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Hyperlactatemia and Lactic Acidosis During Antiretroviral Therapy: Causes, Management and Possible Ætiologies

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Abstract

Nucleoside analogs represent key components of the antiretroviral combinations used to manage HIV infection. Lactic acidosis represents a rare but clinically important and potentially fatal manifestation of NRTI toxicity. The proposed mechanism for this adverse effect is suggested to be via inhibition of mitochondrial DNA polymerase gamma. Depletion of mitochondrial DNA during chronic NRTI therapy may lead to cellular respiratory dysfunction hence both increased production and decreased clearance of lactate. However, NRTI therapy may represent only one of many contributors to lactic acidosis. The development of acidosis may be better seen as a symptom of underlying disorders rather than a disease in itself. In normal conditions the cytosolic (or 'anærobic') metabolism of glucose does not produce hydrogen ions (H^+). Lactic acidosis is likely only to occur when increases in production and defects in clearance of H+ ions is present, this most likely to be when the mitochondrial function of oxidative phosphorylation is disturbed.

Healthy individuals have circulating levels of lactate but maintain normal blood pH. Lactate levels may rise during periods of increased energy needs (such as exercise, hypermetabolic states), hypoxic or hypoperfused states (cardiac, respiratory disease, haemoglobin disorders) when cellular lactate release is increased (such as hyperinsulinæmic states) or when the key tissues involved in clearance (liver, kidneys) dysfunction. However, raised lactate (hyperlactatæmia) does not inevitably lead to acidosis. Indeed, recent surveys of individuals on NRTI therapy indicate hyperlactatæmia to be a relatively common event occurring episodically in 10-20% of individuals whereas acidosis remains rare at less than 0.4% per treatment year. Whilst the treatment of lactic acidosis requires immediate therapy discontinuation and additional supportive measures, the management of hyperlactatæmia initially only requires remeasurement of lactate under controlled resting conditions and careful patient observation.

Key words

Lactil acidosis. Hyperlactatemia. Nucleoside analogs.

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Introduction

Lactic acidosis represents a rare complication of antiretroviral therapy but a common challenge in critical care medicine. Lactic acidosis with or without hepatic steatosis is the most serious presentation of NRTI toxicity. It has been reported during therapy with all NRTIs.

Lactic acidosis is typically classified as types A and B[1]. Type A lactic acidosis occurs when the cells must generate adenosine triphosphate (ATP) without oxygen, a situation usually related to poor tissue oxygenation accompanying, for example hypovolæmic shock, hæmorrhage, circulatory or pulmonary disease and hæmoglobin disorders. Type B is secondary to drugs, toxins or diseases that do not cause poor tissue oxygenation. The key reasons for this differentiation relates to differences in treatment approaches.

Figure 1 shows the fates of pyruvate, the key substrate for cellular energy (in the form of ATP) production. In normal conditions, the majority of cellular energy needs are satisfied via metabolism of pyruvate in Krebs cycle in the mitochondria. This process requires oxygen and produces as by-products carbon dioxide (CO_2) and water (H_2O). An additional small quantity of ATP is derived by the cytosolic (or anærobic) cleavage of pyruvate, producing lactate and water as by-products. Approximately 1400 mmol of lactate is produced daily. Of note, there is no net production of hydrogen ions (H^+) in this process, no production of 'acid'[2]. Hyperlactatæmia occurs when either increased production, increased cellular release of lactate or decreased utilization of lactate occurs and is not, therefore, always accompanied by or a prelude to acidosis.

The source of H^+ key to the development of acidosis is the hydrolysis of ATP to ADP[3]. In normal circumstances this H^+ is rapidly reutilised in the mitochondria-located oxidative phosphorylation process. Thus, for acidosis to occur, oxidative metabolism must be impaired. In the case of lactic acidosis, the acidosis is accompanied by raised lactate. This is a readily understood accompaniment as, firstly, impaired oxidative metabolism will mean more cellular energy requirements will be met by the cytosolic metabolism of glucose, hence producing more lactate, and secondly, the clearance of lactate through its conversion back to pyruvate hence back to glucose (gluconeogenesis) in the Cori cycle is ATP dependent. If the cell is energy deficient this conversion cannot occur. As the primary site of lactate clearance and gluconeogenesis is the liver, it is not surprising that liver disease or dysfunction are commonly present in persons developing lactic acidosis[4]. In both type A and B lactic acidosis it is thought that both overproduction and underutilization of lactate are present albeit to varying degrees[5].

