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ARTICLE

Serum Lactate Levels in Infants Exposed Peripartum to Antiretroviral Agents to Prevent Mother-to-Child Transmission of HIV: Agence Nationale de Recherches Sur le SIDA et les Hépatites Virales 1209 Study, Abidjan, Ivory Coast

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ABSTRACT

BACKGROUND. Mitochondrial toxicity was described in infants exposed to long-term antiretroviral regimens containing nucleoside analogues for the prevention of mother-to-child transmission of HIV. We measured the serum lactate levels in children born to HIV-1 infected African women receiving short-term antiretroviral prevention of mother-to-child transmission of HIV regimens.

METHODS. A prospective study was conducted in women-child pairs from the third trimester of pregnancy to 3 months of life. The exposed group was formed by children exposed in utero to nucleoside analog antiretroviral regimens, zidovudine or zidovudine + lamivudine from 32 to 36 weeks of amenorrhea until delivery. All of these women received nevirapine single dose at the beginning of labor. The children received zidovudine during the first 7 days of life and a nevirapine single dose at day 3. The control group was formed by infants born to HIV-1-infected women who had received nevirapine single dose only and who were not exposed to nucleoside analog antiretroviral regimens. Serum lactate levels were measured at 4, 6, and 12 weeks of life by Cobas Integra 400.

RESULTS. A total of 836 blood samples from 338 infants was collected (262 exposed and 76 controls). Median lactacidemia was 1.8 mmol/L (interquartile range: 1.2–2.7 mmol/L). Overall serum lactate levels ≥2.5 mmol/L, defining hyperlactatemia, were observed in 39 of the 292 infants who had ≥2 serum lactate measurements. The 3-month period prevalence of hyperlactatemia did not differ between the exposed group and the control group. All of the serum lactate levels returned to normal values in all of the subsequent samples. No case of symptomatic hyperlactatemia was detected during the study period.

CONCLUSIONS. Increased lactate levels were identified equally in infants whose mother received short-term nucleoside analogs or nevirapine single dose for prevention of mother-to-child transmission of HIV. Although not rare, hyperlac-

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Key Words
hyperlactatemia, HIV infection, children, mitochondrial injury, vertical transmission, Africa

Abbreviations
ARV—antiretroviral therapy
PMTCT—prevention of mother-to-child transmission of HIV
NVPsd—nevirapine single dose
ANRS—Agence Nationale de Recherches sur le SIDA et les Hépatites Virales
CI—confidence interval
NRTI—nucleoside analog reverse transcriptase inhibitor

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tatemia was not related to short-term exposure to nucleoside analog antiretroviral regimens.

A POSSIBLE MITOCHONDRIAL toxicity has been hypothesized in infants exposed to long-term regimens of antiretroviral therapy (ARV) used for the prevention of mother-to-child transmission of HIV (PMTCT) after a case report of symptomatic severe lactic acidosis.[1] Subsequently, children with neurologic symptoms and biochemical and histologic signs of mitochondrial dysfunction were described within the French Perinatal Study.[2,3] In a systematic screening of neurologic symptoms presented by uninfected children of this large cohort, the 18-month incidence of this phenomenon was estimated at 0.3% in children exposed perinatally to nucleoside analogs.[3] Subsequently, several cohorts reported that a significant number of exposed but asymptomatic children had increased lactate levels within the 6-week postnatal phase of the ARV prophylaxis exposure[4–6] and sometimes persisting several weeks or months later. This biological abnormality was a probable consequence of an acute asymptomatic mitochondrial toxicity.[3] In one of these studies, hyperlactatemia was defined by a lactate value ≥5 mmol/L and was observed in 26% of the infants.[4] The serum lactate measurement was considered there as a surrogate marker of mitochondrial dysfunction and could, thus, be used to investigate mitochondrial toxicity in adults and infants.[4,7] However, the high potential of artifactual values of lactate level is well known for this laboratory measurement.[8] Recently, Noguera et al[6] confirmed these observational data with a control group and adequate biological internal controls, thus strengthening the hypothesis that zidovudine-exposed children had a significant risk of transient asymptomatic hyperlactatemia. Long-term consequences of this mitochondrial injury are not known.

