Hyperlactatemia in Human Immunodeficiency Virus–Uninfected Infants Who Are Exposed to Antiretrovirals

Antoni Noguera, MD*; Claudia Fortuny, MD, PhD*; Carmen Muñoz-Almagro, MD‡; Emilia Sanchez, MD, PhD§; M. Antonia Vilaseca, PhD‡; Rafael Artuch, MD, PhD‡; Jordi Pou, MD, PhD*; and Rafael Jimenez, MD, PhD*

ABSTRACT. *Objective.* **Exposure to nucleoside analogues in fetal or early life has been associated with rare clinically significant mitochondrial toxic effects, mainly neurologic symptoms. Lactate (LA) measurements have been used to monitor nucleoside-related mitochondrial toxicity. Our aim was to determine the prevalence, clinical evolution, and risk factors for hyperlactatemia in our cohort of human immunodeficiency virus (HIV)-uninfected children who were exposed to antiretrovirals.**

Methods. **We conducted a prospective observational study of 127 HIV-uninfected infants who were born to HIV-infected women. Clinical symptoms suggesting mitochondrial dysfunction were analyzed in routine follow-up, and LA and alanine plasma levels were obtained at 6 weeks, 3 months, 6 months, and 12 months in all patients. Elevated alanine levels, together with hyperlactatemia, suggest chronic mitochondrial injury.**

Results. **Most (85%) women received highly active antiretroviral therapy (HAART) during pregnancy (mean duration: 31 weeks) and zidovudine during labor (93%). Most (96%) children received zidovudine alone. Hyperlactatemia with hyperalaninemia was detected in 63 children in at least 1 of the measurements. Mean LA levels were significantly higher in children who were exposed to nucleoside analogue reverse transcriptase inhibitors than in control subjects (2.88 vs 1.61 at 6 weeks, 2.78 vs 1.49 at 3 months, 1.89 vs 1.39 at 6 months, and 1.71 vs 1.24 at 12 months; peak levels: 8.06, 10.1, 7.28, and 4.48 mmol/L, respectively). In 44 patients, LA levels progressed spontaneously to normality within the first year of life. Three girls presented a slight and self-limited delay in psychomotor development, with LA peak levels of 7.3, 4.0, and 4.6 mmol/L. Only the gestational use of didanosine was associated with a higher risk of hyperlactatemia.**

Conclusions. **In our series, almost half of the children (63 of 127) who were exposed to nucleoside analogues developed benign and self-limited hyperlactatemia. When symptomatic, nucleoside analogue–induced toxicity affected neurologic development.** *Pediatrics* **2004; 114:e598–e603. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-0955;** ***alanine, children, HAART, HIV infection, hyperlactatemia, mitochondria, vertical transmission.***

ABBREVIATIONS. HIV, human immunodeficiency virus; ARV, antiretroviral; NRTI, nucleoside analogue reverse transcriptase inhibitor; LA, lactate; HLA, hyperlactatemia; HCV, hepatitis C virus; HBV, hepatitis B virus; ZDV, zidovudine; HAART, highly active antiretroviral therapy; 3TC, lamivudine; d4T, stavudine; NVP, nevirapine; NFV, nelfinavir; ddI, didanosine.

Human immunodeficiency virus (HIV) vertical transmission rates have been dramatically reduced in developed countries thanks to antiretroviral (ARV) treatments, elective cesarean section, and refraining from breastfeeding.[1] The morbidity that ARV may cause in fetal and early life of HIV-uninfected children is still unclear, and thorough research of this condition is warranted.

Nucleoside analogue reverse transcriptase inhibitors (NRTIs) are included in most ARV regimens. These drugs inhibit both HIV reverse transcriptase and DNA polymerase γ, an essential protein for mitochondrial DNA replication in human cells.[2–4] Mitochondria are basic for the generation of adenosine triphosphate through oxidative phosphorylation. When this system is disturbed, an altered oxidoreduction status occurs, shifting the pyruvate/lactate (LA) equilibrium in the direction of LA; similarly, an increase in ketone bodies and alanine is observed.[5,6] Because mitochondria are ubiquitous, impaired oxidative phosphorylation may affect virtually all organ systems, giving rise to a variety of clinical syndromes.[5,7]

