

# Antiretroviral Drugs for Preventing Mother-to-Child Transmission of HIV: A Review of Potential Effects on HIV-Exposed but Uninfected Children

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**Abstract:** The provision of antiretroviral drugs for the prevention of mother-to-child HIV transmission has been rising sharply in low- and middle-income countries. Changes to the World Health Organization guidelines support further extension of these programs. The result will be a greatly expanded population of HIV-exposed but uninfected children with substantial exposure to antiretroviral drugs, both in utero and while breastfeeding. There are limited data on possible toxicities in this burgeoning population, and the large number of confounding factors limits any conclusions. Although the evidence on birth defects and mitochondrial toxicity remains equivocal, considerable data link protease inhibitors to preterm delivery and low birth-weight. Transient hematologic toxicities are also likely. The drug impact later in life is an open question. Larger and longer cohort studies are necessary to properly balance the risks and benefits of large-scale infant exposure to antiretroviral agents.

**Key Words:** antiretroviral, PMTCT, HIV-exposed uninfected infants, childhood growth and development, drug complications

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## INTRODUCTION

The provision of antiretroviral drugs for the prevention of mother-to-child HIV transmission (PMTCT) has been rising sharply in low- and middle-income countries, with the proportion of HIV-infected pregnant women receiving antiretroviral interventions climbing from 10% in 2004 to 53% in 2009.<sup>1</sup> In July 2010, the World Health Organization (WHO) published revisions to its PMTCT guidelines.<sup>2</sup> These revisions significantly expand the eligibility of HIV-infected pregnant women to receive life-long antiretroviral therapy when needed for the women's own health, increasing the CD4 threshold for therapy initiation to a CD4 count <350 cells per cubic millimeter regardless of clinical stage and to WHO stage 3 or 4 disease regardless of CD4 count. For women not requiring therapy for their own health, 2 strategies with similar PMTCT efficacy are offered. One option is zidovudine starting as early as 14 weeks of gestation and intrapartum single-dose nevirapine plus the addition of lamivudine to zidovudine intrapartum and for 7 days postpartum; breastfeeding infants receive daily nevirapine through the end of breastfeeding (up to 12 months postpartum). The other option is maternal triple antiretroviral drug prophylaxis starting as early as 14 weeks of gestation through the end of breastfeeding (up to 12 months postpartum). The infant receives 4–6 weeks of either daily nevirapine or twice-daily zidovudine.

With the availability of antiretroviral drugs increasing globally, WHO's expanded recommendations will lead to a rapidly growing number of antiretroviral-exposed, HIV-uninfected children. The total exposure of these uninfected infants to antiretroviral drugs will start *in utero* and continue until the end of breastfeeding. The exposure period to these drugs could be up to 2 years, yet there are limited data on safety. There is now an urgent need to better understand the consequences of extended exposure to HIV and antiretroviral drugs on HIV-uninfected children to contribute to improved monitoring and management of potential adverse effects. In this report, we review available literature describing the risks that HIV and antiretroviral drug exposure, *in utero* and postpartum, may pose for uninfected children.

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**METHODS**

The authors searched the Medline/PubMed database using several key word Boolean strings (Table 1). Additional literature was located through the database’s “related articles” function. Using the same search terms, abstracts from the International AIDS Conferences in 2008 and 2010, the 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention in 2009, and the Conferences on Retroviruses and Opportunistic Infections for 2009 and 2010 were selected.

Reports not clearly differentiating between infected and uninfected HIV-exposed children were excluded. Focus was on articles and presentations that included information on antiretroviral drug exposure. Except for 2009–2010, conference presentations were ignored in favor of published results. Forty-eight articles formed the basis of the present report.

**RESULTS**

**Birth Defects**

In terms of birth defects, efavirenz, a nonnucleoside reverse transcriptase inhibitor (NNRTI), is of particular interest because primate studies and human case reports indicate a potential for congenital neural tube defects.<sup>3–6</sup> Available data on other commonly used antiretroviral drugs suggest birth defect rates similar to a background rate of 2%–3%.<sup>3</sup>

The Antiretroviral Pregnancy Registry (APR) has data on 604 first-trimester efavirenz exposures, with an overall birth defect rate of 2.8% [95% confidence interval (CI): 1.6% to 4.5%], including a single meningomyelocele case and a single case of anophthalmia with facial clefts and amniotic banding.<sup>3</sup> This rate is not significantly different from the 2.7% overall birth defect prevalence in the general US population.