In Africa, where short-term regimens of ARVs have been frequently used for PMTCT since 2000,[9,10] there has not yet been any study to explore this possible mitochondrial toxicity. We hypothesized that the screening of elevated lactate levels could help in early identification of the infants presenting possible mitochondrial dysfunction. The objective of our study was to estimate the frequency of high lactate levels in infants born to HIV-1-infected women and exposed during pregnancy to short terms of zidovudine or short terms of zidovudine + lamivudine used for PMTCT in comparison with infants exposed to nevirapine single dose (NVPsd) only. We also investigated the risk factors associated with high lactate levels, including the maternal ARV regimen.

METHODS

Design

The Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS) 1209 study was a prospective observational cohort set up in neonates born to HIV-1-infected women within the ANRS 1201/1202 Ditrame Plus project, which evaluated the safety and field effectiveness in reducing mother-to-child transmission of HIV with short-term combinations of zidovudine + NVPsd and zidovudine + lamivudine + NVPsd[11] followed by alternatives to prolonged breastfeeding in Abidjan, Ivory Coast.[12]

Ethical Permissions

The ANRS 1201/1202 Ditrame Plus project was granted ethical permission in the Ivory Coast from the ethical committee of the National AIDS Control Program and in France from the institutional review board of the ANRS. As part of the Ditrame Plus project, the study presented here was included in the institutional review board approval.

Patients

Between May 2002 and February 2005, we enrolled consecutively in this substudy 3 groups of infants born to HIV-1-infected pregnant women (Table 1). Cohort 1 was exposed to maternal short-term zidovudine initiated at 36 weeks of amenorrhea. Cohort 2 was exposed to maternal short-term zidovudine + lamivudine initiated at 32 weeks of amenorrhea. In these 2 cohorts, mothers also received NVPsd at the beginning of the labor, and the newborns received zidovudine syrup (2 mg/kg every

TABLE 1 **Antiretroviral Interventions Among HIV-Infected Mothers and Infants for the PMTCT in the ANRS Ditrame Plus Cohort in Abidjan, 2002–2005**

Regimens	Mother			Infants Postnatal
	Prepartum (Gestational Age at the Beginning, wk)	Intrapartum	Postpartum	
Ditrame Plus 1.0 (cohort 1, exposed)	ZDV 300 mg (36)	ZDV 600 mg + NVP 200 mg		ZDV syrup 2 mg/kg × 4/d for 1 wk and NVP syrup 2 mg/kg on days 2–3
Ditrame Plus 1.1 (cohort 2, exposed)	ZDV 300 mg + 3TC 150 mg (32)	ZDV 600 mg + NVP 200 mg	ZDV 300 mg + 3TC 150 mg (3 d)	ZDV syrup 2 mg/kg × 4/d for 1 wk and NVP syrup 2 mg/kg on days 2–3
National program (cohort 3, control)		NVP 200 mg		NVP syrup 2 mg/kg on days 2–3

ZDV indicates zidovudine; 3TC, lamivudine; NVP, nevirapine.

6 hours) during their first week of life and NVPsd (2 mg/kg) at day 2. The third cohort was used as a control group formed between February 2004 and February 2005 of infants exposed to a NVPsd PMTCT regimen of known efficacy[13] and recommended by the international[14] and national guidelines implemented after the end of the Ditrame Plus cohort.

Biological Analyses

The lactate levels were determined according to AIDS Clinical Trial Group mitochondrial dysfunction focus group guidelines.[15] These guidelines specify in particular how the venous lactate specimens must be collected for this purpose.

