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

Reference	Country	Study type	Result
Geddes *et al*, 2006	South Africa	Observational case series	891 patients; LA: incidence rate of 19/1000 person years (95% CI 9-29)
Wester *et al*, 2007	Botswana	Randomized control trial	650 patients; 2% moderate to severe SH; 1% LA
Boulle *et al*, 2007	South Africa	Cohort	2679 patients; LA/SH related stavudine substitutions in 4.7% (95% CI 3.0-6.8)
Bolhaar *et al*, 2007	South Africa	Retrospective cohort analysis	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.
Sanne *et al*, 2009	South Africa	Cohort	7583 patients; LA/SH: incidence rates of 5.1 per 100 person years (95% CI 4.7-5.5)
van Griensven *et al* , 2009	Rwanda	Cohort	2190 patients; LA/SH 3.1%; incidence rate 20/1000 patient years.
Hernandez *et al*, 2010	South Africa	Retrospective	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).
Menezes *et al*, 2011	South Africa	Prospective	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).

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

Clinical characteristics of different hyperlactataemia syndromes seen in HIV-positive people

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

py=person years

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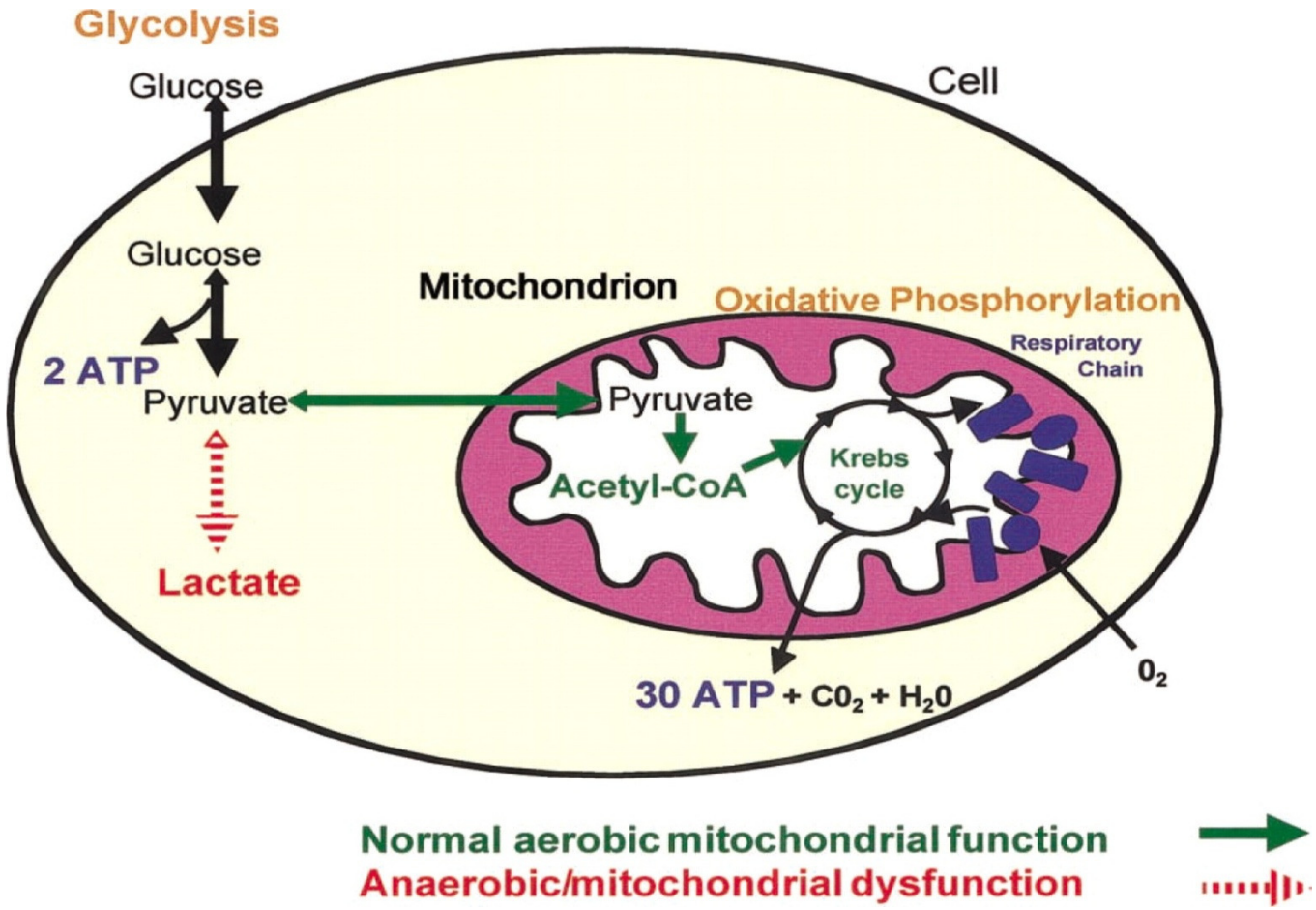
Pathophysiology

