

# Metabolic complications of HIV and HAART: The hyperlactataemia syndromes

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# Outline of the talk

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

# Introduction

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- 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](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 <i>et al</i> , 2006        | South Africa | Observational case series     | 891 patients; LA: incidence rate of 19/1000 person years (95% CI 9-29)   |
| Wester <i>et al</i> , 2007        | Botswana     | Randomized control trial      | 650 patients; 2% moderate to severe SH; 1% LA  |
| Boulle <i>et al</i> , 2007        | South Africa | Cohort                        | 2679 patients; LA/SH related stavudine substitutions in 4.7% (95% CI 3.0-6.8)  |
| Bolhaar <i>et al</i> , 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).<br>Mortality : LA: 30.4% died. SH: None died. |
| Sanne <i>et al</i> , 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 <i>et al</i> , 2009 | Rwanda       | Cohort                        | 2190 patients; LA/SH 3.1%; incidence rate 20/1000 patient years.   |
| Hernandez <i>et al</i> , 2010     | South Africa | Retrospective                 | 1719 patients; LA: incidence rate 13.5 cases/1000 patient years (95% CI 9-29),<br>Mortality: 22.2%<br>SH: Incidence rate 31.79 cases/1000 patient years (95% CI 14-40).  |
| Menezes <i>et al</i> , 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

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- 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:  $\text{pH} < 7.35$  and/or standard bicarbonate  $< 20$  together with  $\uparrow$  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 $\leq$ 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%        |