A meta-analysis including the APR found no increased overall birth defect risk among 1132 women with first-trimester efavirenz exposure compared with 7163 women exposed to other antiretroviral drugs.<sup>7</sup> Across all studies (1256 live births), 1 neural tube defect was observed with first-trimester efavirenz exposure (prevalence 0.08%, 95% CI: 0.002% to 0.44%). However, the limited sample size for the detection of rare outcomes, such as neural tube defects, prevented definitive conclusions.

The PACTG 219/219C study reported a 5.3% birth defect prevalence in children of HIV-infected mothers, not differing by infant HIV status or overall antiretroviral exposure.<sup>8</sup> However, first-trimester efavirenz exposure was associated with 4.3 (95% CI: 1.6 to 11.9) adjusted odds of defect compared with no first-trimester exposure. Of 32 infants with first-trimester efavirenz exposure, 5 serious birth defects were observed. Each infant exhibited different abnormalities, with only 1 neural tube defect.

The Irish–UK National Study of HIV in Pregnancy and Childhood with data on 8242 infants (93.5% with *in utero* antiretroviral exposure) found no increased risk of abnormalities in infants with first-trimester efavirenz exposure compared with infants exposed to other antiretrovirals.<sup>9,10</sup> Moreover, drug exposure or timing did not significantly impact birth defect frequency.

Prospective data are currently insufficient to provide a definitive assessment of neural tube defect risk with first-trimester efavirenz exposure, except to rule out a very large increase in risk.<sup>6</sup> Larger studies are required to more definitively rule out an increased risk.

In PACTG 219/291C, there was a nonsignificant trend toward more frequent birth defects associated with first-trimester lopinavir/ritonavir exposure, and first-trimester zidovudine seemed to be associated with a lower rate of musculoskeletal defects and a higher rate of heart defects.<sup>8</sup> However, a Europe-wide study covering 7353 pregnancies found no difference in birth defects between zidovudine-containing or zidovudine-sparing regimens.<sup>11</sup>

In a study of 195 mother–infant pairs, first-trimester antiretroviral or folate antagonist (cotrimoxazole or pyrimethamine) use was not associated with birth defects, but combined first-trimester antiretroviral and antifolate drug use had a 7.1-fold (95% CI: 1.5 to 34.2) increase in defects.<sup>12</sup> A systematic literature review concluded that the substantial benefits of cotrimoxazole prophylaxis in resource-limited settings support WHO guidelines recommending prophylaxis for HIV-infected pregnant women who require it, regardless of trimester of pregnancy.<sup>13</sup>

**Premature Delivery and Low Birth Weight**

HIV itself was associated with increased prematurity in the preantiretroviral era.<sup>14</sup> Results of studies on pregnancy outcome and antiretroviral use are mixed; divergent results may be partially due to the large number of confounding factors (eg, ethnicity, smoking, alcohol or illicit drug use, viral load, or CD4 count), which are not uniformly measured or considered in all studies.

In an analysis comparing observational data on 19,585 singleton births with prenatal antiretroviral exposure from 2 European and 1 US cohort, a triple-drug regimen was associated with increased prematurity compared with a single-drug regimen in the European but not in US cohorts.<sup>15</sup> However, in a pooled adjusted analysis, a triple-drug compared with a dual regimen was associated with a 1.5-fold increased adjusted odds of prematurity. In a separate analysis of data solely from the United Kingdom and Ireland, triple-drug regimens were associated with prematurity, but there was no

**TABLE 1.** Key Word Boolean Strings Used for the Literature Search

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(HIV-uninfected OR HIV-negative OR HIV-exposed) AND (infant OR child) AND (mortality OR survival OR growth OR height OR weight OR development OR neurocognitive OR neurologic OR immune activation)

(HIV-uninfected OR HIV-negative OR HIV-exposed) AND (antiretroviral OR HAART OR ARV OR ART) AND (infant OR child OR pediatric)

HIV AND antiretroviral AND (PMTCT OR mother-to-child transmission OR vertical transmission OR breastfeeding) [limited to Clinical Trial, Editorial, Letter, Meta-Analysis, Review]

(Antiretroviral OR HAART OR ART) AND (preterm[title] OR premature[title] OR birth weight[title] OR birth defects[title] OR congenital[title])

Antiretroviral AND (uninfected OR HIV-negative) AND (infant OR child) AND (growth OR height OR weight OR development OR neurocognitive OR neurologic OR cancer or malignancy OR delayed effects).

