Lactic Acidosis in HIV-1 Infected Patients Receiving Antiretroviral Therapy

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Case Report

Abstract
Highly active antiretroviral therapy (HAART) has resulted in dramatic declines in morbidity and mortality in HIV-1 infected patients in the developed world. However, with the availability of generic antiretroviral treatments (ART) in India, a large number of patients now receive ART. Increase in experience with ART has led to the detection of drug-related toxicities. We report herein potentially fatal side effects associated with the use of nucleoside analogues in HIV treatment - hyperlactatemia and lactic acidosis/ hepatic steatosis.

INTRODUCTION
Long-term complications with ART like lactic acidosis, hepatic steatosis, pancreatitis, lipodystrophy/ lipoatrophy, neuropathy, lipid abnormalities and hematological toxicities are serious enough to warrant discontinuation of treatment and/or changes in ART regimens. Majority of the long-term toxicities are related to mitochondrial damage associated with NRTIs by inhibiting mitochondrial DNA (mtDNA) enzyme polymerase. NRTIs can precipitate the reduction or mutation of mtDNA and its enzymes leading to mitochondrial dysfunction.1, 2 The relative toxicities of the NRTIs can be rated: zalcitabine (ddC) >/= didanosine (ddI) >/= stavudine (d4T) >/= lamivudine (3TC) >/= zidovudine (ZDV) >/= abacavir (ABC). Combinations of NRTIs have been shown to have a synergistic or additive effect on mitochondrial toxicity in vitro.3

The NRTI-associated lactic acidosis is almost always associated with hepatic steatosis. It is now recognized that by interfering with lactate production or its clearance in an organ or tissues, NRTIs can produce a spectrum of hyperlactatemia syndromes,4 including asymptomatic hyperlactatemia and symptomatic hyperlactatemia which may or may not be associated with hepatic steatosis.

Various case reports and cohort studies conclude that symptomatic hyperlactatemia5, 6 and lactic acidosis6-12 is greater with d4T than with other NRTIs. For example, in the Swiss HIV cohort study, the risk of hyperlactatemia was greater with d4T, with or without ddI, than with ZDV (odds ratio, 2.7).11 In a recent review of 60 cases of NRTI-associated lactic acidosis, Falcó and coworkers12 found that among the 30 patients receiving dual therapy, 15 were using d4T plus 3TC and 11 were using d4T plus ddI.

In the management of hyperlactatemia, the lactate level should be monitored closely, interruption of NRTI therapy is mandatory if the lactate level increases.12 Pancreatitis, lipodystrophy/lipoatrophy, and neuropathy can occur in association with lactic acidosis or separately, requiring careful clinical evaluation.

CASE 1
A 54 years postmenopausal female patient, weight 72 kg, presented at the clinic on June 27, 2001 with Pneumocystis carinii pneumonia (PCP). She had past history of gynecological surgery and history of two episodes of herpes zoster eruptions. She was on antihypertensive medications (Zestril 2.5mg once a day) for the past four years. PCP responded to treatment with TMP-SMX. She was the started with HAART consisting of d4T, 3TC, and nevirapine (NVP), and PCP prophylaxis with TMP-SMX. She developed maculopapular rash and fever within one week of starting HAART. NVP was discontinued and substituted with indinavir. She tolerated the therapy well without any side effects. She had a good immunological recovery after starting ART. Her serial CD4 T cell counts three months apart were 147 (baselines), 232 cells/cmm and 313 cells/cmm.

She presented on March 25, 2002 with complaints of 2-3 loose stools per day, weight loss, weakness, dyspnea on exertion, nausea and epigastric discomfort. Physical examination was pertinent for epigastric tenderness and mild hepatomegaly. Her arterial lactate was 6.5 mmol/L. Serum uric acid was 6.15 mg%, pH = 7.24, pO₂ 88 , pCO₂: 14, HCO₃ : 10, Na:

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ABG showed pH 7.28, PaO2 80, PCO2 20, HCO3: 12. His serum acid 10mg%, and hypoproteinemia (serum albumin-2.5gm%), hyperlactatemia (arterial lactate level = 9.0mmol/L), serum uric mass, and massive hepatomegaly. Investigations revealed and anterior abdominal wall, epigastric tenderness, and edema of feet. On hospitalization, he developed tricyclic antidepressant-induced hyperthermia, which was treated with oral dantrolene. After one week of therapy, he showed symptomatic improvement and reduced arterial lactate level. The patient was discharged on supportive therapy. On follow up, he was feeling well, with only the complaint being mild dyspnea and epigastic discomfort. The arterial lactate level was further reduced to 4 mmol/L. In follow-up, his edema disappears with reduction in hepatomegaly with normalization of serum albumin. He was started with Fortovase + Norvir + Efavirenz.

