

eNeonatal Review

Jointly Presented by The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing

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November 2006 VOLUME 4, NUMBER 3

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World-wide, about 2 million HIV-infected women give birth each year, with about 500,000 of their infants becoming infected. About 5,000-6,000 of these women are in the U.S., but because the large majority of them receive timely and potent intervention, transmission occurs in only about 200 of their infants. How this was accomplished, and the potential risks that these solutions may entail in the form of birth defects or other fetal toxicity are the subject of this issue.

The benefit of antiretroviral prophylaxis to reduce the risk of infection of the fetus was first demonstrated with the use of a single drug, zidovudine, in 1994. By the late 1990's it became evident that highly active antiretroviral therapy with a combination of drugs had the potential to virtually eliminate vertical transmission of HIV. Around the same time, cesarean delivery in combination with single-drug prophylaxis was also shown to reduce transmission to very low rates.

In this issue, we weigh the relative merits of pharmacologic or surgical intervention, and review studies investigating two of the potential risks of antiretroviral drugs in pregnancy — birth defects and mitochondrial damage.

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Guest Editors of the Month



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Unlabelled/Unapproved Uses:

The use of antiretroviral drugs for the indication of prevention of transmission of HIV to the infant is discussed. This is not a labeled indication for these agents.

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Learning Objectives

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CME/CE activity.

At the conclusion of this activity, participants should be able to:

- Discuss the relative merits of pharmacologic or surgical intervention in pregnant HIV-infected women
- Describe the potential risks of using antiretroviral drugs during pregnancy
- Integrate the data presented into current treatment paradigms to minimize mother-child HIV transmission

Commentary

Without intervention, transmission of HIV to the fetus during the first trimester is very rare; the risk is about 2% in the second trimester and about 5% in the 3rd trimester, so that by the onset of labor, about 7% of fetuses are infected. There is a high risk – about 12% – of transmission during vaginal delivery. Thus, through the time of birth, there is roughly a 20% chance of infection. Breastfeeding for 24 months adds an additional 15% risk of infection.

Various factors modify the risk of transmission (particularly maternal viral load, mode of delivery, prematurity, duration of rupture of membranes, type and duration of breastfeeding, and fetal and maternal immunologic characteristics), but maternal antiretroviral therapy and feeding type are the most important modifiers. Although there may be geographic differences in host and pathogen factors, studies around the world have shown a remarkable similarity in the natural history of vertical transmission of HIV.

In 1994, it was demonstrated that transmission of HIV from mother to child could be reduced by about two-thirds with zidovudine prophylaxis begun around the second trimester and continued through 6 weeks of life. Highly active antiretroviral therapy (HAART) with 3 or more drugs was introduced for the treatment of symptomatic HIV infection in 1996. Soon thereafter, several case series noted the absence of mother-to-child transmission (MTCT) among women receiving HAART^[1]. The Women and Infants' Transmission Study, reviewed herein, showed that early, potent antiretroviral therapy can almost entirely eliminate transmission of HIV during pregnancy and parturition^[2]. Also in the late 1990's, it was shown that elective cesarean delivery reduced the risk of transmission – but this was found only in women not receiving potent, effective antiretroviral therapy^[3,4,5].

What is the role of elective cesarean delivery in the HAART era? All evidence to date points to the benefit of cesarean delivery only in women not receiving potent and effective (as measured by viral load) antiretroviral therapy. Thus, when well-counseled, well-managed, and adherent to therapy, most women can be assured that they may safely deliver vaginally.

But at what cost do we reap the benefit of antiretroviral prophylaxis? There are several potential risks that must be considered: birth defects, delayed or subtle toxicity in the exposed child, adverse effects peculiar to the pregnant woman, and effect on duration of pregnancy among them. All of the antiretrovirals are pregnancy category B or C, except for efavirenz, which is category D (based on animal studies and case reports, but not prospective surveillance). Additionally, prospective surveillance suggests that didanosine may cause birth defects. Continued surveillance for birth defects is needed, and all providers of HIV care for pregnant women are strongly encouraged to prospectively enter all pregnant women receiving antiretroviral drugs into the patient-anonymous [Antiretroviral Pregnancy Registry](#).

