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**Serum Lactate Levels in Infants Exposed Peripartum to Antiretrovirals to Prevent
Mother-to-Child Transmission of HIV: ANRS 1209 Study, Abidjan, Côte d'Ivoire.**

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Keys words: hyperlactatemia, HIV infection, children, mitochondrial injury, vertical transmission, Africa

Running head

Hyperlactatemia in neonates in Africa

Abbreviations

ANRS: Agence Nationale de Recherches sur le Sida et les hépatites virales, ARV: antiretroviral therapy, CI: Confidence Interval, HIV : Human Immunodeficiency Virus, NRTI: nucleoside analogue reverse transcriptase inhibitor, NNRTI: non-nucleoside analogue reverse transcriptase inhibitor, SD : Standard Deviation, sdNVP : single-dose of nevirapine, 3TC: lamivudine, ZDV (AZT): zidovudine.

APPENDIX

The ANRS 1209 Ditrane Plus study was coordinated by Didier K. Ekouevi and François Dabis. Ramata Toure and François Rouet were responsible for all laboratory aspects of this study. This study was part of the ANRS 1201/1202 Ditrane Plus project, of which members are listed below.

Composition of the ANRS 1201/1202 and 1209 DITRAME PLUS Study Group

Principal Investigators: François Dabis, Valériane Leroy, Marguerite Timite-Konan, Christiane Welffens-Ekra.

Coordination in Abidjan: Laurence Bequet, Didier K. Ekouévi, Besigin Tonwe-Gold, Ida Viho. Methodology, biostatistics and data management: Gérard Allou, Renaud Becquet, Katia Castetbon, Laurence Dequae-Merchadou, Charlotte Sakarovitch, Dominique Touchard.

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Abstract

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

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

Results: A total of 836 blood samples from 338 infants were 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 at least two serum lactate measurements, 13.4%, 95% confidence Interval [9.6-17.8%]. The three-month period prevalence of hyperlactatemia did not differ between the exposed group (13.1%) and the control group (14.3%) ($p=0.84$). All serum lactate levels returned to normal values in all subsequent samples. No case of symptomatic hyperlactatemia was detected during the study period.

Conclusion: Increased lactate levels were identified equally in infants whose mother received a short-term of nucleoside analogues or NVPsd for PMTCT. Although not rare, hyperlactatemia was not related to short-term exposure to nucleoside analogue ARVs

Introduction

A possible mitochondrial toxicity has been hypothesized in infants exposed to long-term regimens of antiretrovirals (ARVs) used for the prevention of mother-to-child transmission of HIV (PMTCT), following a case report of symptomatic severe lactic acidosis (1). Subsequently, children with neurological symptoms and biochemical and histological signs of mitochondrial dysfunction were described within the French Perinatal Study (2, 3). In a systematic screening of neurological 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 analogues (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 ARVs 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 artefactual 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 (ZDV) 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 are 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 to early identify 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-term of ZDV or short-term of ZDV + lamivudine (3TC) used for PMTCT in comparison to infants exposed to nevirapine single-dose (NVPsd) only. We investigated also the risk factors associated to high lactate levels, including the maternal ARV regimen.

Methods

Design

The ANRS 1209 study was a prospective observational cohort set up in neonates born to HIV-1 infected women within the ANRS 1201/1202 Ditrane Plus project which evaluated the safety and field effectiveness in reducing mother-to-child transmission of HIV with short-term combinations of ZDV+NVPsd and of ZDV+3TC+NVPsd (11) followed by alternatives to prolonged breastfeeding in Abidjan, Côte d'Ivoire (12).

Ethical permissions

The ANRS 1201/1202 Ditrane Plus project was granted ethical permission in Côte d'Ivoire from the ethical committee of the National AIDS Control Programme, and in France from the institutional review board of the French Agence Nationale de Recherches sur le Sida (ANRS). As part of the Ditrane 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 sub-study three groups of infants born to HIV-1 infected pregnant women (Table 1). Cohort 1 was exposed to maternal short-term ZDV initiated at 36 weeks of amenorrhea. Cohort 2 was exposed to maternal short-term ZDV+3TC initiated at 32 weeks of amenorrhea. In these two cohorts, mothers received also NVPsd at the beginning of the labour and the newborns ZDV syrup (2mg/kg/6 hours) during their first week of life and NVPsd (2mg/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 Ditrane Plus cohort.