**CASE 3**

A 50 years female patient, HBsAg positive, weight 85kg, was started with ART on in August 2002. She was asymptomatic with baseline CD4 T cells count of 218/cmm. Her husband died of advanced HIV with disseminated TB and pulmonary aspergillosis. She was also hypertensive and hypothyroid and receiving treatment with an ACE inhibitor and eltorin. She remained asymptomatic and did not have any ADI during the course of illness. She had a good immunological response- her CD4 T cells count increased from 218 to 405 cells/cmm within six months.

She was brought to the emergency room in May 2003 with the chief complaint of sudden onset of severe breathlessness and epigastic discomfort. On physical examination, other than tachypnea, there was no abnormality. The abdomen was soft without hepatomegaly. The laboratory investigations showed: ABG pH: 7.04, PO2 165, PCO2 18, HCO3: 5.0 BE -26 arterial lactate: 21 mmol/lit, S.creatinine: 1.81mg%, K 5.17meq/L, Na 135.3meq/L, Cl: 99.4 meq/L. Anion gap was 36.07. Hb 11.2gm%, TC 20,280/cmm, DC: P 78, L20, M 1,E1, S.uric acid 11.7mg%, SGPT 33u/L, SGOT 40u/L. She was treated with ARVs after one month, he presented with swelling of both lower limbs. As a result, d4T dose was reduced to 30mg bid with ART. He was started with d4T, 3TC and NVP. He improved after starting ART with serial CD4 counts three months apart showing a steady increase- 27, 174, 164, 132, and 221cells/cmm. He remained asymptomatic while on ART. In February 2003, he developed distal sensory neuropathy involving both lower limbs. As a result, d4T dose was reduced to 30mg bid with other supportive treatment. He also had facial lipoatrophy. After one month, he presented with swelling of both lower limbs and face, weakness, dyspnea on exertion, epigastic fullness, nausea and vomiting since three days. On examination he was tachycardia, edema of feet and anterior abdominal wall, epigastric tenderness, and massive hepatomegaly. Investigations revealed hyperlactatemia (arterial lactate level = 9.0mmol/L), serum uric acid 10mg%, and hypoproteinemia (serum albumin-2.5gm%). ABG showed pH 7.28, PaO2 80, PCO2 20, HCO3: 12. His serum cholesterol and triglyceride levels and RFT and liver function tests were normal. Ultrasonography of abdomen showed hepatomegaly with Grade II fatty infiltration.

He was hospitalized with diagnosis of ART induced lactic acidosis with hepatic steatosis. He was treated with withdrawal of ART, IV bicarbonate, niacinamide, carnitine, co-enzyme Q10, IV albumin and other supportive treatment. He showed symptomatic improvement and was discharged from hospital after seven days. He was again hospitalized for complaint of generalized edema, epigastic discomfort, anorexia, dry mouth, breathing difficulty, severe pain and numbness in feet and abdominal distension. He was treated with IV albumin and other supportive treatment. During hospitalization, he developed tricyclic antidepressant-induced hyperthermia, which was treated with oral dantrolene. After one week of therapy, he showed symptomatic improvement and reduced arterial lactate level. The patient was discharged on supportive therapy. On follow up, he was feeling well, with only the complaint being mild dyspnea and hyperlactatemia. His serum acid 10mg%, and hypoproteinemia (serum albumin-2.5gm%), hyperlactatemia (arterial lactate level = 9.0mmol/L), serum uric mass, and massive hepatomegaly. Investigations revealed and anterior abdominal wall, epigastric tenderness, and edema of feet.
one year her ART was changed to d4T, DDI, and indinavir. She responded well with CD4 count rise to 480/cmm. Thereafter, she discontinued ART for 15 months and returned to the clinic with severe itchy dermatosis. Her CD4 T cell count had dropped to 46/cmm. She was started with PCP prophylaxis and d4T, 3TC, and NVP. She again showed immunological response with clinical recovery. After 6 months, she returned with complaints of weakness, nausea, vomiting, epigastric discomfort and dyspnea. Laboratory investigations showed arterial lactate 13.5 mmol/L, serum uric acid level: 11.8 mg%, serum creatinine: 7.4 mg%, SGPT: 104 u/l, serum bilirubin: 1.12 mg%, ABG showed pH: 7.21, HCO₃: 7, PO₂ 88, PCO₂ 16. She was started with peritoneal dialysis for severe acidosis and she died during treatment.

