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Point of Care Capillary Blood Lactate Measurements in Human Immunodeficiency Virus-uninfected Children with *in utero* Exposure to Human Immunodeficiency Virus and Antiretroviral Medications

MARILYN J. CRAIN, MPH, MD¹, PAIGE L. WILLIAMS, PHD², RAY GRINER, MPH², KATHERINE TASSIOPOULOS, DSC, MPH³, JENNIFER S. READ, MD⁴, LYNNE M. MOFENSON, MD⁴, KENNETH C. RICH, MD⁵, and FOR THE PEDIATRIC HIV/AIDS COHORT STUDY

¹Pediatrics and Microbiology, University of Alabama School of Medicine, Maternal and Child Health, UAB School of Public Health, Birmingham, AL

²Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA

³Department of Epidemiology, Harvard School of Public Health, Boston, MA

⁴Pediatric Adolescent and Maternal AIDS Branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD

⁵Pediatrics, University of Illinois at Chicago, Chicago, IL

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INTRODUCTION

Antiretroviral (ARV) therapy of pregnant women has dramatically reduced the transmission rate of HIV infection from mother to child. Monitoring for potential toxicities of individual ARVs and combinations of ARVs used during pregnancy is essential to allow judgments about the best regimens for reducing maternal-to-child transmission with the fewest adverse affects. Concern for possible mitochondrial toxicity associated with ARV medications has led investigators to study blood lactate concentrations in HIV-infected children and adults (1-7) and in infants exposed *in utero* to both HIV infection and ARV. (8-14)

Because elevated blood lactate concentrations are often associated with mitochondrial dysfunction, this laboratory test has been used to screen for mitochondrial dysfunction in

Corresponding author: Marilyn J. Crain, MPH, MD 1600 Seventh Ave S 306A CHB Birmingham, AL 352333
mcrain@peds.uab.edu.

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both clinical care and investigational studies. Obtaining accurate plasma lactate determinations in infants and children is difficult due to requirements that the patient be resting, that venous blood be obtained without use of a tourniquet, and that the sample be tested shortly after being obtained. (15) Technological developments have made analysis of capillary blood lactate at the point of care (POC) possible. The relative ease of POC testing and the reported high level of agreement with venous lactate measurements have led to the introduction of capillary blood POC lactate testing into a variety of clinical care settings, including for conditions unrelated to HIV infection (16-18) and in resource-constrained settings to monitor lactate concentrations in HIV-infected patients receiving ARVs. (19-22)

We established a large US prospective surveillance study, the Surveillance Monitoring for Antiretroviral Therapy Toxicities (SMARTT) of the Pediatric HIV/AIDS Cohort Studies (PHACS), to look for evidence of possible mitochondrial toxicity in a large cohort of uninfected children born to HIV-infected mothers who used ARV medications during that pregnancy. The primary screening laboratory test selected to prompt further evaluation for possible mitochondrial abnormalities in this study was a blood lactate concentration above a threshold of 3mmol/L. Here we report the frequency of elevated POC lactate concentrations in US children born to HIV-infected women receiving ARVs during pregnancy but who remained uninfected. The associations between *in utero* ARV exposure and elevated POC lactate concentrations in these children were evaluated, controlling for other variables. This is the largest cohort study to date reporting lactate concentration in children using a POC testing device.

MATERIALS AND METHODS

SMARTT Study Protocol and Study Population

The multicenter Surveillance Monitoring for Antiretroviral Therapy Toxicities (SMARTT) protocol of the Pediatric HIV/AIDS Cohort Study (PHACS) began enrollment in March, 2007 and includes two cohorts enrolled at 24 sites in the US and Puerto Rico. Newborns and their HIV-infected mothers were enrolled into the Dynamic Cohort between 22 weeks gestation and 72 hours of age, and were prospectively followed. Children from birth to age 12 years who were either previously enrolled and followed in prospective studies such as the Pediatric AIDS Clinical Trials Group (PACTG) 219C Late Outcome Study (23) or the Women and Infants Transmission Study (WITS) (24) (both studies are now closed), other studies approved by the study chair, or participants not previously enrolled in an approved study but who had equivalent data available in their medical records, were enrolled into the Static Cohort, along with their mothers or caregivers. Each clinical site's Institutional Review Board reviewed the study for human use approval and signed informed consent was obtained by the parent or legal guardian both for their own and their child's participation.