Also of concern is the potential for more subtle effects on cellular metabolism and brain development. The nucleoside reverse transcriptase inhibitor (NRTI) class of antiretrovirals are all 2',3'-dideoxyribonucleotide analogues that act by incorporating into and terminating the DNA chain as it is synthesized. Although relatively specific for HIV reverse transcriptase, several NRTIs are substrates for mitochondrial DNA polymerase and damage the mitochondrial chromosome. Symptomatic and even fatal mitochondrial toxicity has been linked to fetal and neonatal exposure to NRTIs^[6,7]. Although a fatal outcome may occur only under unusual circumstances, these reports raise the question as to whether there may be more common but subtle effects. Nucleoside analogue exposure may cause increased plasma lactate levels and decreased mitochondrial DNA content; it has also been suggested that HIV infection in the mother may somehow have an effect on fetal mitochondria, even in the absence of antiretroviral exposure^[6-11]. Whether NRTI exposure affects the long-term development and health of the infant remains an open question that needs continued investigation.

Prevention of mother-to-child transmission has been one of the greatest successes in the fight against the global epidemic of HIV. This success is achieved only with the continued efforts and diligence of all who care for pregnant women and their infants. Every instance of vertical transmission represents a lost opportunity.

Eliminating mother-to-child transmission of HIV requires early engagement in prenatal care, skilled counseling and HIV testing (and sometimes repeat testing), carefully chosen and intensely monitored antiretroviral prophylaxis, testing and close follow up of the exposed infant, and – throughout – sensitive and supportive care. For more details on applying these principles, clinicians are referred to applicable guidelines for resource-rich settings, such as those of the U.S. Public Health Service^[12,13], and for resource-limited settings, such as those of the WHO^[14].

It is within our technical ability to prevent mother-to-child transmission of HIV. But realizing that potential, especially in the resource-limited settings where the vast majority of HIV-exposed infants are born — and doing so safely — remain difficult challenges.

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EARLY POTENT ANTIRETROVIRAL THERAPY REDUCES MOTHER-TO-CHILD TRANSMISSION

Cooper ER. Charurat M. Mofenson L. Hanson IC. Pitt J. Diaz C. Hayani K. Handelsman E. Smeriglio V. Hoff R. Blattner W. Women and Infants' Transmission Study Group. **Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission**. Journal of Acquired Immune Deficiency Syndromes: JAIDS. 29:484-94, 2002.

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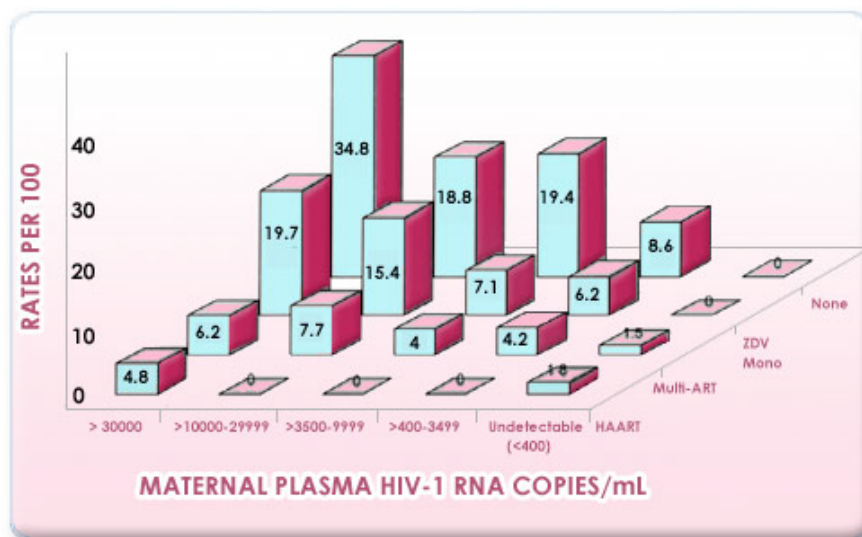
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Although a randomized, controlled trial of highly active antiretroviral therapy (HAART) for prevention of mother-to-child transmission of HIV is unlikely to ever be performed, we have the benefit of large prospective cohort studies. Cooper et al, reporting on data from the Women and Infants' Transmission Study (WITS), examined the relationship between maternal antiretroviral prophylaxis, viral load at term, and risk of transmission in 1542 woman-infant pairs from 1990-2000, a period that spans the eras of no prophylaxis, zidovudine monotherapy, 2-drug therapy ("multi-ART"), and HAART.

