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Lactic acidemia in human immunodeficiency virus-uninfected infants exposed to perinatal antiretroviral therapy

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Objective. **To investigate potential mitochondrial toxicity in HIV-uninfected infants exposed to highly active antiretroviral therapy (HAART) *in utero* and/or neonatal zidovudine.**

Design. **A prospective observational study performed in a tertiary referral center for HIV-infected women and their infants and children.**

Methods. **Plasma lactate was measured repeatedly during the first 6 months of life in a consecutive cohort of infants exposed to HAART *in utero* and/or neonatal zidovudine. Maternal CD4, HIV RNA concentration, antiretroviral and substance use histories, mode of delivery, infant gender, cord pH, Apgar score and birth weight were collected.**

Results. **The plasma lactate was above normal on at least 1 occasion in 35 of 38 (92%) infants and reached levels ≥5 mmol/l in 10 (26%) infants. Overall 78 of 117 (68%) lactate measurements were elevated, with 11 (10%) in the serious (≥5 mmol/l) range. None of the infants received antiretrovirals beyond 6 weeks, yet elevated lactates persisted up to age 6 months. Two infants had reversible symptoms consistent with those of lactic acidemia. No association was found between the infant peak lactate and the type of therapy during pregnancy, its duration or maternal substance use.**

Conclusion. **Transient lactic acidemia was observed in the majority of HIV uninfected infants**

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exposed to HAART *in utero* and/or zidovudine neonatally. We hypothesize that the hyperlactatemia is a consequence of persistent, primarily subclinical, mitochondrial toxicity from the transplacental and neonatal exposure to antiretrovirals and of impaired hepatic lactate clearance. Although the clinical relevance of our findings is unknown, we recommend lactate monitoring in these infants, considering discontinuation of neonatal zidovudine in symptomatic infants with lactate ≥5 mmol/l and careful long term follow up of these children.

INTRODUCTION

Current guidelines for management of HIV-positive pregnant women include use of highly active antiretroviral therapy (HAART) during pregnancy, with the goal of achieving complete plasma viral suppression before delivery.[1, 2] HAART consists of a combination of at least three drugs, usually two nucleoside transcriptase inhibitors (NRTIs) and either a non-NRTI or a protease inhibitor. Recommendations also include the administration of intravenous zidovudine (ZDV) to the woman during labor and oral ZDV to the infant for the first 6 weeks of life. This type of management approach has resulted in decrease in rates of vertical HIV transmission, from ~25% in the absence of any intervention to <1%.[3–5]

Although the use of HAART in pregnancy has significantly decreased rates of vertical transmission, questions remain regarding the safety of these therapies and their potential impact on the uninfected infant. The NRTIs inhibit mitochondrial DNA polymerase gamma, thereby altering mitochondrial replication and inducing mitochondrial dysfunction and elevation of plasma lactic acid.[6, 7] Mitochondrial toxicity with serious hyperlactatemia can lead to life-threatening metabolic acidosis.[8]

Giaquinto et al.[9] reported lactic acid plasma concentrations of >2.5 mmol/l in 17 of 20 infants exposed to perinatal antiretroviral therapy. Of the 17 infants,13 were exposed *in utero* to single or dual NRTI but not HAART. Given that the potential impact of exposure to combination antiretroviral therapy may be quite different from that of exposure to single or dual therapy, data are urgently needed in those infants perinatally exposed to multiple antiretroviral drugs.

The objective of this observational study was to investigate potential mitochondrial toxicity in uninfected infants exposed *in utero* to HAART and neonatal ZDV by determining plasma lactate levels during the first 6 months of life.

MATERIALS AND METHODS

Setting. This was a prospective, observational study performed in a tertiary care multidisciplinary clinic for HIV-infected women and their infected or uninfected children, located in the Children's and Women's Health Centre of British Columbia, Vancouver, Canada.