This review will discuss the possible mechanisms, occurrence, statistical associates or possible risk factors and management of hyperlactatæmia and lactic acidosis during antiretroviral NRTI therapy.

Diagnostic criteria

Laboratory upper limits of normal (based on standard deviations) for lactate are generally 2-2.5 mmol/l. Lactic acidosis is rarely seen in individuals with lactate levels below 5 mmol/l. Values of lactate between 2-5 mmol/l are of no established clinical significance. Additionally, acidosis requires a pH value below 7.35[6]. Lactic acidosis is accompanied

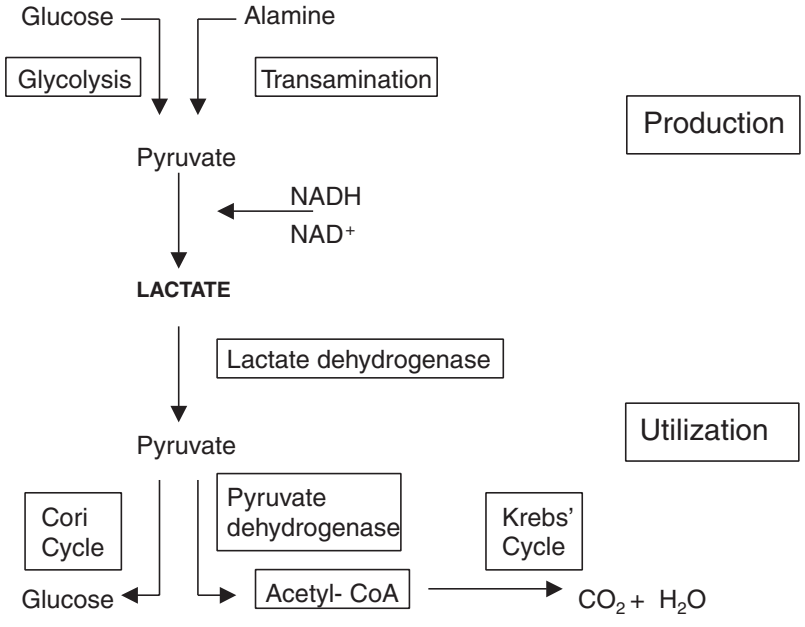

Figure 1. *The production and utilization of lactate and the fates of pyruvate.*

by a broad anion gap [generally calculated as (sodium plus potassium) minus (chloride plus bicarbonate)].

Lactic acidosis and NRTIs

During a development study for the fluorinated thymidine analogue fialuridine (FIAU) for Hepatitis B virus infection, 7 of 15 treated patients developed severe hepatotoxicity and lactic acidosis, with 3 patients showing milder changes. Subsequently, 5 participants died and 2 patients survived after liver transplantation. Pancreatitis, neuropathy, and myopathy often accompanied the syndrome. The liver appeared to be most substantially affected with liver histology showing macro- and microvesicular steatosis and abnormal mitochondria. The problem had not been predicted from animal or *in vitro* studies[7]. This presentation is similar to the presentation of lactic acidosis with antiretroviral NRTIs, viz. the acidosis is typically accompanied by liver dysfunction and often dysfunction in other tissues. Lactic acidosis represents proof that antiretroviral NRTIs can (at least rarely) cause disease probably via toxicity to hepatic mitochondria. There is clearly mitochondrial dysfunction in these individuals as diminished oxidative phosphorylation and hence diminished acid clearance are required for acidosis to occur.

However, FIAU may be more likely to trigger mitochondrial dysfunction than antiretroviral thymidine analogs for two reasons. Firstly, it is not an obligate DNA chain terminator hence may trigger high rates of mitochondrial DNA damage, which persists through mitochondrial division. Secondly, it is preferentially activated by thymidine kinase (TK)-2 located within mitochondria relative to the cytosolic, cell cycle dependent TK-1. The converse is true for AZT and d4T. This may explain why mitochondrial toxicity, almost invariably accompanied by lactic acidosis, was common with FIAU but remains rare with antiretroviral NRTIs[8].

Lactic acidosis has been reported in persons receiving both single- and dual-NRTI regimens including combinations of AZT or d4T with ddI, ddC, or 3TC. Differences in the relative incidence of lactic acidosis between different agents or different combinations have not been established. Lactic acidosis remains a rare problem with an annual incidence of <0.5% of treated individuals.

