A high incidence of nucleoside reverse transcriptase inhibitor (NRTI)-induced lactic acidosis in HIV-infected patients in a South African context

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Objective. To determine the incidence of and predisposing risk factors for lactic acidosis in HIV-infected patients on antiretroviral drugs in South Africa.

Design. Observational case series.

Setting. Sinikithemba HIV Clinic, McCord Hospital, Durban.

Subjects. Eight hundred and ninety-one HIV-positive patients on highly active antiretroviral therapy (HAART) during an 18-month period commencing in January 2004.

Measurements and results. Fourteen cases of lactic acidosis (incidence rate of 19 (95% confidence interval (CI): 9 - 29) cases per 1 000 person-years of treatment) were reported. All cases were female, with a median age of 36 years and a median weight of 81 kg. The median time on HAART before developing lactic acidosis was 7.5 months and the median peak lactate level was 9.3 mmol/l. All cases were on stavudine (d4T), lamivudine (3TC) and 1 non-NRTI. The case mortality rate was 29% (4 patients).

Conclusions. The incidence rate is higher than reported in studies in developed countries. This may be due to d4T, which is recommended as a first-line antiretroviral drug in South Africa. This implication raises the question whether it is an appropriate drug in first-line treatment of patients with predisposing risk factors such as female gender and being overweight.

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By February 2005 there were 29 000 HIV-infected patients on highly active antiretroviral therapy (HAART) at 113 public-sector health facilities in South Africa.[1] As more people are prescribed antiretroviral therapy (ART) adverse events and complications of therapy will be increasingly common.

The South African National Antiretroviral Guidelines[2] recommend that for adult HIV-infected patients 2 nucleoside reverse transcriptase inhibitors (NRTIs), viz. stavudine (d4T) and lamivudine (3TC), be used in the first-line HAART regimen.

NRTIs inhibit mitochondrial DNA polymerase-γ, the enzyme responsible for DNA synthesis. The ensuing mitochondrial toxicity may result in lactic acidosis, hepatic steatosis and other adverse events including myopathy, neuropathy and myelotoxicity.[3] A recognised sign of mitochondrial impairment is a raised serum lactate level. Mild hyperlactataemia (lactate level of 2.1 - 5 mmol/l) is often asymptomatic or may cause nausea, vomiting and abdominal discomfort. If severe (lactate level > 5 mmol/l) it can cause metabolic acidosis (standard bicarbonate level < 20 mmol/l), hepatic steatosis, coma and multi-organ failure.[4] Lactic acidosis syndrome has a mortality rate of 80% if lactate levels are > 10 mmol/l.[5]

Not all NRTIs precipitate hyperlactataemia equally. A rank order exists, with zalcitabine more likely to cause hyperlactataemia than didanosine > d4T > zidovudine (AZT) > abacavir = 3TC = tenofovir.[6] Reported risk factors for developing lactic acidosis include being female, obese, pregnant and having a low CD4 nadir before starting a regimen containing a NRTI.[7,8]

The reported incidence rate of lactic acidosis in HIV-infected patients on HAART ranges from 1.3 to 3.9 cases per 1 000 person-years on treatment.[4]

This study aimed to determine the incidence rate and to identify predisposing factors for developing lactic acidosis among HIV-infected patients on HAART attending an HIV clinic at McCord Hospital in Durban, South Africa.

Methods

This case series was based on a study population of 891 HIV-positive patients of all ages who had commenced HAART between January 2004 and June 2005 and who had been on treatment for at least 3 months.

NRTI-induced lactic acidosis was defined as a lactate level > 5 mmol/l and an arterial blood bicarbonate level < 20 mmol/l (or a total venous CO_2 < 20 mmol/l) with other causes such as septicaemia and dehydration excluded. Cases of lactic acidosis were identified and reported by clinicians or identified from the hospital's electronic database.