The serum lactate levels were systematically measured in children at 4, 6, and 12 weeks of life by Roche Cobas Integra 400 at the Treichville Hospital University CeDReS laboratory in Abidjan. All of the measures were performed on the supernatant after deproteineization with internal quality control as suggested by the manufacturer (Roche Diagnostics, Mannheim, Germany). CeDReS also participated in an external quality control program of lactate measurements organized by a Necker University Hospital laboratory (Paris, France). The quality control was performed in Assurance de Qualité des Laboratories D'analyses Médicales (ASQUALAB) in Corentin Celton Hospital (Moulineaux, France).

Capillary blood was collected in ethylenediaminetetraacetic acid microtainer tubes (Becton Dickinson, Plymouth, United Kingdom) in newborns at weeks 4 and 6 for the diagnosis of pediatric HIV infection. All of the samples collected at week 4 were systematically processed for a plasma HIV-1 RNA viral load measurement using the branche DNA assay or a real-time polymerase chain reaction with the quantitative Taqman technology.[16] The same technique was applied to the 6-week sample if the first one tested was positive. Maternal CD4 count was measured using flow cytometry (FACScan, Becton Dickinson, San Jose, CA).

Outcomes

We defined hyperlactatemia as ≥2 consecutives measures of lactate levels ≥2.5 mmol/L at either 4 weeks and 6 weeks or 6 weeks and month 3. Repeated measurements were also realized at 4 to 6 months in case of diagnosis of hyperlactatemia at an earlier age for further studying the kinetics of the lactate levels in this subgroup.

The available infant data included in the analysis of the determinants of hyperlactatemia were gender, HIV infection status, anthropometric data at birth (weight and length), and compliance to zidovudine syrup intake for the postexposure prophylaxis. Maternal data included the ARV regimen (type and term) during pregnancy, intrapartum dose intake, age, clinical stage, and CD4 count.

Statistical Analysis

The prevalence of hyperlactatemia was estimated with its 95% confidence interval (CI). The group comparisons used Student's t test, the nonparametric Mann-Whitney U test, or 1-way analysis of the variance for quantitative variables and the χ^2 test or Fisher's exact test for qualitative variables.

All of the factors potentially associated with hyperlactatemia were studied in univariate and then multivariate logistic regression. All of the tests were 2-sided, and a $P < .05$ was considered significant. All of the analyses were performed with Stata 8.0 (Stata Corporation, College Station, TX).

RESULTS

Description of the Study Sample

Between May 2002 and February 2005, 836 blood samples were collected from 338 infants (140 in cohort 1, 122 in cohort 2, and 76 in the control group). Altogether, 23 infants were diagnosed as HIV infected at 4 weeks: 6 (4.4%) in the zidovudine group, 6 (4.9%) in the zidovudine + lamivudine group, and 11 (14.9%) in the NVPsd group. Among these infants, 159 (47%) initiated breastfeeding, and 179 (53%) received formula feeding. Overall, 3 lactate measurements were performed in median per infant (range: 1–5), and the mean lactate level was 2.2 mmol/L (SD: 1.4 mmol/L). No statistical difference of mean lactate level was observed between the 3 groups ($P = .242$) and between the exposed and the controls groups ($P = .530$) when adjusting the timing of the blood samples collected (Table 2).

Frequency of Hyperlactatemia

A total of 292 infants (86%) who had ≥2 consecutive lactate measurements were available for this estimation, and 39 of them had hyperlactatemia. Thus, the prevalence of hyperlactatemia in this population was 13.4% (95% CI: 9.6%–17.8%). It was 11.6% (95% CI: 6.3%–19.0%) among 112 infants from cohort 1, 14.5% (95%CI: 8.5%–22.5%) in 110 infants of cohort 2, and 14.3% (95% CI: 7.1%–24.7%) in 70 infants of control group ($P = .79$; Fig 1). The prevalence of hyperlactatemia was 13.1% in the overall exposed group and 14.3% in the control group ($P = .84$). Serious lactate levels (≥5 mmol/L) were identified in 34 (4.0%) of 836 blood samples collected, and 5 children presented confirmed (≥2 samples) severe hyperlactatemia among 292 infants who had 2 consecutive measurements. No difference was observed between the 3 groups ($P = .574$).

