the doors to a competitive market in generic drugs in the developing world as a way to deal with the epidemic in a sustainable manner. He noted that pilot HAART projects using generic drugs that combine prevention and treatment, such as the one conducted by Médecins Sans Frontieres in Khayelitsha (Abstracts 1095 and 3685), have proved that HAART can be feasible in limited-resource settings and should be expanded. Achmat lives with HIV and has free access to antiretrovirals, yet he declared he would not take the lifesaving drugs until the South African government agreed to an action plan to provide HAART in the public hospitals in South Africa.

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CONCLUSION

The XIVth International AIDS Conference will be remembered as the meeting that emphasised the need for both prevention and treatment of HIV/AIDS. It will also be remembered for the presentation of the first reports of pilot HAART projects that demonstrated the feasibility and effectiveness of such interventions in developing countries.

REFERENCES

1. Marseille E, Hofmann PB, Kahn JG. HIV prevention before HAART in sub-Saharan Africa. *Lancet* 2002; **359:** 1851-1856.
2. Creese A, Floyd K, Alban A, Guinness L. Cost-effectiveness of HIV/AIDS interventions in Africa: a systematic review of the evidence. *Lancet* 2002; **359:** 1635-1643.
3. Farmer P, Leandre F, Mukherjee JS, *et al.* Community-based approaches to HIV treatment in resource-poor settings. *Lancet* 2001; **358:** 404-409.
4. Weidle PJ, Malamba S, Mwebaze R, *et al.* Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance. *Lancet* 2002; **360:** 34-40.

KEY PRACTICE POINT

NRTI-ASSOCIATED HYPERLACTATAEMIA AND LACTIC ACIDOSIS

Jennifer Pitt, *MB ChB, Dip Obstet*
Clinical Research Unit, Somerset Hospital and University of Cape Town

Since the advent of highly active antiretroviral therapy (HAART), the prognosis of patients with HIV infection has improved dramatically – as evidenced by the decrease in mortality and morbidity rates.[1] However, this increase in life expectancy carries the risk of significant drug toxicities, such as the nucleoside reverse transcriptase inhibitor (NRTI)-associated mitochondrial toxicity.

BACKGROUND

Mitochondria are organelles which are present in all cells except erythrocytes. They generate cellular energy in the form of adenosine triphosphate (ATP) by aerobic oxidative phosphorylation (Fig. 1). This process is dependent on DNA polymerase-γ, an enzyme that replicates the major components of mitochondrial DNA.[2,3]

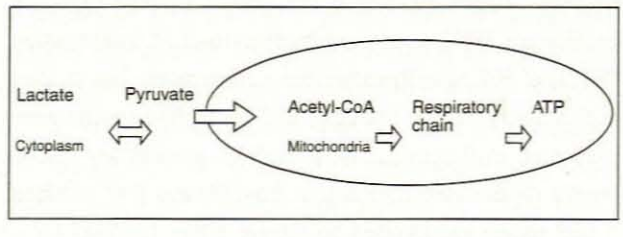

Fig. 1. Aerobic oxidative phosphorylation.

The inhibition of DNA polymerase-γ impairs the synthesis of mitochondrial enzymes and leads to the dysfunction of the respiratory chain and the accumulation of acetyl-CoA within the mitochondria. This build-up of acetyl-CoA shifts the balance of pyruvate metabolism towards lactate reduction. The result is the accumulation of lactate in the blood (Fig. 2).[2,3]

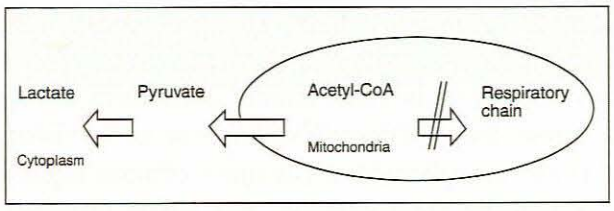

Fig. 2. Inhibition of DNA polymerase-γ and shift to lactate production.