Inherited mitochondrial diseases may affect infants to different degrees: from a severe multisystemic illness that leads to death in some to an oligosymptomatic syndrome with nonspecific mild symptoms or signs that can easily be associated with other conditions such as prematurity, maternal drug addiction, acute fetal distress, or congenital infections.[5,7,8] The latter evolution is more likely to occur in the HIV-uninfected infant, considering that exposure to ARV does not exceed the age of 6 weeks and in light of the reassuring data from large observational studies.[9] Therefore, the identification of children who are affected by NRTI-induced mitochon-

From the *Infectious Diseases Unit, Pediatrics Department, Integrated Unit Hospital Sant Joan de Déu, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain; ‡Laboratory Department, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain; and §Catalan Agency for Health Technology Assessment and Research, Catalan Health Service, Department of Health and Social Security, Generalitat de Catalunya, Barcelona, Spain.
Accepted for publication Jun 8, 2004.
doi:10.1542/peds.2004-0955
This work was partially presented at the 10th Conference on Retrovirus and Opportunistic Infections; Feb 10–14, 2003; Boston, Massachusetts (abstract no. 777); and the 9th European AIDS Conference; Oct 25–29, 2003; Warsaw, Poland (abstract no. F 10/5).
Reprint requests to (C.F.) Servei de Pediatria, Hospital Sant Joan de Déu, Passeig Sant Joan de Déu 2, 08950 Esplugues (Barcelona), Spain. E-mail: cfortuny@hsjdbcn.org

drial toxicity has become a great challenge for pediatricians. Moreover, the potential for long-term adverse effects on a developing organism, especially regarding high-energy-requirement tissues (nervous system or muscle), remains unknown. Although sophisticated diagnostic procedures are often required to confirm a mitochondrial disease, blood LA levels have been used as a screening tool for mitochondrial dysfunction[5,8] despite its lack of specificity and its technical and physiologic variability.[10]

To date, reports concerning NRTI toxicity in children who are exposed perinatally to ARV are contradictory. Although large population-based studies have failed to demonstrate signs or symptoms suggesting mitochondrial injury in NRTI-exposed HIV-uninfected children,[9,11–13] other authors have reported rare severe neurologic damage consistent with mitochondrial dysfunction[14,15] and a higher risk of febrile seizures below the age of 18 months[16] in these otherwise healthy patients. The aim of our study was to determine the prevalence, clinical consequences, evolution, and risk factors for hyperlactatemia (HLA) in our cohort of HIV-uninfected infants who were exposed to ARV during gestation, labor, and/or the neonatal period.

METHODS

A prospective observational study was conducted between January 2000 and December 2002 in a tertiary care pediatric hospital in Barcelona. The study cohort consisted of all infants who were born to HIV-infected mothers and referred to our outpatient clinic by several maternity hospitals. Informed consent was obtained from their parents or legal guardians.

Demographic, clinical, and laboratory data were routinely collected on all of our patients. The variables that were relevant to this study included mother's age, third-trimester HIV-RNA viral load and CD4 T-cell count, type and timing of ARV therapy, and history of substance abuse during pregnancy; mother's hepatitis C virus (HCV) and hepatitis B virus (HBV) co-infection; mode of delivery; intrapartum use of zidovudine (ZDV); infant's gender, Apgar scores, gestational age, and birth weight; and vertical transmission of HIV, HBV, and/or HCV and exposure to ARV during the neonatal period.

A complete physical examination was performed, and height, weight, and head circumference were measured at every visit (at birth and at 15 days; 6 weeks; and 3, 6, and 12 months of life). Full blood picture and serum biochemistry, including venous blood gas, pH measurements, and liver enzyme tests, were obtained together with plasma proviral HIV-DNA (Amplicor HIV; Roche, Basel, Switzerland) and HIV-RNA load quantification (CA HIV-1 Monitor; Roche; limit of <50 copies/mL) at every visit.

Infants were eligible for the study when 2 negative results in HIV-DNA molecular tests were available, usually at birth and at the age of 2 weeks; had been exposed to ARV during gestation, labor, and/or the neonatal period; and did not present any other medical condition capable of raising plasma LA levels (eg, congenital heart defects, inborn errors of metabolism, prematurity). Ulterior HIV-DNA and/or HIV-RNA molecular tests were performed in all cases to confirm absence of HIV infection beyond the age of 4 months, in accordance with current guidelines.[17]

