Safety of Tenofovir Disoproxil Fumarate-Based Antiretroviral Therapy Regimens in Pregnancy for HIV-Infected Women and Their Infants: A Systematic Review and Meta-Analysis

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Background: There are limited data on adverse effects of tenofovir disoproxil fumarate (TDF)-based antiretroviral therapy (ART) on pregnant women and their infants.

Methods: We conducted a systematic review of studies published between January 1980 and January 2017 that compared adverse outcomes in HIV-infected women receiving TDF- vs. non–TDF-based ART during pregnancy. The risk ratio (RR) for associations was pooled using a fixed-effects model.

Results: Seventeen studies met the study inclusion criteria. We found that the rate of preterm (<37 weeks gestation) delivery (RR = 0.90, 95% confidence interval [CI]: 0.81 to 0.99, I² = 59%) and stillbirth (RR = 0.60, 95% CI: 0.43 to 0.84, I² = 72%) were significantly lower in women exposed (vs. not) to TDF-based ART regimen. We found no increased risk in maternal severe (grade 3) or potentially life-threatening (grade 4) adverse events (RR = 0.62; 95% CI: 0.30 to 1.29), miscarriage (RR = 1.09; 95% CI: 0.80 to 1.48), very preterm (<34 weeks gestation) delivery (RR = 1.08, 95% CI: 0.72 to 1.62), small for gestational age (RR = 0.87, 95% CI: 0.67 to 1.13), low birth weight (RR = 0.91; 95% CI: 0.80 to 1.04), very low birth weight (RR = 3.18, 95% CI: 0.65 to 16.53), congenital anomalies (RR = 1.03; 95% CI: 0.83 to 1.28), infant adverse outcomes or infant mortality (age >14 days) (RR = 0.65; 95% CI: 0.23 to 1.85), but increased neonatal mortality (age <14 days) risk (RR = 5.64, 95% CI: 1.70 to 18.79) with TDF-based ART exposure. No differences were found for anthropomorphic parameters at birth; one study reported minor differences in z-scores for length and head circumference at age 1 year.

Conclusions: TDF-based ART in pregnancy seems generally safe for women and their infants. However, data remain limited and further studies are needed, particularly to assess neonatal mortality and infant growth/bone effects.

Key Words: pregnancy, HIV, tenofovir, toxicity

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INTRODUCTION

The current World Health Organization (WHO) guidelines recommend antiretroviral therapy (ART) administration to all pregnant HIV-infected women, regardless of clinical or immune status, for maternal health benefits and prevention of mother-to-child HIV transmission, with tenofovir disoproxil fumarate (TDF) + lamivudine (3 TC) or emtricitabine (FTC) + efavirenz (EFV) as a fixed-dose combination, once-daily tablet, as the recommended first-line ART regimen. TDF has a good safety profile for treatment of HIV infection and is also active against hepatitis B. However, chronic TDF treatment has been associated with renal tubular dysfunction and decreases in bone mineral density in adults and young children with HIV infection as well as in adults taking TDF as pre-exposure prophylaxis.

Data on the use of TDF-based ART in human pregnancy for treatment of HIV or hepatitis B have been generally reassuring regarding maternal toxicity and lack of association with birth defects. Pharmacokinetic studies indicate a slight increase in clearance of tenofovir, the active form of TDF that circulates in the bloodstream, in pregnant compared with nonpregnant women, but decreased exposure is not associated with viral rebound and standard dosing during pregnancy is recommended. Tenofovir readily crosses the placenta, with cord-to-maternal blood ratio ranging from 0.60 to 1.03 with chronic dosing and 0.55–0.73 with single-dose TDF in labor. Subcutaneous administration of TDF at high doses to pregnant monkeys (exposure equivalent to 25-times the area under the curve achieved with therapeutic dosing in humans) resulted in lower fetal circulating insulin-like growth factor–1, higher insulin-like growth factor binding protein–3 levels, lower fetal body weight, and a slight reduction in fetal bone porosity. Data on the effects of fetal tenofovir exposure on growth and bone development in the infant have been limited and conflicting, with some studies suggesting an effect of in utero tenofovir exposure on fetal/infant growth/bone, and others showing no effect.