Several cohorts have evaluated the incidence although definitions of lactic acidosis have varied between groups. One observational cohort study of 1836 patients during 5 years estimated the incidence of nucleoside-related hepatomegaly and steatosis at 1.3 (95% confidence intervals 0.2-4.5) per 1000 person-years of therapy[9]. However, these estimates are derived from the monotherapy era. More recent estimates in HAART treated patients are around 3.9/1000 person years[10] although 'symptomatic hyperlactatemia' and lactic acidosis may occur as commonly as 13.6-14.5/1000 patient years[11,12]. The possible increase in risk in the HAART era may relate several factors including the greater effects of two (or more) nucleosides, the longer duration of continuous therapy, the impact of concomitant therapies (particularly on hepatic function) and the impact of drug related lipid and insulin disturbances (on hepatic steatosis and lactate release).

The US Food and Drug Administration (FDA) has reported on spontaneous reports of 46 episodes of lactic acidosis during single-NRTI treatment and 60 episodes during dual-NRTI treatment. Among those in the dual-therapy group, 36/60 (60%) were receiving d4T/3TC, 9/60 (15%) were on ddI/d4T, 7/60 (12%) were on 3TC/AZT, 7/60 (12%) were receiving ddI/AZT, and 1/60 (2%) were on d4T/AZT. Since d4T/3TC is the most widely used NRTI combination, it is possible that the greater number of reports involving these agents simply reflects the relatively more common use of these drugs. Deaths were noted to be more common among women, hepatitis co-infected and heavier patients[13]. A clinical cohort which recently reported 9 individuals with severe hyperlactatæmia (>5 mmol/l) including 4 persons with acidosis noted that women and the combination of ddI/d4T was over represented relative to the total cohort although acidosis was also seen with 3TC/AZT and 3TC/d4T. Of interest, all 4 individuals with lactic acidosis had concurrent infections at the time of presentation. Earlier lactate samples available in 6 patients indicated lactate had been above 2.5 mmol/l in the recent past in 5[14]. In another clinical cohort of 349 HIV-infected patients followed over approximately 18 months, 2 of 5 episodes of severe hyperlactatæmia occurred in persons *not* on ART (one secondary to malignancy and multi-system failure, one consequent to multiple HIV-related infections and cardiomyopathy). A third episode was in a poorly adherent individual with lactic acidosis thought to be triggered by alcohol abuse. Of the individuals thought to have NRTI related lactic acidosis, one had had lactate values <2 mmol/l on 2 occasions in the previous 5 months and the other had been stable on NRTI therapy for I year[10]. These data are consistent with many (but not all) previous anecdotes of individuals developing lactic acidosis: individuals are well and stable on therapy before suddenly developing lactic acidosis. This suggests an additional trigger for the development of lactic acidosis may be needed.

Of note, metformin-related lactic acidosis may also require additional triggers to occur. Suggested triggers or risk factors for metformin related lactic acidosis include renal impairment, heart failure, respiratory disease, and liver dysfunction[5,15]. Indeed, reports of lactic acidosis with this agent are exceedingly rare in the absence of additional disease complications or additional triggers. As metformin is a mitochondrial toxin[16] it may be seen as a model for NRTI-related lactic acidosis. If this is the case, we may be able pre-identify may individuals at risk of lactic acidosis and endeavour to limit NRTI exposure particularly during periods of increased risk.

Lactic acidosis most commonly occurs in persons on prolonged (>6 months) therapy, although there may be additional risk factors. In particular,

initial reports were most often of women with factors such as obesity and HBV or HCV co-infection and advanced HIV disease often being present[13]. However, lactic acidosis has now been reported across the range of patients infected with HIV. Additionally, transient, non-fatal lactic acidosis has been reported in neonates receiving prophylactic AZT or AZT/3TC therapy[13,17].

Presentation and management of lactic acidosis in persons on antiretroviral therapy

The onset of lactic acidosis may be either abrupt or insidious. Initial symptoms often include nausea, vomiting, and abdominal pain although in more insidious cases fatigue and weight loss may predominate. A tender enlarged liver may be palpable. Subsequently, shortness of breath, tachypnea and hyperventilation, liver and/or renal failure, clotting abnormalities, seizures, cardiac arrhythmia, and death ensue. Biochemical abnormalities include elevated lactate and lactate:pyruvate ratio, acidosis with pH <7.35, low bicarbonate, widened anion gap, elevated lactate dehydrogenase and often (but not invariably) elevated hepatic transaminases, and creatinine kinase. Histologic examination of the liver may reveal diffuse microvesicular steatosis with slightly enlarged mitochondria.