Patients. A sample of consecutive infants born between December 1999 and June 2001 to HIV-infected women who were treated with at least three antiretroviral agents during pregnancy and/or intravenous ZDV during delivery and the neonatal period were included in this study. Two to six blood specimens were obtained between 1 week and 6 months of age from all infants during routine clinic visits.

Patient care. HIV-infected pregnant women were offered HAART according to British Columbia and Canadian consensus guidelines,[1] which are consistent with US Centers for Disease Control and Prevention guidelines.[2] Women received triple combination therapy including two NRTIs and either a non-NRTI or a protease inhibitor. HIV-infected women who began therapy before their pregnancy were offered continuation of antiretroviral therapy throughout the pregnancy. In women with CD4 cell counts >300/mm^3, therapy was deferred until after screening obstetric ultrasound was performed at or near 18 weeks of gestation. The women were closely monitored with CD4 counts, HIV RNA concentrations, ultrasound and toxicity screening throughout pregnancy at 4- to 6-week intervals. Plasma lactate was measured in the pregnant women close to term. A cesarean section was performed if complete viral suppression was not achieved at the end of the pregnancy and for usual obstetric indications. Intravenous ZDV was administered during delivery, and oral ZDV started in the infant on the first day of life and continued for 6 weeks postdelivery, per the protocol in AIDS Clinical Trials Group 076.[10] If complete viral suppression was not achieved at the end of the pregnancy, an oral dose of nevirapine was given to the mother during delivery and to the infant after birth. Infants were examined at 2 weeks and 1, 2, 3, 4 and 6 months of life. Infant HIV PCR, hematologic counts, liver transaminases and plasma lactates were monitored at each clinic visit.

Variable definition and laboratory methods. HIV PCR tests were performed at the Province reference laboratory at the British Columbia Centre for Disease Control using Roche HIV-1 DNA PCR assays. Infants were defined as HIV-uninfected if they had at least two negative HIV PCR tests on separate occasions after the age of 1 month. Infant data collected from the records included gender, cord pH, Apgar scores and birth weight.

Infant venous lactate samples were collected at least 1 min after releasing the tourniquet to minimize the accumulation of lactate in the arm. Blood was collected in sodium fluoride and potassium oxalate tubes (gray top), transported on ice to the laboratory and processed within 45 min by a colorimetric method (Vitros 950;

Ortho). A lactate concentration of >2.1 mmol/l was considered abnormal, and a lactate concentration of ≥5 mmol/l was considered in the serious range.[11]

Maternal CD4 counts were measured using flow cytometry at the immunology laboratory of the tertiary center at Children's and Women's Health Centre of British Columbia.

Maternal plasma HIV RNA concentrations were determined at the University of British Columbia Diagnostic Virology and Reference Laboratory at Saint Paul's Hospital in Vancouver, with the Roche HIV-1 RNA monitor test. The threshold for the detection of HIV RNA concentration using the ultrasensitive method was 50 copies/ml.

Maternal data included type and timing of antiretroviral therapy and substance use during pregnancy (patient self-report and urine test at delivery), CD4, HIV RNA concentration, plasma lactate and mode of delivery.

Ethics. This study was approved by the Clinical Research Ethics Board, Faculty of Medicine, University of British Columbia (Approval No. C01-0535) and by the Research Review Committee of Children's and Women's Health Centre of British Columbia (Approval No. W02-0176), both in Vancouver, Canada.

Statistics. Data were analyzed with the use of Statistical Solutions Program TM and Microsoft Excel TM. Pearson chi squares were conducted to compare event rates within the cohort. Yates correction was not used. Fisher's exact test was used when expected variables of cell sizes were <5. Odds ratios with 95% confidence intervals (CI) were calculated. Means with standard deviations were calculated, and unpaired *t* tests were used to compare independent means. All *t* tests were two sided, and a *P* value of <0.05 was defined as significant.

