States,³⁰ we made a very approximate estimate of the denominator of patients receiving ART, from the estimated number of patients with less than 500 CD4 cells × 10⁶/l. Of the total of 209 756 patients likely to be

exposed to ART, 44 892 (21%) were female. Assuming no sex bias in publication of cases, if there were no association between sex and LA, among the 56 US cases, the expected number of females would be 11, but the observed number was 30. These data suggest that the risk of developing LA could be 2.5 times higher in women than in men (table 4).

Combination therapy is not randomly allocated, patients switch treatments and have long ART histories which are poorly recorded. It is therefore difficult to estimate the contribution of individual drugs to a toxicity, particularly if the event is the result of cumulative exposure to a drug class rather than an individual drug exposure. A background of HIV infection is not required for NRTI to produce LA, as there are reports of LA in HIV negative neonates exposed to prophylactic ZDV.^{31–32}

ZDV associated LA events were reported mainly during the monotherapy era.²⁵ In our series, 90% of those cases on ZDV at the time of the LA episode were taking it as monotherapy. The cases of LA associated with ZDV therapy had more advanced disease compared with patients exposed to NRTI other than ZDV. Additionally, the case fatality rate (CFR) among ZDV treated patients was 68%, compared with 37% for patients not exposed to ZDV. These differences probably reflect the use of ZDV monotherapy in patients with more advanced HIV disease in the late 1980s and early 1990s.

The association between d4T use and hyperlactataemia or LA has been highlighted in previous studies.^{21–33} However, 51 of the 53 patients on d4T in our review were taking it as part of combination therapy, which included at least one additional NRTI. Cumulative toxicity has been proposed as a risk factor for mitochondrial toxicity and the total duration of exposure to NRTI could be important.³⁴ The median NRTI exposure of patients included in our review was 8 months, but in most cases this period refers to the regimen on which LA occurred and not the total time exposed to NRTI. If cumulative toxicity is important^{17–24–35} some of the association of LA with d4T might be confounded by a long duration of NRTI exposure. Previous ART regimens were reported in only 13 of the 52 patients on d4T and all of them had a previous history of ZDV use. Carr *et al* found that an important proportion of patients on d4T had received previous treatment with ZDV.³⁶ By contrast, John *et al* reported that the association between d4T and hyperlactataemia was not confounded by previous treatment with ZDV.³ The contribution of other NRTI to the development of LA events is difficult to evaluate because the majority of patients taking ddI or 3TC (92%) were also taking d4T. Lonergan *et al* recently reported improvements in both laboratory abnormalities and clinical symptoms when d4T was replaced by either ABC or ZDV in symptomatic patients with hyperlactataemia.³⁷

Key messages

- Female patients might be at a greater risk of developing lactic acidosis than males, once they are exposed to ART
- The total exposure to NRTI might be an important variable, but this is poorly reported in case reports and case series
- Hepatic steatosis and mild to moderate elevation in liver function test are frequently reported in patients with lactic acidosis. The implications of these findings are not well understood to date
- Mitochondrial toxicity is believed to be the cause of lactic acidosis in HIV infected patients exposed to NRTI; however, the number of cases that have had studies of mitochondrial morphology or function are small.

This review also highlights that a common presentation of LA is with non-specific gastrointestinal symptoms. A high level of suspicion is required if an early diagnosis is to be made.

Previous reviewers have reported high case-fatality ratio (CFR) associated with LA, of around 60%,^{25,35} but in a more recent study it was 33%.²⁶ In our review CFR was 48% overall. In the first 45 cases, published between 1991 and 1999, the CFR was 64%. In contrast, for the second 45 cases, published between 2000 and June 2001, it was 33%. The lower CFR among more recently published cases might be due to a higher level of awareness among clinicians about LA and earlier identification of cases.

