



**Recommendations for the Use of Antiretroviral Drugs in  
Pregnant Women with HIV Infection and Interventions to Reduce  
Perinatal HIV Transmission in the United States**

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## Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs (Last updated December 7, 2018; last reviewed December 7, 2018)

### Panel's Recommendation

- Children with *in utero* or neonatal exposure to antiretroviral (ARV) drugs who develop significant organ system abnormalities of unknown etiology, particularly of the nervous system or heart, should be evaluated for potential mitochondrial dysfunction (CIII).
- It is important that the long-term medical record of a child without HIV includes information about *in utero* and neonatal ARV exposure (BIII).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion

Beginning in the 1990s, evolving long-term monitoring studies, outcomes studies, and other types of surveillance and research have been conducted to assess whether *in utero* exposure to antiretroviral (ARV) drugs may pose later risks to children's health. These include studies of children without HIV born to women with HIV infection, e.g., the Pediatric AIDS Clinical Trial Group (PACTG) Late Outcomes Study, and the Surveillance Monitoring for ART Toxicities (SMARTT) from the Pediatric HIV/AIDS Cohort Study (PHACS). Participation of children and their parents in these types of observational studies provides an essential contribution to the research needed to monitor and identify long-term health outcomes from *in utero* HIV and ARV exposure. Available evidence does not permit definitive conclusions about whether exposure to ARV agents *in utero* might affect the long-term risk of malignancy, cardiometabolic, or neuropsychological outcomes in children; however, the balance of evidence accumulated during the past 2 decades, particularly related to zidovudine exposure, is reassuring. Potential toxicities require further, long-term investigation, especially as individual antenatal ARV drugs and ARV drug combinations continue to evolve. Initial data from follow-up of PACTG 076 infants through age 6 years did not indicate any differences in immunologic, neurologic, or growth parameters between infants who were exposed to the zidovudine regimen and those who received placebo, and no malignancies were noted.<sup>1,2</sup> However, concerns remain that exposure to ARV drugs may have long-term effects on mitochondrial and immunologic function. Ongoing studies within the PHACS and other cohorts of children who are HIV-exposed but uninfected may help to identify the long-term risks of ARV drug exposure in infancy.

### Potential Mitochondrial Toxicity

Nucleoside reverse transcriptase inhibitor (NRTI) drugs induce some degree of mitochondrial dysfunction reflecting varying affinity for mitochondrial gamma DNA polymerase. This affinity can interfere with mitochondrial replication, resulting in mitochondrial DNA (mtDNA) depletion and dysfunction.<sup>3-5</sup> Aberrant histological morphology of mitochondria, mtDNA mutations, alterations in mtDNA levels in cord blood mononuclear cells, and even aneuploidy in cord blood cells have all been described in both non-human primates and neonates exposed *in utero* to NRTI drugs.<sup>6-11</sup> Reported increased and decreased alterations in mtDNA levels add further complexity to interpretation of their clinical significance; in addition, the data may be confounded by stage of maternal HIV infection, differences in laboratory assays and cell lines used and duration of elevation.<sup>8,10,12-15</sup> One study has reported that respiratory chain mitochondrial function is subtly and transiently perturbed, with an increased incidence of abnormal newborn metabolic screen results for products of intermediary metabolism (elevated amino acids and acylcarnitines) in infants who are HIV exposed but uninfected compared with infants without HIV exposure.<sup>16</sup> The degrees to which these theoretical concerns and documented mitochondrial abnormalities are clinically relevant are unknown, but they are significantly outweighed by the robust, proven efficacy of maternal and infant ARV prophylaxis in preventing perinatal HIV transmission.<sup>8,17</sup>

Evidence of clinically apparent effects of mitochondrial toxicity are also conflicting. A low rate of hyperlactatemia (3.4%) is documented among infants who are HIV-exposed but uninfected born to U.S. women receiving antiretroviral therapy (ART).<sup>18</sup> However, earlier studies from the French Perinatal Study Group cohort noted a significantly increased incidence of clinical effects possibly reflecting mitochondrial dysfunction including seizures, cognitive and motor delays, abnormal neuroimaging, hyperlactatemia, cardiac dysfunction,

and two deaths, with abnormal mitochondrial histology noted among some infants without HIV born to women with HIV (who received or did not receive ARV drugs during pregnancy: 12/2,644 vs. 0/1,748, respectively,  $P = 0.002$ ).<sup>19,20</sup> Further clinical studies from the United States and Europe have not duplicated these reported findings from the French Studies.<sup>21-27</sup> In a report from a long-term follow-up study in the United States (PACTG 219/219C), 20 children with possible symptoms of mitochondrial dysfunction were identified among a cohort of 1,037 infants who were HIV-exposed but uninfected.<sup>26</sup> Definitive diagnosis was not possible because none of the children had biopsies for mitochondrial function; however, 3 of the 20 children had no exposure to ARV drugs. In the other 17 children, there was an association between symptoms and first exposure to zidovudine/lamivudine limited to the third trimester, but overall exposure to NRTI drugs was not associated with symptoms. Some small alterations in mtDNA and oxidative phosphorylation enzyme activities were documented in stored specimens from these children, but the clinical significance of these observations remains unknown.<sup>28,29</sup>