TABLE 2 **Lactate Values (mmol/L) According to the Exposure to Antiretroviral Prophylaxis and the Timing of the Blood Collection: ANRS 1209 Study, Abidjan, 2002–2005**

Variable	Overall	Control Group Cohort 3 NVPsd	Exposed Group			P^a	P^b	P^c
			All	Cohort 1 ZDV+ sdNVP	Cohort 2 ZDV + 3TC+ sdNVP			
Lactate values (total)								
No. of samples	836	194	642	323	319			
Minimum to maximum	0.2–11.7	0.6–6.3	0.3–11.7	0.3–10.5	0.2–11.7			
Mean (SD) mmol/L	2.2 (1.4)	2.3 (1.1)	2.2 (1.5)	2.0 (1.1)	2.3 (1.6)	.009	.530	.242
Lactate values (week 4)								
Age of infants, d	29 (28–31)	31 (29–34)	28 (28–30)	29 (28–30)	28 (28–30)		.570	
No. of samples	299	73	226	117	109			
Minimum to maximum	0.2–11.7	0.9–5.7	0.2–11.7	0.6–7.5	0.2–11.7			
Mean (SD) mmol/L	2.2 (1.4)	2.2 (0.9)	2.2 (1.5)	2.1 (1.1)	2.3 (1.8)	.283	.976	.499
Lactate values (week 6)								
Age of infants, d	44 (42–46)	46 (44–50)	44 (42–46)	44 (42–46)	44 (42–46)		.270	
No. of samples	264	65	199	101	98			
Minimum to maximum	0.3–10.5	0.9–5.7	0.3–9.9	0.6–10.5	0.3–9.9			
Mean (SD) mmol/L	2.4 (1.5)	2.3 (1.2)	2.2 (1.5)	2.2 (1.5)	2.6 (1.9)	.149	.638	.273
Lactate values (month 3)								
Age of infants, d	92 (90–93)	93 (92–100)	91 (90–92)	93 (92–94)	91 (90–92)		.690	
No. of samples	264	65	170	79	91			
Minimum to maximum	0.3–8.1	0.9–6.3	0.3–8.1	0.3–6.3	0.4–8.1			
Mean (SD) mmol/L	2.1 (1.1)	2.3 (1.1)	2.0 (1.2)	1.7 (1.1)	2.2 (1.1)	.006	.104	.006

ZDV indicates zidovudine; 3TC, lamivudine.
[a] Comparison between the 2 exposed groups.
[b] Comparison between exposed (all) and control groups.
[c] Comparison between the 3 groups.