The WHO recommendation to initiate all HIV-infected pregnant women on ART irrespective of CD4+ cell count has been adopted by almost all countries, leading to a rapid increase in the number of pregnant women receiving a TDF-containing regimen. This systematic review meta-analysis was conducted to inform the process of revising the WHO consolidated guidelines on the use of ART for treating and preventing HIV infection. We aimed to compare rates of maternal and child adverse outcomes in pregnant HIV-infected women receiving TDF-based ART compared with those not receiving TDF-based ART.

METHODS

Protocol and Registration

The study background, rationale, and methods were specified in advance and documented in a protocol to be published at the international prospective register of systematic reviews (PROSPERO; Number: CRD42015025189; http://www.crd.york.ac.uk/PROSPERO/).
risk ratio (RRs) with 95% confidence intervals (CIs). Data from trials and observational cohorts were pooled together given the lack of difference in average risk estimates between study types. Heterogeneity was quantified using the I² statistics (the proportion of variation due to between study heterogeneity). Review Manager 5.1 was used for statistical analyses.

RESULTS

Study Characteristics

The process of study identification and selection is shown in Figure 1. The literature search yielded 5305 citations after removing duplicates. After reviews of the title and abstract, 38 full-text articles were selected for critical reading. Seventeen studies met the inclusion criteria. Table 1 shows the characteristics of these studies. Most of the included studies were prospective cohorts (n = 14) studies, 2 were from the same randomized controlled trial studies, and 1 was a cross-sectional study. The studies recruited participants from 1993 to 2014 and were published between 2007 and 2016. Eight publications including 6 cohorts (with 1 cohort having 3 publications) were from the United States, Malawi, Italy, and France. Four studies were multi-country studies: 1 study recruited participants from Uganda and Zimbabwe; 1 from Malawi, South Africa, Uganda, and Zimbabwe; 1 from India, Malawi, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe; and 1 from 17 centers across European countries.

Risk of Maternal and Obstetrical Adverse Outcomes

The pooled RRs for the association between receipt of TDF-based ART during pregnancy and maternal and obstetric adverse outcomes are provided in Figure 2. We found that the rate of preterm (<37-week gestation) delivery (RR = 0.90, 95% CI: 0.81 to 0.99, I² = 59%, 4 studies) and stillbirth (RR = 0.60, 95% CI: 0.43 to 0.84, I² = 72.0%, 3 studies) were significantly lower in women exposed to TDF-based ART compared with those exposed to non-TDF-based ART (Fig. 2). We found no increased risk in maternal grade 2 or 3 or 4) adverse events (AEs) (RR = 0.62, 95% CI: 0.30 to 1.29, 1 study), small for gestational age (RR = 0.87, 95% CI: 0.67 to 1.17).
TABLE 1. Summary Characteristics of the Included Studies (TDF-ART Exposed Versus TDF ART Nonexposed)