Deproteinized venous blood LA levels (normal range: 0.77–2.44 mmol/L until the age of 1 year[18]) were measured by a spectrometric procedure in a Cobas Fara II Analyzer (Roche) at 6 weeks and 3, 6, and 12 months of life. Because of great physiologic variability of LA levels, all samples not obtained under optimal conditions (previous rest for 15 minutes, avoiding tourniquets when possible, and immediate blood flowing after venipuncture) were excluded from the study. Samples were immediately placed on ice and assayed within 20 minutes. Whenever LA values were above the reference range, plasma alanine concentrations (reference range [mean ± SD]: 312 ± 78 μmol/L) were measured by ion exchange chromatography with ninhydrin detection in the same blood sample (Biochrom 20; Pharmacia, Biotech, Cambridge, United Kingdom). Chronic mitochondrial dysfunction leads to HLA and hyperalaninemia; therefore, ARV toxicity–related HLA was considered only when both LA and alanine concentrations were elevated; otherwise, these were regarded as transient HLA values as a result of blood drawing and excluded from the study as well. Finally, LA levels from infants who were exposed to ARV were compared with LA concentrations, age and gender adjusted, obtained from anonymous blood samples of children who were referred to our laboratory for presurgical routine blood analysis. Analytical procedures and normal gender- and age-matched concentrations for LA and alanine techniques were previously validated in our laboratory and have been reported elsewhere.[18,19]

Statistical Analysis

Patients were initially defined as HLA or non-HLA. Univariate assessment of risk factors for HLA was conducted using the χ^2 test for categorical variables and the t test for continuous variables. To measure further the independent association between the exposure to different NRTIs (weeks of exposure) and elevated LA concentrations, we used multiple logistic regression allowing for the repeated measures. Other statistical tests were used when appropriate. All tests were 2-tailed, and $P < .05$ was considered significant. Statistical analysis was performed with the SPSS 10.0 Program.

RESULTS

From January 2000 to December 2002, 132 children who were born to HIV-infected mothers were referred to our outpatient clinic. Five of them were excluded from the study because of HIV infection ($n = 1$), congenital heart defects ($n = 2$), and extreme prematurity ($n = 2$). The final cohort consisted of 127 children who were born to 121 HIV-infected mothers (including 6 sets of twins). Data regarding gestation, birth, and neonatal clinical variables are summarized in Table 1. The most frequently used highly active antiretroviral therapy (HAART) regimens during gestation were lamivudine (3TC) plus ZDV ($n = 51$) and stavudine (d4T) plus 3TC ($n = 40$), either with nevirapine (NVP, $n = 49$) or with nelfinavir (NFV, $n = 44$; Table 2). HIV infection was diagnosed in 7 mothers at labor. Most (96%) of the neonates received ZDV up to the age of 6 weeks, whereas 5 (4%) of them received ZDV, 3TC, and NVP because of intrapartum diagnoses of HIV infection in their mothers. Vertical transmission rate for HCV was 15% (8 infants of 54 HCV-infected mothers). No child was infected with HBV.

Overall, 292 plasma LA measurements were included in the study (Table 3). When compared with control subjects, LA from NRTI-exposed infants was higher at all ages ($P < .0001$) and showed a linear trend toward normalization with age that was also statistically significant (Fig 1). LA values were above normal at least once in 63 (49.6%) of 127 of our patients and, at the age of 1 year, 44 (70%) of 63 of those infants had normalized their LA concentrations, whereas 30% (19 of 63) still showed HLA. Among these, elevated LA values with hyperalaninemia at the age of 2 years (normal range: 0.66–1.88 mmol/L) were still observed in 3 children (range: 2.17–2.81 mmol/L). Seven patients were exposed to ARV only during labor and/or the neonatal period, and 2 of them developed asymptomatic HLA (LA peaks of 2.48 and 5.5 mmol/L at the age of 3 months) that had spontaneously normalized 3 months later.

The only independently HLA-associated factor by

TABLE 1. Clinical and Laboratory Data From HIV-Infected Mothers and Their HIV-Uninfected Newborns