RESULTS

Among 38 infants (21 girls and 17 boys, including 3 pairs of twins), 35 were exposed to triple antiretroviral therapy (ART) *in utero*, all were exposed to ZDV during delivery and the neonatal period (mean, 5.4 weeks), and 9 also received nevirapine at delivery. All 38 infants had 2 or more negative HIV PCR tests between 1 and 6 months of age and were confirmed HIV-uninfected. The mean duration of HAART during pregnancy was 17 weeks (range, 2 to 38). Before delivery the mean maternal CD4 count was 520 cells/mm^3 (range, 10 to 1310), HIV RNA concentration was undetectable in 32 women, and mean maternal plasma lactate was 1.3 mmol/l (n = 26; range, 0.7 to 2.7).

Results of 117 infant plasma lactate measurements (median, 3 per infant) are shown in the Figure. Lactate was above normal (2.1 mmol/l) at least once in 35/38 (92%) infants, including in the three infants (one pair of twins) exposed to ART only during delivery and the neonatal period. In 25 (64%) infants, the peak values were mildly elevated (mean, 3.4 mmol/l; 95% CI 3.1 to 3.7; range, 2.2 to 4.9) and in 10 (26%) seriously elevated (mean, 6.1 mmol/l; 95% CI 5.5 to 6.7; range, 5.0 to 7.4).

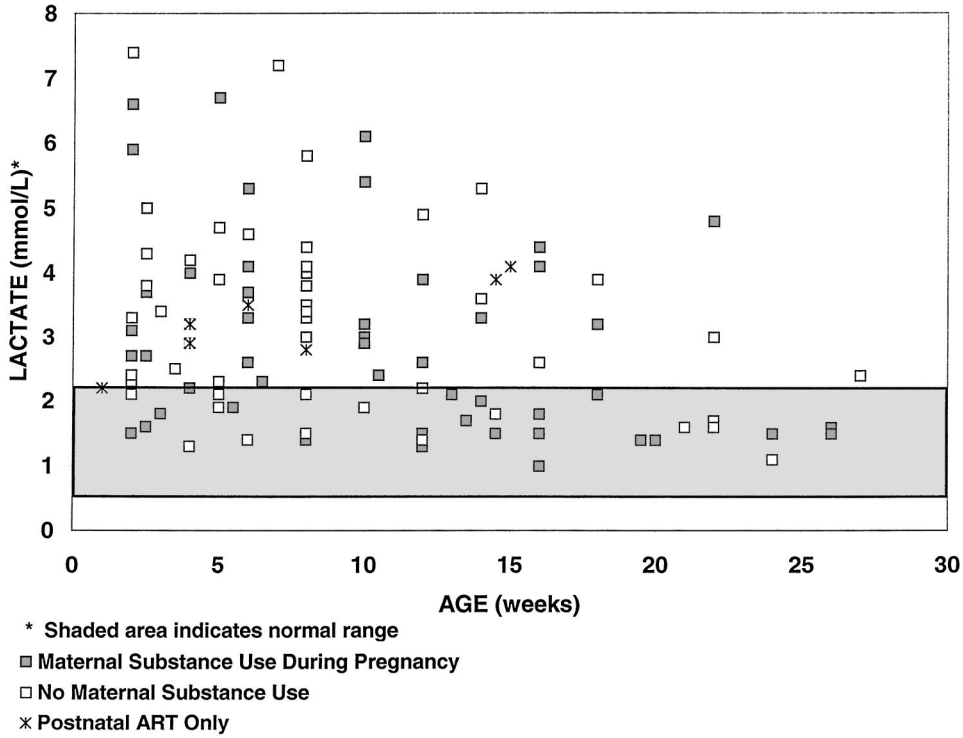

FIG. 1. Lactate measurements in 38 HIV-uninfected infants exposed to ART *in utero* and/or during the neonatal period.

Overall 78 (67%) of all lactate measurements were elevated, and 11 (10%) were in the serious range (≥5 mmol/l). In 33/38 infants, plasma lactate concentrations were available after 28 weeks of age; it had normalized in 31 of 33 (94%) and remained elevated in 2. In 5 of 38 infants, the last documented lactate before 28 weeks remained elevated.