Maternal medical histories of illnesses and complications during pregnancy and ARV use were obtained. For participants in the Dynamic Cohort, these data were gathered within two weeks after delivery. For participants in the Static Cohort, the same information was gathered from computerized data records from the previously enrolled natural history studies or from clinical medical records, through medical record abstraction, or maternal interview. Information on maternal drug use during pregnancy was obtained by maternal self-report (shortly after delivery for the Dynamic Cohort, and at the entry visit for the Static Cohort). For both the Dynamic and Static Cohort participants, HIV viral load results (VL) and absolute CD4 cell counts and CD4 % both early in pregnancy and again prior to or at labor and delivery were collected as indicators of maternal HIV disease characteristics. Sex, race and ethnicity, estimated gestational age, birth weight, and any clinical diagnoses were abstracted from medical records. Children and their mothers were followed at annual study visits for the SMARTT study and new clinical diagnoses were recorded for the children and

laboratory testing was performed. In addition to laboratory studies required by the study, infants and children received complete physical examinations. The study population for this analysis included all subjects enrolled in SMARTT with at least one POC lactate measurement reported as of October 1, 2009.

POC Lactate Measurement

At each annual study visit, capillary blood was obtained and assayed using the Lactate Pro™ analyzer device [KDK Corporation Lactate Pro System, CLIA record K980908, waived 7/27/2001, ARKRAY Inc., Kyoto, Japan] and the Lactate Pro™ Test Strip. The device was calibrated at least weekly at each site using the device Check Strip and results were recorded in a log. If a child's measured POC lactate exceeded 3mmol/L, POC lactate testing was repeated at the same visit.

Statistical Methods and Covariate Definitions

Our primary analysis considered the first available POC lactate measurement for each participant, or repeat POC lactate for elevated POC lactate >3mmol/L if obtained at that visit. The prevalence of elevated POC lactate was estimated overall and by age group. Differences in percent with elevated POC lactate by age group were assessed via a Chi-square test and differences in median POC levels across age groups were assessed via a Kruskal-Wallis test.

Associations of elevated POC lactate with *in utero* ARV exposure were evaluated using logistic regression models. ARV exposure *in utero* was classified by drug class, trimester of exposure to individual ARV drugs, trimester of exposure to any ARV, and whether the exposure was to highly active antiretroviral therapy (HAART, defined as use of at least three drugs from at least two drug classes, whether used for treatment or prevention of HIV transmission). Potential confounders also were evaluated, including the child's age at POC assessment, maternal health status during pregnancy reflected by VL and CD4 percent measurement closest to labor and delivery, maternal substance use during pregnancy (alcohol, tobacco, cocaine, opiates, or marijuana), and infant characteristics including low birth weight (<2.5 kg), preterm birth (< 37 weeks gestation), gender, race, and ethnicity.

Each potential confounder described above was first evaluated for univariate association with elevated POC lactate. Multivariate models were then fit, including all covariates with $p < 0.20$ in univariate models and reduced to a core model including only those covariates with $p < 0.10$. Associations of elevated POC lactate with ARV exposure were adjusted for covariates in this core model. SAS Version 9.1 (SAS Institute Inc, Cary, NC) was used to conduct all statistical analyses, and two-sided p -values < 0.05 were considered statistically significant. Because the number of individual ARV drugs assessed leads to a relatively high number of statistical comparisons, we considered the results exploratory and placed emphasis on consistency of findings. However, since our analysis is a safety assessment, we considered minimizing Type II errors (failing to detect significant associations when they exist) equally important to reducing Type I error rates.