Characteristic	
Mother's age, y	
Mean ± SD	30.8 ± 5.1
Median (range)	32 (17–42)
Substance abuse during pregnancy, *n* (%)	49 (40)
Cigarettes	39 (32)
Methadone	17 (14)
Heroin	7 (6)
Cocaine	4 (3)
Alcohol	4 (3)
Others	5 (4)
Multidrug (≥2 drugs) users	14 (12)
Gestational ARV treatment, *n* (%)	
No treatment	7 (6)
ZDV	11 (9)
HAART	103 (85)
HCV coinfection, *n* (%)	51 (42)
HBV coinfection, *n* (%)	5 (4)
Antepartum CD4 cell count/mm^3	
Mean ± SD	555 ± 275
Median (range)	572 (78–1690)
Antepartum RNA-HIV measurement, $\log_{10}$ copies/mL	
Mean ± SD	0.85 ± 1.51
Median (range)	0 (0–4.88)
Mode of delivery, *n* (%)	
Vaginal	10 (8)
Elective cesarean section	98 (81)
Urgent cesarean section	13 (11)
Intrapartum ARV treatment, *n* (%)	
No treatment	8 (7)
ZDV	113 (93)
Female gender, *n* (%)	64 (53)
1-min and/or 5-min Apgar score <8, *n* (%)	6 (5)
Gestational age at birth, wk, mean ± SD	37.1 ± 1.5
Birth weight, g, mean ± SD	2786 ± 464
Neonatal ARV treatment, *n* (%)	
ZDV	122 (96)
ZDV + 3TC + NVP	5 (4)

TABLE 2. Individual and Cumulative Gestational Exposure to Different NRTIs (in weeks)

	No. of Patients	Mean	SD	Median	Range
ZDV	81	25.9	11.3	27.1	2–40
3TC	92	29.4	10.3	36	2–40
d4T	46	28.4	12.9	36	1–40
ddI	22	27.3	12.9	36.5	2–40
Gestational cumulative exposure to different NRTIs	120	58.3	23.4	72	3–113
Prenatal and postnatal cumulative exposure to different NRTIs	127	61.3	25.8	78	6–119

Note that some children were exposed to >2 NRTIs because of changes in maternal HAART regimens during pregnancy.

logistic regression was gestational use of didanosine (ddI; odds ratio: 1.06 per 1 week of fetal exposure; 95% CI: 1.01–1.11; $P = .025$). No other statistically significant associations were found between HLA and other specific types of ARV agents or regimens, duration of treatments, or the rest of the described clinical and laboratory variables (data not shown).

Three female infants developed neurologic symptoms consistent with mitochondrial dysfunction together with HLA. Patient 1 had been exposed to ddI, d4T, and NFV during gestation and intrapartum ZDV at 37 weeks of gestational, and she received ZDV during her first 6 weeks of life. At 2 months of age, she presented with mild axial hypotonia and poor head control and needed early stimulation for 5 months, with good clinical evolution. Patient 2 was exposed to ZDV, 3TC, NVP, and benzodiazepines from the fifth month of gestation, when HIV infection was diagnosed in her mother. She was born at 38 weeks of gestational, with ZDV use during labor, and she also received a 6-week course of ZDV. At 2 months of age, she presented with mild limb spasticity, axial hypotonia, and retention of primitive reflexes, symptoms that had settled down by the age of 6 months. Patient 3 was exposed to 3TC, d4T, and NVP during the whole gestation; her mother was a heavy smoker. Born at 37 weeks of gestational, she also received intrapartum and neonatal ZDV. At 6

TABLE 3. LA Plasma Values From HIV-Uninfected NRTI-Exposed Infants and Control Subjects, at Various Ages

	Age			
	6 wk	3 mo	6 mo	12 mo
Cases				
Blood samples excluded because of nonoptimal conditions when obtained and/or processed	55	56	44	44
HLA samples excluded because of normal alaninemia	5	8	1	3
LA samples included in the study	67	63	82	80
HLA samples	35	30	15	20
LA maximum, mmol/L	8.06	10.1	7.28	4.1
LA samples >5 mmol/L	4	5	2	0
Mean LA values, mmol/L	2.88	2.78	1.89	1.71
Controls				
Number of subjects	159	160	158	160
Mean LA values, mmol/L	1.61	1.49	1.39	1.24
P value	<.0001	<.0001	<.0001	<.0001