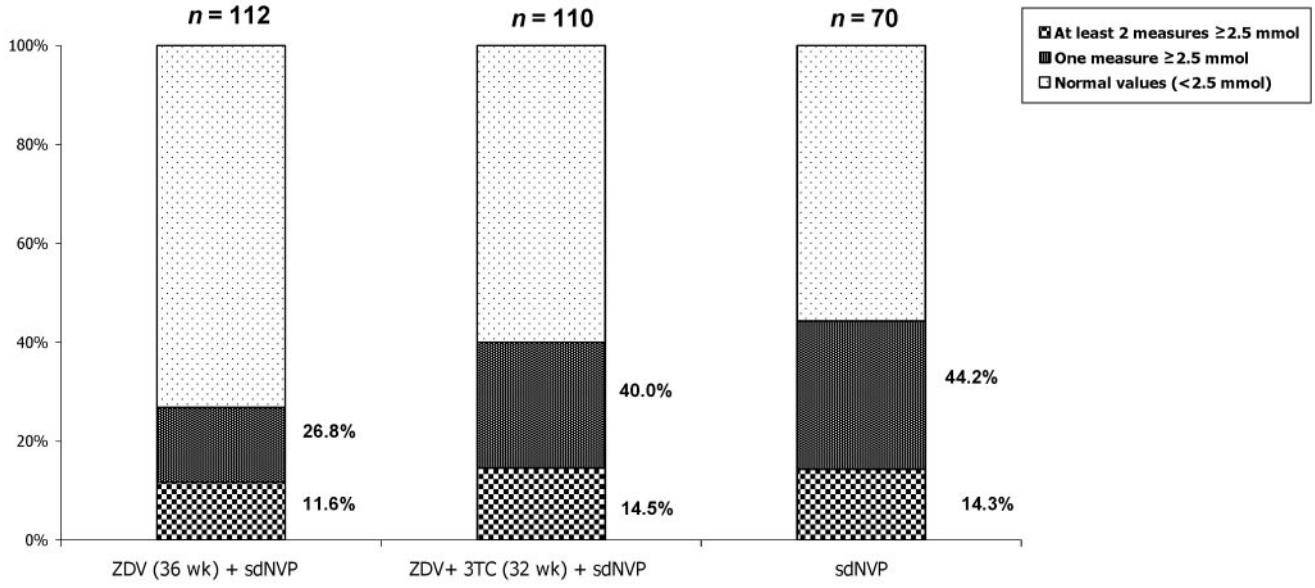

FIGURE 1
Frequency of hyperlactatemia (≥2.5 mmol/L on 2 consecutive measurements in a series of 3) in infants born to HIV-infected mothers and exposed to antiretroviral agents during pregnancy, according to the ANRS 1209 study, Abidjan (2002–2005). ZDV + sdNVP indicates zidovudine from 36 weeks of gestation and sdNVP; ZDV + 3TC+ sdNVP, ZDV + lamivudine from 32 weeks of gestation and sdNVP.

Factors Associated With Hyperlactatemia in Infants Exposed to Nucleoside Antiretroviral Agents

In univariate and then multivariate analyses, none of the following variables was found to be significantly associated with hyperlactatemia: child characteristics (gender, HIV status at week 4, twin birth, infant zidovudine prophylaxis, and birth weight) and maternal characteristics (duration of prepartum prophylaxis with zidovudine, CD4, World Health Organization clinical stage, and age). No difference of frequency of hyperlac-

tatemia was found according to the infant HIV status at week 4 (4.8% in HIV-infected infant vs 14.0% among the non–HIV-infected; $P = .229$).

Evolution of Neonatal Hyperlactatemia

The kinetics of hyperlactatemia are documented in 28 of 31 infants exposed to zidovudine ($n = 12$) or zidovudine + lamivudine ($n = 19$) and show a return to normal values for 25 children (Fig 2). Three infants had persistent hyperlactatemia at month 6, and their lactate levels were, respectively, 3.3 (zidovudine group), 3.6 (zidovudine group), and 5.7 mmol/L (zidovudine + lamivudine group) at that time.

Clinical Manifestations

None of the children who presented a biologically confirmed hyperlactatemia in the first 3 months of life developed any of the following symptomatic clinical manifestations: abdominal pain or muscular or neurologic symptoms either before or after the biological diagnosis was made. There was not record of special clinical manifestation in the 3 children with persistent hyperlactatemia. All of these infants with abnormal biological values were subsequently clinically followed at least until their second birthday, and 1 male infant death was reported at week 38, of which the presumptive cause was severe anemia. His serum lactate values were 2.6 mmol/L at week 4, 3.3 mmol/L at week 6, 1.8 mmol/L at month 3, and 2.7 mmol/L at month 6.