Staff had been trained to take blood without a tourniquet and to delay or repeat the test if patients had been exercising. Blood

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Table I. Characteristics of 14 HIV-infected patients with nucleoside-induced lactic acidosis (1 January 2004 - 30 June 2005)

Patient no.	Sex	Age (yrs)	Ethnic group	Weight (kg)	1st CD4 (cells/µl)	Most recent CD4 (cells/µl)	Last viral load (copies/ml)	HAART			Peak laboratory levels				Time for lactate to normalise (months)	New HAART
								Agents	Time (months)†	Symptoms	Lactate (mmol/l)	Bicarb (mmol/l)	Anion gap	Outcome		
1	F	35	Black	82	77	308	< 400	D4T/3TC/ EFV	7	LOA/abdominal pain/ diarrhoea/SOB	9	7	26	Died		
2	F	45	Black	75	127	124	< 50	D4T/3TC/ EFV	7	Vomiting	8.9	15	13	Resolved	2	AZT/3TC Kaletra
3	F	37	White	103	200	471	652	D4T/3TC/ EFV	5.5	N&V/heartburn Loss of energy/SOB	6.6	8.3	18	Died		
4	F	35	Black	78	136	136	< 50	D4T/3TC/ NVP	4	Vomiting/ epigastric pain	9.6	12.7	23	Resolved	4.5	AZT/3TC Kaletra
5	F	37	Black	140	32	429	< 50	D4T/3TC/ EFV	7.5	N&V/SOB/ malaise	13.4	12	25	Resolved	5.5	AZT/3TC Kaletra
6	F	36	Black	58	48	99	< 50	D4T/3TC/ EFV	12	Epigastric pain	6.7	15	14	Resolved	2.5	AZT/3TC Kaletra
7	F	35	Black	83	47	470	< 50	D4T/3TC/ EFV	12	Epigastric pain/ joint pain	5.6	17	15	Resolved	2	AZT/3TC Kaletra
8	F	55	Black	79	157	529	< 50	D4T/3TC/ EFV	8.5	Abdominal discomfort	10.6	17	17	Resolved	3	Not yet restarted
9	F	40	Black	98	186	76	< 50	D4T/3TC/ NVP	12	Vomiting/abdominal pain/fatigue	14.7	13.9	30	Died		
10	F	32	Indian	66.6	3	134	< 50	D4T/3TC/ EFV	10.5	Nausea/vomiting abdominal pain	8.5	18	24	Resolved	3.5	AZT/3TC Kaletra
11	F	34	Black	82	2	53	< 50	D4T/3TC/ EFV	7.5	Headache/ vomiting	10.6	17.7	20	Resolved	2.5	Not restarted
12	F	36	Black	70	147	143	< 50	D4T/3TC/ EFV	8	SOB/LOA N&V/abdominal pain	17.5	10.8	30	Resolved	2	AZT/3TC Kaletra
13	F	35	Black	57	142	335	< 50	D4T/3TC/ EFV	7.5	Tender calves/ SOB/epigastric pain	7.5	19.5	18	Resolved	2.5	AZT/3TC EFV
14	F	39	Black	97	178	271	< 50	D4T/3TC/ EFV	7.5	Vomiting/SOB/ epigastric pain	18.1	6.3	23	Died		
Median		36		80.5	132	207	< 50		7.5		9.3	15	22		2.5	
Normal range											0.7 - 2.1	24 - 31	10 - 12			

*First CD4 count before commencing HAART.
†Time (months) from starting ART to developing lactic acidosis.
SOB = shortness of breath; N&V = nausea and vomiting; LOA = loss of appetite; AZT zidovudine; 3TC = lamovudine; EFV = efavirenz.

specimens were transported on ice and processed within 4 hours to ensure reliable lactate measurement. A single laboratory used a standardised method to measure the lactate levels (Beckman Coulter, Synchron systems, California, USA). An open cohort was used to calculate the incidence rate. Incident cases were censored from the cohort.