Biological Analyses

The lactate levels were determined according to ACTG 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 400TM in Treichville Hospital University, CeDReS laboratory in Abidjan. All 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 ASQUALAB “Assurance de qualité des laboratoires d’analyses médicales” in Corentin Celton Hospital (Moulineaux, France).

Capillary blood was collected in EDTA microtainer tubes (Becton Dickinson) in newborns at weeks 4 and 6 for the diagnosis of pediatric HIV infection. All samples collected at week 4 were systematically processed for a plasma HIV-1 RNA viral load measurement using the bDNA assay or a real time polymerase chain reaction (PCR) 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 (FASCAN).

Outcomes

We defined hyperlactatemia as at least two consecutives measures of lactate levels higher than 2.5 mmol/L at either 4 weeks (S4) and 6 weeks (S6) or S6 and month 3 (M3). Repeated

measurements were also realized at 4-6 months in case of diagnosis of hyperlactatemia at an earlier age, for studying further 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, length) and compliance to ZDV syrup intake for the post-exposure 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 percent confidence interval (CI). The group comparisons used Student's t-test or the non parametric Mann-Whitney U test or one-way analysis of the variance (ANOVA) for quantitative variables and the Chi-2 test or Fisher's exact test for qualitative variables.

All factors potentially associated with hyperlactatemia were studied in univariate then multivariate logistic regression. All tests were two-sided and a p-value <0.05 was considered significant. All the analyses were performed with STATATM 8.0 (Stata Corporation, College Station, TX, USA).

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 ZDV group, 6 (4.9%) in the ZDV+3TC group and 11 (14.9%) in the sdNVP group. Among these infants, 159 (47%) initiated breastfeeding and 179 (53%) received formula feeding. Overall, three lactate measurements were performed in median per infant (range: 1-5) and the mean lactate level was 2.2 mmol/L, (standard deviation [SD] 1.4 mmol/L). No statistical difference of mean lactate level was observed between the three groups ($p=0.242$) and between the exposed and the controls groups ($p=0.530$) when adjusting on the timing of the blood samples collected (Table 2).

Frequency of hyperlactatemia

A total of 292 infants (86%) who had at least two 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%, (CI: 9.6-17.8%). It was 11.6% (CI: 6.3-19.0%) among 112 infants from cohort 1, 14.5%, (CI: 8.5-22.5%) in 110 infants of cohort 2 and 14.3%, (CI: 7.1%-24.7%) in 70 infants of control group ($p=0.79$) (Figure 1). The prevalence of hyperlactatemia was 13.1% in the overall exposed group and 14.3% in the control group ($p=0.84$). Serious lactate levels (≥ 5 mmol/L) were identified in 34/836 (4.0%) blood samples collected and five children presented confirmed (≥ 2 samples) severe hyperlactatemia among 292 infants who had two consecutive measurements. No difference was observed between the three groups ($p=0.574$).

Factors associated with hyperlactatemia in infants exposed to nucleoside antiretrovirals

In univariate 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 ZDV prophylaxis, birth weight) and maternal characteristics (duration of prepartum prophylaxis with ZDV, CD4, WHO clinical stage and age). No difference of frequency of hyperlactatemia was found according to the infant HIV status at week-4 (4.8% in HIV-infected infant versus 14.0% among the non HIV-infected, $p=0.229$).

Evolution of neonatal hyperlactatemia

The kinetics of hyperlactatemia is documented in 28 of 31 infants exposed to ZDV ($n=12$) or ZDV+3TC ($n=19$) and shows a return to normal values for 25 children (Figure 2). Three infants had persistent hyperlactatemia at month 6 and their lactate levels were respectively 3.3 mmol/L (ZDV group), 3.6 mmol/L (ZDV group) and 5.7 mmol/L (ZDV+3TC group) at that time.

Clinical manifestations

None of the children who presented a biologically confirmed hyperlactatemia in the first three months of life developed any of the following symptomatic clinical manifestations: abdominal pain, muscular or neurological symptoms, either before or after the biological diagnosis was made. There was not record of special clinical manifestation in the three children with persistent hyperlactatemia. All these infants with abnormal biological values were subsequently clinically followed at least until their second birthday and one male infant death was reported at week 38, whose 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 at month 6.