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difference between protease inhibitor- (PI-) and NNRTI-based regimens.<sup>16</sup>

The US-based Pediatric Spectrum of HIV Disease study evaluated prematurity and low birth-weight in HIV-exposed infants between 1989 and 2004, when PMTCT evolved from zidovudine alone to triple-drug regimens.<sup>17</sup> During this period, MTCT rates fell from 28% to 1%, whereas the proportion of low birth-weight infants and prematurity dropped from 35% to nearly 20%. The study found no association between low birth-weight and maternal antiretroviral use, but prematurity was significantly associated with no maternal antiretrovirals or PI-based regimens and symptomatic maternal HIV disease, black race, infant HIV infection, and illicit drug use. These conclusions were echoed by another US study, in which PI-based triple-drug regimens were associated with increased prematurity compared with single drug or combination without a PI, whereas low birth-weight and stillbirth rates were similar between groups.<sup>18</sup> The Botswana Mma Bana study reported that an antepartum lopinavir ritonavir-based combination regimen was associated with a significant increase in prematurity compared with a triple nucleoside regimen.<sup>19</sup> Data from the APR suggest an increase in low birth-weight infants since the introduction of combination therapy, with PI-containing regimens a significant risk factor.<sup>20</sup> In contrast, other studies have not reported an association of pregnancy outcome with antepartum antiretroviral or PI use.<sup>21,22</sup>

Variations between studies in the timing of antiretroviral initiation may account for some differences between studies. A Brazilian study reported that women receiving triple-drug regimens before conception had a significantly increased risk of prematurity and low birth-weight compared with women who initiated drugs later in pregnancy.<sup>23</sup> A Dutch matched case-control study similarly reported that first-trimester triple-drug regimen use was associated with a 44% preterm delivery rate compared with 21% when starting in the second or third trimesters and 14% among HIV-uninfected women.<sup>24</sup>

## Mitochondrial Toxicity

Mitochondrial toxicity is a classwide effect of nucleoside reverse transcriptase inhibitors (NRTIs), associated most strongly with stavudine, zidovudine, didanosine, and zalcitabine.

Mitochondrial dysfunction (due to antiretroviral drug exposure before, during, or after birth) is a broader toxicity that could have a continuing influence on childhood development.<sup>25</sup>

The impact of mitochondrial toxicity in HIV-infected infants receiving NRTI-based treatment has been well described<sup>26</sup>; the impact of mitochondrial dysfunction related to NRTI exposure perinatally in HIV-uninfected infants is unclear.

The French Perinatal Cohort Study Group identified biopsy evidence of mitochondrial toxicity in 12 out of 2644 uninfected children exposed to HIV and antiretroviral drugs in utero.<sup>27</sup> All 12 presented neurologic symptoms and 7 also had hyperlactatemia. Another 14 infants had symptoms possibly explained by mitochondrial dysfunction but lacked biopsy evidence. At 18 months, the total incidence of definite mitochondrial dysfunction in this cohort was 0.26% compared with 0.01% in the general population. Risk was higher in infants exposed to antenatal combination NRTIs compared with when exposed to zidovudine alone.

PACTG 219/219C did not report any significant association between overall *in utero* antiretroviral exposure and mitochondrial dysfunction in 1037 HIV-exposed uninfected children.<sup>28</sup> However, in unadjusted models, children with symptoms suggestive of mitochondrial dysfunction were more likely to have been exposed to lamivudine or zidovudine/lamivudine in the third trimester compared with children without signs of mitochondrial dysfunction. However, possible confounding by earlier year of birth and higher maternal viral load in cases was noted.<sup>29</sup>

Results from the Women and Infants Transmission Study (WITS) support the hypothesis that maternal viral load may contribute to mitochondrial toxicity.<sup>30</sup> Lymphocyte mitochondrial DNA levels in HIV-exposed children were lower than in children born to HIV-uninfected mothers. Some of the children were also exposed to prenatal antiretrovirals, but these children had higher mitochondrial DNA levels than those without perinatal drug exposure. Mitochondrial DNA levels progressively approached normal during the children's first 5 years, and none of the children exhibited symptoms of mitochondrial dysfunction.

