Safety of Tenofovir During Pregnancy for the Mother and Fetus: A Systematic Review

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Tenofovir disoproxil fumarate (TDF) safety during pregnancy has important public health implications. This review summarizes TDF safety during pregnancy, focusing on pregnancy outcomes, congenital anomaly risk, and other potential toxicities on neonates. Although information is limited, TDF appears to be safe during pregnancy. In 6 studies of human immunodeficiency virus type 1 (and/or hepatitis B virus)–infected women receiving TDF during pregnancy, adverse events were mild to moderate; none were considered to be TDF-related. Five studies that followed in utero TDF-exposed infants showed no increased risk of growth or bone abnormalities. One study showed slightly lower infant height at age 1 year, but the significance is unclear. The Antiretroviral Pregnancy Registry database, with 1800 pregnancies exposed to TDF in the first trimester, does not indicate increased congenital anomaly risk with TDF exposure. More evidence collected prospectively, ideally with bone density measurements and randomized trial design, will be optimal to determine the effects of antenatal TDF exposure on children’s health.

Keywords. HIV; PMTCT; TDF; pregnancy; safety.

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TDF for the mothers and infants, including the adverse events and outcomes, risk of congenital anomalies for infants exposed in utero, and other potentially toxic effects in the neonates (growth, bone, or other abnormalities).

METHODS

We searched PubMed on 6 August 2013 and reviewed all English-language literature published up until that time using the search terms of pregnancy, gestation, antenatal, prenatal, fetal, fetus, neonate, infant, intrauterine, and tenofovir or tenofovir disoproxil fumarate. We examined the abstracts of all identified articles; if no abstract was available, the full article was examined. When the abstract included clinical information for pregnant women on any form of TDF for any length of time, and when it contained original information (not a review), we considered the article relevant. We only looked at articles in peer-reviewed journals (including articles published online ahead of print) and did not attempt to identify unpublished articles such as abstracts at conferences.

In addition, we also reviewed the most recent interim report of the Antiretroviral Pregnancy Registry (APR) [18]. APR is the largest safety database for antiretroviral drugs in pregnancy. It is a prospective, voluntary registration system collecting information from health providers aiming at detecting any major teratogenic or other toxic effect of antiretroviral drugs.

RESULTS

We identified 130 nonduplicate journal articles, and 111 were excluded due to lack of relevance. Among the remaining 19 articles, 3 pertained to TDF exposure in rhesus macaques [19–21] and 16 pertained to humans [18, 22–36]. These included case reports, case series, retrospective or prospective observational studies, and clinical trials.

Prenatal and Postpartum TDF Exposure in Animal Studies

Three articles were found in the literature reporting on the safety of prenatal and postnatal TDF use among rhesus macaques [19–21]. Maternal administration of a high dose of TDF (30 mg/kg/day) did not impair fetal growth in utero. Sonographic assessments showed normal growth patterns in fetuses regardless of whether maternal treatment was initiated during the first [19] or the second trimester [20]. However, if the same dose of TDF was given to infant rhesus macaques postnatally, one-quarter of experimental infants developed severe growth restriction and reduction of bone porosity [20]. Further studies showed that these toxicities tended to occur at high-dose and long-term exposures rather than short-term high-dose or prolonged low-dose exposures [21].

For infants with maternal exposure to similar doses of TDF starting from the first trimester, birth crown–rump length and birth weight were either below or at the lower range of normal compared with age-matched controls [19]. There were also significantly lower serum insulin-like growth factor 1 (IGF-1) concentrations in fetuses, which could explain the observed low growth at delivery [19].

Prenatal TDF Use in Humans

Safety Profile of TDF for Pregnant Women

Because patients exposed to single-dose nevirapine frequently develop nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) resistance [37], several studies attempted to evaluate a short course of TDF/emtricitabine (FTC) at labor and delivery and the early postpartum period for PMTCT and prevention of antiretroviral drug resistance development. In the trial in Zambia, women were randomized at labor to either the local standard-of-care regimen (short-course zidovudine and single-dose nevirapine) or single-dose TDF/FTC plus the local standard of care. The results showed that NNRTI resistance development was significantly decreased in the TDF/FTC arm at both 2 and 6 weeks postpartum [22]. Mothers and infants had a similar proportion of serious adverse event (SAEs) occurrence in both groups: mothers, 4% in the TDF/FTC arm and 5% in the control arm; infants, 10% in the TDF/FTC arm and 12% in the control arm [22]. None of the SAEs were judged to be attributable to TDF use [22].