In our review, only a small number of cases had investigation of mitochondrial morphology or function. At least 43 studies have shown evidence of NRTI related mitochondrial toxicity in vitro, and in animal models.¹⁰ Most of the evidence for mtDNA depletion in clinical studies has been in cases of ZDV related myopathy.³⁸

The proposed mechanism for LA is inhibition of mtDNA polymerase γ leading to mtDNA depletion. Walker *et al* showed that ZDV and the combination ZDV/3TC can produce raised lactate levels and cell death without a reduction in or deletions of mtDNA in an in vitro study.³⁹ Bartley *et al* have reported multiple hepatic mtDNA deletions in a patient with LA.⁴⁰ Recently we have described a case of LA with marked reduction in respiratory chain enzyme activity but not mtDNA depletion and direct NRTI induced toxicity on the respiratory chain has also been proposed.^{41,42}

Mitochondrial dysfunction would be expected to lead to an increase in endogenous lactate production. Leclercq *et al*, using an exogenous lactate challenge test in 11 symptomatic and three asymptomatic patients with hyperlactataemia, showed a marked increase in endogenous lactate production even in patients with a moderate increase in serum lactate.⁴³ In addition, in the face of this overproduction of lactate, factors which affect lactate clearance such as hepatic dysfunction, might also be expected to contribute to hyperlactataemia and lactic acidosis.⁴⁴ Concomitant use of drugs such as ribavirin with other NRTI—that is, ddI, has also proposed as a risk factor to develop mitochondrial dysfunction and LA but in patients with hepatic dysfunction caused by hepatitis C.⁴⁵

In summary, LA is likely to be an NRTI related adverse effect, which affects female patients more frequently. It is difficult to evaluate the precise role of individual NRTI drugs from case reports. It is possible that d4T, and probably also ZDV, may be more likely to induce LA than other NRTI. Since the clinical presentation of LA is frequently non-specific and because raised levels of lactate occur in asymptomatic patients, a standard case definition is required to assess risk factors and prognostic factors accurately. A large case-control study is needed to better define risk factors for severe LA.

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CONTRIBUTORS

AAP performed the systematic review and wrote the first and final drafts of the manuscript; ADG reviewed the searching strategy, critically reviewed the data analysis and the manuscript; SE critically reviewed the proforma used to collect cases information and the manuscript drafts; IVDW proposed the project, reviewed the analysis strategy, and assisted in the writing of the manuscript.



Further references can be found on the STI website (www.stijournal.com/supplemental)

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ECHO

HAART homes in on lymphocyte mitochondria in lactic acidosis



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A severe adverse reaction to highly active antiretroviral treatment (HAART) has shown for the first time the treatment's potential for damaging lymphocyte mitochondria and increasing lymphocyte death. This has prompted speculation that cell death follows mitochondrial disruption.

The case of severe lactic acidosis occurred in a 39 year old woman who had been HIV positive for nearly 10 years and receiving HAART with stavudine, didanosine, and indinavir for just over two and a half years. Viral load was <50 copies/ml and CD4+ lymphocytes >500/ml. When treatment was stopped serum lactic acid concentration was about 5 mmol/l and γ -glutathione 14 times higher than normal. Acidosis started to decrease only one month afterwards and returned to normal only two months later. Mitochondria in the lymphocytes dropped in number and those remaining appeared swollen and their internal structure disrupted, with loss of cristae. These traits persisted for a month after treatment was withdrawn, during which time apoptosis of CD3+ lymphocytes peaked. Apoptosis and mitochondrial abnormalities gradually resolved as lactic acid concentration dropped, and despite an increased viral load of 21 000 copies/ml. CD4+ lymphocyte numbers were unaffected.

Lymphocytes were typed by flow cytometry after staining with monoclonal antibodies. Apoptosis was measured by counting stained lymphocytes under fluorescence microscopy and by flow cytometry.

Lactic acidosis is a rare, but increasing, serious adverse reaction. This case provided a chance to see whether lymphocyte mitochondria are affected, given the importance of lymphocytes in HIV infection and reported mitochondrial damage in liver and skeletal muscle in similar cases.

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