

# Nucleoside Analogue-Induced Fatal Lactic Acidosis in Two HIV-Infected Patients in Singapore

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## ABSTRACT

The introduction of antiretroviral therapy has led to a significant decrease in the mortality and morbidity associated with human immunodeficiency virus (HIV) infection. Nucleoside reverse transcriptase inhibitors (NRTI) have been widely used as part of the antiretroviral therapy against HIV. However, one recently recognised serious complication of NRTI is the development of lactic acidosis. We report two cases of fatal NRTI-induced lactic acidosis, which occurred within five months of each other. Both were being treated with didanosine (ddI) and stavudine (d4T). Physicians involved in the care of HIV patients should recognise and be alert to the possibility of this highly fatal complication.

**Keywords:** HIV infection, lactic acidosis, nucleoside reverse transcriptase inhibitors, anti-retroviral therapy

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## INTRODUCTION

The use of nucleoside reverse transcriptase inhibitors or NRTIs in the treatment of patients with human immunodeficiency virus (HIV) has led to the decrease in mortality and morbidity associated with HIV infection<sup>(1)</sup>. Currently, there are three main classes of anti-retroviral agents: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors. NRTI can be used with either, other NRTIs, or in combination with NNRTI or protease inhibitors as part of highly active antiretroviral therapy (HAART). The occurrence of lactic acidosis is an infrequent but increasingly recognised and highly fatal adverse effect of some NRTIs<sup>(2)</sup>. Common NRTIs implicated include zidovudine (AZT), didanosine (ddI) and stavudine (d4T)<sup>(2-7)</sup>. This particular complication of NRTI therapy has, as yet, not been reported in South East Asia. We report on two HIV patients who developed fatal lactic acidosis while being treated with didanosine and stavudine in Singapore.

## CASE REPORT

### Case 1

A 24-year-old Thai woman was diagnosed to have HIV infection after presenting with *pneumocystis carinii* pneumonia (PCP) in July 1998. She was also found to be a chronic hepatitis B carrier with a positive HBeAg.

Anti-retroviral therapy (ART) was commenced in November 1998. The patient was given lamivudine (3TC) 150 mg bid and stavudine (d4T) 30 mg bid. The regimen was changed to didanosine (ddI) 125 mg bid and stavudine (d4T) 30 mg bid one month later. There was significant improvement in her CD4 cell count and HIV viral load. In April 1999, the dose of her ddI and d4T were increased to 200 mg bid and 40 mg bid respectively in tandem with the patient's weight gain.

In July 1999, eight months after commencing ART, the patient was admitted to hospital with a three week history of nausea, vomiting, anorexia and epigastric discomfort. She had a low-grade fever, but her other vital signs were normal. Examination of her heart and lungs were unremarkable. The abdomen was found to be soft, with a slightly enlarged liver. Her full blood count revealed a normal haemoglobin and white cell count but there was thrombocytopenia of  $70 \times 10^9/L$ . There was a mild transaminitis as follows: ALT 76 (7-36) U/L, AST 113 (15-33) U/L and ALP 74 (32-103) U/L. She has also a mildly elevated triglyceride level. The serum amylase level was 154 (0-100) U/L. She was managed as probable ddI-induced pancreatitis and ART was stopped.

On day three of admission, the patient was noted to be hyperventilating. An arterial blood gas showed: pH 7.10, pCO<sub>2</sub> 10 mmHg, pO<sub>2</sub> 134 mmHg, base excess -24 mmol/L, bicarbonate 3 mmol/L. The lactate level was markedly elevated at 29.4 (0.7 - 2.1) mmol/L. Other investigations included a salicylate level < 0.1 mmol/L and a toxicology screen of the blood and urine that showed no evidence of methanol or ethanol ingestion.