RESULTS

Size and characteristics of the Study Population

As of October 2009, 1934 subjects had enrolled in SMARTT (1240 in the Static Cohort and 694 in the Dynamic Cohort). Among the 1790 children who had completed a baseline visit, 1641 (92%) had at least one POC lactate measurement (Static Cohort: 1098; Dynamic Cohort: 543) and were included in our analysis.

Characteristics of the study population overall are shown in Table 1. Aside from children's ages at the time of study entry and POC lactate measurement, which were determined by the study protocol, characteristics of subjects in the two cohorts were similar except for maternal health status. Maternal viral load was higher in the mothers of children enrolled in the Static Cohort than in those of the Dynamic (viral load >1000 copies/ml in 20% of the mothers of Static Cohort participants compared to 15% of Dynamic Cohort participants, Fisher's Exact $p=0.01$). This difference is likely due to less effective antiretroviral therapy in earlier eras of the HIV epidemic, resulting in poorer virologic control for mothers of Static Cohort children.

Of the 1641 subjects, 98% reported neonatal prophylaxis (90% with ZDV monotherapy or other single agent, 8% with combination ARV therapy), with a median duration of 43 days (IQR: 42-45 days). Ninety-nine percent of the children in the 0 to 6 month age group had POC measurements conducted in the first 6 weeks of life, corresponding to the standard period of neonatal ARV prophylaxis. Because of the very low percentage of children who could be confirmed to have had no neonatal prophylaxis, it was not feasible to compare those with ARV exposure in the neonatal period vs. those without ARV exposure. The odds of elevated POC for those infants with combination vs. monotherapy ARV prophylaxis during the neonatal period were evaluated, and no association was found (adjusted OR=1.49, 95% CI 0.57 - 3.90).

The overall prevalence of SMARTT subjects with POC lactate levels above the study-defined threshold (>3mmol/L) was 3.4% (95% CI 2.5%, 4.3%), and did not differ among age groups (0 - < 6 months, 3.4% (95% CI 2.0%, 5.4%); 6 - < 24 months, 3.6% (95% CI 1.7%, 6.7%) and ≥ 24 months, 3.2% (95% CI 2.2%, 4.6%). POC lactates were performed in the first two weeks of life for 96% of the infants under 6 months of age; 99% of infants < 6 months of age had a POC lactate measurement by 6 weeks of age. Although the overall proportion of those with elevated POC lactate was similar in each age group, there was a significant difference in median POC lactate concentrations across age groups, with higher concentrations in infants < 6 months of age compared to older ages (median POC lactate 1.9 mmol/L for 497 infants < 6 months of age, 1.7 mmol/L for 250 children ages 6 - < 24 months, and 1.6 mmol/L for 894 children ≥ 24 months, $p < 0.001$).

In unadjusted models (Table 2), the odds of POC lactate >3mmol/L was significantly lower among infants of non-white race [odds ratio (OR) = 0.47, 95% CI: 0.27, 0.82, $p = 0.01$], but significantly higher among those reporting Hispanic/Latino ethnicity (OR = 1.74, 95% CI: 1.02, 2.99, $p = 0.05$) (Table 2). The odds of elevated POC lactate were also significantly higher for those reporting maternal cocaine or opiate use at any time during pregnancy (OR: 3.77, 95% CI: 1.42, 9.99, $p = 0.01$) or during the first trimester (OR: 3.75, 95% CI: 1.27, 11.02, $p = 0.02$). In a multivariate model which included age at POC assessment, birth characteristics, demographic factors, cocaine or opiate use, and alcohol or tobacco use during pregnancy, race [adjusted OR (aOR): 0.39 for non-white vs. white race, 95% CI: 0.22, 0.70, $p = 0.002$] and maternal cocaine or opiate use (aOR: 4.52, 95% CI: 1.67, 12.18, $p = 0.003$) remained significantly associated with elevated POC lactate.