However, a Canadian study suggests that compensatory changes in mitochondrial proliferation and gene expression may take place during and after antiretroviral exposure in response to toxicity.<sup>31</sup> During the early neonatal period, peripheral blood mononuclear cell mitochondrial DNA levels were increased, but mitochondrial gene expression (mitochondrial RNA) was decreased in infants with *in utero* antiretroviral exposure compared with infants of HIV-uninfected mothers. These higher mitochondrial DNA levels persisted after antiretroviral exposure ceased, whereas the difference in mitochondrial RNA content lessened over time.

As with other direct signs of mitochondrial toxicity, definitive results on hyperlactatemia incidence due to *in utero* antiretroviral exposure have proved elusive. A Spanish study reported that half (63 of 127) of antiretroviral-exposed, HIV-uninfected infants had elevated blood lactic acid and alanine at least once, returning to normal by age 6 months.<sup>32</sup> Similar data have been reported by others in the United States and Italy.<sup>33,34</sup> In contrast, in neonates in Cote d'Ivoire, hyperlactatemia prevalence was only 13% and similar in infants exposed to short-course single or dual NRTI drugs compared with single-dose nevirapine.<sup>35</sup> Study differences may relate to the complexity and the duration of regimens: in resource-rich settings, triple-drug combination regimens started in the second trimester plus 6-week infant zidovudine are standard, whereas in Cote d'Ivoire, single or dual NRTI drugs were started at 32–36 weeks' gestation, and infants received only 1 week of zidovudine.

## Hematologic and Other Laboratory Abnormalities

Hematologic side effects are well described in HIV-infected children receiving antiretroviral therapy. A number of studies have suggested that uninfected infants exposed to both HIV and antiretroviral drugs have hematologic abnormalities, generally subclinical, with some persisting for prolonged periods.

Transient hemoglobin abnormalities in HIV- and antiretroviral-exposed uninfected infants have been noted in most

studies.<sup>36–42</sup> In general, these have resolved by age 3–6 months, after discontinuation of infant antiretroviral prophylaxis. *In utero* exposure to combination antiretroviral regimens seems to be associated with increased anemia severity.

Several studies have suggested small, clinically irrelevant, but statistically significant reductions in other hematologic cell lineages. In a French longitudinal cohort of HIV-exposed uninfected children, platelet, neutrophil, and lymphocyte counts were significantly lower in antiretroviral-exposed infants compared with those in unexposed infants until the age of 18 months.<sup>36</sup> There was a negative relationship with the duration of exposure, and *in utero* exposure to combination drugs was associated with a greater reduction than exposure to single drug. In a German study, *in utero* combination-drug exposure in uninfected children was independently associated with neutropenia severity; thrombocytopenia was not observed.<sup>39</sup> In the European Collaborative Study, neutrophil counts were significantly lower in uninfected antiretroviral-exposed children than in unexposed children until the age of 8 years, with a trend toward association with increasing duration (*in utero* plus neonatal exposure) and complexity of exposure (combination vs. single drug).<sup>41</sup> Similarly, in a study in The Netherlands, neutrophil count was significantly lower in uninfected, antiretroviral-exposed than in unexposed infants until the age of 8 months.<sup>42</sup> In a US study, although hemoglobin and neutrophil count abnormalities resolved by the age of 6 months, persistent lymphocyte reductions were observed through age 24 months.<sup>37</sup> Similar to the French data, *in utero* combination-regimen exposure was associated with a greater reduction.

More recent international trials have evaluated extended infant or postnatal maternal antiretroviral prophylaxis to prevent transmission through 6 months of breastfeeding. The Breastfeeding and Nutrition (BAN) trial compared intrapartum single-dose nevirapine and 1 week of zidovudine/lamivudine as control with 28 weeks of either postnatal maternal triple antiretroviral prophylaxis or infant daily nevirapine. By 36 weeks, similar proportions of infants had experienced grade 3 or 4 anemia (20–21%) or neutropenia (1%) despite differences in drug exposure.<sup>43</sup> Similarly, the Kesho Bora study compared the same BAN control regimen with maternal triple-drug prophylaxis through 6 months in breastfeeding infants and found no statistically significant differences in grade 3 or 4 anemia (12%–15% at birth, 1% at 3 months) or neutropenia (8% at birth, 1% at 3 months) between groups.<sup>44</sup> However, there was no maternal antepartum regimen in BAN and a median of only 6 weeks of antepartum drugs in the Kesho Bora trial.