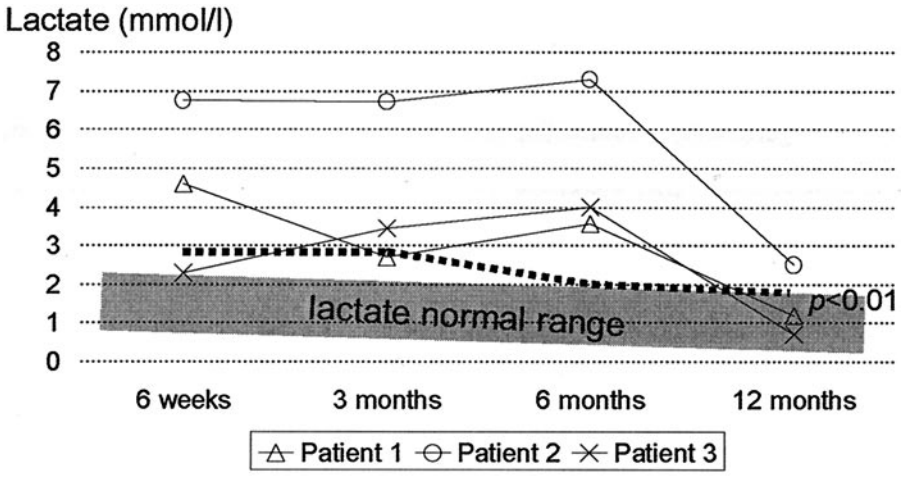

Fig 1. Mean LA plasma value evolution for HIV-uninfected NRTI-exposed children (thicker dotted line) and for the 3 girls who developed neurologic symptoms.

months of age, she developed poor head control, was unable to sit unaided, and showed upper limb spasticity and adduced thumbs at physical examination. Additional clinical controls have shown a good clinical evolution toward normalization at the age of 1 year. Cerebral ultrasounds were normal in all cases. Evolution of LA levels for these 3 patients is shown in Fig 1. Additional neurologic evolution and LA levels have been normal in all of them to date (23, 30, and 27 months of age, respectively).

No symptoms consistent with LA acidosis were observed during the study. However, an inverse correlation was found between LA plasma levels and pH values (Pearson correlation test: $r = -0.491$, $P < .0001$).

DISCUSSION

LA acidosis is the most fearful syndrome associated with NRTI-induced mitochondrial toxicity described in HIV-infected adult patients,[20,21] with an estimated incidence rate that ranges from 1.3 to 3.9 cases per 1000 person-years of NRTI exposure.[3,22] Recent studies have documented asymptomatic or mildly symptomatic HLA in HIV-infected NRTI-treated adult patients,[23–25] with prevalence rates as high as 65% for symptom-free HLA.[22] To date, the reason that some HLA patients develop LA acidosis is unknown; some individual susceptibility probably plays a role in this evolution.[10]

Data regarding NRTI-induced HLA in the pediatric age are still scarce. To our knowledge, only 1 case of LA acidosis in an HIV-infected infant has been described, by Church et al.[26] We recently documented a prevalence rate of 17% (14 of 80) for asymptomatic HLA in our cohort of HIV-infected pediatric patients,[27] after using the same inclusion criteria for LA measurements. These data are similar to those reported by Desai et al[28] (prevalence rate: 32%, 41 of 127 patients) in the other pediatric series in which LA levels have been investigated.

The results in our study are similar to those reported by the only 2 series of HIV-uninfected infants in whom LA plasma levels were documented. Giaquinto et al[29] described 17 (85%) of 20 infants who were followed up to a mean age of 7 months with transient asymptomatic HLA (>2.5 mmol/L) at least once during the study, whereas Alimenti et al[30] reported a prevalence rate of 92% for HLA in their cohort (35 of 38 infants; LA levels ≥2.1 mmol/L) that was followed up to the age of 6 months. Both groups of authors described a trend toward normalization of LA levels with time, which has been found to be statistically significant in our cohort. Compared with our series, a higher incidence of HLA is reported; this

may be attributable to the more restrictive inclusion criteria that we used. The physiologic and technical variability of plasma LA determination is a widely recognized drawback of this technique. The exclusion of blood samples that were obtained under nonoptimal conditions and the concomitant determination of alanine levels probably minimized this problem in our study. Moreover, the use of a large control group at every age with statistically significant lower LA values compared with those from NRTI-exposed infants strengthens our findings.

It is remarkable that the prevalence for HLA is higher in HIV-uninfected infants who are exposed perinatally to ARV than in HIV-infected pediatric patients on chronic HAART. These findings may be partially explained by a chronic adaptation to NRTI toxicity, similar to that reported in HIV-infected adult patients.[22,23,31] However, one could also hypothesize that the higher energy requirements of a developing organism in the first months of life may make these patients more vulnerable to NRTI toxicity. In fact, in our previous study in HIV-infected pediatric patients,[27] only a younger age at the beginning of antiretroviral treatment was found to be a statistically significant risk factor to develop HLA.