The relationships reported between viral load, intensity of antiretroviral therapy, and risk of transmission are depicted as below:

Material Plasma HIV-1 RNA Levels and Antiretroviral use during Pregnancy



J Acquir Immune Defic Syndr. 2002 Apr 15;29(5): 484-94.

The data across the back row (the risk of transmission on no therapy) show a strong relationship between maternal viral load and risk of transmission. A similar though less pronounced relationship is seen moving left to right across viral load strata for monotherapy, 2-drug therapy, or HAART. If we look at transmission rates within a viral load stratum and move from back to front on the graph we see a striking decrease in risk of transmission with increasing number of drugs used, independent of viral load. This observation, which is consistent with data for the original placebo-controlled trial of zidovudine, indicates that antiretrovirals act both by decreasing maternal viral load and by a mechanism independent of maternal viral load. Risk of transmission also decreased with increasing duration of antiretroviral therapy during pregnancy, independent of the number of drugs taken. The observation of transmission in 1.8% of women taking HAART and having an undetectable viral load at delivery (the lower right data bar) might suggest that even fully suppressive HAART does not prevent all transmission. However, all three of the women who received HAART and transmitted virus to their infant were receiving HAART only for short durations (1 of 4 study visits), suggesting that infection was acquired in utero prior to late institution of HAART. None of the 128 women taking 2-drug or multi-drug antiretroviral therapy at 3 or more of the 4 scheduled study visits (at entry and 18, 25, and 34 weeks gestation) delivered an infected infant, even though not all would have had undetectable viral loads.

The WITS data show that early, potent antiretroviral therapy was associated with "complete" (within the statistical limits) protection against mother-to-child transmission. This study, along with several randomized studies of shorter courses of antiretroviral prophylaxis in developing countries, helped to establish the risk of transmission at various points during pregnancy.

The WITS data also give us clues as to the mechanism of protection. Reduction of maternal viral load must be part but not all of the effect. The authors postulate that antiretrovirals: 1) may provide pre-exposure prophylaxis for the fetus; 2) may affect vaginal viral load independent of plasma viral load; or 3) may select for less infectious strains of virus. Studies of pre- or post-exposure prophylaxis in other settings suggest that the first hypothesis probably accounts for most of the viral load-independent effect. Of the 3 major classes of antiretroviral drugs - nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors - the NRTIs and NNRTIs cross the placenta well, while protease inhibitors do not. However, there are no reports suggesting that a 3-drug combination of 2 NRTIs plus a protease inhibitor is any less effective than 2 NRTIs plus an NNRTI. Thus, bringing maternal viral load down below the limit of detection while loading the fetus with therapeutic levels of at least 2 drugs appears to be sufficient to provide potent protection.


IS THERE A ROLE FOR CESAREAN DELIVERY IN THE ERA OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY?

The International Perinatal HIV Group. **The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1 – a meta-analysis of 15 prospective cohort studies.** *New England Journal of Medicine.* 340:977-87, 1999.

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The European Mode of Delivery Collaboration. **Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial.** *Lancet.* 353:1035-9, 1999.

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European Collaborative Study. **Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy.** *Clinical Infectious Diseases* 40:458-65. 2005.

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Recognizing that there is a high risk of HIV transmission during parturition, the potential protective effect of cesarean delivery was examined in two major studies. The International Perinatal HIV Group conducted a meta-analysis of 15 prospective cohort studies including 8533 mother-infant pairs delivering between 1982 and 1996, most of whom did not receive any antiretroviral prophylaxis. Among 7840 mother-infant pairs with complete data, a multivariate analysis adjusting for receipt of antiretroviral therapy, advanced maternal disease, and low birth weight (all known to correlate with risk of infection), elective cesarean delivery was associated with a lower risk of vertical transmission (odds ratio, 0.43, 95% confidence interval 0.33-0.56).