Given the above data, mitochondrial dysfunction should be considered in children without HIV, but with perinatal exposure to ARV drugs who present with severe clinical findings of unknown etiology, particularly neurologic findings. It is important that the long-term medical record of a child without HIV includes information about ARV exposure in the event that the child develops unusual symptoms later in life, or if adverse late effects of HIV or ARV exposure in children without HIV are identified in the future.<sup>8,30,31</sup>

### ***Potential Cancer Risk and Exposure to Nucleoside Reverse Transcriptase Inhibitor Drugs***

Although older studies have not found an association between *in utero* ARV exposure and malignancies, follow-up was limited to early childhood.<sup>1,2,27</sup> Animal studies have reported potential transplacental genotoxicity of nucleoside analogue therapy in monkeys, and micro-nucleated erythrocytes have been identified among infants with *in utero* nucleoside analogue exposure.<sup>32,33</sup> In an initial report from the French Perinatal Cohort in 2008, which included cross-check with the French National Cancer Registry, the incidence of cancer among 9,127 children who were HIV-exposed but uninfected (median age 5.4 years) was not significantly different from that expected for the general population; however, the relative risk of cancer for children was higher **with exposure to** a didanosine/lamivudine combination **than to** zidovudine monotherapy.<sup>34</sup> An updated report from the French Perinatal Cohort described 21 cancers in 15,163 children without HIV (median age 9.9 years) exposed *in utero* to HIV and  $\geq 1$  NRTI drug.<sup>35</sup> Among the NRTIs studied, didanosine (which **is no longer recommended**) was potentially associated with risk of cancer. In a study in the United States, there were 4 cancer diagnoses among 3,087 children exposed to HIV; cancer incidence in children who were HIV exposed but not exposed to ARV prophylaxis was not significantly different than incidence in children exposed to any ARV prophylaxis, and the number of cancer cases did not differ significantly from cases expected based on national reference rates.<sup>36</sup> Continued follow-up of children who are HIV- and ARV-exposed but uninfected is needed to evaluate the potential risk of cancer as these children age into adulthood.

### ***Potential Immunologic Dysfunction***

The potential impact of HIV exposure on the immune system of an infant without HIV is unclear. One study reported lower CD4 T lymphocyte (CD4) cell counts in HIV-exposed but uninfected infants born to mothers whose viral load at delivery was  $>1,000$  copies/mL than in HIV-exposed but uninfected infants whose mothers had a viral load  $<50$  copies/mL at delivery.<sup>37</sup> Other data suggest that exposure to HIV *in utero* may be associated with alterations in CD4 and CD8 cell-mediated immune responses in infants to vaccines and non-specific antigens in infants.<sup>38</sup> **More recent data indicate immune activation and proinflammatory responses are greater in infants who are HIV exposed than in infants who are HIV unexposed.**<sup>39-43</sup>

### ***Potential Increased Morbidity and Mortality***

The French Perinatal Cohort Group has reported an increased risk of serious bacterial infections with encapsulated organisms in infants HIV-exposed born to mothers with low CD4 numbers near the time of delivery.<sup>44</sup>

Data from Botswana also show higher rates of morbidity and mortality in infants and children HIV-exposed but uninfected than in infants HIV-unexposed.<sup>45-47</sup> A meta-analysis assessing all-cause mortality in infants and children HIV-exposed but uninfected consistently observed increased risk in this group compared to HIV-

unexposed infants.<sup>48</sup> Further study is needed regarding the reproducibility of these data, and whether there is an immunological basis for the increased susceptibility of infants and children HIV exposed but uninfected to infectious diseases.<sup>49</sup>

## Conclusion

Ongoing evaluation of the early and late effects of *in utero* exposure to ARV drugs and infant feeding approaches include the Pediatric HIV/AIDS Cohort Study Surveillance Monitoring of Antiretroviral Toxicity study, natural history studies, and HIV/AIDS surveillance conducted by state health departments and the Centers for Disease Control and Prevention. Because much of the available follow-up data to date relate to *in utero* exposure to antenatal zidovudine or other NRTIs alone, and most pregnant women with HIV currently receive ART regimens, it is critical that studies to evaluate potential adverse effects of *in utero* drug exposure continue to be supported. HIV surveillance databases from states that require HIV reporting provide an opportunity to collect population-based information concerning *in utero* exposure to ARV drugs. To the extent permitted by federal law and regulations, data from these confidential registries can be compared with information from birth defect and cancer registries to identify potential adverse outcomes.

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