

# Does maternal use of tenofovir during pregnancy affect growth of HIV-exposed uninfected infants?

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Transmission of HIV from mother to child can be almost eliminated by antiretroviral drugs started early in pregnancy [1,2]. If HIV disease in a pregnant woman is more advanced (i.e., CD4 cell count below 350 cells/ $\mu$ l), then antiretroviral drugs are given as treatment for the woman herself with the additional benefit that transmission to the child is prevented. If HIV disease in a pregnant woman is less advanced, then combination antiretroviral regimens can be provided during pregnancy and lactation as prophylaxis. There is also gathering support for implementing universal test-and-treat strategies during pregnancy as a public health approach to preventing vertical transmission and optimizing coverage of treatment for women who need it [3–5]. Tenofovir disoproxil fumarate (TDF) is an attractive drug to recommend as part of first-line antiretroviral drug treatment regimens because of its generally favorable safety profile, excellent durability, and high efficacy [6,7]. It is also available in the United States and many other countries as part of fixed-dose combinations. Thus, determining whether or not there are untoward side effects of intrauterine exposure is of great public health importance.

There is another reason why the safety of intrauterine TDF exposure needs careful consideration. Oral TDF combined with emtricitabine used preexposure and postexposure (PrEP) has now been shown in three independent studies to be significantly associated with reduced risk of HIV acquisition among adult men and women [8–10]. In settings, particularly in sub-Saharan

Africa, with high HIV incidence, PrEP has the potential to make sizable gains in terms of adult HIV infections prevented [11]. The young, at-risk, but still uninfected, women most in need of antiretroviral prophylaxis against sexual HIV transmission are also those most likely to become pregnant. Thus, not only will infants born to HIV-infected women potentially be exposed to TDF, but infants born to uninfected women may also be exposed in the future, with the optimistic scenario that these prevention programs are able to gather momentum. Vaginal gel formulations of TDF have produced promising [12] but some inconsistent results and have not yet garnered support for implementation without further studies. Vaginal gel formulations are attractive, from the potential toxicity point of view, as systemic drug concentrations are considerably lower [13].

Guidelines in the United States have generally advised caution in the use of TDF during pregnancy for HIV-infected women based on findings from treatment studies that have implicated TDF in declining bone health in HIV-infected adults and children [14]. HIV infection itself appears to have adverse effects on bone health, and is a consequence not corrected by antiretroviral therapy, rather it may be exacerbated if regimens include TDF [15]. Studies in pregnant rhesus macaques have found adverse effects of high-dose TDF given during pregnancy on intrauterine growth measured at birth, but growth restriction is not observed at lower doses more consistent with the doses used in human pregnancies [16–18].

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The findings reported in this issue by Siberry *et al.* [19] from the multisite, US-based Pediatric HIV/AIDS Cohort Study (PHACS) are reassuring about the safety of TDF used during pregnancy. Among over 2000 births to HIV-infected women all of whom received combination antiretroviral therapy during pregnancy, those uninfected infants whose mothers received TDF as part of their regimen (median duration 4.8 months) were at no greater risk of low birth weight, low birth length, small head circumference, or reduced weight for gestational age than those not exposed to TDF. Remarkably, TDF use more than doubled in the last 5 years in this US-based cohort and 43% of pregnant HIV-infected women in 2010 were treated using a TDF-based combination regimen.

PHACS also reported a small but statistically significant association between TDF use and lower length-for-age  $z$ -scores at 1 year of age among uninfected infants. This finding raises the question of whether there may be adverse effects of intrauterine TDF exposure that are not detectable at birth but which become detectable later. This is a concerning possibility as the mechanisms by which TDF may exert influence on bone health, especially on the developing fetus, are unknown. Studies of nutritional insults during pregnancy in animal models, have found adverse consequences for bone development of the fetus [20]. However, it should be noted that in these animal studies, including those directly examining TDF effects, consequences are detectable at birth. But the results from PHACS challenge our complacency about what safety parameters need to be assessed for antiretroviral drugs utilized during pregnancy. It is important that early markers of bone health be directly evaluated in newborns. This has only been done in one small study, with reassuring results about TDF safety [21,22].

Establishing the safety of drugs used during pregnancy for the unborn child is a methodological challenge. Randomized trials are generally unhelpful and reliance on observational epidemiologic studies is critical. There are serious weaknesses with the data presented from the PHACS: notably, less than a third of the study participants had data that could be included in the 1 year analysis – the risk of selection bias is quite severe with such sizable rates of attrition/exclusion. Measurement of potential confounders was also rather limited. The size of the difference between the TDF-exposed and unexposed ( $\sim 0.10$   $z$ -score) is small and does not remain significant after adjustment for multiple comparisons (although the authors argue that adjustment is not necessary in this circumstance). Nevertheless, replication of this unexpected finding is essential before clinical advice should be influenced.

Antiretroviral drugs used during pregnancy and lactation have the capacity to prevent most HIV infections in infants and young children. But several of the drugs in current use may have untoward consequences for exposed

infants. For example, mitochondrial toxicity is associated with zidovudine use, particularly in combination with lamivudine [23]. Efavirenz use in the first trimester of pregnancy is contraindicated due to animal data and case reports indicating a potential association with neural tube defects; nevertheless, in a recent meta-analysis, no increased relative risk of birth defects was noted among infants whose mothers received efavirenz-based regimens [24]. Common manifestations of intrauterine antiretroviral drug exposures have uncertain clinical relevance, and the more serious side effects seem to be rare justifying continued, unequivocal support for programs utilizing these drugs to prevent mother-to-child HIV transmission. But prudent choice between the available agents based on toxicity profiles is advisable [25].

Some special populations, for example hepatitis B virus (HBV) and HIV co-infected pregnant women, could particularly benefit from antiretroviral drug regimens including both TDF and lamivudine (or emtricitabine) [6]. Even with appropriate vaccination of infants against HBV and use of hepatitis B immune globulin, 5–15% of infants of hepatitis B surface antigen-positive women become HBV-infected, and this proportion may be higher among HIV co-infected pregnant women. This is particularly important in south-east Asia and other countries with high dual HBV and HIV infection rates among pregnant women [26,27]. Shorter peripartum regimens including TDF have been shown to be highly effective in preventing development of drug resistance to nevirapine [28]. Given the largely favorable results with TDF in extended regimens during pregnancy seen in PHACS [19], these short postpartum regimens are also likely to have a favorable risk–benefit profile, but this requires evaluation.

The results from PHACS are generally reassuring about the safety of TDF use during pregnancy but remind us of the importance of vigilance. Active and passive surveillance, such as the Antiretroviral Pregnancy Registry, as well as targeted research are necessary to understand the possible effects of antiretroviral drugs used during pregnancy on the infant [29]. Better understanding of the effects of the different antiretroviral agents may facilitate development of adjunctive interventions, for example vitamin D supplementation [30,31], to minimize potential adverse outcomes in the HIV-exposed infants who have been saved from HIV infection. Programs to expand access to and improve coverage of antiretroviral drugs for treatment and prevention remain a critical public health priority.

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## Conflicts of interest

The conclusions in this report are those of the authors and do not necessarily represent the views of the US Centers for Disease Control and Prevention.

The authors have no conflicts of interest to declare.

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