Discussion

In adults and children, the rise of lactate levels may be observed in physiological 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 inhibitors related hyperlactatemia requires exclusion of others causes, such as dehydration, vigorous exercise, alcohol intoxication, renal failure, hyperthyroidism and exposure to others drugs (17). However, hyperlactatemia is commonly artefactual due to 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).

In order to understand the significance of elevated lactate levels in infants exposed to ARVs, our study included also a control group formed by infants born to HIV-infected mothers and exposed to sdNVP, a non nucleoside reverse transcriptase inhibitor.

We have also undertaken internal and external quality controls with an independent laboratory to validate the lactate measurements. Moreover, we defined high lactate levels as two consecutives levels >2.5 mmol/L, thus taking into account only high and sustained lactatemia. We believe therefore our estimates are minimally biased regarding an artefactual 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 exposed children presented hyperlactatemia (6). This discrepancy could be explained by a longer exposure to NRTIs in the Spanish study, both for prenatal and postnatal periods. In industrialized countries, prophylactic treatment 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 ZDV is given intravenously during labor, while children in our study were exposed in utero to oral ZDV alone in median for four weeks or to ZDV+3TC in median for eight 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 cohort 1 or 3. This could be related to either the longer period of exposure or an exposure to two analogues nucleosides such as ZDV and 3TC.

It is also important to underline that our control group took into account the pregnancy effect as well as the maternal HIV infection status, that 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 analogues.

There are potential limitations to our investigation. An enrolment 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 as all 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 logistical 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 a 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 Nogurera et al (6).

Our study allows drawing some public health conclusions. It appears clearly 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 abnormalities which 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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Table 1. Antiretroviral interventions among HIV-infected mothers and infants for the prevention of mother-to-child transmission of HIV in the ANRS Ditrane Plus cohort in Abidjan, Côte d'Ivoire (2002-2005).

Regimens	Mother			Infants
	Prepartum (gestational age at the beginning)	Intrapartum	Postpartum	Postnatal
Ditrane Plus 1.0 (Cohort 1, exposed)	ZDV 300 mg (36 weeks)	ZDV 600 mg + NVP 200 mg	-	ZDV syrup 2mg/kg x 4/ day for one week and NVP syrup 2mg/kg on day 2-3
Ditrane Plus 1.1 (Cohort 2, exposed)	ZDV 300 mg + 3TC 150 mg (32 weeks)	ZDV 600 mg + NVP 200 mg	ZDV 300 mg + 3TC 150 mg (3 days)	ZDV syrup 2mg/kg x 4/ day for one week and NVP syrup 2mg/kg on day 2-3
National Program (Cohort 3, control)	-	NVP 200 mg	-	NVP syrup 2mg/kg on day 2-3

ZDV= zidovudine, 3TC = lamivudine, NVP= nevirapine

Table 2. Lactate values (mmol/L) according to the exposure to antiretroviral prophylaxis and the timing of the blood collection. ANRS 1209 study, Abidjan, Côte d'Ivoire (2002-2005).

	Overall	Control group		Exposed group		p*	p**	p***
		Cohort 3 sdNVP	All	Cohort 1 ZDV+ sdNVP	Cohort 2 ZDV+3TC+ sdNVP			
Lactate values (total)								
Number of samples	836	194	642	323	319			
Min-Max	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)	0.009	0.530	0.242
Lactate values (week-4)								
Age of infants (days)	29 [28-31]	31 [29-34]	28 [28-30]	29 [28-30]	28 [28-30]		0.570	
Number of samples	299	73	226	117	109			
Min-Max	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)	0.283	0.976	0.499
Lactate values (week-6)								
Age of infants (days)	44 [42-46]	46 [44-50]	44 [42-46]	44 [42-46]	44 [42-46]			
Number of samples	264	65	199	101	98			
Min-Max	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)	0.149	0.638	0.273
Lactate values (month-3)								
Age of infants (days)	92 [90-93]	93 [92-100]	91 [90-92]	93 [92-94]	91 [90-92]			
Number of samples	264	65	170	79	91			
Min-Max	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)	0.006	0.104	0.006

sdNVP = single-dose of nevirapine, ZDV = zidovudine, 3TC = lamivudine

* Comparison between the two exposed groups, **Comparison between exposed (all) and control groups, *** Comparison between the three groups