Management of lactic acidosis involves recognition and removal of the cause(s) and supportive therapy, and correction of the biochemical abnormalities. In persons on antiretroviral therapy this will include immediate cessation of antiretroviral therapy and any additional potentially contributory drugs. Additionally, a search for additional triggers of lactic acidosis, such as sepsis, malignancy, hæmoglobin transfer disorders, cardiac or respiratory disease, etc., should be made.

Supportive management is likely to include admission to an intensive care unit, intravenous fluids to minimise risk of hypervolæmia, oxygen and if necessary augmentation of cardiac function and treatment of sepsis. Approaches used in critical care medicine include administration of bicarbonate either intraperitonelly or via haemofiltration, carbicarb solution, and the pyruvate dehydrogenase stimulant dichloracetic acid (DCA)[5]. Whilst DCA reduces lactate, a randomised study in type A lactic acidosis did not demonstrate as survival benefit[18]. Use of intravenous bicarbonate is not popular and may be risky[19]. Use of thiamine (vitamin B_1) is appropriate if alcohol-related triggering of lactic acidosis is thought likely. In metformin-related lactic acidosis insulin is required[5].

Additional agents that have been suggested as adjuncts to management of NRTI-related lactic acidosis include administration of either oral or intravenous riboflavin (vitamin B_2)[20,21], carnitine and ubiquinone or coenzyme Q-10[22]. Riboflavin has been associated with possible benefit in some cases, although it is unclear from these reports if recovery had not already begun when riboflavin was introduced[20, 21].

The prognosis of clinically apparent lactic acidosis appears poor. Of cases reported to the FDA, 56% were fatal[13]. Other short series have indicated a 100% fatality rate[22,23] although in other series 1 death in 102 patients with lactate values above 2.5 mmol/l was reported[14] and 10/11 patients with hyperlactemia (definition not provided, mean 4.42 mmol/L) recovered[24]. The level of lactate and severity of acidosis appear the key issues in prognosis in critical care medicine: the higher the lactate, the more acidotic the patient the worse the prognosis[25]. This does not mean that sustained support should not be considered in individuals with high lactates and severe acidosis. For example, when associated with metformin use, risk of death appears to be associated with the presence of other hypoxic disease or underlying ill health rather than lactate levels[5]. This may also be the situation with HIV where risk factors such as obesity, hepatitis co-infection and advanced HIV infection have been suggested from reports of (mostly fatal) cases reported to the FDA[13].

Hyperlactatæmia: a separate syndrome or part of a spectrum?

Raised lactate may occur secondary to increased production, increased release or reduced clearance or utilization of lactate. It remains to be fully established to what extent each of these potential contributors are involved in hyperlactaemia, although reduced hepatic clearance looks most likely to be critical. Clearly, elevated lactate is relatively common (8-18.3% above 2-2.5 mmol/l in cross-section and/or partially longitudinal studies) whereas lactic acidosis is rare (0.3-0.4% per patient year).

Several possible explanations arise for this difference. Firstly, elevated lactate may be related to sampling error either due to recent patient activity, tourniquet use or delayed sample processing. The largest reported studies on hyperlactatemia which have included cohorts of untreated individuals find that the range of lactate values for these patients lie below 2.5 mmol/l (usually a mean around 1 mmol/l) and have described techniques to limit sampling error.

Patients treated for HIV infection may have increased cellular energy requirements. Both elevated basal lipolysis and increased fat turnover[26] and elevated endogenous glucose production and glucose turnover[27] have been reported. Lipid[28] and glucose oxidation[27] appears normal suggesting adequate adipocyte and myocyte mitochondrial function. However, as adipocytes have limited mitochondrial reserve the increase energy needs may be provided by cytosolic pyruvate metabolism, leading to lactate release. This explanation is unlikely as high lactate may be seen even in individuals with low fat mass and without metabolic or morphologic manifestations.

More possible is that adipocytes and myocytes are releasing lactate into the systemic circulation more readily. Persons on antiretrovirals for prolonged periods commonly have metabolic disturbances including hyperinsulinaemia and glucose intolerance with hyperglycaemia. Both hyperinsulinaemia and hyperglycaemia stimulate increase lactate release from adipocytes *in vivo*[29]. This effect of

insulin is also observed in skeletal muscle *in vivo* probably by activating Na^+-K^+-ATPase[30] and thus may stimulate increased lactate release from other tissues. Again, however, hyperinsulinæmia does not appear necessary for hyperlactatemia in treated patients.