In the Tenofovir Emtricitabine in Africa and Asia (TEmAA) trial, TDF/FTC (600 mg/400 mg), given to the mothers starting from the onset of labor until 7 days postpartum, was well tolerated and resulted in no peripartum HIV-1 transmissions [23]. No maternal drug resistance to NNRTIs or NRTIs was observed [23]. In the second phase of the same trial, single-dose TDF/FTC (TDF 13 mg/kg and FTC 2 mg/kg) was provided to neonates within 12 hours of life. The results also showed no peripartum HIV-1 transmissions [24]. The observed SAEs (eg, grade 3 anemia, gastroenteritis, respiratory symptoms) were not thought to be TDF-related [24].

A pharmacokinetic study of 28 HIV-1–infected women in the United States who received single-dose TDF (either 600 mg or 900 mg) at labor found that both mothers and infants tolerated TDF well without TDF-associated SAEs reported [25].

In addition to the above studies, there are other studies where TDF was used for longer periods of time. In an evaluation of 127 HIV-1–infected women receiving HAART during pregnancy, 15 women received a TDF-based regimen with a median in utero TDF exposure of 127 days [26]. TDF was generally well tolerated in this study. Although 73% (11/15) of the women on TDF experienced laboratory abnormalities, none were attributable to TDF [26]. In a European study, 34 HIV-1–infected pregnant women receiving TDF and/or FTC before...
and during pregnancy were evaluated; the median antiretroviral treatment duration before delivery was 50 months, and no TDF-related SAEs were reported [27]. In the Development of AntiRetroviral Therapy in Africa (DART) Trial conducted in Uganda and Zambia, no significant difference was found in the distribution of miscarriages/terminations, stillbirths, and live births between pregnant women on TDF (111 patients) vs those not on TDF (62 patients) [28].

In an Italian study of trends of antiretroviral use during pregnancy and pregnancy outcomes in 2002–2008, a significant increase in the use of TDF/FTC was found from almost none in 2005 to >10% in 2007–2008 [29]. During the same period, a similar increasing trend was observed in the United States [30]. This increased use of TDF/FTC was not accompanied by changes in preterm delivery, Appgar scores of newborns, birth weight, or congenital anomalies at the population level [29]. Because no information was provided at the individual level in these 2 articles, they were not further included in this review.

We identified only 1 study where TDF was used in HBV-monoinfected mothers. Eleven mothers with high HBV viremia received daily oral TDF 300 mg during the third trimester [31]. In addition to HBV vaccine and hepatitis B immune globulin administered to the exposed newborn babies, TDF appeared to be effective in preventing HBV transmission to the infant with no adverse pregnancy outcomes and/or congenital anomalies [31].

Use of TDF 1% vaginal gel precoitally was demonstrated to lower the risk of HIV-1 acquisition sexually by 39% in 1 study in South Africa [12]. Women may become pregnant while on TDF gel for preventing HIV-1 infection; a study investigating the pharmacokinetics and placental transfer of TDF vaginal gel showed that single-dose 1% TDF vaginal gel in term pregnancy resulted in very low TDF concentrations in maternal serum and did not result in any safety issues [32]. Table 1 lists all studies that reported on TDF safety during pregnancy or in the perinatal period.

**Teratogenicity**

APR was the main source of data on teratogenic effects related to antiretroviral drugs [18]. Each year, there are approximately 1300 pregnant women enrolled, representing 15%–20% of HIV-1–infected women who give birth to live infants annually in the United States. The most recent APR interim report was issued in June 2013. A total of 17,978 pregnancies and 16,159 outcomes after exposure to antiretroviral drugs at any time during pregnancy from 1 January 1989 through 31 January 2013 were reported [18]. The overall congenital anomaly rate with exposure to any antiretroviral agent at any time during pregnancy was 2.9 per 100 live births (95% confidence interval [CI], 2.6%–3.2%) [18], which was not significantly different from the prevalence of congenital anomalies of 2.7% reported by the US Centers for Disease Control and Prevention congenital anomalies surveillance system [18]. For TDF in particular, the prevalence of congenital anomalies reported was 2.3% (42/1800; 95% CI, 1.7%–3.1%) with exposure during the first trimester, and 2.4% (20/894; 95% CI, 1.4%–3.4%) with exposure during the second/third trimester. There were sufficient numbers of first-trimester exposures to TDF to detect at least a 1.5-fold increase in risk of overall congenital anomalies and a 2-fold increase in risk of congenital anomalies in the more common classes, such as cardiovascular and genitourinary system defects. No such increases have been detected to date, nor was any specific pattern of major congenital anomalies observed. However, we should note that the registry might not always provide sufficient information about the specific nature of congenital anomalies.