Mean birth weight of the infants was 2993 g (range, 1480 to 4760 g; median, 2972 g). Mean cord pH ($n = 19$) was 7.26 (range, 6.99 to 7.33). The only very low cord pH (6.99) was after an emergency cesarean section for placental abruption. The Apgar scores for all infants varied between 6 and 9 at 1 min and 9 and 10 at 5 min. Liver transaminases were normal during the study period in all but 1 hepatitis C-infected infant.

Two neonates with plasma lactate >5 mmol/l at 2 weeks of age had recurrent vomiting and irritability. Oral ZDV was discontinued; symptoms resolved and lactate decreased to <4.2 mmol/l during a 2-week period in both infants. These infants had been exposed to triple antiretroviral therapy *in utero* (ZDV, lamivudine, nelfinavir for 17 weeks and didanosine, stavudine, indinavir for 37 weeks), and the first was also exposed to heroin, cocaine and methadone. The pregnancies were otherwise uncomplicated and both infants were delivered by elective cesarean section at 38 weeks gestational age. All the other infants remained asymptomatic, even with lactate concentrations as high as 7.4 mmol/l. In the infant with vertical hepatitis C virus infection, the lactate value reached a peak of 6.7 mmol/l at the age of 5 weeks and gradually decreased to normal at 20 weeks.

The highest plasma lactate reached in each infant (peak lactate) was compared with various maternal, delivery and infant factors (Table 1). No association was found between mean peak lactate and mode of delivery, gender, maternal CD4 count or duration of ART during pregnancy. The peak lactate could not be associated with maternal HIV RNA concentration, which was undetectable at the end of pregnancy in the majority of the mothers. There was no significant difference between infants exposed to nevirapine *vs.* protease inhibitor regimens, or stavudine and non-stavudine regimens. The mean peak lactate in infants coexposed to maternal substance use and antiretrovirals was not significantly different from that in infants not exposed to recreational drugs.

No risk factor was identified for peak lactate in the serious range (≥5 mmol/l) when odds ratios were analyzed for maternal CD4 count, duration or type of ART (Table 2).

DISCUSSION

In this study, hyperlactatemia was observed in 92% of 38 HIV-uninfected infants exposed to HAART *in utero* and/or ZDV during the neonatal period, with peak lactate values of >5 mmol/l in 26% of infants. Our findings contrast markedly with those found in normal infants not exposed to HAART, where the plasma lactate has been shown to be mildly elevated at the time of delivery, but rarely reaches levels of 5 mmol/ and returns to normal values within days, with an estimated half-life of 35 h.[12–20] In infants older than 1 week, normal adult plasma lactic acid levels are to be

TABLE 1. Peak plasma lactate concentration in 38 HIV-uninfected infants exposed to ART

Maternal/Obstetric/Infant Variables	Peak Plasma Lactate Concentration (mmol/l)				
	No. of infants	Mean	Range	95% CI	*P**
Mode of delivery					
Vaginal	14	3.6	1.6–7.2	2.6–4.6	0.29
Cesarean	24	4.2	1.4–7.4	3.6–4.8	
Gender					
Male	17	3.9	1.6–7.2	3.1–4.7	0.86
Female	21	4.0	1.4–7.4	3.3–4.7	
Maternal CD4 at delivery					
≤350 cells/mm^3	11	3.9	1.4–6.6	2.9–4.9	0.86
>350 cells/mm^3	27	4.0	1.6–7.4	3.4–4.6	
Duration of ART					
<20 wk	24	4.2	1.4–7.2	3.5–4.8	0.28
>20 wk	14	3.6	1.6–7.4	2.8–4.5	
In utero exposure to					
Nevirapine	23†	3.8	1.4–6.7	3.1–4.5	0.41
Protease inhibitor	12†‡	4.3	1.6–7.4	3.3–5.3	
In utero exposure to stavudine					
Yes	9	4.0	1.6–7.4	2.9–5.1	0.95
No	29	4.0	1.4–7.2	3.4–4.6	
In utero coexposure to recreational drugs§					
Yes	20	4.1	2.0–6.7	3.4–4.8	0.59
No	18	3.8	1.4–7.4	3.1–4.6	

* $P < 0.05$ determined significant.