Results

In 18 months, 14 cases of lactic acidosis were diagnosed in 737 person-years of treatment. The incidence rate was 19 (95% confidence interval (CI): 9 - 29) cases per 1 000 person-years of treatment (Table I). All cases were adult females, although 40% of patients attending the HIV clinic were male. The median age of the cases was 36 years, with the interquartile (IQ) range 35 - 39.3 years (the average age in the clinic was 36 years). The median mass was 81 kg (IQ range 69.2 - 97.3 kg), with the average mass of females in the clinic being 66 kg.

Twelve of the patients (86%) were black, with 1 Indian and 1 white patient (98% of the cohort were black). The median time on HAART before developing lactic acidosis was 7.5 months (IQ range 7 - 11.6 months) and the median peak lactate level was 9.3 mmol/l (IQ range 7.3 - 14.4 mmol/l). All patients were on 2 NRTIs, d4T and 3TC, with 12 (86%) on efavirenz (EFV) and 2 on nevirapine as the third (non-NRTI) drug. The median CD4 count on starting HAART was 132 cells/µl (IQ range 43 - 173 cells/µl) for the cases. More than 90% of patients at McCord HIV Clinic have a CD4 count of < 200 cells/µl on commencing HAART. At the time of developing lactic acidosis the median CD4 count of the patients was 207 cells/µl (IQ range 118 - 460 cells/µl), with 86% (N = 12) patients having a viral load < 50 copies/ml.

Four patients died, giving a case fatality rate for NRTI-induced lactic acidosis of 29%. In 10 patients lactate levels returned to normal in a median of 2.5 months (IQ range 2 - 3.75 months) off HAART. By the end of the study period 8 patients had been restarted on HAART, 7 on AZT, 3TC and Kaletra, and 1 on AZT, 3TC and EFV. One patient chose not to restart HAART and 1 died of an opportunistic infection before HAART had been recommenced. No recurrence of hyperlactataemia occurred.

Discussion

The incidence rate of lactic acidosis was higher in HIV-infected patients on HAART in Durban than that reported in developed countries.[4] Predisposing factors for lactic acidosis were being on a d4T-containing regimen, being female and being overweight. The association between these factors and the development of NRTI-induced lactic acidosis has been confirmed by other studies.[6-8]

A poor response to HAART does not appear to be a predisposing risk factor for developing lactic acidosis as 86% of patients had achieved undetectable viral loads and had improved CD4 counts.

Not all possible confounding factors were considered in this study. Age, diet, alcohol intake and concurrently taking other drugs including traditional remedies were not considered. Patients were not routinely asked if they had taken any traditional remedies. The effect of these and other pharmacological substances on HAART, liver metabolism and lactate levels is not clear.

The choice of the alternative HAART regimen was based on the drugs available in the country, cost, likelihood of resistance developing and the risk of recurrence of symptomatic hyperlactataemia.[9]

This observational study may be limited by selection bias as all cases may not have been identified from the database. Information bias is possible as case data were collected retrospectively from hand-written patient records. Body mass index (BMI) would have been a better measure of obesity but height was not routinely recorded.

Conclusion and recommendations

d4T, one of the drugs in the first-line HAART regimen in South Africa, is being prescribed to increasing numbers of HIV-positive patients. This effective NRTI can cause potentially fatal complications including lactic acidosis. The incidence rate in obese female patients is higher than previously reported.

It is essential that all health care providers and patients be trained to recognise the symptoms and signs of lactic acidosis early on. Protocols for management of the condition should be readily available. Adverse event surveillance at facilities offering HAART and national auditing need to be formalised. Proper surveillance of side-effects will enable evidence-based decisions to be taken to avoid potentially fatal complications like severe lactic acidosis.

BMI should be measured routinely. Genetic predisposition, the influence of traditional remedies and other drug interactions need to be studied. Until surveillance can properly inform policy-makers of the true risk associated with d4T, health workers should have a high index of suspicion for lactic acidosis in obese female patients.

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