A recent study by Poirier et al,[32] based on a small group of children, demonstrated that infants who are born to HIV-infected untreated mothers have significantly lower mitochondrial DNA content in peripheral blood leukocytes when compared with control subjects. This depletion in mitochondrial DNA persists up to the age of 2 years and is further increased when mothers receive ZDV during pregnancy. Similar genetic findings have been reported in naïve HIV-infected adult patients,[33] suggesting that HIV may play a role in mitochondrial damage. Our study confirms a high prevalence of HLA in HIV-uninfected infants who are exposed to ARV. Similarly, 3 patients in our cohort still showed elevated LA levels at the age of 2 years. These genetic and biochemical findings strongly hint at the possibility of a clinical syndrome caused by NRTI toxicity, despite the population-based studies that have failed to demonstrate signs or symptoms suggesting mitochondrial injury in these patients.[9,11–13]

In adult patients, several NRTI-associated adverse effects have been recognized: myopathy,[34] LA acidosis,[20,21] osteopenia,[35] neuropathy,[36] fat maldistribution, and dyslipidemias[37] are the most important and frequent of these. The few articles regarding NRTI-induced toxicity in the pediatric age mainly describe neurologic symptoms similar to those of inherited mitochondrial diseases[5,7,8]: developmental retardation, seizures, and HLA. In the French cohort,[14,15] which included 2644 HIV-uninfected NRTI-exposed infants, the 18-month incidence for demonstrated mitochondrial dysfunction was 0.26%. Most of these patients presented neurologic symptoms (mainly delay in cognitive development, motor abnormalities, and seizures), abnormal cerebral magnetic resonance imaging, and HLA, either with a typical histologic pattern or a deficit in the enzymologic study of the respiratory chain complexes; 2 deaths were described.[14] The same authors reported a higher incidence of first febrile seizure in HIV-uninfected children who were younger than 18 months and had been exposed to ARV drugs.[16] Finally, neurologic symptoms (spastic gait and a generalized developmental regression) appeared 5 months before LA acidosis was identified and steadily improved after discontinuation of NRTIs in the only case of LA acidosis in a pediatric HIV-infected patient reported to date.[26]

According to the classification of probability level for the diagnosis of a mitochondrial respiratory chain deficit by Barret et al,[15] analogous to that used for inherited mitochondrial diseases, the 3 patients that we report would be classified as "possible" mitochondrial dysfunction cases (symptoms compatible with those described in inherited mitochondrial diseases plus persistent significant HLA). Our prevalence rate of "possible" mitochondriopathy was 2.4% (95% confidence interval: 0%–5.1%), whereas the prevalence rate in the French cohort for "established" plus "possible" mitochondriopathy was 1.05% (28 of 2644 patients).[15] However, the French authors excluded 61 children with self-limited symptoms consistent with mitochondrial dysfunction, about whom complementary investigations were not available. These latter patients exactly match our girls who were affected with developmental retardation, except for the systematic determination of LA plasma values. In any case, the transient nature of elevated LA levels and the benign evolution of the infrequent HLA-associated neurologic syndrome in our series should be emphasized.

In our study, HLA was associated with gestational exposure to ddI but not to other NRTIs or ARV regimens, neither during pregnancy nor later. However, it should be kept in mind that these results are based on a small group of patients. It seems plausible that an additive or synergistic effect from different NRTIs contributes to mitochondrial toxicity in the fetus. Actually, only 1 of the 3 girls who developed neurologic symptoms had been exposed to ddI, and HLA was also documented in 2 infants who had been exposed to ZDV only in the neonatal period. A control group of HIV-uninfected infants who were not exposed to NRTIs or were exposed to NRTI monotherapy probably would have enhanced our study, but these were not available. Current guidelines[17] discourage the use of ddI in HIV-infected pregnant women because of several reports describing maternal mortality secondary to LA acidosis/hepatic steatosis in patients who receive long-term ddI and d4T.[38,39] This recommendation is reinforced by our findings.

The benefit obtained from ARV in preventing HIV vertical transmission has been well demonstrated in recent series similar to ours, with HIV mother-to-child transmission rates $<2\%$.[40] This success outweighs the potential toxicity of these agents in the newborn, and HAART should continue to be used in pregnant HIV-infected women. However, additional investigations regarding the efficacy and safety of ARV therapies in the neonate are warranted, and an effort to choose the least toxic therapeutic regimen in every single case is mandatory. In our opinion,

plasma LA may provide some benefit in both the etiologic identification and the evolution of children who develop a clinical syndrome. Moreover, long-term follow-up is recommended, with special attention paid to neurologic symptoms and cognitive and behavioral development.