Associations between *in utero* ARV exposure and elevated POC lactate were explored (see Table, Supplemental Digital Content 1 "Association between *in utero* ARV Exposure and Elevated POC lactate in 1641 Infants and Children Enrolled in SMARTT"), with and without adjustment for the clinical and historical covariates described above. Although POC lactate was more likely to be elevated in children exposed to non-nucleoside reverse transcriptase inhibitors (NNRTIs) in unadjusted analysis, after adjustment for race and maternal opiate and cocaine use (aOR: 1.77, 95% CI: 0.88, 3.57, $p = 0.11$) there were no

significant associations of elevated POC lactate with trimester of ARV exposure or trimester of HAART exposure.

Associations between *in utero* exposure to individual ARVs and elevated POC lactate are shown in Table 3. A significant increase in odds of elevated POC lactate was observed for children with *in utero* exposure to emtricitabine compared with children unexposed (5.6% vs. 2.9%, uOR: 2.02, 95%CI: 1.04, 3.92), even after adjustment for non-white race and maternal cocaine and opiate use during pregnancy (aOR: 2.23, 95% CI: 1.12, 4.42). *In utero* exposure to efavirenz, was also associated with an increased risk of elevated POC lactate (aOR: 4.05, 95% CI: 1.62, 10.1), but exposure to zidovudine or lamivudine alone or in combination (data not shown) or to protease inhibitors (PIs) was not.

Timing of first reported trimester of exposure to specific ARVs was also evaluated for association with elevated POC, as summarized in Supplemental Digital Content 2 (Table). Emtricitabine exposure was associated with elevated POC lactate when first exposure during pregnancy occurred during the first trimester (aOR: 2.39, 95% CI: 1.07, 5.35, $p=0.03$), but not during the second or third trimesters, as compared to those unexposed to emtricitabine during pregnancy. Although most efavirenz use by pregnant women in this study occurred during the first trimester, likely prior to diagnosis of pregnancy, some women used efavirenz which was first reported in the second or third trimester. Efavirenz use first reported in the second or third trimester of this pregnancy was associated with significantly elevated POC lactates (aOR: 26.4, 95% CI: 7.10, 97.8, $p<0.001$) but no significant association was observed with the first exposure to efavirenz in the first trimester.

DISCUSSION

Mitochondrial dysfunction is known to occur in some patients receiving ARVs. (25-27) Since most infants born in resource-rich settings and an increasing number in resource-limited parts of the world, are transplacentally exposed to ARV either for maternal health reasons or to prevent maternal-to-child transmission of HIV, it is important to understand any risks of this potential complication in infants exposed to maternal ARVs. In the present multisite study of 1641 HIV-exposed but uninfected children with *in utero* ARV exposure, the occurrence of blood lactate above 3mmol/L was relatively low at 3.4%, in contrast with previous studies reporting much higher proportions of HIV- and ARV-exposed infants and children with transient or sustained venous lactate above the individual study thresholds (49-92%). (8-10)

The current study differs from previous studies in several important respects. First, a POC device was used to measure capillary blood lactate in the participants of this study, thereby potentially avoiding falsely elevated lactate measurement due to crying, need for a tourniquet, and other technical issues related to obtaining appropriate samples. This FDA-approved and CLIA-waived device and test strips may be more representative of actual blood lactate in these infants because of avoidance of the technical issues of obtaining appropriate venous samples of blood from young infants. Venous lactate concentration was not determined each time POC lactate was done but only when POC lactate concentration was above the study threshold. The lactate concentration threshold selected for this surveillance study (>3 mmol/L) has been used in studies of HIV infected adults (7) and was chosen as a threshold to identify those in need of additional venous lactate evaluation and clinical correlation while eliminating additional evaluations for those with only minor elevations. Other studies have used lactate concentrations defining hyperlactatemia from just above the laboratory upper limit of normal (2.1-2.44 mmol/L) to 5 mmol/L. (8-11) Lactates > 5 mmol/L are usually associated with clinical lactic acidosis. (26). It is recognized that some children in this study may not have been identified as having a clinical condition

associated with hyperlactatemia, since this laboratory abnormality may be only intermittent. (28-30)