DISCUSSION

In adults and children, the rise of lactate levels may be observed in physiologic circumstances, such as during and immediately after exercise, in hypermetabolic states, and in the context of disease conditions.[8] Thus, the diagnosis of nucleoside reverse transcriptase inhibitor-related hyperlactatemia requires exclusion of other causes, such as dehydratation, vigorous exercise, alcohol intoxication, renal failure, hyperthyroidism, and exposure to others drugs.[17] However, hyperlactatemia is commonly artifactual because of sampling methods: in vivo by the use of tourniquets or as a consequence of fist clenching or hand pumping when venous specimens are drawn and in vitro if adequate plasma collection tubes are not used.[18,19]

To understand the significance of elevated lactate levels in infants exposed to ARVs, our study also included a control group formed by infants born to HIV-infected mothers and exposed to NVPsd, a non–nucleoside reverse transcriptase inhibitor. We have also undertaken

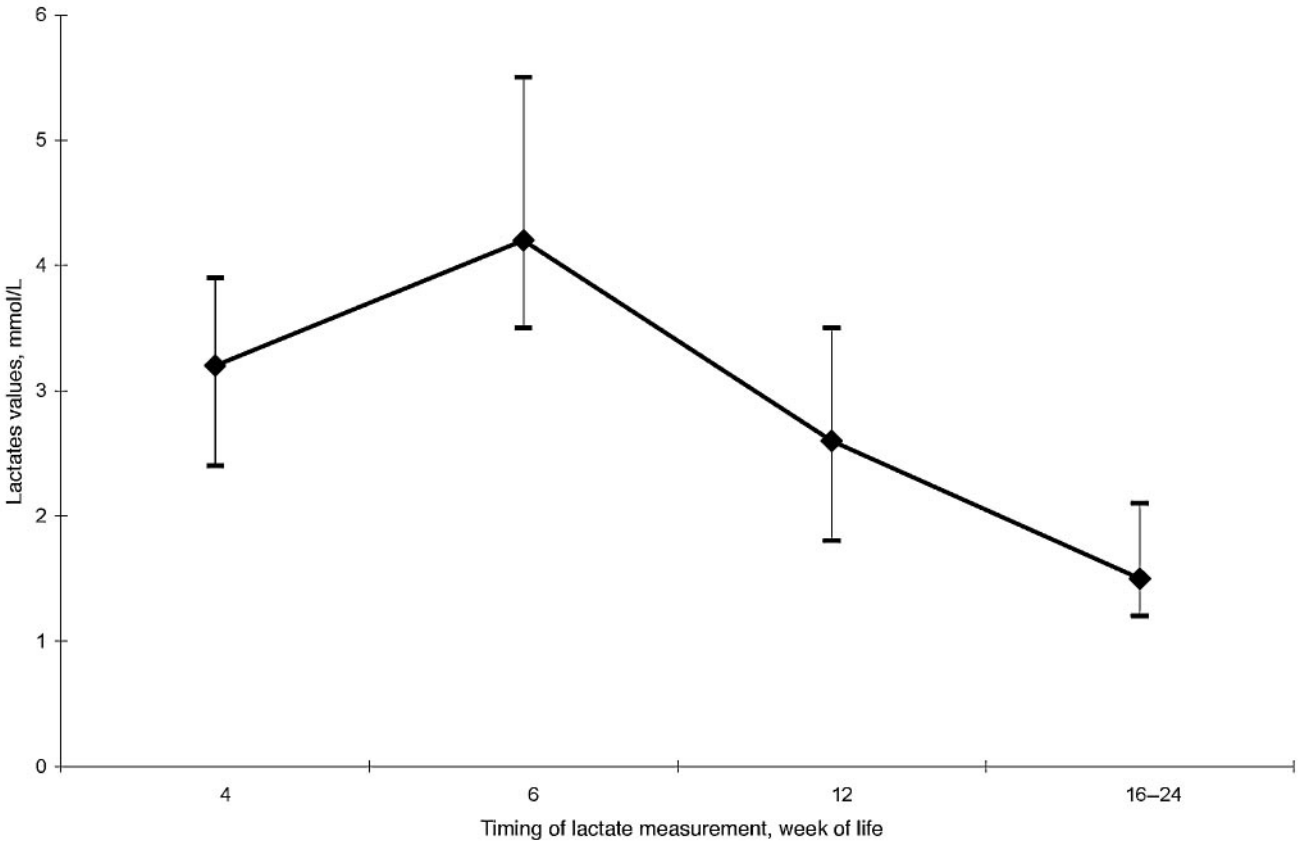

FIGURE 2
Kinetics of evolution of lactate measurements (median range and interquartile values of lactate measurements) in 28 infants born from HIV-infected mothers presenting hyperlactatemia in the first 3 months of life, according to the ANRS 1209 study in the Ditrame Plus cohort in Abidjan (2002–2005).

internal and external quality controls with an independent laboratory to validate the lactate measurements. Moreover, we defined high lactate levels as 2 consecutives levels ≥2.5 mmol/L, thus taking into account only high and sustained lactatemia. We believe, therefore, that our estimates are minimally biased regarding an artifactual measure.

In our study, the overall frequency of high lactate levels was estimated at 13% and did not differ according to the type of ARV exposure. No difference was also found between groups when comparing the mean value of serum lactates of the exposed and control groups.

These results are in relative contradiction with those from a controlled study in Spain where half of the exposed children presented hyperlactatemia.[6] This discrepancy could be explained by a longer exposure to nucleoside analog reverse transcriptase inhibitors (NRTIs) in the Spanish study, both for prenatal and postnatal periods. In industrialized countries, prophylactic treatments are generally initiated at the beginning of the second trimester of pregnancy and continued in the newborn for 6 weeks.[20,21] In addition, a high dose of zidovudine is given intravenously during labor, whereas children in our study were exposed in utero to oral zidovudine alone in median for 4 weeks or to zidovudine + lamivudine in median for 8 weeks, and the labor dose was only given orally. As expected, we observed that the infants from cohort 2 had higher mean lactates than infants from cohorts 1 or 3. This could be related to either the longer period of exposure or an exposure to 2 analogs nucleosides, such as zidovudine and lamivudine.