Vaginal delivery and non-elective cesarean delivery were associated with similar risks of transmission of HIV. However, when the time between rupture of membranes and delivery in non-elective cesarean deliveries was examined, the risk of transmission was lower than with vaginal delivery if cesarean delivery was accomplished within 4 hours of rupture of membranes (odds ratio 0.53, 95% confidence ratio 0.4-0.7).

The authors found that cesarean delivery lowered the risk of transmission among mother-infant pairs receiving antiretroviral prophylaxis (mostly zidovudine monotherapy) during pregnancy, labor, and the neonatal period (2.0% transmission, 95% confidence interval 0.1-4.0% with antiretroviral therapy and cesarean delivery, compared to 7.3%, 95% confidence interval 5.9-8.8, with antiretroviral therapy alone).

The European Mode of Delivery Collaboration conducted a randomized controlled trial of cesarean versus vaginal delivery for prevention of vertical HIV infection. Among the 370 mother-infant pairs for whom outcome data were available, 64% received antiretroviral prophylaxis. Among women assigned to cesarean delivery, 11.7% gave birth vaginally; among women assigned to vaginal delivery, 26.8% had operative deliveries, 54% of which were emergent. Infants of 1.8% of women assigned to the cesarean delivery group became infected with HIV, and 10.5% of infants of women assigned vaginal delivery became infected ($p < 0.001$). By actual mode of delivery, 3.5% of cesarean births and 10.2% of vaginal births produced infected infants. Among 119 women taking zidovudine and undergoing cesarean delivery, only 1 infant (0.8%) was infected.

There is a clear conclusion from these studies: elective cesarean delivery decreases the risk of HIV transmission in women receiving either no antiretroviral prophylaxis or zidovudine monotherapy alone. However, the response among clinicians differed depending generally on which side of the Atlantic they were located. In the U.S., caution about generalization of the results to women receiving HAART was urged and cesarean delivery rates did not increase as much as they did in Europe, where between 1999 and 2003 elective cesarean delivery was performed for about 65% of HIV-infected women.

The European experience in the HAART era (data from 1997 through mid-2004) was reviewed in the European Collaborative Study report on 1983 mother-child pairs. During this period, the use of HAART increased from about 5% of pregnancies to about 85%. This study confirmed key findings of the WITS — that a lower viral load and potent antiretroviral therapy dramatically reduces risk of transmission.

In addition, the authors stated that among women receiving HAART whose most recent viral load was undetectable, cesarean delivery was associated with an additional reduction in the risk of transmission. Yet the confidence interval for this association in the data was 0.08-5.37 ($p = 0.7$). Only 1 woman receiving HAART and delivering vaginally transmitted the virus, and her viral load at term and the duration of HAART therapy

were unclear. We do know that of the 11 infected children of mothers receiving HAART (10 of whom had cesarean deliveries, half of which were emergent), the median duration of HAART was only 38 days and most had advanced HIV disease. While the authors conclude that "offering an elective Caesarean delivery to all HIV-infected women, even in areas where HAART is available, is appropriate clinical management, especially for persons with detectable viral loads", their data, along with the data from WITS and other case series, show that early, effective HAART is sufficient to prevent HIV transmission and additional benefit from cesarean delivery could not be demonstrated.

DO ANTIRETROVIRAL DRUGS CAUSE BIRTH DEFECTS?

Antiretroviral Pregnancy Registry Steering Committee. **Antiretroviral pregnancy registry international interim report for 1 January 1989 through 31 January 2006.**

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The Antiretroviral Pregnancy Registry (APR), managed by Charles River Laboratories Clinical Services and supported financially by antiretroviral manufacturers, reports data on teratogenic effects from two large European registries and the published literature. The APR's most recent semi-annual review of the outcome of 6893 instances of antiretroviral use in pregnancy (prospectively reported directly to the APR) describes birth defects in 2.9% of the 2117 reported first trimester antiretroviral exposures. This is comparable to the rate reported by the CDC's population-based surveillance system – 2.2% for defects diagnosed by the first day of life and 3.1% for defects discovered at any time.