Although 2 cases of pyelectasis, a dilation of the renal pelvis, were reported in children exposed to maternal TDF during pregnancy [33], this may not be considered a congenital anomaly as it usually resolves spontaneously. Furthermore, there are no studies in the literature so far showing an association of TDF use during pregnancy with increased risk of teratogenicity. In the DART trial, congenital anomalies were reported in 3% of TDF-exposed and 4% of non-TDF-exposed live births [28]. In the European study mentioned earlier, there were no congenital anomalies reported among any of the infants born to 31 TDF/FTC-treated HIV-1–infected mothers [27].

**Fetal Growth and Bone Health**

Decreases in bone mineral density have been observed with use of TDF in macaques (intravenously) [19, 20] and humans (orally) [7, 38, 39]. In light of this concern, studies to explore fetal/infant bone and growth outcomes after TDF exposure during pregnancy are needed.

Currently, the information is very limited. In the case series mentioned previously by Nurutdinova et al [26], growth was assessed by measuring birth weight and reviewing growth charts during follow-up visits. The results showed that the majority of infants (14/15) with in utero TDF exposure had normal growth development both at birth and at 12 months of age. One infant failed to thrive due to parental neglect. In the DART trial, no significant evidence of lower birth weight or other growth parameters up to age 4 years and no fractures during follow-up were reported among 120 children who were exposed to TDF prenatally [28].