ACKNOWLEDGMENTS

This work was supported by grants REDEMETH 903/054 and FIS 99/0051/01E from Ministerio de Educación y Ciencia. Dr Noguera is the recipient of a grant from Hospital Sant Joan de Déu.

We are very grateful to Josep Maria Martin for skillful technical assistance.

REFERENCES

1. Mofenson LM. Advances in the prevention of vertical transmission of human immunodeficiency virus. *Semin Pediatr Infect Dis.* 2003;14:295–308
2. White AJ. Mitochondrial toxicity and HIV therapy. *Sex Transm Inf.* 2001;77:158–173
3. Ogedegbe AO, Thomas DL, Diehl AM. Hyperlactataemia syndromes associated with HIV therapy. *Lancet Infect Dis.* 2003;3:329–327
4. Brinkman K, Hofstede HJM, Burger DM, Smeitink JAM, Koopmans PP. Adverse effects of reverse transcriptase inhibitors: mitochondrial toxicity as common pathway. *AIDS.* 1998;12:1735–1744
5. Munnich A. Defects of the respiratory chain. In: Fernandes J, Saudubray JM, Van den Berghe, eds. *Inborn Metabolic Diseases. Diagnosis and Treatment.* Berlin, Germany: Springer; 2000:158–168
6. Ruitenbeek W, Wendel U, Trijbels F, Sengers R. Mitochondrial energy metabolism. In: Blau N, Duran M, Blaskovics ME, eds. *Physician's Guide to the Laboratory Diagnosis of Metabolic Diseases*. London, United Kingdom: Chapman & Hall; 1996:390–406
7. DiMauro S, Schon EA. Mitochondrial respiratory-chain diseases. *N Engl J Med.* 2003;348:2656–2668
8. Ogier H, Aicardi J Metabolic diseases. In: Aicardi J, ed. *Diseases of the Nervous System in Childhood*. London, United Kingdom: Mac Keith Press; 1998:254–322
9. European Collaborative Study. Exposure to antiretroviral therapy in utero or early life: the health of uninfected children born to HIV-infected women. *J Acquir Immune Defic Syndr.* 2003;32:380–387
10. Brinkman K. Management of hyperlactatemia: no need for routine lactate measurements. *AIDS.* 2001;15:795–797
11. Dominguez K, Bertolli J, Fowler M, et al. Lack of definitive severe mitochondrial signs and symptoms among deceased HIV-uninfected and HIV-indeterminate children ≤5 years of age, Pediatric Spectrum of HIV disease project (PSD), USA. *Ann N Y Acad Sci.* 2000;918:236–246
12. Lindegren ML, Rhodes P, Gordon L, Fleming P. Drug safety during pregnancy and in infants: lack of mortality related to mitochondrial dysfunction among perinatally HIV-exposed children in pediatric HIV surveillance. *Ann N Y Acad Sci.* 2000;918:222–235
13. Bulterys M, Nesheim S, Abrams EJ, et al. Lack of evidence of mitochondrial dysfunction in the offspring of HIV-infected women. Retrospective review of perinatal exposure to antiretroviral drugs in the Perinatal AIDS Collaborative Transmission Study. *Ann N Y Acad Sci.* 2000;918:212–221
14. Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet.* 1999;354:1084–1089
15. Barret B, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort. *AIDS.* 2003;17:1769–1785
16. Landreau-Mascaro A, Barret B, Mayaux MJ, Tardieu M, Blanche S. Risk of early febrile seizure with perinatal exposure to nucleoside analogues. *Lancet.* 2002;359:583–584
17. Public Health Service Task Force. Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States. Available at: www.hivatis.org. Accessed November 26, 2003
18. Artuch R, Vilaseca MA, Farre C, Ramon F. Determination of lactate, pyruvate, beta-hydroxybutyrate and acetoacetate with a centrifugal analyser. *Eur J Clin Chem Clin Biochem.* 1995;33:529–533
19. Moyano D, Vilaseca MA, Artuch R, Lambruschini N. Plasma amino acids in anorexia nervosa. *Eur J Clin Nutr.* 1998;52:684–689
20. Falco V, Rodriguez D, Ribera E, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. *Clin Infect Dis.* 2002;34:838–846
21. Coghlan ME, Sommadossi JP, Jhala NC, Many WJ, Saag MS, Johnson VA. Symptomatic lactic acidosis in hospitalized antiretroviral-treated patients with HIV: a report of 12 cases. *Clin Infect Dis.* 2001;33:1914–1921