There were enough reports in the APR to provide ample power for the detection of a two-fold increase in birth defects associated with first trimester exposure for 9 antiretrovirals. For 8 of these there was no increase over the expected prevalence. For didanosine, 6.0% of first trimester exposures were associated with birth defects (95% confidence interval 3.3-9.8%), although there was no specific pattern to the reported defects.

Efavirenz exposure was of special theoretical concern because in a preclinical study exposing 20 pregnant cynomolgus monkeys to levels of drug comparable to human use, 3 offspring had serious defects: anencephaly, microphthalmia, and cleft palate (described in the efavirenz [product labeling](#)). The APR recorded the outcome in 244 cases of first trimester efavirenz exposure and found 6 cases with birth defects, which is within the expected natural rate. Importantly, the defects seen were similar to common defects in the general population and did not resemble the defects seen in exposed monkeys. Although these data are reassuring, retrospective reports of 4 cases of neural tube defects after first trimester efavirenz exposure prompted the U.S. Food and Drug Administration to reclassify efavirenz as a pregnancy category D drug.

The data on birth defects after antiretroviral exposure are generally reassuring. There is enough data in humans to say that efavirenz may cause birth defects in humans – however, at a much lower rate or with more subtle manifestations than the disturbing outcomes seen in monkeys. Pending further data, we must also remain concerned about the increased prevalence of all birth defects associated with early didanosine exposure.

NUCLEOSIDE ANALOGUES & MITOCHONDRIAL DYSFUNCTION IN ANTIRETROVIRAL-EXPOSED INFANTS

Blanche S. Tardieu M. Rustin P. Slama A. Barret B. Firtion G. Ciraru-Vigneron N. Lacroix C. Rouzioux C. Mandelbrot L. Desguerre I. Rotig A. Mayaux MJ. Delfraissy JF. **Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues.** *Lancet.* 354:1084-9, 1999.

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Barret B. Tardieu M. Rustin P. Lacroix C. Chabrol B. Desguerre I. Dollfus C. Mayaux MJ. Blanche S. For the French Perinatal Cohort Study Group. **Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in a large prospective cohort.** *AIDS.* 17:1769-85, 2003.

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The Perinatal Safety Review Working Group. **Nucleoside exposure in the children of HIV-infected women receiving antiretroviral drugs: absence of clear evidence for mitochondrial disease in children who died before 5 years of age in five United States cohorts.** *Journal of Acquired Immune Deficiency Syndromes: JAIDS.* 25:261-8, 2000.

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In 1999 Blanche and colleagues reported 8 cases of mitochondrial dysfunction with abnormally low absolute or relative activities of respiratory-chain complexes months or years after the end of antiretroviral treatment. The cases were identified from 1754 infants exposed to antiretrovirals in a prospective French cohort study. Two of the infants were asymptomatic and five of the infants had seizures, 2 of whom had progressive brain disease followed by death at around one year of age. Various other abnormalities such as lactic acidosis, increased serum levels of hepatic, pancreatic, or muscle enzymes, cardiomyopathy, brain MRI images, or electroretinography were seen inconsistently. In the three infants in whom it was evaluated, mitochondrial DNA content was normal. Potential causes, including known genetic diseases affecting mitochondria, were excluded.

In 2003, the same group described the retrospective search for mitochondrial disease in a prospective cohort study of 2644 antiretroviral-exposed and 1748 non-antiretroviral-exposed infants, in addition to cases included in a national registry of HIV-exposed infants. The study relied primarily on enzymatic and ultrastructural studies of muscle biopsies from children with suspicious symptoms. After systematic review of the records, 14 cases of possible and 7 cases of established mitochondrial disease were identified among the antiretroviral-exposed infants (these included the 8 original cases). In contrast, no instances of possible or established mitochondrial disease were found among the infants of HIV-infected mothers who were not exposed to antiretrovirals.