The toxicity of NRTIs is related to their antiretroviral mechanism of action: the selective inhibition of viral DNA replication. If the selectivity of the NRTI is not absolute, cellular targets such as mitochondrial DNA polymerase-γ will be affected.[2,3]

All currently available NRTIs inhibit human mitochondrial DNA polymerase-γ to some degree. The relative potency of inhibition of DNA polymerase-γ by NRTIs is as follows: zalcitabine > didanosine > stavudine > lamivudine > zidovudine > abacavir.[4-7] Abacavir has a very low affinity for mitochondrial DNA polymerase-γ.[8] The risk for developing NRTI-related mitochondrial toxicity increases with length of time on therapy.[9]

The resultant mitochondrial dysfunction may manifest biochemically as hyperlactataemia and lactic acidosis or clinically as hepatic steatosis, pancreatitis, peripheral neuropathy and myopathy.

The following three cases illustrate the spectrum of hyperlactataemia.

CASE 1: ASYMPTOMATIC HYPERLACTATAEMIA

A 29-year-old woman (height 169 cm, weight 106 kg, body mass index (BMI) 37) was commenced on therapy with a protease inhibitor/ddI 400 mg 4 times a day/d4T 40 mg twice a day. The baseline viral load was 26 000 copies/ml and the baseline CD4 count 279/µl.

At week 48, she was noted to have an asymptomatic increase in transaminase and lactate dehydrogenase (LDH) levels. This biochemical picture raised suspicions of an increase in lactate. Her lactate level was measured at week 52 and found to be elevated at 2.4 mmol/l (upper limit of normal (ULN) 2.0 mmol/l).

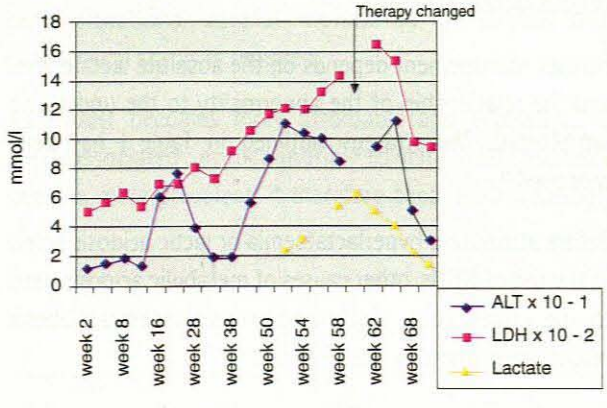

Fig. 3. Changes over time of biochemical parameters in case 1.

As she was asymptomatic, her lactate levels were monitored over the next 6 weeks. This demonstrated a linear increase in lactate (Fig. 3). Based on the rate of rise, it was predicted that her lactate levels would soon reach 10 mmol/l. As the mortality rate associated with a lactate level >10 mmol/l is 80%, she was changed to a non-d4T-NRTI regimen at week 59. The biochemical abnormalities settled on the new therapy.

CASE 2: SYMPTOMATIC LACTIC ACIDOSIS WITH RECOVERY

A 34-year-old woman (height 163 cm, weight 87 kg, BMI 33) was commenced on therapy with a protease inhibitor/d4T 40 mg twice a day/3TC 150 mg twice a day. The baseline viral load was 54 600 copies/ml and the baseline CD4 count 145/µl.

She presented at week 32 with a 2-week history of nausea, vomiting and epigastric pain. She was treated for gastroenteritis. Liver function tests showed a mild transaminitis and an elevated LDH level. She returned at week 33 with ongoing gastrointestinal (GIT) symptoms and a worsening of the biochemical abnormalities (Fig. 4).

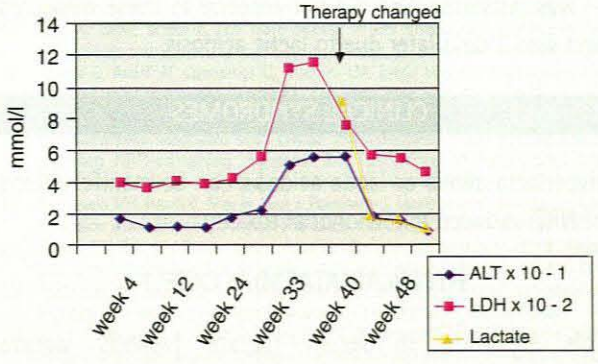

Fig. 4. Changes over time of biochemical parameters in case 2.