Most likely, diminished lactate clearance is likely to be critical to lactate levels. Reduced clearance of lactate generally requires hepatic mitochondrial dysfunction. Hyperlactatæmia is not, however, an invariable accompaniment of liver failure as extrahepatic tissues such as the kidney and muscle may compensate[5]. Patients with HIV infection may have several reasons for diminished hepatic clearance of lactate: NRTI effects on mitochondria, dyslipæmia and insulin resistance contributing to steatosis, direct toxic effects of some agents (e.g. nevirapine), alcohol use, additional concomitant therapy (particularly NSAIDs, valproate, metformin) and hepatitis B or C co-infection.

In vitro cultures of single NRTIs with a human hepatocyte cell line (HepG2) have provided evidence for a number of mitochondrial defects with AZT, ddC, and ddI but not d4T and 3TC. However, only AZT induced a marked rise in lactic acid levels. Only in mitochondria isolated from AZT (50 μM)-treated cells was significant inhibition of cytochrome c oxidase and citrate synthase found. Additionally, whilst AZT, d4T, and 3TC did not affect the synthesis of the 11 polypeptides encoded by mitochondrial DNA, ddC caused 70% reduction of total polypeptide content and ddI reduced by 43% the total content of 8 polypeptides (including NADH dehydrogenase subunits 1, 2, 4, and 5, cytochrome c oxidase subunits I to III, and cytochrome b) (Table I). The authors hypothesized that in hepatocytes the reserve capacity for mitochondrial respiration is such that inhibition of respiratory enzymes is unlikely to become critical unless an additional insult was present[31].

Amongst drugs some but not all cross-sectional studies have found associations with d4T and higher lactate levels on therapy. The problem with analyses of a mixture of patients receiving different lines of therapy lies in the difficulty in adjusting for the duration of past NRTI exposure and the treatment sequence most commonly used (AZT first, followed by d4T second). Thus, individuals who are receiving d4T may have both a longer duration of antiretroviral exposure (as mentioned for the Western Australian cohort[10]) and a proportion of these individuals may be receiving d4T due to intolerance of AZT. As AZT intolerance is potentially related to mitochondrial toxicity, the d4T population may be at greater risk of having lactate elevations by the selection process that has led them to discontinue their initial AZT therapy. These data should therefore be interpreted with caution.

The Western Australian cohort study[10] presented data on 349 individuals, in whom 1,379 lactate measurements were drawn between January 1999 and June 2000. During the observation period, 65% of individuals had a lactate above 1.5 with 18.3% with at least one value above 2.5 and 5.7% of individuals had at least one value above 3.5 mmol/l. None of these individuals went on to develop clinical disease. Across the population, lactate levels in antiretroviral therapy *naïve* individuals were 1.34 mmol/l, with AZT-based regimens 1.45 mmol/l and with d4T-based combinations 1.65 mmol/l, these differences being significant by ANOVA. The clinical relevance of these tiny differences, if any, is not apparent from these data. No differences were reported between 3TC and ddI use or between the choice of PI versus NNRTI.

In an observational cohort of 871 antiretroviral treated patients from France, 14 cases of symptomatic hyperlactatemia, were recognized during 18 months, an incidence of 0.8% per annum. All patients who developed hyperlactemia were receiving d4T. In the subset of 299 patients treated with d4T/ddI, the incidence rose to 1.56%[24].

The largest cross-sectional study reported to date looked at 1,239 individuals who had been receiving antiretroviral therapy for at least 4 months and an additional 253 individuals who had never received antiretroviral therapy. Of the 1,239 who had at least one lactate sample, 8.7% had a serum lactate level greater than or equal to 2.5 mmol/l with 9 (0.8%) of individuals above 5 mmol/l, a level considered severe. High lactate was observed in similar frequency with male and female patients and duration of therapy was similar between those individuals with normal and raised lactate values. Overall the median lactate levels for the population of 1,239 treated patients were 1.4 mmol/l and

Table I. In vitro *studies of effects of NRTIs on hepatocyte mitochondria*[31]