It is also important to underline that our control group took into account the pregnancy effect, as well as the maternal HIV infection status, which was not performed in the Spanish study.[6] We can conclude, therefore, that, in our study, the high lactate levels, although not rare, were not related to short-term exposure to the nucleoside analogs.

There are potential limitations to our investigation. An enrollment bias could be discussed, because we have enrolled the control group in a more limited time period than the other groups. However, the impact of this selection procedure on the lactate measurements should be limited, because all of the laboratory assessments were performed by the same laboratory. We were not able to measure arterial pH to identify lactic acidosis, as well as the lactate-pyruvate ratio to explore mitochondrial function, for logistic reasons. However, the strengths of this observational study remain the large sample size and the use of a control group, which has taken into account both the HIV infection status of the mother and the exposure to ARV drugs. Indeed, with 53 infants in each group, we had an 80% statistical power to detect a mean difference between the infants exposed to NRTIs with mean lactate levels estimated at 2.88 mmol/L and those not exposed to NRTIs with mean lactate levels estimated at 1.61 mmol/L according to the results by Noguera et al.[6]

Our study allows us to draw some public health conclusions. It seems clear that lactate measurement is neither a specific nor a sensitive marker of mitochondrial injury in this context, although one cannot rule out the occurrence of mitochondrial injury in these cohorts.[2,3] Based on our findings, as well as the literature from industrialized countries,[3] there is no argument to justify any routine screening of hyperlactatemia in infants exposed perinatally to ARVs. Long-term follow-up, including clinical investigations, as well as more advanced biological investigations of HIV-infected infants exposed perinatally to ARVs for PMTCT, could help to detect all of the abnormalities that could be drug-related. The creation of an international registry to collect short- and long-term ARV toxicity in such infants could help in the future to document the overall impact of all ARV drugs used for PMTCT.

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