The patient was admitted at week 34 with ongoing GIT symptoms, dyspnoea and paraesthesiae. Her lactate level was 9.1 mmol/l and arterial blood gas measurement revealed a metabolic acidosis: pH 7.3/partial pressure carbon dioxide (pCO_2) 1.5 kPa/partial pressure oxygen (pO_2) 8.4 kPa/standard bicarbonate (SB) 5.9 mmol/l. She was diagnosed with lactic acidosis. She had stopped her HAART on admission. Her symptoms settled by week 35 and she was discharged.

She has been clinically well since then. Her lactate levels have remained normal on continued therapy.

CASE 3: SYMPTOMATIC LACTIC ACIDOSIS RESULTING IN PATIENT DEATH

A 34-year-old woman (height 158 cm, weight 75 kg, BMI 30) was commenced on nelfinavir 1 250 mg twice a day/ddI 400 mg 4 times a day / d4T 40 mg twice a day.

The baseline viral load was 547 152 copies/ml and the baseline CD4 count 125/µl.

The initial regimen failed virologically and the patient was changed to indinavir 800 mg twice a day/RTV 100 mg twice a day/ddI 400 mg 4 times a day/d4T 40 mg twice a day, based on viral genotyping.

She was fully suppressed (viral load < 50 copies/ml) and clinically well after 24 weeks of therapy.

She presented at week 32 with a 2-day history of nausea, vomiting and epigastric pain. She had suffered an episode of diarrhoea during the previous week. She was admitted with suspected acute pancreatitis. She had stopped taking her HAART before admission.

Arterial blood gas measurement revealed a partially compensated metabolic acidosis: pH 7.29/pO_2 16.23 kPa/pCO_2 1.98 kPa/SB 7.3 mmol/l. Her lactate level was reported as 21.6 mmol/l. She was diagnosed with lactic acidosis and admitted to the ICU. Aggressive supportive therapy – including intravenous rehydration, intravenous sodium bicarbonate and parenteral vitamin B, including riboflavin – was instituted. She did not respond to these measures and died 2 days later due to lactic acidosis.

CLINICAL SYNDROMES

Hyperlactataemia or lactic acidosis can be manifestations of NRTI-induced mitochondrial toxicity.

HYPERLACTATAEMIA: CASE 1

This elevation in serum lactate (venous lactate > 2.0 mmol/l) in the absence of metabolic acidosis (arterial pH < 7.3) can be asymptomatic or symptomatic.

The symptoms may include fatigue, asthenia, malaise, GIT symptoms (loss of appetite, loss of weight, nausea, vomiting, abdominal pain, dyspepsia ± bloating), dyspnoea and neurological symptoms (paraesthesiae, muscle weakness). An elevated LDH level, mild transaminitis and a decrease in bicarbonate often precede the onset of symptoms.[10]

The reported incidence of asymptomatic hyperlactataemia in NRTI-treated patients ranges from 8% to 21%, while that for symptomatic hyperlactataemia is only 1 - 2%.[11-13]

At present we are unable to predict which patients with asymptomatic hyperlactataemia will go on to develop lactic acidosis.[14] However, recent literature reviews have reported an increased risk in female patients[10] and patients with an increased BMI.[3,14] This trend is supported by our three cases. Deficiencies in riboflavin and thiamine, cofactors required for oxidative phosphorylation, may further predispose patients to the development of hyperlactataemia.[15]

LACTIC ACIDOSIS: CASES 2 AND 3

This symptomatic elevation in serum lactate accompanied by metabolic acidosis is often associated with a mild transaminitis and a rise in LDH.[10] Liver biopsy reveals hepatic steatosis.

The reported rate of lactic acidosis varies from 0.85 cases per 1 000 patient-years of treatment[14] to 8.4 cases/1 000 patient-years,[16] with an even higher rate reported among patients taking only stavudine and didanosine.[16] There are some indications that the rate may be even higher in South African patients.[10] Although development of lactic acidosis is not a frequent event, it is important because of the associated high mortality rate, which approaches 80% in patients with a serum lactate level >10 mmol/l.[3]

MANAGEMENT

Routine monitoring of lactate levels is not recommended for all patients receiving NRTIs.[3] However, Adda *et al.*[10] propose a diagnostic index for monitoring patients on therapy and predicting the occurrence of hyperlactataemia. This index includes an elevated LDH level (> 2 x ULN) together with elevated transaminases (aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 2 x ULN) and the presence of nausea and/or vomiting. This index showed 100% sensitivity, 98% specificity, 100% negative predictive value and 50% positive predictive value for hyperlactataemia.

