Metabolic complications of HIV and HAART: The hyperlactataemia syndromes

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Outline of the talk

- Understanding the problem
- Do not miss the diagnosis
- Managing the patient appropriately
Introduction

• Until 2010, SA’s guidelines recommended d4T-based therapy as first line therapy in the public-sector.

• Cheap and easy to administer but significant morbidity, particularly hyperlactataemia syndromes with long-term risks of lipoatrophy, and peripheral neuropathy. (Boulle et al, Antivir Ther 2007; Menezes et al. BMC Infectious Diseases 2011).

• Several resource-limited countries yet to phase out d4T - according to the WHO (2010) ~56% of HAART regimens within such countries still contained d4T. (http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf)

• Despite the change in SA guidelines, shortages of abacavir and tenofovir reported at health facilities - d4T advised as a possible alternative. (Schowalter L et al, S Afr J HIV Med 2012)

• Rates of the hyperlactataemia syndromes vary in HIV-infected patients using NRTIs worldwide – higher in African countries.
# Epidemiology – African Countries

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Study type</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geddes et al, 2006</td>
<td>South Africa</td>
<td>Observational case series</td>
<td>891 patients; LA: incidence rate of 19/1000 person years (95% CI 9-29)</td>
</tr>
<tr>
<td>Wester et al, 2007</td>
<td>Botswana</td>
<td>Randomized control trial</td>
<td>650 patients; 2% moderate to severe SH; 1% LA</td>
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<tr>
<td>Boulle et al, 2007</td>
<td>South Africa</td>
<td>Cohort</td>
<td>2679 patients; LA/SH related stavudine substitutions in 4.7% (95% CI 3.0-6.8)</td>
</tr>
<tr>
<td>Bolhaar et al, 2007</td>
<td>South Africa</td>
<td>Retrospective cohort analysis</td>
<td>1735 patients; incidence rate 10.6 /1000 patient years; 16.1/1000 patient years (females); 1.2/1000 patient years (males). Mortality: LA: 30.4% died. SH: None died.</td>
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<tr>
<td>Same et al, 2009</td>
<td>South Africa</td>
<td>Cohort</td>
<td>7583 patients; LA/SH: incidence rates of 5.1 per 100 person years (95% CI 4.4-5.5)</td>
</tr>
<tr>
<td>van Griensven et al, 2009</td>
<td>Rwanda</td>
<td>Cohort</td>
<td>2190 patients; LA/SH 3.1%; incidence rate 20/1000 patient years.</td>
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<tr>
<td>Hernandez et al, 2010</td>
<td>South Africa</td>
<td>Retrospective</td>
<td>1719 patients; LA: incidence rate 13.5 cases/1000 patient years (95% CI 9-29), Mortality: 22.2% SH: Incidence rate 31.79 cases/1000 patient years (95% CI 14-40).</td>
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<tr>
<td>Menezes et al, 2011</td>
<td>South Africa</td>
<td>Prospective</td>
<td>9040 patients; SH:3.6 cases/100 person-years (95%CI 1.2-7.5), LA:1.6 cases/100 person-years (95%CI 0.4-5.2).</td>
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Presentations – the hyperlactataemia syndromes

- Usually transient and have no symptoms however may be symptomatic, and occasionally life-threatening when accompanied by a metabolic acidosis – the lactic acidosis syndrome.

- Asymptomatic hyperlactataemia: common but does not predict for the symptomatic form of the disease.

- Symptomatic hyperlactataemia: good prognosis if recognised early and if no liver dysfunction.

- Lactic acidosis: pH < 7.35 and/or standard bicarbonate < 20 together with ↑ lactate. There is invariably multiple organ dysfunction, especially liver dysfunction.
Presentations: differences between the types of syndromes

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Subclinical</th>
<th>Symptomatic</th>
<th>Lactic acidosis syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency in HIV+ patients</td>
<td>8–18%</td>
<td>8–14·5 cases/1000 py</td>
<td>1·3–3·9 cases/1000 py</td>
</tr>
<tr>
<td>Specificity for current NRTI use</td>
<td>Poor</td>
<td>Very high</td>
<td>Very high</td>
</tr>
<tr>
<td>Serum lactate (mmol/L)</td>
<td>2·1–5·0</td>
<td>Usually ≤5·0</td>
<td>Usually &gt;5·0</td>
</tr>
<tr>
<td>Acid/base abnormalities</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Liver abnormalities</td>
<td>Rare</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Extrahepatic organ failure</td>
<td>No</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Usually benign</td>
<td>Mild to moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Usually excellent</td>
<td>Usually good</td>
<td>Mortality &gt;50%</td>
</tr>
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</table>

py=person years
Pathophysiology

- Both NRTIs and HIV infection directly influence mitochondrial function:

  - NRTIs by binding to various enzymes such as the mtDNA polymerase $\gamma$ and thymidine kinase 2 causing depletion of mtDNA; and reducing mitochondrial gene expression.

  - HIV infection through its viral proteins (Env, Nef, Tat and Vpr) activate mitochondrial apoptotic pathways to trigger cell death and through the massive inflammatory response and immune activation (TNF$\alpha$, IL2, INF$\alpha$) induce apoptosis.
Schematic representation of glycolysis and oxidative phosphorylation metabolism in the presence and absence of mitochondrial toxicity.
Pathophysiology: A South African experience (Adults)

- 29% ↓ mean mtDNA copies/cell from week 0 to 4 in std dose d4T and 32% ↓ in low dose d4T arm vs. 4% ↓ in TDF arm.