The initial French report was alarming, and in response the Perinatal Safety Review Working Group was formed in the U.S. to examine deaths among subjects into 5 cohort studies that included 16,313 HIV-exposed, uninfected infants, of which 75% definitely or probably were exposed in utero to antiretrovirals. A total of 252 deaths were categorized in 5 groups: 1) unrelated to mitochondrial disease; 2) consistent with mitochondrial disease but unlikely; 3) mitochondrial disease "might reasonably be included in the differential diagnosis"; 4) mitochondrial disease suggestive or proven; or 5) SIDS.

There were 30 deaths among uninfected children, 14 of whom were definitely or probably antiretroviral-exposed, and 16 of whom were not or probably not antiretroviral-exposed. SIDS was the cause of death for 4 of the uninfected children. All of the other 26 HIV-uninfected, antiretroviral-exposed infants died of causes deemed to be unrelated to mitochondrial disease. Death from all causes was several-fold more common in children whose HIV status was indeterminate. These included 3 for whom mitochondrial disease might reasonably be included in the differential; however, 2 of these children were definitely not exposed to antiretrovirals and the other's prenatal exposure was unknown.

There were no deaths among HIV-uninfected children exposed to both zidovudine and lamivudine. Among infants of negative or indeterminate HIV status, there were 14 SIDS deaths among about 10,000 zidovudine-exposed infants and 14 deaths among about 3,000 antiretroviral-unexposed infants. Considering the demographics of SIDS at the time of the deaths under review, the authors did not find evidence of an increased incidence of SIDS over what was expected.

So how do we resolve the apparent discrepancy between these two studies? While the 2 fatal French cases are striking, it seems unlikely that the U.S. study would have missed similar events. It is more plausible to assume that cases similar to the more subtly affected French infants could be missed without active surveillance.

In addition, there is an important distinction between the antiretroviral exposure in four of the French cases (including both fatal cases) and the practice in the U.S. In the U.S., combination antiretroviral therapy for pregnant women commonly includes zidovudine and lamivudine – but only zidovudine is given to the newborn if the mother received prenatal treatment. In France, however, it was common practice to give zidovudine and lamivudine to both the mother and to the infant. But even if we accept that this difference in exposure pattern may account for the absence of fatal mitochondrial disease in the U.S., legitimate concern must remain over the potential for more subtle effects.

NUCLEOSIDE ANALOGUE ANTIRETROVIRALS & SUBCLINICAL MITOCHONDRIAL DAMAGE

Alimenti A. Burdge DR. Ogilvie GS. Money DM. Forbes JC. **Lactic acidemia in human immunodeficiency virus-uninfected infants exposed to perinatal antiretroviral therapy.** *Pediatric Infectious Disease Journal.* 22:782-9.

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Noguera A. Fortuny C. Munoz-Almagro C. Sanchez E. Vilaseca MA. Artuch R. Pou J. Jimenez R. **Hyperlactatemia in human immunodeficiency virus-uninfected infants who are exposed to antiretrovirals.** *Pediatrics.* 114:e598-603, 2004.

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Divi RL, Walker VE, Wade NA, Nagashima K, Seilkop SK, Adams ME, Nesel CJ, O'Neill JP, Abrams EJ, Poirier MC. **Mitochondrial damage and DNA depletion in cord blood and umbilical cord from infants exposed in utero to Combivir.** *AIDS.* 18:1013-21, 2004.

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Poirier MC, Divi RL, Al-Harthi L, Olivero OA, Nguyen V, Walker B, Landay AL, Walker VE, Charurat M, Blattner WA. Women and Infants Transmission Study (WITS) Group. **Long-term mitochondrial toxicity in HIV-uninfected infants born to HIV-infected mothers.** *Journal of Acquired Immune Deficiency Syndromes: JAIDS.* 33:175-83, 2003.

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Alimenti et al. prospectively measured plasma lactate levels during the first 6 months of life in 38 British Columbian infants, 35 of whom were exposed to antiretroviral regimens containing 2 nucleoside analogues starting a mean of 17 weeks prior to delivery. A lactate level greater than the upper limit of normal (2.1 mM) was found on at least one measurement in 92% of infants and 26% had levels >5 mM. Among 33 infants followed beyond 28 weeks of life, lactate levels normalized in all but 2 (94%). Other than two infants with irritability and vomiting in the first 2 weeks of life, no infant had symptoms suggestive of mitochondrial dysfunction. There was no association between lactate level and duration of antiretroviral therapy or exposure to stavudine (a nucleoside analogue with more potent inhibition of mitochondrial DNA polymerase).