Patients who manifest persistent symptoms, signs or laboratory abnormalities (transaminitis/raised LDH) suggestive of hyperlactataemia should be evaluated with venous lactate sampling.

Further management depends on the absolute lactate level and the relationship of the abnormality to the underlying symptom(s). The strategy outlined in Table I has been proposed.[17]

Before attributing hyperlactataemia or lactic acidosis solely to the use of NRTIs, other causes of metabolic acidosis need to be ruled out, including sepsis/uraemia/diabetic ketoacidosis/thyrotoxicosis/lymphoma.[18]

Once the diagnosis of NRTI-related mitochondrial toxicity is made, NRTI therapy should be stopped. Cessation of treatment should lead to the resolution of symptoms.[19,20]

TABLE I. PROPOSED STRATEGY FOR INTERPRETING LACTATE LEVELS

Lactate	Symptoms	Action
< 2 mmol/l	No	No intervention
	Yes	Investigate other causes
2 - 5 mmol/l	No	Observe
	Yes	Exclude other causes Consider discontinuation of NRTI
5 - 10 mmol/l	No	Observe
	Yes	Discontinue NRTI Exclude other causes
>10 mmol/l	Any	Discontinue NRTI Exclude other causes

Further treatment is largely supportive. Hyperlactataemia can be managed on an outpatient basis, but patients with lactic acidosis require hospitalisation with aggressive intravenous rehydration and alkalinisation with high-dose bicarbonate infusions.[3]

A recent case series has shown that specific therapy using the cofactors of oxidative phosphorylation (thiamine, riboflavin, L-carnitine, prostaglandin E and coenzyme Q) are associated with a lower mortality rate.[14] This supports previous anecdotal information of patients with lactic acidosis who responded dramatically to administration of essential cofactors: high-dose riboflavin 50 mg once daily, thiamine 100 mg by intravenous infusion, or L-carnitine 50 mg/kg daily respectively.[21-23]

Brinkman *et al.*[24] propose twice-daily vitamin supplementation for the treatment of lactic acidosis, including 50 mg thiamine/10 mg riboflavin/100 mg nicotinamide/10 mg pyridoxine/10 mg dexpanthenol/100 mg intravenous L-carnitine. The regimen is continued until serum lactate levels fall below 3 mmol/l.

On recovery from hyperlactataemia or lactic acidosis, rechallenge with NRTI-sparing regimens is preferred.[14] However, in cases of moderate hyperlactataemia there have been reports of rechallenge with non-d4T NRTI-containing regimens, which were not associated with relapse.[25-27] In both situations, careful monitoring of clinical and biochemical status is required.

As HAART becomes more affordable and accessible, so NRTI-associated mitochondrial toxicity will probably become more prevalent. It therefore becomes increasingly important for clinicians to be aware of these rare but potentially life-threatening drug toxicities and the need to diagnose them early and intervene appropriately.

