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 Frontiéres 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.

Reprinted with permission, Dr Jean Nachega, Johns Hopkins HIV Report, 2002.

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

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).
CASE 1: ASYMPTOMATIC HYPERLACTATAEMIA

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. 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. Abacavir has a very low affinity for mitochondrial DNA polymerase-γ. The risk for developing NRTI-related mitochondrial toxicity increases with length of time on therapy.

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).

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 (GI) symptoms and a worsening of the biochemical abnormalities (Fig. 4). She has been clinically well since then. Her lactate levels have remained normal on continued therapy.

**CASE 3: HYPERLACTATAEMIA WITH ASYMPTOMATIC ACIDOSIS**

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 GI symptoms and a worsening of the biochemical abnormalities (Fig. 4). 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/ddl 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 125M.

The initial regimen failed virologically and the patient was changed to indinavir 800 mg twice a day/RN 100 mg twice a day/ddl 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/pO2 16.23 kPa/pCO2 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.18

The reported incidence of asymptomatic hyperlactataemia will go on to develop lactic acidosis.19 However, recent literature reviews have reported an increased risk in female patients19 and patients with an increased BMI.20 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.18

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.21 Liver biopsy reveals hepatic steatosis.

The reported rate of lactic acidosis varies from 0.85 cases per 1 000 patient-years of treatment22 to 8.4 cases/1 000 patient-years,23 with an even higher rate reported among patients taking only stavudine and didanosine.24 There are some indications that the rate may be even higher in South African patients.25 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.26

MANAGEMENT

Routine monitoring of lactate levels is not recommended for all patients receiving NRTIs.21 However, Adda et al.21 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 1 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/uremia/diabetic ketoacidosis/thyrotoxicosis/lymphoma.27

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.28 29
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. 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. 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.

Brinkman et al. 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. However, in cases of moderate hyperlactataemia there have been reports of rechallenge with non-d4T NRTI-containing regimens, which were not associated with relapse. In both situations, careful monitoring of clinical and biochemical status is required.

As HAART becomes more accessible and affordable, 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**

6. Martin, J.L. et al. Neopterin levels fall below 3 mmol/l.