- With each d4T dose (20 mg, 30 mg and 40 mg) - ↓ in mean mtDNA copy numbers (22%, 35%, and 31% respectively) vs. 4% ↓ TDF at 4 weeks of HAART.

- Despite the significant depletion in mtDNA, expression levels of only 2 of 8 adipocyte genes (*MTCYB* and *NRF-1*) associated with mitochondrial energy metabolism and biogenesis were significantly affected by std dose d4T when compared with TDF. Minimal effects on gene expression were noted with low dose d4T.

Menezes *et al*, HIV Medicine 2012
Value of measurements of mtDNA routinely?

• Several studies have been performed using PBLs and tissue biopsies to assess mitochondrial function.

• Most studies conclude that measurements of mtDNA in PBLs and tissue contributes little to predicting functional mitochondrial toxicity.

• Suggest that measurements of mtDNA should not be used in routine practice, although there may still be some value in performing this in patients at risk.
At risk groups?

- ddI > d4T > AZT.

- ↑BMI – several SA cohorts suggest this.

- Gender - women are at greater risk.

- Pregnancy – especially when ddI and d4T are used in combination.

- Underlying liver disease: may impair lactate clearance.

- Genetic predisposition: mitochondrial haplotype L1c– a higher incidence of NRTI associated neuropathy (Canter JA et al, JID 2010).

- Age: unusual in children but some studies have reported otherwise.
Diagnosis

• Diagnosis of exclusion - life threatening. Symptoms/signs usually nonspecific and vague.

• Symptoms include:
  ▪ loss of weight, weakness and fatigue.
  ▪ Nausea, vomiting, loss of appetite, abdominal pain.
  ▪ Dyspnoea.
  ▪ Myalgia.

• Signs
  ▪ Peripheral oedema.
  ▪ Hepatomegaly
  ▪ Peripheral neuropathy and lipoatrophy often herald the onset of symptomatic hyperlactataemia.
Examination and investigations

• Clinical examination: respiratory and abdominal examination and assessment for peripheral neuropathy.

• Investigations:
  ▪ Lactate.
  ▪ Blood gas.
  ▪ Other tests: U+E, glucose, urine dipstix, liver function test, other tests depending on the clinical picture.
Differential diagnosis

- Sepsis
- Renal failure
- Diabetic ketoacidosis
- Pancreatitis
- Cardiac failure
- Severe anaemia
- Severe dehydration
- Liver failure
- Other drugs (e.g. metformin, INH overdose)
Management

• Stop HAART even before the diagnosis is confirmed if high index of suspicion.

• Sepsis/opportunistic infections should be excluded.

• SA guidelines based on anecdotal experience and other published guidelines. No prospective studies on the treatment of hyperlactataemia or lactic acidosis.
Management: lactate < 5 mmol/l and bicarbonate > 20 mmol/l.

- Switch NRTI regimen - less likely to cause lactic acidosis - ABC or TDF (or AZT if both unavailable) with 3TC or FTC. Monitor lactate – decrease slowly over weeks.

- If despite the switch - symptoms are severe or lactate continues to rise - HAART should be stopped.
Management: lactate >5 mmol/l and bicarbonate >15 mmol/l

• Stop HAART. Admit. Vitamins. Hydrate.

• HAART only be recommenced (alternative regimen) when lactate and bicarbonate normal (may take months).

• Options:
  - If on NNRTI regimen, boosted PI should be added.
  - If already failed on NNRTI and is on a boosted PI, RAL or ETV should be added if available
  - Otherwise should be continued on the boosted PI only.
  - When lactate normalised – should be switched to TDF/3TC/NNRTI or ABC/3TC/NNRTI.

Management: lactate > 5 mmol/l and bicarbonate < 15 mmol/l)

- Stop HAART. Admit to ICU. IVI fluids and IVI vitamins. Septic work up - Antibiotics - sepsis may mimic or precipitate the lactic acidosis.

- Consider IVI NaHCO3 if profound acidosis. Ventilation if respiratory fatigue occurs. Dialysis, inotropes and other supportive measures as necessary. If pancreatitis is present - keep NPO.

- Avoid NRTIs in future regimens. If on NNRTI regimen, boosted PI should be added. If already failed on NNRTI and is on a boosted PI, RAL or ETV should be added if available. Otherwise should be continued on the boosted PI only.

Poor prognostic markers

- High lactate level
- Severe acidosis
- Coexistent pancreatitis
- Patients who require ventilation and/or dialysis appear to have an extremely poor prognosis.
Prevention

• Mortality rates as high as 60%. Avoid d4T or ddI: WHO and SA guidelines changed but we still continue to use them because of shortage of TDF/ABC.

• Recognise the syndrome before the patient becomes acidotic. Symptoms tend to occur long before laboratory abnormalities are present.

• Monitoring weight: at every visit and when drops by > 5%, lactate should be measured even if no other symptoms present.

• Peripheral neuropathy - lactate measured.

• BMI: start women with a BMI > 28 on ABC or TDF—or to switch them to these NRTIs if they gain weight to a BMI > 28 on HAART).

• Routine lactate monitoring not recommended - correlation with the development of symptoms poor. Up to 25% of patients on NRTIs have asymptomatic hyperlactataemia with mild elevations in lactate levels, and only minority develop symptoms.
Conclusion

• Avoid use of d4T!

• Important to identify hyperlactataemia syndromes complicate NRTI therapy.

• Exclude other causes.

• Lactic acidosis, being the most serious manifestation, can progress to liver failure and death.