A multicenter observational study, which included 68 infants exposed to HAART in utero, indicated that in utero exposure to TDF did not impair growth and bone health in HIV-1–infected infants [34]. Similar distribution of low weight and length measurements were found between groups with or without in utero exposure to TDF both at birth and at a median age of 23 months [34]. Bone mineral status was measured by quantitative ultrasound; axially transmitted tibial speed of
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Country</th>
<th>Study Population</th>
<th>Intervention</th>
<th>Serious Adverse Events</th>
<th>SAE Is Related to TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi et al 2007</td>
<td>RCT</td>
<td>Zambia</td>
<td>HIV-infected pregnant women and their 397 infants</td>
<td>198 of 397 women received peripartum sd of TDF/FTC + intrapartum sd NVP + short course of ZDV from 32 wk gestation</td>
<td>4% (7/198) had SAEs; The most common SAE was postpartum anemia; Most common causes of morbidity were septicemia (22) and pneumonia (8)</td>
<td>No</td>
</tr>
<tr>
<td>Arrive et al 2009</td>
<td>Multicenter open-label phase 1/2</td>
<td>Cote d’Ivoire, Cambodia, and South Africa</td>
<td>38 women infected with HIV-1 or HIV-2 and their 39 infants</td>
<td>38 women received twice-daily ZDV from 28 wk gestation + sd NVP + 2 tablets of TDF/FTC at delivery, and once-daily TDF/FTC for 7 d postpartum</td>
<td>23.7% (9/38) had SAEs postpartum; Neutropenia (5); Liver enzyme elevation (1); Neonatal sepsis and urinary tract infection (1)</td>
<td>No</td>
</tr>
<tr>
<td>Arrive et al 2010</td>
<td>Multicenter open-label phase 2/3</td>
<td>Cote d’Ivoire, Cambodia, and South Africa</td>
<td>36 women infected with HIV-1 and their 36 infants</td>
<td>Twice-daily ZDV from 28 wk gestation + sd NVP + 2 tablets of TDF/FTC at delivery, and once-daily TDF/FTC for 7 d postpartum</td>
<td>5.6% (2/36) had SAEs postpartum; Grade 3 leucopenia (1); Grade 4 neutropenia (1); Acute brain injury at birth (1); Grade 3 neutropenia (1); Grade 3/4 hyperbilirubinemia (2)</td>
<td>No</td>
</tr>
<tr>
<td>Flynn et al 2011</td>
<td>Pharmacokinetic study</td>
<td>US, Puerto Rico</td>
<td>HIV-infected mothers and their 26 infants</td>
<td>13 women received sd of 600 mg TDF at labor + standard ZDV prophylaxis intravenously and 15 women received sd of 900 mg TDF (8 with FTC and 7 without FTC) at labor</td>
<td>10 infants were exposed to TDF prenatally; 7 infants received 4 mg/kg of TDF only after birth and 9 infants received 4 mg/kg of TDF plus 3 mg/kg of FTC after birth</td>
<td>None</td>
</tr>
<tr>
<td>Kinai et al 2012</td>
<td>Case report</td>
<td>Japan</td>
<td>One HIV-infected woman</td>
<td>Abacavir + LPV/r + raltegravir in the first 33 wk of pregnancy with change to abacavir + LPV/r + TDF at 35 wk gestation (3 wk prior to delivery)</td>
<td>NA; Modest proximal tubular dysfunction; Decreased fetal growth, biparietal diameters, and femur length</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pan et al 2012</td>
<td>Retrospective case series</td>
<td>US</td>
<td>11 HBV-monoinfected pregnant women</td>
<td>TDF 300 mg daily during the third trimester</td>
<td>None; None; NA</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Study Type</td>
<td>Country</td>
<td>Study Population</td>
<td>Intervention</td>
<td>Serious Adverse Events</td>
<td>SAE Is Related to TDF</td>
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<tr>
<td>Beigi et al 2011 [32]</td>
<td>Pharmacokinetic study</td>
<td>US</td>
<td>16 HIV-uninfected women</td>
<td>1% TDF vaginal gel single use in term pregnancy</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Sabbatini et al 2007 [33]</td>
<td>Retrospective case series</td>
<td>Italy</td>
<td>33 HIV-infected mothers and their 33 infants</td>
<td>7 of 33 women received TDF as their regimens were continued during pregnancy</td>
<td>7 infants with prenatal TDF exposure</td>
<td>None</td>
</tr>
<tr>
<td>Nurutdinova et al 2008 [26]</td>
<td>Retrospective case series</td>
<td>US</td>
<td>127 pregnancies in HIV-infected women</td>
<td>15 women (16 pregnancies) received TDF either as part of treatment or for prevention of mother-to-child transmission of HIV</td>
<td>15 infants had prenatal TDF exposure</td>
<td>73% (11/15) experienced laboratory abnormalities One case with SAE (grade 3 hyperbilirubinemia)</td>
</tr>
<tr>
<td>Vigano et al 2011 [34]</td>
<td>Multicenter observational study</td>
<td>Italy</td>
<td>68 mothers taking HAART during pregnancy</td>
<td>HAART that included TDF was initiated from second or third trimester with a median duration of exposure of 25 wk</td>
<td>33 of 68 infants had prenatal TDF exposure</td>
<td>None</td>
</tr>
<tr>
<td>Colbers et al 2013 [27]</td>
<td>Nonrandomized open-label multicenter phase 4 study</td>
<td>Europe</td>
<td>34 HIV-infected pregnant women and their 34 infants</td>
<td>34 women received TDF and/or FTC as part of HAART during pregnancy for at least 2 wk</td>
<td>34 infants had prenatal TDF exposure</td>
<td>5.9% (2/34) developed SAEs Postpartum anemia due to blood loss during delivery (1) Postnatal uterine atony (1)</td>
</tr>
<tr>
<td>Gibb et al 2012 [28]</td>
<td>RCT</td>
<td>Uganda Zimbabwe</td>
<td>382 pregnancies in 302 HIV-infected pregnant women and their 226 live infants</td>
<td>120 of 182 pregnancies included in the analysis received a TDF-containing regimen</td>
<td>120 infants included in the analysis had prenatal TDF exposure</td>
<td>• 3% (7/226) had congenital abnormalities (no difference in TDF exposed and nonexposed infants, $P = .69$) • 10% (22/225) were premature (no difference in TDF exposed and nonexposed infants, $P = .67$) • 16% (34/209) had low birth weight (no difference in TDF exposed and nonexposed infants, $P = .44$) • 10% (6/62) with no in utero TDF exposure and 6% (7/111) with in utero TDF exposure died ($P = .42$)</td>
</tr>
</tbody>
</table>
sound was similar in the 2 groups [34]. In addition, unlike the finding in the macaque study [19], infants exposed to TDF had IGF-1 serum concentration comparable to those of unexposed infants [34]. Lower serum concentrations of parathyroid hormone and higher urinary calcium excretion were detected in the exposed group, but all values were within the reference range for age [34]. However, this study had a relatively small sample size (33 infants in the TDF-exposed group and 35 infants in the nonexposed group), and the subjects’ age when enrolled and evaluated was 12–78 months. This could lead to selection bias and does not allow for evaluation of differences at birth that may change over time.