On the same day, there was a rapid deterioration in the patient's clinical status. Pulmonary oedema was seen on her chest X-ray. She was transferred to the Intensive Care Unit where she was mechanically hyperventilated and was started on intravenous

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**Table 1. Summary of HIV-patients on nucleoside analogue therapy presenting with lactic acidosis.**

Cases	Reference	Age/Sex	NRTI used at time of presentation	NRTI dose	Duration used (mths)	pH	Lactate (mmol/L) (0.7 - 2.1)	HCO <sub>3</sub> <sup>-</sup> (mmol/L)	Presenting symptoms	Outcome of patient after admission
Patient 1		24/F	Didanosine Stavudine	250mg/d 60mg/d	7	7.10	29.4	3	Nausea, vomiting, Anorexia, abdo** discomfort	Died
Patient 2		49/M	Didanosine Stavudine	400mg/d 80mg/d	15	7.35	9.2	12	Nausea, vomiting, anorexia	Died
3	2	33/M	Zidovudine	500mg/d	3	NS*	Not done	19	Fever	Died
4	2	48/M	Zidovudine	NS*	NS*	NS*	20.2	5	Nausea, vomiting, abdo** pain, dyspnoea	Died
5	3	35/F	Zidovudine	100mg q4h	5	7.17	105	5	Nausea, vomiting, dyspnoea	Died
6	4	47/M	Zidovudine	500mg/d	6	7.41	17.9	17	Nausea, vomiting, diarrhoea, abdo** pain	Died
7	4	57/F	Zidovudine	1200mg/d	9	NS*	NS*	NS*	Diarrhoea, fatigue, wt + loss	Died
8	5	31/M	Didanosine Zidovudine	400mg/d 500mg/d	5	7.25	13.7	4.7	Nausea, wt + loss, dyspnoea	Recovered after haemodialysis
9	6	36/M	Didanosine	12mg/kg/d	4	7.32	27	NS*	Nausea, anorexia, diarrhoea, abdo**pain	Died
10	9	45/M	Didanosine Zidovudine	7.5mg/kg/d 500mg/d	4	7.12	43	3	Abdo** pain, wt + loss, dyspnoea	Died in spite of haemodialysis
11	9	69/M	Didanosine	11mg/kg/d	4	7.21	26	7	Vomiting, diarrhoea, dyspnoea	Died in spite of haemodialysis
12	10	57/M	Zidovudine	750mg/d	6	7.34	8	17	Diarrhoea, abdo** pain	Died
13	17	35/F	Didanosine Stavudine	NS*	3	7.1	70.7	2.3	Nausea, vomiting, diarrhoea	Recovered after haemodialysis

\* NS: Not Stated      \*\* abdo: abdominal      + weight loss

bicarbonate infusion, but to no avail. Intravenous broad-spectrum antibiotics including erythromycin, metronidazole and ceftazidime were given to cover for the possibility of underlying sepsis. Despite the above aggressive measures, the patient became hypotensive requiring inotropic support and developed acute oliguric renal failure. A vascular catheter was inserted in preparation for haemofiltration but this was not carried out because of her labile blood pressure. The patient died six days after admission.

#### Case 2

A 49-year-old bisexual seaman was diagnosed with HIV infection in September 1997 after presenting with cerebral toxoplasmosis. He was treated successfully for his toxoplasmosis and ART was commenced soon after diagnosis. He was started on zidovudine (AZT) 200 mg bid and lamivudine (3TC) at 150 mg bid.

Due to failure of this regimen, his treatment was switched in September 1998 to highly active antire-

troviral therapy (HAART) consisting of ddI 200 mg bid, d4T 40 mg bid and a protease inhibitor, nelfinavir 750 mg tid. Two months after HAART, his absolute CD4 count was 76 cells/ul with an undetectable viral load. This regimen was continued except for a brief period between January 1999 and March 1999 when the ART was stopped because of probable ART-induced hepatitis. A hepato-biliary ultrasound done then showed fatty infiltration of the liver; there was no focal intrahepatic lesion. The same regimen of ART was restarted at the previous dose after the liver dysfunction resolved.

In November 1999, the patient started complaining of numbness of a glove and stocking distribution. The development of peripheral neuropathy was attributed to ART. However, no modifications were made to his ART regimen as the symptoms were mild.