SD : Standard deviation

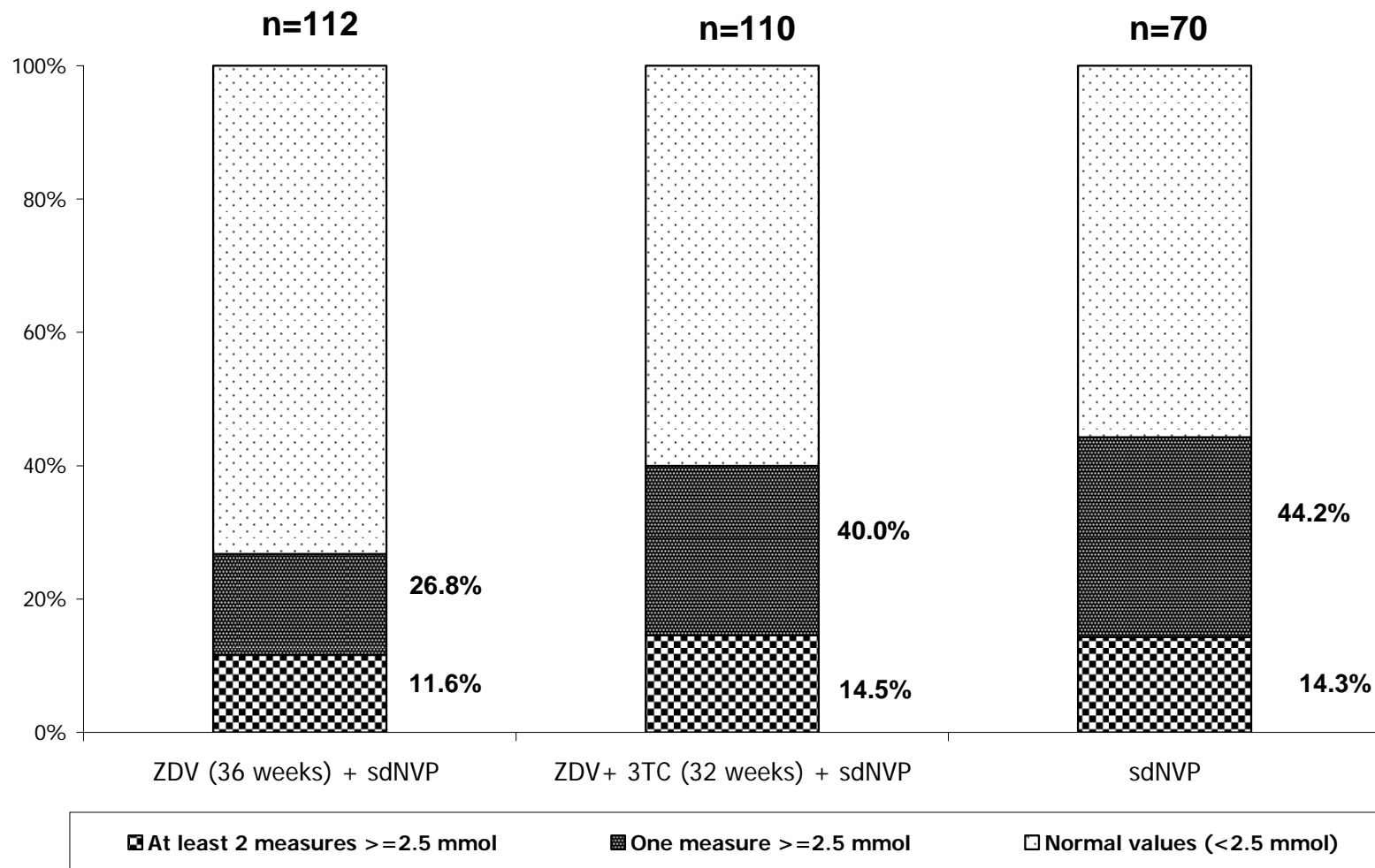


Figure 1

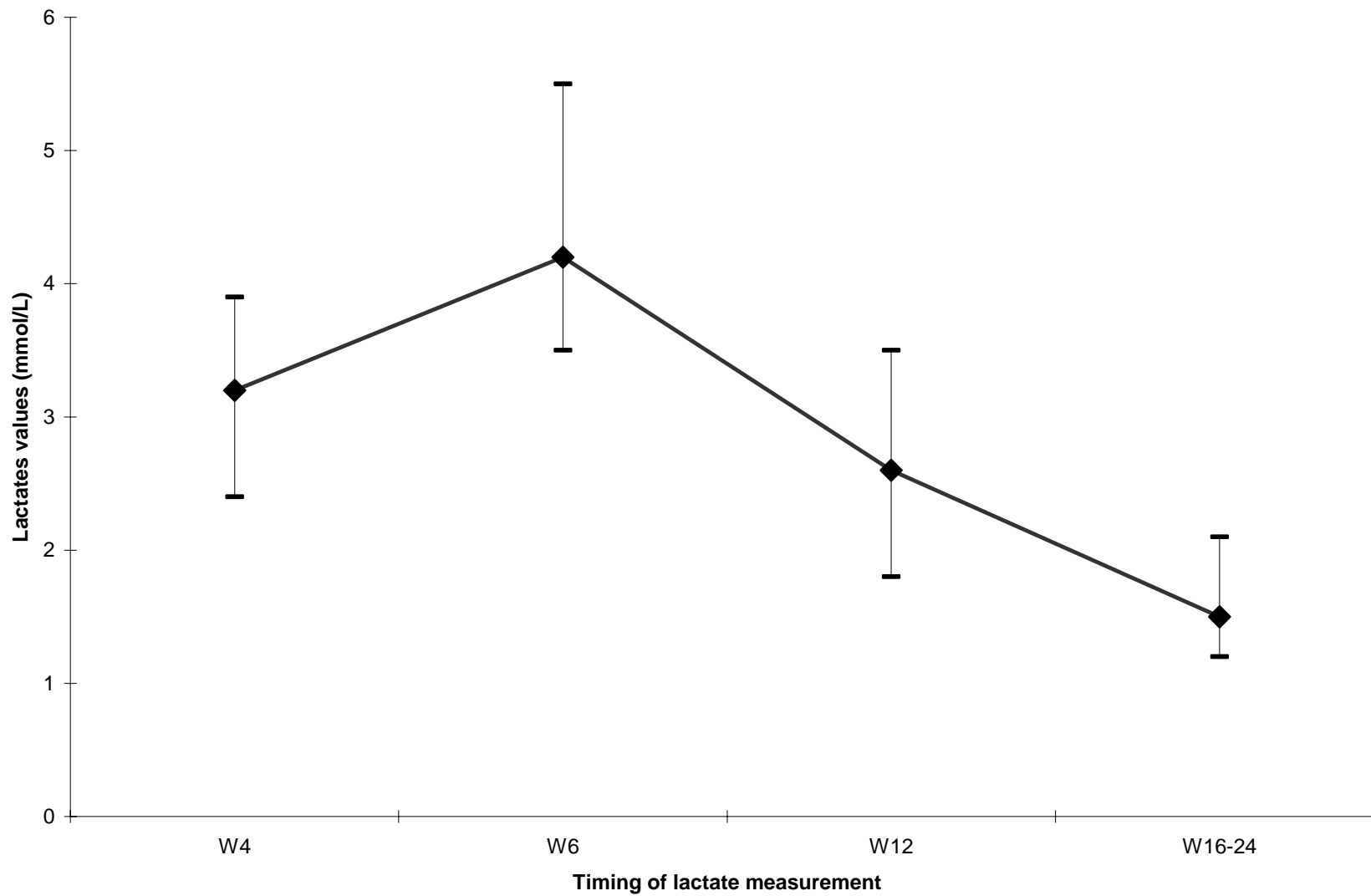


Figure 2

Figure 1. Frequency of hyperlactatemia* in infants born to HIV-infected mothers and exposed to antiretrovirals during pregnancy. ANRS 1269 study, Abidjan, Côte d'Ivoire (2002-2005).

sdNVP : single-dose of nevirapine

ZDV+sdNVP : zidovudine (ZDV) from 36 weeks of gestation and single-dose of nevirapine

ZDV+3TC+sdNVP: zidovudine (ZDV) + lamivudine (3TC) from 32 weeks of gestation and single-dose of nevirapine

* \geq 2.5 mmol/L on two consecutive measurements in a series of three

Figure 2. Kinetics of evolution of lactate measurements & in 28 infants born from HIV-infected mothers presenting hyperlactatemia in first three months of life. ANRS 1269 study in the Ditrane Plus cohort in Abidjan, Côte d'Ivoire (2002-2005).

W4 = 4 weeks of life

W8 = 6 weeks of life

W12=12 weeks of life

W16-W24=between 16 and 24 weeks of life

& Median range and interquartile values of lactate measurements