In this study the proportion of children with elevated POC lactate results was not increased for specific age groups, although the median lactate decreased with increasing age. Other studies of lactic acid in HIV- and ART- exposed but uninfected infants also reported a decrease in lactic acid levels with increasing age, with most previously elevated values becoming normal at later time periods. (8, 10, 11) Our results also differed from previous reports in that older children were included in this cohort and elevated POC lactate were observed in older children at the same frequency as younger age groups. This suggests that mitochondrial injury may persist after early infancy in some cases and is in contrast to previous reports suggesting that most NRTI-related abnormalities reported to date in HIV-infected persons have resolved once the offending ARV has been discontinued. (31-33) Further longitudinal follow-up of individual study participants will be necessary to formally determine whether elevated POC lactate is persistent or related to an intercurrent event causing elevated POC lactate. To date there appear to be no correlations between the elevated POC lactate measurements and clinical symptoms of mitochondrial abnormalities. As this study is ongoing, more definitive answers to this question will be available in the future.

We identified relationships between elevated POC lactate and race, ethnicity, and maternal use of opiates and cocaine not previously reported. Risk of POC lactate $>3\text{mmol/L}$ was higher in the offspring of mothers of white race and of Hispanic ethnicity than among non-white and non-Hispanics. These results are of interest since pathogenic mtDNA mutations vary by race and ethnicity and suggest areas of future study. (34, 35) In our multivariate analysis, maternal cocaine or opiate use during this pregnancy remained significantly associated with elevated POC lactate. The mechanism of increased risk of elevated POC lactate concentration with maternal use of opiates or cocaine during pregnancy is unknown, and has not been found in other studies of lactate measurement in HIV exposed but uninfected infants exposed to *in utero* ARVs (8).

The relationship between specific ARV exposure *in utero* and elevated lactate was also examined. Most previous studies of mitochondrial abnormalities with ARV have found associations with the NRTI class, (7, 25) but these associations were not observed in this cohort study. In contrast, in this cohort a small proportion of children with *in utero* exposure to emtricitabine (14%) and efavirenz (4%) were more likely to have elevated POC lactate, findings not previously reported in HIV-uninfected children. The proportion of children with elevated POC lactate was increased, even after adjustment for ethnicity and maternal use of cocaine or opiates during pregnancy. The reason for the elevated lactate associated with exposure to this subset of ARVs in children is not known. Emtricitabine is known to reduce mitochondrial transmembrane potential in PBMCs from HIV-uninfected adults treated with post-exposure prophylaxis (36). NNRTIs have also been associated with mitochondrial effects *in vitro*. Efavirenz has been shown to affect mitochondrial oxidative phosphorylation and apoptosis *in vitro* and could account for increased lactate concentrations (1, 19, 37); however further studies will be needed to confirm this observation and its clinical relevance. Analysis of maternal ARVs used in pregnancy by mothers of SMARTT participants between the years of 1995 and 2009 found that US medication prescribing practices for HIV infected pregnant women have changed over time. By 2009 tenofovir disoproxil fumarate and emtricitabine had become the most commonly used NRTIs after zidovudine and lamivudine. Although use of NNRTIs in pregnancy peaked in 2003 with nevirapine most common overall in this class, by 2009 efavirenz use had become more prevalent than nevirapine. (38) Secular trends in maternal ARV usage provides an indication that prescribing practices for HIV infection during pregnancy are likely to continue to evolve,

with need for ongoing monitoring for infant and childhood toxicities, however routine POC lactate monitoring for these ARV exposures are not clearly indicated currently.

POC capillary blood lactate determination was advantageous in this large epidemiologic study conducted at multiple centers since the assay avoids some of the issues which make venous testing procedures complex in an infant or child. Several POC lactate devices have been used in human studies and offer simplicity of assay performance with standardization to an external control sample, but it is necessary to obtain a free flowing drop of capillary blood in order for the test to be valid. Site personnel receive technical training for POC lactate measurements, but adherence to performance standards cannot be absolutely assured and may account for some of the discrepancies between elevated POC lactate measurements and normal venous lactate observed at the same visit.