He was admitted in the following month with symptoms of severe shortness of breath and abdominal discomfort for four days. There was no history of recent alcohol, salicylate or biguanide

ingestion. On examination, the patient was observed to be hyperventilating but the rest of the examinations were unremarkable. His chest X-ray on admission was normal. The liver function test revealed the following: ALT 80 U/L, AST 91 U/L and ALP 95 U/L. An arterial blood gas on room air showed pH 7.35 mmHg, pCO<sub>2</sub> 14 mmHg, pO<sub>2</sub> 122 mmHg, base excess -15 mmol/L, bicarbonate of 12 mmol/L and oxygen saturation 98%. The plasma lactate was 9.2 mmol/L.

Diagnosis of lactic acidosis was made and antiretroviral therapy was discontinued. He continued to hyperventilate but remained relatively well otherwise. Serial arterial blood gases through the next four days showed little improvement in the bicarbonate level in spite of bicarbonate replacement.

On day six of admission, the patient became progressively dyspnoeic. Another ABG revealed that the patient had decompensated metabolic acidosis. The pH was 7.21, pCO<sub>2</sub> was 15 mmHg, pO<sub>2</sub> was 59 mmHg and standard bicarbonate was 9 mmol/L. A chest X-ray showed the presence of bilateral pulmonary oedema. There were no acute ischaemic changes and no suggestive features of pulmonary embolism on the electrocardiogram. The creatine kinase was 343 U/L (normal range: 40-210) with a MB fraction of 30 U/L.

Oral riboflavin 50 mg was added in addition to bicarbonate replacement but the patient continued to deteriorate clinically and died of cardiopulmonary arrest the following day.

## DISCUSSION

The development of lactic acidosis in HIV patients treated with NRTI is rare with a reported incidence of 1.3 per 1000 person-years of follow up in a retrospective study<sup>(2)</sup>. The NRTIs implicated include zidovudine (AZT)<sup>(3,4)</sup>, didanosine (ddI)<sup>(5,6)</sup> and stavudine (d4T)<sup>(7)</sup>. Lactic acidosis has also been reported with the use of fialuridine, another nucleoside analogue that was being evaluated in a trial for treatment of chronic hepatitis B virus infection<sup>(8)</sup>. This phase II trial was terminated prematurely after lactic acidosis and liver failure developed suddenly and unexpectedly in seven patients, of whom five died. However, there has been no literature citing the occurrence of lactic acidosis with the use of non-nucleoside analogues and protease inhibitors.

The clinical manifestations of the two described patients are similar to those that have been reported<sup>(2-7,9,10)</sup>. Common symptoms consist mainly of gastrointestinal symptoms including nausea, vomiting, abdominal pain and diarrhoea and respiratory

symptoms such as tachypnoea. A rapid decline in mental status, hypotension and cardiorespiratory arrest may follow. The fatal outcome commonly occurred at three to eight days after hospitalisation. A summary of the literature of the features of HIV patients who develop lactic acidosis whilst on nucleoside analogue therapy is presented in Table I.

In both cases described here, they were on didanosine as well as stavudine, both of which have been reported to give rise to lactic acidosis<sup>(7,9)</sup>. It is possible that the two medications, when used together, could give rise to a combined potentiating effect, thereby imparting an even greater risk of lactic acidosis than if they were to be used separately.

Neither of the patients was found to have any other cause that could have precipitated lactic acidosis. In particular, there was no history of recent alcohol, salicylate or biguanide consumption. There had been no ingestion of traditional medications and we were unable to find any evidence of sepsis.

Lactic acidosis is categorised into either type A or type B. Type A acidosis occurs when there is underlying tissue hypoxia, whereas Type B occurs in the absence of tissue hypoxia. Examples of Type B acidosis include that caused by sepsis, alcohol, malignancy, seizures, diabetes mellitus, hepatic failure, salicylates, and glycogen storage diseases. NRTI induced lactic acidosis is a Type B acidosis. The underlying pathogenesis is mitochondrial dysfunction induced by the nucleoside analogues<sup>(8,10)</sup>. The muscle and liver are the organs primarily involved. The increase in lactate levels arises from either an increased production of lactic acid from abnormal muscle mitochondria, or from inadequate hepatic clearance of lactic acid due to liver dysfunction.