Other clinical cases: Three other cases, two males and one female, presented with hyperlactatemia without acidosis. All three were having fatigue, nausea, epigastric discomfort and leg cramps while receiving d4T, 3TC and NVP. They recovered with supportive care and subsequently tolerated AZT, 3TC and NVP without rise in arterial lactate levels.

**DISCUSSION**

Long-term metabolic complication related to ART is increasingly recognized with increasing use in HIV infected patient. Cheaper generic ARTs are available in India. Fix dose d4T+3TC + nevirapine cost around 30 US$ per month. Many patients can afford Nevirapine based ART. Patients do adhere to prescribe ART and have completed two years of follow-up on ART. We are describing important and fatal if not recognized early, metabolic side effects due to ART. Six patients out of seven were receiving fixed dose combination of d4T+3TC+nevirapine. One patient was receiving d4T+3TC+Efavirenz. Except one (48kg) all patients were weighing > 70kg with highest of 93kg. Four patients with acidosis were hyperurecemic. One patient had facial and limb lipoatrophy, rest of the patients were free from other long-term metabolic side effects. Moderate to massive Hepatomegaly with steatosis was seen in six patients. Only one patient was hepatitis B co-infected.

Small studies show that patients with higher body weight on d4T and 3TC-based regimen are more susceptible to lactic acidosis. There is no gender difference, hypertension was found in four out of seven patients. The median time to the development of lactic acidosis after ART exposure was 16 months. Hyperurecemia was found in five patients and impaired renal function test was seen in two patients. Long-term metabolic side effects were seen in only one patient. Hyperlactatemia may be an independent of other long-term side effects. All of our patients were treated with supportive care, and all except one improved. Intensive care is required to treat acidosis as patients may have serious acid base and fluid and electrolyte imbalance.

Lactic acidosis rather than infectious causes should be considered for patients receiving d4T-based ART and whose CD4 T cell counts are above 350/cmm who present with weakness, breathlessness and epigastric discomfort. Routine screening for lactate in a patients receiving NRTI based therapy is not recommended, as mild hyperlactatemia does not predict development of lactic acidosis and as the onset of lactic acidosis can be abrupt, without preceding elevation of lactate levels.

Case reports have suggested that vitamins and cofactors required for oxidative phosphorylation may help induce recovery from lactic acidosis. These include riboflavin, thiamine, a vitamin B complex, carnitine, and coenzyme Q. There is no standardized treatment of NRTI-induced mitochondrial toxicity, but several authors have recommended a combination of vitamins with CoQ. Hepatic steatosis is usually associated with lactic acidosis, responsible for delayed clearance of lactate from the circulation.

**Spectrum of hyperlactatemia: Symptoms**

- Symptoms of lactic acidosis are nonspecific like nausea and vomiting, abdominal pain, weight loss, malaise, dyspnea/tachypnea
- Laboratory findings are increased anion gap, increased lactate levels, metabolic acidosis (pH < 7.25)
- Lactate level > 9 mmol/L-
- Widespread energy deficits contribute to organ failure
- Mortality exceeds 75%

**Table 1 : Demographic Information**

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<th>Patients</th>
<th>1</th>
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<td>March 03</td>
<td>May 2003</td>
<td>March 02</td>
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<td>Metabolic side effect</td>
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* Triomune = d4T+3TC+Nevirapine, EFV= Efavirenz; Dx = diagnosis, LA = Lactic acidosis
Features of hepatic dysfunctions are common which includes tender hepatomegaly, peripheral edema, ascites, and encephalopathy. Mild elevation of liver enzymes is common but jaundice is rare. Hepatic steatosis is frequently observed on imaging and on biopsy. Lactic acidemia with no or mild symptoms has been detected in 8% to 21% of patients receiving at least one NRTI as compared to 0% to 1% of patients receiving no ART. Hyperuricemia has been found in up to 60% of patients with lactic acidosis.

In conclusion, increase in experience with HAART in Indian patients has led to the identification of potentially fatal lactic acidosis. High index of suspicion is required to diagnose lactic acidosis, as initial symptoms are nonspecific. We found lactic acidosis in obese patients who were receiving d4T-based ART. Hyperuricemia, hypertension and renal failure were also detected in these patients. Further studies are required to identify any association between obesity, hypertension and use of ACE inhibitors with the development of lactic acidosis.

REFERENCES


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