We observed a low frequency of elevated blood lactate concentrations overall (3.4%) but the relationship of elevated lactate in infancy and childhood to later clinical outcome is currently unknown. There was an increased risk of elevated lactate in the modest number of children exposed *in utero* to emtricitabine and efavirenz, to cocaine and opiate use, and those of Hispanic/Latino ethnicity. In the current study, the risk of elevated lactate with *in utero* ARV exposure was low.

Over the last fifteen years, the rate of vertical transmission of HIV infection from mothers to their infants has decreased dramatically in this country, and efforts are in force to make these advances available to women around the globe. ARV drugs used in combination for treatment of HIV disease in pregnant women or to prevent maternal-to-child transmission may result in complex interactions and adverse effects. Furthermore, the role of individual genetic susceptibility in adverse reactions to ARV medications is being investigated. (38) Ongoing studies to determine the safest and most effective regimens to prevent HIV transmission to infants while preserving maternal health should remain a priority. The SMARTT study continues to enroll and follow infants with *in utero* exposure to ARVs, including new antiretroviral agents and combinations as they enter clinical usage. POC lactate measurements as well as other evaluations continue to be monitored as new infants enter this longitudinal study. These ongoing assessments will help to determine which evaluations are most important for defining infant toxicities and whether POC lactate monitoring should be recommended for HIV uninfected infants exposed prenatally to ARV medications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of 1641 Infants and Children Enrolled in the SMARTT Study with Point of Care (POC) Lactate Measurements

Characteristic	Total (N=1641)
Female	810 (49%)
Age in years at Entry, Median (IQR) ^a	2.1 (0 – 5.6)
Age in years at POC, Median (IQR)	3.0 (1.0 – 6.8)
<i>Race/ethnicity^b</i>	
Black/African-American	1061 (65%)
White or Other	475 (29%)
Hispanic/Latino	565 (34%)
<i>Infant characteristics</i>	
Preterm Birth (gestation < 37 wks) ^c	318 (20%)
Low Birth Weight (< 2500 g) ^d	306 (19%)
<i>Maternal Health Status Prior to Labor and Delivery</i>	
Viral load >1000 copies/mL ^e	267 (18%)
CD4 count <250 cells/ mm ^{3f}	248 (17%)
CD4% <25% ^g	442 (30%)
<i>Maternal Substance Use During Pregnancy^h</i>	
Alcohol/Tobacco use	339 (23%)
Cocaine or opiate use	48 (3%)

Percentages calculated excluding those with missing or unknown characteristics:

^a IQR- Inter-quartile range

^b 105 subjects had unknown race or did not wish to report race

^c 36 missing information on gestational age at birth

^d 26 missing birth weight

^e 171 missing maternal viral load

^f 146 missing maternal CD4 count

^g 182 missing maternal CD4 percent

^h 156 missing maternal substance use during pregnancy, primarily due to non-enrollment of mothers of some Static Cohort participants.

Table 2

Associations of Subject and Maternal Characteristics with Elevated POC Lactate (>3 mmol/L)

Characteristic	Sample Size	Percent with characteristic	Percent with high POC, among those with characteristic	Percent with high POC, among those without characteristic	OR	95% Confidence Interval	P-value
Female	1639	49.4	2.7	4.0	0.67	(0.39, 1.17)	0.16
Nonwhite	1536	68.2	2.6	5.3	0.47	(0.27, 0.82)	0.01
Hispanic/Latino	1638	34.5	4.6	2.7	1.74	(1.02, 2.99)	0.05
Age < 6 months	1641	20.5	3.6	3.3	1.09	(0.57, 2.09)	0.80
Infant Characteristics							
Preterm	1605	19.8	3.5	3.3	1.04	(0.53, 2.03)	0.92
LBW ^a	1615	18.9	2.6	3.5	0.74	(0.34, 1.58)	0.43
LBW and full term	1614	6.4	4.8	3.2	1.51	(0.59, 3.86)	0.40
Maternal Exposures and Health Status During Pregnancy							
Viral load > 1000 copies/ml*	1470	18.2	2.6	3.7	0.71	(0.32, 1.59)	0.41
CD4 < 250/mm ^{3b}	1495	16.6	3.6	3.3	1.11	(0.53, 2.31)	0.79
CD4% <25% ^b	1459	30.3	2.5	3.8	0.64	(0.32, 1.26)	0.20
Alcohol or tobacco use during pregnancy	1485	22.8	1.8	3.7	0.47	(0.20, 1.12)	0.09
Alcohol or tobacco use during 1 st trimester	1476	21.3	1.6	3.7	0.42	(0.16, 1.07)	0.07
Cocaine or opiate use during pregnancy	1485	3.2	10.4	3.0	3.77	(1.42, 9.99)	0.01
Cocaine or opiate use during 1 st trimester	1483	2.6	10.5	3.0	3.75	(1.27, 11.02)	0.02