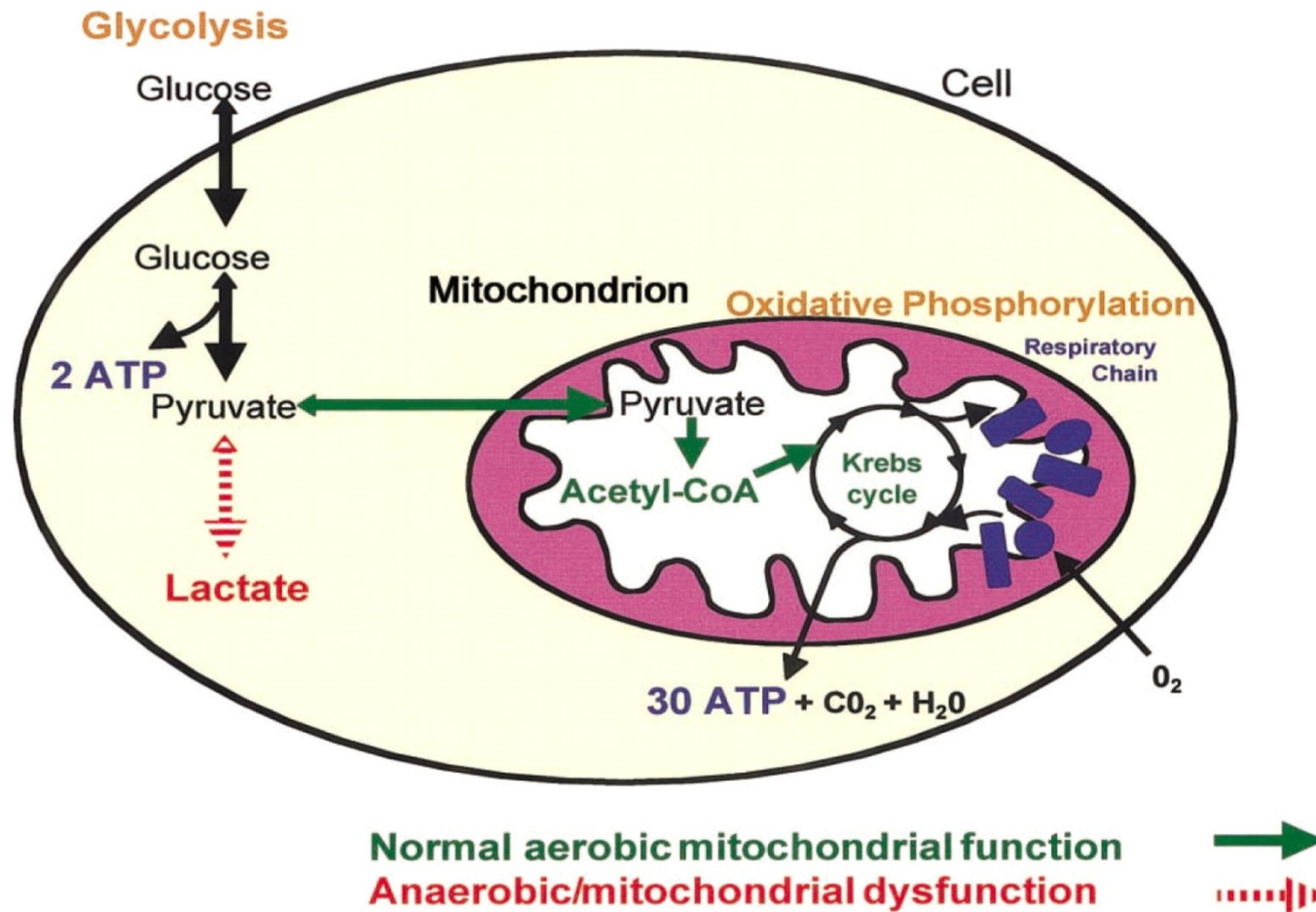
py=person years

# Pathophysiology

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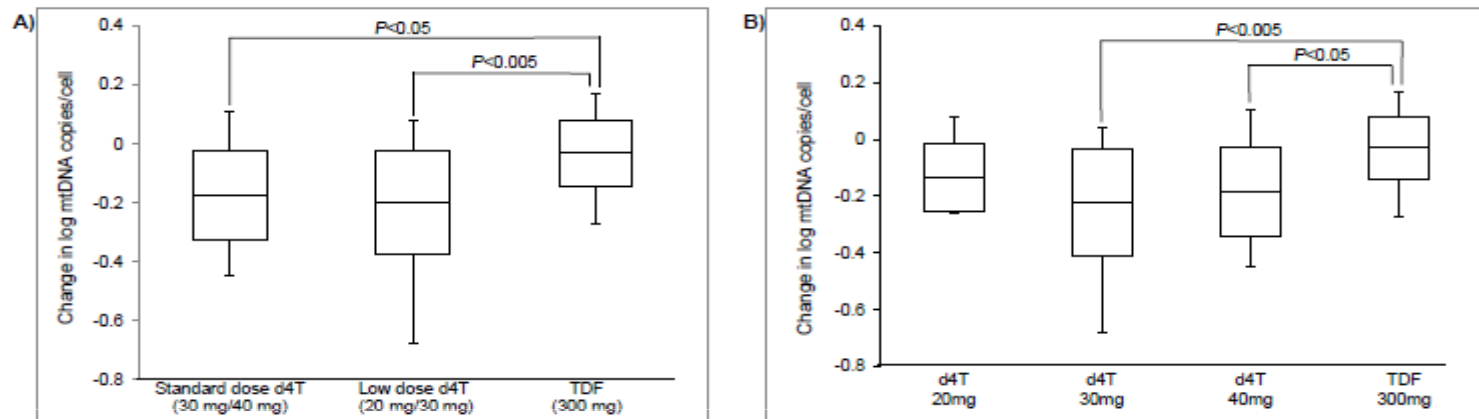
- Both NRTIs and HIV infection directly influence mitochondrial function:
  - NRTIs by binding to various enzymes such as the mtDNA polymerase  $\gamma$  and thymidine kinase 2 causing depletion of mtDNA ; and reducing mitochondrial gene expression.
  - HIV infection through its viral proteins (Env, Nef, Tat and Vpr) activate mitochondrial apoptotic pathways to trigger cell death and through the massive inflammatory response and immune activation (  $\text{TNF}\alpha$ , IL2,  $\text{INF}\alpha$ ) 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.

## Value of measurements of mtDNA routinely?

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- 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?

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- 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

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- 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 lipotrophy often herald the onset of symptomatic hyperlactataemia.

# Examination and investigations

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- 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

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

# Management

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- 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.

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- 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

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- 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)

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- Stop HAART. Admit to ICU. IVI fluids and IVI vitamins. Septic work up - Antibiotics - sepsis may mimic or precipitate the lactic acidosis.
- Consider IVI NaHCO<sub>3</sub> 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

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

# Prevention

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- 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

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- 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.