Noguera and colleagues in Spain prospectively followed 127 infants exposed to antiretrovirals, mostly zidovudine or stavudine plus lamivudine and nevirapine or nelfinavir, for a mean duration of 31 weeks during pregnancy, followed by intrapartum and neonatal zidovudine. Results were considered abnormal only when both lactate and alanine were elevated. Control levels were obtained from aged-matched infants undergoing venipuncture for routine presurgical testing. The mean lactate level in antiretroviral-exposed infants was 2.88 mM at 6 weeks and decreased steadily to 1.71 mM by 12 months, significantly different ($p < 0.0001$) at each of the 4 time points from controls, which was 1.61 mM at 6 weeks and 1.24 mM by 12 months. Three of the exposed infants had transient neurologic abnormalities, one of whom had especially high lactate levels (about 7 mM through the first 6 months of life).

The authors point out that the prevalence of hyperlactatemia in HIV-uninfected, antiretroviral-exposed infants they describe is higher than the prevalence among HIV-infected children receiving antiretroviral therapy at their institution (17%).

Divi and colleagues found moderate to severe damage to umbilical cord arterial endothelium mitochondria by transmission electron microscopy in blinded specimens from 6 of 9 infants exposed in utero to zidovudine and lamivudine, whereas specimens from unexposed controls were normal. The severity of damage correlated with duration of prenatal exposure. The ratio of copies of the mitochondrial mtD loop gene to copies of the nuclear 18S RNA gene in both cord blood mononuclear cells and umbilical cord was higher in infants of HIV-uninfected controls than in antiretroviral-exposed infants. Review of medical records did not reveal associations between maternal health, other exposures, maternal age, or morphologic and genetic findings.

Poirier and colleagues from the WITS Group compared mitochondrial DNA content (using the same genes as Divi et al) and telomere length in peripheral blood leukocytes from control infants of 20 HIV-uninfected mothers, 10 antiretroviral-unexposed infants of HIV-infected mothers, and 10 infants with prenatal and neonatal zidovudine exposure. The mitochondrial:nuclear copy ratio was 146 at birth for the zidovudine-exposed infants and 442 for the controls, and the difference remained significant at 1 and 2 years ($p < 0.05$ at all 3 time points). Interestingly, the ratio was intermediate in the zidovudine-unexposed, HIV-exposed infants; significantly less than controls at birth, 1 year, and 2 years; and significantly greater than zidovudine-exposed infants at birth and 2 years. There were no differences in telomere length between the three groups. The authors did not offer speculation on how HIV status in the mother, without antiretroviral exposure, could affect mitochondrial DNA content in the infant.

Taken together, these studies of plasma lactate levels and mitochondrial DNA content suggest that antiretroviral-exposed infants have measurable effects on mitochondria. The clinical significance of any metabolic, ultrastructural, or genetic abnormalities is unknown. Obtaining plasma lactate levels free of artifact from hypoxia or ischemia related to phlebotomy is difficult. The Alimenti study purports to have taken precautions to prevent artifact; the Noguera study describes the control population and confirmed high lactate levels with elevated alanine. The finding of Poirier and colleagues that infants of HIV-infected mothers who were not exposed to antiretrovirals have decreased mitochondrial DNA copy number in peripheral leukocytes is surprising.

Various metabolic abnormalities, including evidence of mitochondrial damage, can be observed in antiretroviral-naïve adults infected with HIV. Potential mechanisms for a chronic systemic infection to cause such abnormalities can be envisioned, but how an uninfected fetus might be affected by a mother's HIV infection is less clear. It should be noted that the Poirier study was performed in the era when only zidovudine was given to pregnant women. The routine use of HAART for prevention of mother-to-child transmission of HIV might conceivably ameliorate effects of maternal HIV infection on the fetus.

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Ask a Question about this Newsletter 

Ask the Authors

LAST MONTH'S Q & A October 2006 - Volume 4 - Issue 2

Last issue we reviewed several recent studies on the effectiveness and potential risks of caffeine use in neonates.