† Total 35; 3 infants were not exposed to HAART *in utero.*

‡ The mothers of 3 infants in this group briefly took nevirapine; then treatment was changed to a PI.

§ Heroin, cocaine, opioid derivatives and/or methadone, with or without alcohol and cigarettes.

TABLE 2. Odds ratio of infant peak lactate ≥ 5 mmol/l

Maternal Variables	Infants with Peak Lactate ≥ 5 mmol/l				
	No.	%	Odds ratio	95% Cl	*P**
CD_4 count (/mm^3)					
≤350	2/11	18	0.53	(0.06–3.67)	0.75
>350	8/27	30			
Duration of ART					
<20 wk	7/24	29	1.51	(0.26–9.45)	0.89
≥20 wk	3/14	21			
Exposure to stavudine					
Yes	2/9	22	0.75	(0.09–5.48)	1.00
No	8/29	28			
Exposure to					
Nevirapine	6/23†	26	0.71	(0.12–4.14)	0.95
Protease inhibitor	4/12†	33			

* $P < 0.05$ determined significant.

† Total - 35; 3 infants were not exposed to HAART *in utero.*

expected, and the adult range of normal values can be used. Hyperlactatemia occurs in rare genetically acquired metabolic diseases as a result of mitochondrial dysfunction[21–24] and in extremely severe acute diseases with hypoxia and shock. The significant hyperlactatemia observed here in otherwise healthy infants exposed to perinatal antiretroviral therapy is a newly described phenomenon.

In HIV-infected adults and children receiving combination antiretroviral therapy, some of the most frequently observed effects of mitochondrial toxicity are myopathy, myelosuppression, pancreatitis, peripheral neuropathy and hepatic steatosis.[6, 7] The clinical effects vary according to the antiretroviral medication itself, the duration of therapy and the individual's susceptibility. Profound mitochondrial toxicity accompanied by lactic acidemia is not an uncommon finding in patients taking NRTI-containing regimens.[25–27] Brinkman[11] proposed discriminating plasma concentrations for the degree of hyperlactatemia: mild for a lactate of ≥2.1 to 5 mmol/l; and serious for a lactate of ≥5 mmol/l.

The potential for short or long term adverse effects related to mitochondrial toxicity in HAART-exposed uninfected infants is a concern. The most frequent early side effect in infants with perinatal exposure to ZDV monotherapy is transient anemia.[10] Long term follow-up of ZDV-exposed children has been reassuring to date in terms of growth and neurologic development,[28] except for a French report on 8 infants with possible mitochondrial toxicity after perinatal exposure to ZDV with or without lamivudine.[29] Two of the infants with severe encephalopathy died at ~1 year of age, 3 had neurologic symptoms and 3 were asymptomatic. In that study mitochondrial toxicity was diagnosed by tissue biopsies; plasma lactic acid was not measured. In a subsequent safety review of 223 deaths among >20 000 children born to HIV-infected women included in US cohorts, there were no deaths attributable to mitochondrial toxicity in children exposed to NRTIs during the perinatal period.[30] Similarly a review of neurologic events in relation to mitochondrial dysfunction in living children exposed to ZDV or lamivudine reported no clear cases of mitochondrial dysfunction.[31]

A number of factors can falsely increase the measured plasma lactate, including venostasis caused by the tourniquet, inappropriate handling of the specimens, muscular activity and nonfasting state.[32–34] Ideal collection conditions are difficult to achieve in young infants, but we minimized unwanted effects and believe that the elevated lactates were genuine. Furthermore the infants were their own controls, because normalization occurred in the majority of infants longitudinally. We recognize that our study could be enhanced by a control group of uninfected infants born to HIV-positive women and not exposed to antiretrovirals. However, such a group was not available in our setting for a longitudinal study.