REFERENCES

1. Mocroft A, Vella S, Benfield TL, *et al.* Changing patterns of mortality across Europe in patients infected with HIV-1. *Lancet* 1998; **352:** 1725-1729.
2. Khouri S, Cushing H. Lactic acidosis secondary to nucleoside analog antiretroviral therapy. *Infect Med* 2000; **17:** 547-554.
3. Landovitz RJ, Sax PE. NRTI-associated mitochondrial toxicity. *AIDS Clin Care* 2001; **13:** 343-349.
4. Brinkman K. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. *AIDS* 1998; **12:** 1735-1744.
5. Chen CH, Vazquez-Padua M, Cheng YC. Effect of anti-human immunodeficiency virus nucleoside analogs on mitochondrial DNA and its implication for delayed toxicity. *Mol Pharm* 1991; **39:** 625-628.
6. Martin JL, Brown CE, Matthews-Davis N, Reardon JE. Effects of antiviral nucleoside analogs on human DNA polymerases and mitochondrial DNA synthesis. *Antimicrob Agents Chemother* 1994; **38:** 2743-2749.
7. Daluge SM, Good SS, Faletto MB, *et al.* 1592U89, a novel carbocyclic nucleoside analog with potent, selective anti-human immunodeficiency virus activity. *Antimicrob Agents Chemother* 1997; **41:** 1082-1093.
8. Cihlar T, Chen MS. Incorporation of selected nucleoside phosphonates and anti-human immunodeficiency virus nucleotide analogues into DNA by human DNA polymerases α, β and γ. *Antiviral Chem Chemother* 1997; **8:** 187-195.
9. Boubaker K, Flepp M, Sudre P, *et al.* Hyperlactatemia and antiretroviral therapy: The Swiss HIV Cohort Study. *Clin Infect Dis* 2001; **33:** 1931-1937.
10. Adda N, Pallcia S, Wakeford C, Kargl D, Rousseau. Lactic acidemia in HIV infected patients receiving triple combination therapy: Predictive factors and clinical features. 39th Congress of the Infectious Disease Society of America, San Francisco, 25 - 28 Oct 2001 (Abstract 201669).
11. Carr A, Miller J, Law M, Cooper DA. A syndrome of lipoatrophy, lactic acidemia and liver dysfunction associated with HIV nucleoside analogue therapy contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS* 2000; **14:** F25-F32.
12. Boubaker K, Flepp M, Sudre P, *et al.* Hyperlactatemia and antiretroviral therapy in the Swiss HIV Cohort Study (SHCS). 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, Feb 2000 (Abstract 57).
13. Vrouenraets SM. Hyperlactatemia in HIV-infected patients: The role of NRTI treatment. 8th Conference on Retroviruses and Opportunistic Infections, Chicago, 5-8 Feb 2001 (Abstract 625).
14. Falco V, Rodriguez D, Ribera E, *et al.* Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. *Clin Infect Dis* 2002; **34:** 838-846.
15. Fouty B, Frerman F, Reeves R. Riboflavin to treat nucleoside analogue induced lactic acidosis. *Lancet* 1998; **352:** 291-292.
16. Gerard Y, Maulin L, Yazdanpanah Y, *et al.* Symptomatic hyperlactatemia: an emerging complication of antiretroviral therapy. *AIDS* 2000; **14:** 2723-2730.
17. Carr A. Lactic acidemia and bone disease in HIV disease. 8th Conference on Retroviruses and Opportunistic Infections, Chicago, 5 - 8 Feb 2001 (Abstract L12).
18. Chatta G, Arieff AI, Cummings C, Thierney LM. Lactic acidosis complicating the acquired immunodeficiency syndrome. *Ann Intern Med* 1993; **118:** 37-39.
19. Lonergan JT, Havlir D, Barber E, Mathews WC. Incidence and outcome of hyperlactatemia associated with clinical manifestations in HIV-infected adults receiving NRTI-containing regimens. 8th Conference on Retroviruses and Opportunistic Infections, Chicago, 5 - 8 Feb 2001 (Abstract 624).
20. Mokrzycki MH, Harris C, May H, Laut J, Palmisano J. Lactic acidosis associated with stavudine administration: a report of 5 cases. *Clin Infect Dis* 2000; **30:** 198-200.
21. Dalton SD, Rahimi AR. Emerging role of riboflavin in the treatment of nucleoside analogue-induced type B lactic acidosis. *AIDS Patient Care STDs* 2001; **15:** 611-614.
22. Posteraro AF, Mauriello M, Winter SM. Riboflavin treatment of antiretroviral induced lactic acidosis and hepatic steatosis. *Conn Med* 2001; **65:** 387-390.
23. Arici C, Tebaldi A, Quinzan GP, Maggiolo F, Ripamonti D, Suter F. Severe lactic acidosis and thiamine administration in an HIV-infected patient on HAART. *Int J STD AIDS* 2001; **12:** 407-409.
24. Brinkman K, Vrouenraets S, Kaufmann R, Wiegel H, Frissen J. Treatment of lactic acidosis. 2nd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, Toronto, 12 - 15 Sep 2000 (Abstract P15).
25. Miller KD, Cameron M, Wood LV, Dalakas MC, Kovacs JA. Lactic acidosis and hepatic steatosis associated with use of stavudine: report of four cases. *Ann Intern Med* 2000; **133:** 192-196.
26. Lenzo NP, Garas BA, French MA. Hepatic steatosis and lactic acidosis associated with stavudine treatment in an HIV patient: a case report. *AIDS* 1997; **11:** 1294-1296.
27. John M, Moore CB, James IR, *et al.* Chronic hyperlactatemia in HIV-infected patients taking antiretroviral therapy. *AIDS* 2001; **15:** 717-723.