Data analysis of a large cohort of 2029 children (426 of whom had antenatal exposure to TDF) in the US Pediatric HIV/AIDS Cohort Study (PHACS) showed that maternal TDF use during pregnancy did not impair fetal growth at birth but may have had a delayed effect on infant growth 1 year later [35]. The mechanisms and significance of this finding are not yet fully understood [16, 35]. In addition, a case report from Japan noted blunted fetal biparietal diameter and femur length after the mother started TDF at 35 weeks of gestation until delivery at 38 weeks [36]. Despite lower weight and height at birth and throughout the first 3 months of life, there was no sign of osteomalacia or rickets detected later on [36]. The causal link is unclear given late and short exposure to TDF. Currently, no published study has evaluated bone density measurements to assess bone development in TDF-exposed infants. Table 2 lists a summary of studies reporting effects of TDF use during pregnancy on infant growth and bone health.

### Other Toxicities

Postmarketing surveillance has reported nephrotoxicity in patients receiving TDF, but the majority of these patients were adults and had preexisting risk factors for renal insufficiency [38, 40]. Therefore, TDF dosage modification is required for patients whose creatinine clearance (CrCl) is <50 mL/min [41]. Normally, CrCl may increase by as much as 50% in pregnancy because of increased glomerular filtration rate and renal plasma flow [42]. Data from a pooled analysis of 5 clinical trials in Malawi found that only 0.4% of HIV-1–infected pregnant women had a baseline CrCl <50 mL/min, suggesting that assessment of baseline CrCl may not be necessary before TDF initiation in pregnancy in resource-limited settings [43].

Mitochondrial toxicity, presenting with a variety of clinical symptoms such as lactic acidosis, liver steatosis, pancreatitis, lipodystrophy, or myopathy, is a potential adverse effect of NRTI use [44, 45] due to possible inhibition of DNA polymerase-γ [46, 47]. There are no human data linking TDF use in pregnancy with emergence of mitochondrial toxicity. An in vitro study showed that TDF is a weaker inhibitor of DNA
polymerase-γ than most of the other NRTIs, and it was not concentration dependent; therefore, TDF is less likely to cause mitochondrial toxicities [48].

**Toxicities of TDF in Pregnant Women Infected With HBV**

The use of antiviral approaches during pregnancy has been suggested as a complementary means of minimizing MTCT of HBV, particularly among women with high HBV DNA loads and e antigen (HBeAg) expression, in whom rates of breakthrough HBV transmission to the infant despite immunization can be high [49, 50]. Lamivudine and telbivudine have been evaluated in late pregnancy among HBV-infected women to prevent vertical transmission in a few studies [50–54], but TDF has not yet been evaluated. As mentioned before, a small cohort of 11 Asian HBV-monoinfected, HBeAg-positive pregnant women were treated with TDF in the third trimester [31]. After a median duration of 10 weeks' exposure, a significant reduction in serum HBV DNA was achieved at delivery. No HBV MTCT occurred, and no obstetric complications or congenital anomalies were observed.

In HIV-1/HBV-coinfected individuals, elevation in liver enzymes can occur after initiation of antiretroviral drugs, particularly in those with low CD4+ T-cell counts and advanced immunosuppression, as a result of immune reconstitution [55]. Such immune-mediated flares can also occur postpartum in HBV-monoinfected women, even in the absence of therapy [56, 57]. Pregnant women who are started on TDF-based regimens should be counseled about signs and symptoms of liver toxicity, and liver enzymes should be assessed regularly after antiretroviral drug initiation. Differentiation between HBV disease flare or drug toxicity can be difficult and requires expert consultation for further management. Five ongoing clinical trials (NCT01745822, NCT01125696, NCT01066858, NCT01488526, NCT01312012) in women monoinfected with HBV or coinfected with HIV-1 and HBV will hopefully shed more light on the safety of TDF use during pregnancy.