The Mma Bana trial compared 2 triple-drug regimens (zidovudine/lamivudine with either abacavir or lopinavir-ritonavir) during pregnancy and 6 months of breastfeeding; median antepartum drug duration was 11 weeks.<sup>19</sup> Infants received single-dose nevirapine plus zidovudine for 4 weeks. By the age of 6 months, grade 3 or 4 anemia was seen in 13%–16% of infants and neutropenia in 15%–18%, without significant differences between arms. The neutropenia rate was higher in the Mma Bana study (15%–18%) than BAN (1%) or Kesho Bora (1–8%), but this is complicated by differing definitions of neutropenia between studies.

Hematologic toxicity in 691 infants in the Mma Bana trial was compared with toxicity in 1028 infants in a previous Botswana study, the Mashi trial, in which only antepartum zidovudine was given, with 4 weeks of infant zidovudine if formula-feeding and 6 months if breastfeeding. In a multivariate analysis, *in utero*/postpartum maternal triple-drug regimen exposure was associated with severe infant anemia, with a 5.8-fold increase compared with formula-fed infants exposed to antepartum/4 weeks' infant zidovudine and 2.2-fold increase compared with breastfed infants exposed to antepartum/6 months' infant zidovudine.<sup>45</sup> These investigators had previously shown that *in utero* triple-drug exposure was associated with an increased risk of grade 3 or 4 neutropenia in infants through age 1 month compared with *in utero* zidovudine-only exposure.<sup>46</sup> In contrast, no difference was observed in hepatic toxicity between triple-drug and zidovudine-only exposure.

In summary, hematologic abnormalities with *in utero* antiretroviral exposure have been observed in studies from multiple geographic locations and seem to be more severe with exposure to multiple drugs. Although anemia seems to be transient, neutropenia and lymphopenia may be more prolonged. Although the clinical significance of these findings is unclear, they do provide biomarkers suggesting that antiretroviral exposure may have potential long-term effects in uninfected infants.

## Growth, Development, and Other Long-term Impacts

Research on long-term effects of *in utero* antiretroviral drug exposure on growth, development, and possible malignancies is limited, and follow-up time is relatively brief.

The European Collaborative Study reported no association between *in utero* exposure to zidovudine alone and growth through 18 months, though they did observe a small growth deficit in children exposed to combination-drug regimens *in utero*.<sup>47</sup> Using data derived from the Botswana Mma Bana and Mashi trials, at-birth HIV-uninfected infants exposed *in utero* to triple-drug regimens had significantly lower weight, length and weight for length than did uninfected infants exposed to zidovudine alone, although these differences were no longer significant by the age of 3 months.<sup>48</sup> However, length-for-age z-scores remained significantly lower through the age of 6 months in infants exposed to triple drugs compared with those exposed to zidovudine alone.

PACTG 219/219C evaluated neurologic development in HIV-exposed uninfected children and found no overall association between antiretroviral exposure *in utero* and abnormal neurologic assessment at 2 years of age.<sup>49</sup> However, HIV-exposed uninfected children with low birth weights had significantly better assessment scores if exposed to antiretroviral *in utero*. Notably, children without antiretroviral exposure were born before 1994, whereas the antiretroviral-exposed children were largely born after 1994, and 42% of their mothers had viral loads <400 copies per milliliter. The study found a trend toward delayed neurodevelopment associated with higher maternal viral load.

Another recent study from a Buenos Aires public clinic<sup>50</sup> concluded that *in utero* exposure to HIV alone or in

combination with antiretroviral drugs did not influence infants' growth and development during their first 2 years.

### Malignancies

A number of studies have found that NRTI exposure is associated with both mutagenesis and other forms of DNA damage.<sup>51–54</sup> This has raised concerns about *in utero* antiretroviral exposure elevating the risk of cancers later in life, although available data have been reassuring regarding short-term risk.

The PACTG 219/219C study found no increase in early childhood cancer associated with antiretroviral exposure,<sup>55</sup> when comparing HIV-uninfected children with or without exposure to any antiretrovirals. The children's median age at last study visit was 3.1 years (range: 0.5 months to 14.9 years).

Similarly, the French Perinatal Cohort found overall incidence of cancer in HIV-exposed uninfected children followed to median age 5.4 years did not differ significantly from that expected for the general population.<sup>56</sup> However, 5 cases of central nervous system cancer were observed compared with 1.6–2.1 expected cases; a higher cancer risk was observed with exposure to didanosine lamivudine-containing regimens compared with exposure to zidovudine alone, although only 4% of women received such regimens.