^aLow birth weight^bMaternal viral load and CD4 measurements were the latest available prior to or during labor and delivery.

Table 3

Association Between Overall *in utero* Exposure to Individual Antiretroviral Agents and Elevated POC Lactate in HIV-exposed Uninfected Infants and Children

Antiretroviral Agent ^a	Percent exposed	%POC > 3 mmol/L among exposed	%POC > 3 mmol/L among unexposed	Unadjusted OR (95% CI) ^b	P-value	Adjusted OR ^c (95% CI)	P-value
Nucleoside Reverse Transcriptase Inhibitor (NRTIs)							
Zidovudine	82%	3.0%	4.2%	0.70 (0.36, 1.36)	0.30	0.77 (0.37, 1.58)	0.48
Stavudine	6%	1.1%	3.4%	0.32 (0.04, 2.33)	0.26	0.32 (0.04, 2.35)	0.26
Didanosine	5%	6.4%	3.1%	2.16 (0.83, 5.59)	0.11	1.56 (0.47, 5.20)	0.47
Lamivudine	80%	3.0%	4.2%	0.72 (0.38, 1.36)	0.31	0.77 (0.37, 1.59)	0.48
Abacavir	22%	4.7%	2.8%	1.69 (0.92, 3.09)	0.09	1.82 (0.96, 3.45)	0.07
Tenofovir	19%	5.0%	2.8%	1.81 (0.98, 3.36)	0.06	1.85 (0.96, 3.54)	0.07
Emtricitabine	14%	5.6%	2.9%	2.02 (1.04, 3.92)	0.04	2.23 (1.12, 4.42)	0.02
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)							
Efavirenz	4%	9.4%	3.0%	3.36 (1.38, 8.20)	0.008	4.05 (1.62, 10.1)	0.003
Nevirapine	12%	4.3%	3.1%	1.42 (0.66, 3.07)	0.37	0.92 (0.35, 2.38)	0.86
Protease Inhibitors (PIs)							
Atazanavir	9%	5.6%	3.0%	1.91 (0.88, 4.15)	0.10	1.97 (0.89, 4.35)	0.09
Indinavir	3%	4.4%	3.2%	1.40 (0.33, 5.96)	0.65	1.63 (0.38, 7.09)	0.51
Ritonavir	15%	3.3%	3.2%	1.03 (0.48, 2.23)	0.93	1.14 (0.52, 2.49)	0.74
LPV/RTV ^d	28%	2.7%	3.5%	0.77 (0.40, 1.48)	0.43	0.91 (0.46, 1.78)	0.77
Nelfinavir	30%	2.8%	3.4%	0.80 (0.42, 1.51)	0.49	0.65 (0.32, 1.34)	0.25
Saquinavir	4%	0.0%	3.3%	---	---	---	---

^aOf the 1641 participants with POC Lactate measurements, 69 did not have maternal ARV exposure available; models above are based on 1572 with both POC Lactate and maternal ARV exposure.

^bConfidence interval

^cAdjusted for non-White race and maternal use of any hard drug (cocaine, opiates) during pregnancy.

^dLopinavir/Ritonavir