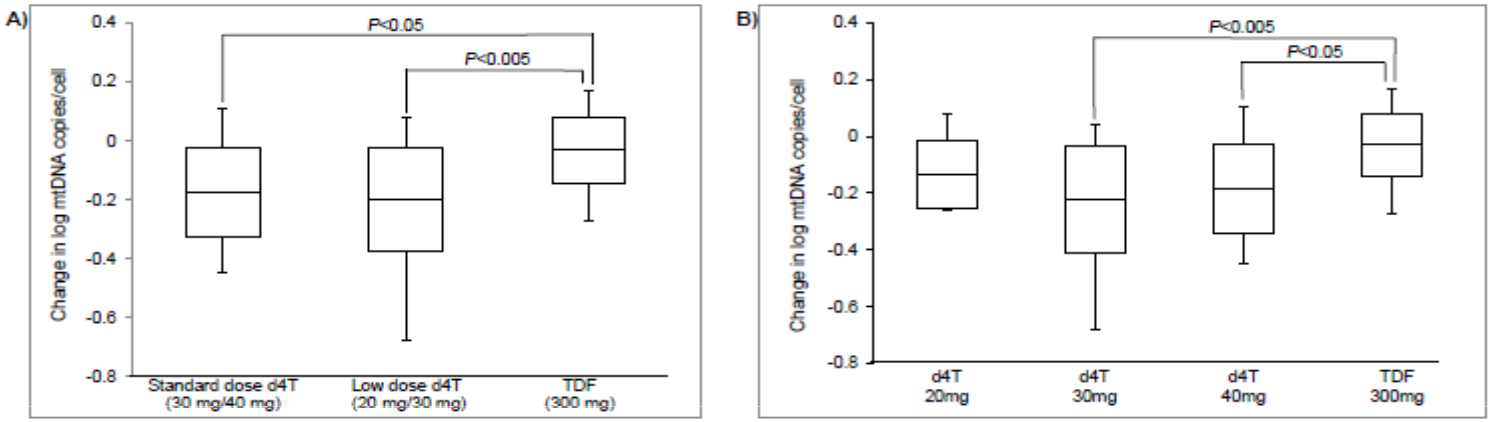
- Both NRTIs and HIV infection directly influence mitochondrial function:
  - NRTIs by binding to various enzymes such as the mtDNA polymerase γ and thymidine kinase 2 causing depletion of mtDNA ; and reducing mitochondrial gene expression.
  - HIV infection through its viral proteins (Env, Nef, Tat and Vpr) activate mitochondrial apoptotic pathways to trigger cell death and through the massive inflammatory response and immune activation (TNFα, IL2, INFα) induce apoptosis.

Schematic representation of glycolysis and oxidative phosphorylation metabolism in the presence and absence of mitochondrial toxicity.



Montaner J S et al. Clin Infect Dis. 2004;38:S73-S79
Clinical Infectious Diseases

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.

Southern African HIV Clinicians Society Guidelines 2006 & 2012

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.

Southern African HIV Clinicians Society Guidelines 2006 & 2012

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.

Southern African HIV Clinicians Society Guidelines 2006 & 2012

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.