22. John M, Moore CB, James IR, et al. Chronic hyperlactatemia in HIV-infected patients taking antiretroviral therapy. *AIDS.* 2001;15:717–723
23. Boubaker K, Flepp M, Sudre P, et al. Hyperlactatemia and antiretroviral therapy: the Swiss HIV Cohort Study. *Clin Infect Dis.* 2001;33:1931–1937
24. Lonergan JT, Behling C, Pfander H, Hassanein TI, Mathews WC. Hyperlactatemia and hepatic abnormalities in 10 human immunodeficiency virus-infected patients receiving nucleoside analogue combination regimens. *Clin Infect Dis.* 2000;31:162–166
25. Gérard Y, Maulin L, Yazdanpanah Y, et al. Symptomatic hyperlactataemia: an emerging complication of antiretroviral therapy. *AIDS.* 2000;14:2723–2730
26. Church JA, Mitchell WG, González-Gómez I, et al. Mitochondrial DNA depletion, near-fatal metabolic acidosis and liver failure in an HIV-infected child treated with combination antiretroviral therapy. *J Pediatr.* 2001;138:748–751
27. Noguera A, Fortuny C, Sanchez E, et al. Hyperlactatemia in human immunodeficiency virus-infected children receiving antiretroviral therapy. *Pediatr Infect Dis J.* 2003;22:778–782
28. Desai N, Mathur M, Weedon J. Lactate levels in children with HIV/AIDS on highly active antiretroviral therapy. *AIDS.* 2003;17:1565–1568
29. Giaquinto C, Romeo AD, Giacomet V, et al. Lactic acid levels in children perinatally treated with antiretroviral agents to prevent HIV transmission. *AIDS.* 2001;15:1074–1075
30. Alimenti A, Burdge DR, Ogilvie GS, Money DM, Forbes JC. Lactic acidemia in human immunodeficiency virus-uninfected infants exposed to perinatal antiretroviral therapy. *Pediatr Infect Dis J.* 2003;22:782–788
31. Boffito M, Marietti G, Audagnotto S, Raiter R, Di Perri G. Lactacidemia in asymptomatic HIV-infected subjects receiving nucleoside reverse-transcriptase inhibitors. *Clin Infect Dis.* 2002;34:558–559
32. Poirier MC, Divi RL, Al-Harthi L, et al. Long-term mitochondrial toxicity in HIV-uninfected infants born to HIV-infected mothers. *J Acquir Immune Defic Syndr.* 2003;33:175–183
33. Côté HCF, Brumme ZL, Craib KJP, et al. Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. *N Engl J Med.* 2002;346:811–820
34. Dalakas MC, Illa I, Pezeshkpour GH, Laukaitis JP, Cohen B, Griffin JL. Mitochondrial myopathy caused by long-term zidovudine therapy. *N Engl J Med.* 1990;322:1098–1105
35. Carr A, Miller J, Eisman JA, Cooper DA. Osteopenia in HIV-infected men: association with asymptomatic lactic acidemia and lower weight pre-antiretroviral therapy. *AIDS.* 2001;15:703–709
36. Simpson DM, Tagliati M. Nucleoside analogue-associated peripheral neuropathy in human immunodeficiency virus infection. *J Acquir Immune Defic Syndr.* 1995;9:153–161
37. Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. *Lancet.* 1999;364:1112–1115
38. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Inf.* 2002;78:58–59
39. Mandelbrot L, Kermarrec N, Marcollet A, et al. Case report: nucleoside analogue-induced lactic acidosis in the third trimester of pregnancy. *AIDS.* 2003;17:272–273
40. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV-1 transmission: a randomized trial. *JAMA.* 2002;288:189–198

Hyperlactatemia in Human Immunodeficiency Virus–Uninfected Infants Who Are Exposed to Antiretrovirals

Antoni Noguera, Claudia Fortuny, Carmen Muñoz-Almagro, Emilia Sanchez, M. Antonia Vilaseca, Rafael Artuch, Jordi Pou and Rafael Jimenez

Pediatrics 2004;114;e598
DOI: 10.1542/peds.2004-0955 originally published online October 18, 2004;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Hyperlactatemia in Human Immunodeficiency Virus–Uninfected Infants Who Are Exposed to Antiretrovirals

Antoni Noguera, Claudia Fortuny, Carmen Muñoz-Almagro, Emilia Sanchez, M. Antonia Vilaseca, Rafael Artuch, Jordi Pou and Rafael Jimenez

Pediatrics 2004;114;e598
DOI: 10.1542/peds.2004-0955 originally published online October 18, 2004;