It is important to note that childhood studies will not provide definitive answers on the ultimate effect of antiretroviral drugs in this area; follow-up into adulthood will be required.

### CONCLUSIONS

Since the PACTG076 trial results in 1994, the benefits of antiretroviral drugs for PMTCT have been clear.<sup>57</sup> Additionally, combination antiretroviral regimens provided to HIV-infected mothers for their own health are critical for maternal survival, and protecting children requires protecting the health of those who nurture them. Thus, the immense benefits of antiretroviral drug use during pregnancy for PMTCT and maternal health far outweigh potential adverse effects identified to date. However, there are limited data on long-term effects of *in utero* antiretroviral exposure on uninfected children, and combination regimens have been in use for only about 10–15 years. Potential serious adverse effects are likely to be rare and occur later in life.

This literature review regarding the effects of prophylactic antiretroviral drugs on infants and children highlights the many areas in which disagreement exists or research is lacking (Table 2). One concern is that much of the research has been conducted in developed countries. Clinical, social, and economic factors in these lands differ greatly from the resource-poor environments, where combination antiretroviral regimens in pregnant women for PMTCT and therapy are now gaining ground after years of delay.

The multitude of potential confounding factors is a significant obstacle to conducting research in this area. If HIV-exposed but uninfected children have elevated mortality or delayed development, does this imply a drug effect or is it because their parents are sick and their homes disrupted? Alternatively, adverse outcomes in the children could be a result of the biologic effects of exposure to the virus rather than the result of treatment. A further difficulty is that studies usually last for a short time, whereas definitive research will require years of follow-up.

**TABLE 2.** Summary of Potential Adverse Effects of *In Utero* Antiretroviral Exposure in HIV-Exposed but Uninfected Children

#### Birth Defects

Sample size to date can only rule out very large increase in risk of neural tube defects with first-trimester EFV exposure.

Larger numbers with first-trimester exposure are needed to rule out the risk for rare outcomes such as neural tube defects.

Available data for other commonly used antiretroviral drugs suggest birth defect rates similar to a background rate of 2%–3%.

#### Premature Delivery, Low Birth-Weight

Mixed results regarding association with *in utero* antiretroviral exposure, possibly due to a large number of confounding factors that are not uniformly measured, including the timing of antiretroviral drug initiation.

Some data suggest elevated prematurity risk with antepartum combination antiretroviral regimens, particularly if protease inhibitor based.

Fewer data suggest association of combination regimens with low birth-weight.

#### Mitochondrial Toxicity

Severe, clinically evident mitochondrial diseases secondary to *in utero* antiretroviral exposure are likely to be rare.

Further studies are needed that account for confounding factors, include maternal disease severity

#### Hematologic Abnormalities

Transient anemia is frequent and more severe with *in utero* exposure to combination-drug regimens but generally resolves by the age of 3–6 months.

Small but persistent abnormalities in neutrophil and/or lymphocyte cell count with *in utero* antiretroviral exposure have been observed in studies from multiple geographic locations and seem to be more severe with *in utero* exposure to multiple drugs.

Clinical relevance of abnormalities is unclear but may be providing biomarker suggesting potential long-term effect of antiretroviral drug exposure.

#### Growth and Development

Mixed data on effect of *in utero* exposure to combination drug regimens on growth; effect, if exists, seems transient.

Very limited studies on neurodevelopment suggest that more advanced maternal disease may be an additional important confounder.

#### Malignancies

Limited data are reassuring regarding the risk of malignancy in the short term (to age <5–10 years).

No reports with follow-up into adolescence or young adulthood, when the effect on promotion of malignancies may be more likely to be observed.

To systematize the required research, it is necessary to ensure that antiretroviral drug exposure monitoring is established through registries or cohorts in resource-restricted settings and includes extended drug exposure through maternal or infant prophylaxis through breastfeeding. The long-term effects of the present interventions can best be determined by following a large group of antiretroviral-exposed, HIV-uninfected children into adulthood.

### AUTHORS' CONTRIBUTIONS

S. Hediari, with the support of medical writer David Gilden, wrote the first draft. L. Mofenson and M. Cotton contributed substantially to the manuscript by extensively editing and providing expert comments. All other authors contributed equally to the manuscript by providing comments

on subsequent drafts. All the authors have read and approved the final version.

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