Although infants received ZDV for a maximum of 6 weeks postnatally, elevated lactate concentrations persisted up to 6 months before returning to normal levels. These findings are consistent with those of Giaquinto,[9] who also reported slow normalization of lactates in antiretroviral exposed infants. A slow return to normal has also been observed in adults with hyperlactatemia after discontinuation of ART.[25] We hypothesize that the self-limiting hyperlactatemia is a consequence of persistent mitochondrial toxicity from the transplacental and/or neonatal exposure to antiretroviral drugs. As suggested by Brinkman,[11] both an increased production of lactate by the muscle mass and an impaired hepatic (and to a lesser extent, renal) clearance likely play a role in the persistence of the lactic acidemia. This occurs as a result of mitochondrial toxicity affecting different tissues, including the muscular and the hepatic tissues. One can hypothesize that the liver of the infant may be even more vulnerable to this toxicity during the first months of life.

The peak lactate in the infant was not associated

with the specific type of antiretroviral regimen or the duration of HAART during pregnancy. Stavudine has been incriminated in adult cases of lactic acidemia,[26, 35–37] but because hyperlactatemia was so generally observed in this study and stavudine was used in only 9 patients, we were unable to identify it as an independent risk. The sample size in this study was relatively small, and there is the possibility that significant relationships were not identified. Further investigation with larger sample size is needed regarding the relative risk of different antiretroviral drugs or combinations in the development of infant lactic acidemia.

More than one-half of the infants in this study were coexposed to HAART and substances like heroin, cocaine and methadone, with or without alcohol and tobacco. Published data are lacking regarding the possible toxic effect of these substances on lactate metabolism. In this limited sample there was no clear difference in the severity or duration of the hyperlactatemia in infants exposed to HAART alone *vs.* those coexposed to HAART and other substances. The possible role of coexposure to substance use during pregnancy must be clarified in larger studies.

The relative contributions of the antiretroviral agents transferred transplacentally *vs.* the oral ZDV taken by the infant are unknown. In this study elevated lactate values were also observed in three infants exposed to ART only during delivery and the neonatal period. All but one of the maternal plasma lactates measured at term were normal. The optimal duration of antiretroviral therapy in infants born to mothers with undetectable HIV RNA concentration at term also remains unknown. A number of studies investigating the efficacy of shorter antiretroviral regimens have been performed in developing countries, resulting in partial success in the prevention of vertical transmission.[38] As more and more infants will be exposed *in utero* to HAART, gaining a better understanding of the potential toxicities with the purpose of reducing the toxicity of the antiretroviral regimens becomes imperative.

The clinical relevance of our findings remains to be determined. Despite the high number of abnormal plasma lactate values, only two of the infants in our series had symptoms suggestive of lactic acidemia, which rapidly resolved on discontinuation of oral ZDV. Additionally none of our children has shown symptoms of mitochondrial toxicity during subsequent follow-up up to 36 months. Plasma lactate is an indirect marker of mitochondrial function, and we believe it will be important in the future to compare lactate levels with new assays for the evaluation of mitochondrial toxicity, such as mitochondrial DNA assays.[39]

In summary this study demonstrates that many HIV-uninfected infants exposed to HAART *in utero* and neonatal ZDV may have elevated plasma lactate levels (some in the "serious" range) during the first months of life. These findings suggest that mitochondrial damage may occur as a consequence of this antiretroviral exposure. However, it is important to recognize the immense and proven benefit of ART in pregnancy and the neonatal period for prevention of perinatal HIV transmission. The clinical relevance of our findings remains unknown, and HAART should continue to be recommended to all pregnant women. However, our findings indicate the importance of monitoring of plasma lactate in all infants taking antiretroviral therapy. We believe that consideration should be given to discontinuing medication in symptomatic infants with a lactate of >5 mmol/l. We also believe that our study reinforces the need for long term surveillance of these infants and for more study regarding the efficacy and toxicity of antiretroviral therapies in pregnancy and the neonate.

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