In nucleoside induced lactic acidosis, mitochondrial dysfunction occurs as a result of the inhibition of the enzyme DNA polymerase  $\gamma$  by nucleoside analogues. DNA polymerase  $\gamma$  is responsible for mitochondrial DNA synthesis and the inhibition of this enzyme led to a marked depletion in the levels of mitochondrial DNA. There is an associated inhibition of oxidative phosphorylation resulting in a compensatory increase in glycolysis, and thence, lactic acid (the product of glycolysis). Only the mitochondrial form of this enzyme is affected. Eukaryotic DNA polymerase activity is unaffected. Abnormal mitochondrial DNA in the muscle has been demonstrated in cases of zidovudine induced myopathy<sup>(11)</sup>, and a similar abnormality could occur in the use of didanosine. The myopathy may manifest as an elevation in the level of creatine kinase. Comparisons have been made between zidovudine-induced myopathy and inherited mitochondrial

myopathies where abnormal mitochondrial DNA occurs as a result of mutations in the affected DNA. Both of these conditions are associated with the occurrence of lactic acidosis. In this report, lactic acidosis occurred 7-15 months after nucleoside analogue treatment in comparison with others ranging from 3-9 months as summarised in Table I<sup>(2-7,9,10)</sup>. The delayed occurrence of the clinical presentation suggests that a sufficient level of mitochondrial dysfunction must be present before lactic acidosis can occur.

It is of note that both patients developed pulmonary oedema after the onset of lactic acidosis. Mitochondrial DNA mutations have been known to be associated with cardiac changes such as left ventricular hypokinesia and dilated cardiomyopathy<sup>(12)</sup>. High-output cardiac failure as a result of decreased systemic vascular resistance has been reported in one patient with mitochondrial myopathy complicated by lactic acidosis<sup>(13)</sup>. Both, left ventricular dysfunction and high output cardiac failure could have led to the development of pulmonary oedema in our patients.

Literature review of liver biopsies from these HIV patients who develop lactic acidosis have shown a diffuse, predominantly macrovacuolar hepatic steatosis with minimal hepatocellular necrosis<sup>(10,14)</sup>. At autopsies, these livers were markedly enlarged. The impaired mitochondrial metabolism is believed to cause inadequate oxidation of fatty acids in the mitochondria. This may manifest as raised triglyceride levels and the appearance of a fatty liver on ultrasound as in the cases we presented.

Concurrent riboflavin or thiamine deficiency may contribute to the pathogenesis of NRTI induced lactic acidosis. Riboflavin is the precursor of co-factors involved in oxidative phosphorylation. Thiamine is needed as a co-factor for the entry of substrates into Krebs's cycle. Deficiency of either riboflavin or thiamine leads to the disruption of aerobic metabolism with the consequent accumulation of lactate. There have been anecdotal reports regarding the successful use of riboflavin and thiamine in NRTI-induced lactic acidosis resulting in improvement of clinical symptoms and resolution of lactic acidosis<sup>(15,16)</sup>.

Another treatment option is haemodialysis together with intensive care monitoring. Chodock et al<sup>(17)</sup> reported a case where a 35-year-old woman with severe lactic acidosis associated with nucleoside use was intubated, hyperventilated and underwent haemodialysis, which resulted in an improvement in her lactate level and eventual recovery. In most cases, however, the development of lactic acidosis has a poor prognosis with a mortality rate of as high as 75% in those with lactate levels above 9 mmol/L<sup>(18)</sup>.

## CONCLUSION

With the establishment of NRTI as an essential part of HIV therapy in combination with NNRTIs and protease inhibitors, there is an associated increase in incidence of NRTI-related mitochondrial dysfunction leading to the development of hepatic steatosis, lactic acidosis and myopathy.

We report two fatal cases of lactic acidosis secondary to the use of NRTIs. Further work is needed to assess the true incidence of this complication amongst those exposed to nucleoside analogue therapy in our local population. It has been suggested that liver enzymes, prothrombin time and bicarbonate level be checked regularly in any patient on nucleoside analogue therapy known to precipitate lactic acidosis<sup>(8)</sup>. A high index of suspicion is needed, and the onset of tachypnoea or gastrointestinal related symptoms in a HIV patient receiving NRTI should alert the physician to the possibility of lactic acidosis.

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