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The eNeonatal Review Team asked the October faculty a few questions.

Q Has evidence shown monitoring of caffeine levels to be of any value while treating apnea of prematurity?

A Caffeine levels used for the short-term prevention/treatment of apnea of prematurity (AOP) have been cited as 5-20 mg/l, with the goal of providing adequate therapy while minimizing toxicity. Two reports of accidental overdose show transient physiologic changes associated with and without caffeine levels being obtained.

One case report^[1] of short-term toxicity from an accidental overdose of 160 mg/kg in a premature infant documented hypertonia, sweating, tachycardia, cardiac failure, pulmonary edema and metabolic acidosis with hyperglycemia (plus elevation of creatine kinase and gastric dilatation) at a caffeine level of 217 mg/l at 36 hours post-dose, with resolution of signs at a corresponding level of 60-70 mg/l. Another case report^[2] of an accidental dose of 300 mg/kg in a 30 day old premature infant described similar signs with resolution after 96 hours without levels being obtained (due to lack of facilities).

In a pharmacologic study^[3] of caffeine metabolism in premature infants, researchers measured caffeine metabolites and associated higher clearances with higher weights, higher post-natal ages and female gender. Another study of premature Asian infants with apnea^[4] documented levels of 10-20 mg/l with tolerable adverse effects (gastrointestinal disturbances, diuresis and hyperglycemia), and researchers concluded that weight was the sole parameter associated with therapeutic dosing.

Caffeine levels may be an important adjunct for monitoring the balance between adequate therapy and toxicity. Less invasive methods of measuring plasma caffeine levels such as urinary caffeine levels^[5] are being explored and may be of interest and clinical utility.

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[pharmacokinetics](#). Anaesth Intensive Care. 1999 Jun;27(3):307-11.

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5. Cattarossi L, Violino M, Macagno F, Logreco P, Savoia M. [Correlation between plasma and urinary caffeine levels in preterm infants](#). J Perinat Med. 2006;34(4):344-6.



While there are "encouraging" results from the CAP study regarding the potential effect of caffeine on neurodevelopmental outcomes of preterm infants, other studies suggest alteration of cerebral blood flow after caffeine administration, which in theory could adversely affect the brain. How premature are we in reassuring ourselves that caffeine is indeed safe for these infants?



Such questions are aims of the international CAP trial^[1] to examine the long-term effects and safety of caffeine in the management of AOP. Mortality and neurodevelopmental morbidity, including cerebral palsy, cognitive deficit, bilateral blindness and deafness, are measured at 18 months and are planned for follow up (mortality and morbidity in cognition, neuromotor function, behavior, vision, hearing, and general health) at 5 years.

Methylxanthines increase oxygen consumption and inhibit/alter the expression of receptors for adenosine, which is neuroprotective in hypoxia/ischemia of the developing brain. Experimental evidence shows that mice deficient in these receptors display anxious and aggressive behavior, but its effect on the growth, neurologic and cognitive development and childhood behavior of premature infants is unknown^[1,2]. Continuing follow-up data from the CAP trial will provide the data for rigorous evaluation of this neonatal therapy to answer the question.

References:

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2. Millar D, Schmidt B: [Controversies surrounding xanthine therapy](#). Semin Neonatol 2004; 9:239-244.

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Target Audience · [back to top](#)

This activity has been developed for Neonatologists, NICU Nurses and Respiratory Therapists working with Neonatal patients. There are no fees or prerequisites for this activity.

Learning Objectives · [back to top](#)

At the conclusion of this activity, participants should be able to:

- Discuss the relative merits of pharmacologic or surgical intervention in pregnant HIV-infected women
- Describe the potential risks of using antiretroviral drugs during pregnancy

- Integrate the data presented into current treatment paradigms to minimize mother-child HIV transmission

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- Dr. Nogee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.
- Dr. Lehmann has indicated a financial relationship in the form of honorarium from the Eclipsys Corporation.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

Unlabelled/Unapproved Uses · [back to top](#)

The use of antiretroviral drugs for the indication of prevention of transmission of HIV to the infant is discussed. This is not a labeled indication for these agents.

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