	HepG2 Cell Response				
Effect	**AZT**	**ddC**	**d4T**	**ddI**	**3TC**
Increased lactic acid levels	++	+	–	+	–
Mitochondrial morphologic changes	Enlarged mitochondria	Loss of cristae	–	Loss of cristae	–
Inhibition of mitochondrial polypeptides	–	+++	–	++	–
Inhibition of COX and citrate synthase	+	–	ND	ND	ND

amongst the untreated individuals 1.1 mmol/l 5 untreated individuals had lactate values above 2.5 mmol/l on a single occasion with one individual having elevated lactate on 2 consecutive occasions (in both cases <3 mmol/l). Raised lactate had a poor (40%) predictive value for future raised lactate, however, individuals who went on to have severe hyperlactatæmia or acidosis generally had modest lactate elevations in the weeks or months prior to the severe event. Regarding the whole population, regimens containing ddI appeared to have an increased relative hazard of a raised lactate whereas those regimens that contained ABC appeared to have a significantly diminished relative hazard of hyperlactataemia. Rates of hyperlactataemia where highest in individuals receiving the combination of d4T/ddI (17%). The hazard of a high lactate relative to d4T/ddI was significantly lower in individuals receiving the combination of ABC/3TC or d4T/3TC. No significant differences between the relative hazard of hyperlactataemia on d4T/ddI were observed with combinations of AZT/ddI or AZT/3TC. Overall and in a subset of 312 individual on first line therapy, rates of hyperlactatæmia were similar when d4T was compared with AZT, the incidence in both groups being dependent on whether combined with ddI or 3TC. These data all suggest that ddI use but not thymidine analog choice may be a relevant risk for high lactate. Associations with d4T in previous studies may relate to the relatively more common use of this agent with ddI. This association with ddI rather than d4T would be consistent with the effects of these drugs on hepatocytes *in vitro*[31].

Additionally, associations with biochemical parameters were observed with hyperlactataemia. In a multivariate model, hyperlactataemia was associated with higher ALT levels and higher glucose levels although the median values were not outside of the normal range. Additionally, hyperlactataemia was associated with a wider anion gap. Individuals with an anion gap of 12-18 had a 4.9-fold greater chance of hyperlactataemia than those with an anion gap of less than 12. Furthermore, individuals with an anion gap of greater than 18 had an 8-fold higher chance of having an elevated lactate value than those individuals with an anion gap of less than 12. These data raise the possibility that, at least for some individuals, elevated lactates may be a reflection of a shift in acid base homeostasis. However, only 4 events of lactic acidosis were reported in this population[14].

Overall, these data suggest that lactate may exist in a spectrum from normal through mild to moderate elevation or 'compensated' hyperlactatæmia to severe and often 'decompensated' hyperlactatæmia and acidosis. The risks for shifting from normal to raised but compensated hyperlactatæmia may include duration of NRTI therapy, ddI use (at least relative to 3TC or ABC with a thymidine analog), hyperglycæmia and transaminitis. Decompensation may require additional triggers including respiratory or other intercurrent infection, alcohol bingeing, or introduction of additional drugs.

Summary

Patients receiving NRTI therapy are at risk of lactic acidosis. This event may be preceded by asymptomatic or minimally symptomatic hyperlactatæmia and may require additional triggers such as infection, cardiac or respiratory problems or the introduction of additional toxic agents. Commonly, hepatic disease including hepatitis B or C co-infection may be present. Additionally, female patients may be at greater risk. Amongst drug combinations, ddI/d4T appears over represented in recent case-cohort series with data on hyperlactatemia implicating ddI rather than d4T as the agent associated with risk. Higher lactate values on therapy with d4T observed in some cohorts are likely to be a reflection of the more common association of d4T, relative to AZT, with ddI. Screening of lactate in asymptomatic individuals has not be demonstrated to be beneficial although physicians should consider lactate evaluation in individuals presenting with fatigue, weight loss or abdominal pain as well as more acute symptoms. The interpretation of a lactate value between 2.5 and 5 mmol/l is not currently known and should prompt carefully re-sampling and monitoring of the patient. Individuals with severe lactate elevation (>5 mmol/l) should be evaluated with arterial blood gases to assess blood pH and should stop antiretroviral therapy promptly. Lactic acidosis has a range of other causations including cardiac, respiratory and haemoglobin disorders, as well as sepsis, alcohol bingeing and other drugs. These problems should also be ruled out in individuals presenting on NRTIs with lactic acidosis.

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