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**Table 2. Summary of Studies Reporting Potential Effects of Tenofovir Used in Pregnancy on Infant Growth and Bone Health, 2008–2013**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Country</th>
<th>Study Population</th>
<th>No. of Infants Exposed to TDF</th>
<th>Infant Growth and Bone Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurutdinova et al 2008 [26]</td>
<td>Retrospective case series</td>
<td>US</td>
<td>127 pregnancies in HIV-infected women who received HAART with or without TDF</td>
<td>14 live infants with antenatal TDF exposure</td>
<td>Normal growth and development at birth and during 12-month follow-up One failed to thrive due to parental neglect</td>
</tr>
<tr>
<td>Vigano et al 2011 [34]</td>
<td>Multicenter observational study</td>
<td>Italy</td>
<td>68 HIV-exposed uninfected infants born to mothers who received HAART with or without TDF</td>
<td>33 exposed to maternal TDF</td>
<td>No difference in incidence of LBW and length in TDF-exposed and unexposed groups</td>
</tr>
<tr>
<td>Siberry et al 2012 [35]</td>
<td>Prospective cohort study</td>
<td>US</td>
<td>2029 HIV-exposed uninfected children whose mothers received maternal ARV with or without TDF</td>
<td>426 with maternal TDF use</td>
<td>No difference in small for gestational age, LBW, birth length for age, or birth head circumference for age z scores with TDF exposure Slightly decreased infant length at 1 y of age among those with in utero TDF exposure (mean z scores of length-for-age at 1 year of age: −0.17 vs −0.03, P = .04)</td>
</tr>
<tr>
<td>Gibb et al 2012 [28]</td>
<td>Randomized controlled trial</td>
<td>Uganda, Zimbabwe</td>
<td>382 pregnancies in 302 HIV-infected pregnant women who took HAART with or without TDF during pregnancy</td>
<td>120 with in utero TDF exposure</td>
<td>z scores for weight, mid-upper arm circumference, and head circumference for age were not different in children with or without in utero TDF exposure at birth or during follow-up Height-for-age z scores were similar in TDF-exposed and nonexposed groups during 2 y follow-up No bone fractures reported during 2 y of follow-up</td>
</tr>
<tr>
<td>Kinai et al 2012 [36]</td>
<td>Case report</td>
<td>Japan</td>
<td>One case with in utero TDF exposure between 35 and 38 wk of gestation</td>
<td>One</td>
<td>Lower weight and height at birth and throughout the first 3 mo of life No sign of osteomalacia or rickets detected by hand radiography at 1 and 3 mo of age</td>
</tr>
</tbody>
</table>

Abbreviations: ARV, antiretroviral; HAART, highly effective antiretroviral therapy; HIV, human immunodeficiency virus; LBW, low birth weight; TDF, tenofovir.
CONCLUSIONS

Our systematic review indicates that TDF appears to be generally safe for HIV-1 (and/or HBV)—infected pregnant women. The available safety data of TDF in pregnancy are generally reassuring for pregnancy outcomes and for lack of congenital or other severe anomalies in exposed infants. The evidence on the effects of TDF on bone health and growth of infants is limited but also generally reassuring, in contrast to data from animal studies, where extremely high doses and prolonged use might have led to the adverse outcomes observed. However, the PHACS study suggested slightly lower mean length and head circumference at 1 year of age among infants exposed to maternal TDF in utero [35], and a case of blunted fetal growth in an infant exposed to TDF for a brief period of time during late gestation was reported from Japan [36]. Therefore, more research on the safety of TDF in pregnancy is needed. Prospectively collected data, randomized study designs, and maternal/infant bone density measurements would be particularly useful. Research on the long-term effects of antenatal TDF exposure on child health will also be necessary. Given the anticipated increase in TDF use among pregnant women and the rapidly changing antiretroviral drug use guidance, the need for and importance of such studies are urgent and compelling.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References