| First Author | Study Design | Study Period | Study Setting | Study Population | TDF-ART Exposed | TDF-ART Nonexposed | Outcomes |
|--------------|-------------|--------------|---------------|------------------|-----------------|-------------------|----------|
| Brogley et al²⁶ | Cohort | 05/1993 to 08/2010 | Pediatric AIDS Clinical Trials Groups (PACTGs) 219/219C protocols | 2202 children born to HIV-infected women; [117 (5.3%) had ≥1 birth defects] | 45 exposed to TDF-based ART first trimester (unspecified regimens) | 1988 exposed to non–TDF-based ART first trimester (unspecified regimens) | Congenital anomalies |
| Mirochnick et al²⁹ | Cohort | 11/2004 to 05/2009 | International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) | 38 HIV-infected pregnant women receiving care at IMPAACT sites | 20 receiving ATVr (300 mg/100 mg daily)-based ART plus TDF | 18 receiving ATVr (300 mg/100 mg daily)-based ART without TDF | Birth weight |
| Vigano et al²⁰ | Cohort | Not reported | Not reported | 68 HIV-uninfected children born to HIV-infected mothers who received PI-based ART during pregnancy (evaluated at median age 23 mo) | 33 exposed to TDF-based ART (unspecified regimens) | 35 exposed to non–TDF-based ART (unspecified regimens) | Low birth weight, bone health (quantitative bone ultrasound) |
| Gibb et al¹⁷ | Cohort | 01/2003 to 10/2004 | Development of AntiRetroviral Therapy (DART) in Africa | 302 ART-naive women with CD4 <200 cells/mm³ enrolled in trial who became pregnant; substudy follow-up selected infants | 251 women on TDF-based ART (follow-up substudy 111 TDF-ART–exposed infants: 94 TDF/ZDV/3TC; 11 TDF/d4T/3TC; 1 TDF/ZDV/3TC/LPVr; 5 other TDF based) | 115 women on non–TDF-based ART (ZDV, d4T, or ABC-based ART regimens) (follow-up substudy 62 TDF-unexposed infants: 49 ZDV/3TC-based; 2 ABC/3TC-based; 11 other non–TDF based) | Infant mortality, miscarriages, premature, low birth weight, still births, congenital anomalies, and growth delay |
| Knapp et al³⁰ | Cohort | 10/2002 to 10/2007 | International Maternal Pediatric Adolescent AIDS Clinical Trials Group protocol P1025 | 1112 children born to HIV-infected women receiving ART during pregnancy | 138 exposed to TDF-based ART first trimester; 97 exposed to TDF-based ART second/third trimester (unspecified regimens) | 876 exposed to non–TDF-based ART (unspecified regimens) | Congenital anomalies |
| Siberry et al¹¹ | Cohort | 2003 to 2010 | Surveillance Monitoring for Antiretroviral Toxicity (SMARTT) of Pediatric HIV/AIDS Cohort Study (PHACS) | 2029 children aged 1–12 yrs with maternal ART use during pregnancy (2006 children with birth weight, 1.980 with birth weight and gestational age) | 449 mothers receiving TDF-based ART (unspecified regimens); 426 infants | 1580 mothers receiving non–TDF-based ART (unspecified regimens); 1156 infants | Low birth weight, prematurity, growth delay |
| Ransom et al¹⁹ | Cohort | 2002 to 2011 | International Maternal Pediatric Adolescent AIDS Clinical Trial Group protocol P1025 | 2,099 HIV-uninfected children born to HIV-infected mothers (2,2025 with birth weight and 1496 with 6 mo weight) | 630 TDF-based ART (different regimens; 91% included PI) | 1395 infants with non–TDF-based ART exposure (different regimens; 79% included PI) | Preterm birth, birth weight |
### TABLE 1. (Continued) Summary Characteristics of the Included Studies (TDF-ART Exposed Versus TDF ART Nonexposed)

| First Author | Study Design | Study Period | Study Setting | Study Population | TDF-ART Exposed | TDF-ART Nonexposed | Outcomes |
|--------------|--------------|--------------|---------------|-----------------|-----------------|-------------------|----------|
| Sibiude et al\(^{32}\) | Cohort | 01/1994 to 12/2010 | French Perinatal Cohort (ANRS CO1/CO11) | 13,124 live births to HIV-infected women receiving ART during pregnancy | 823 first trimester TDF-based ART; 208 second/third trimester TDF-based ART (unspecified regimens) | 12,043 non–TDF-based ART (unspecified regimens) | Congenital anomalies |
| Colbers et al\(^{33}\) | Cohort | 02/2010 to 05/2013 | European HIV 17 treatment centers | 36 HIV-infected pregnant women receiving ATVr-based ART | 21 receiving TDF-based ATVr ART | 10 receiving ATVr-based ART without TDF | Birth weight |
| Siberry et al\(^{35}\) | Cohort | 04/2011 to 06/2013 | Substudy of the Surveillance Monitoring for Antiretroviral Toxicity (SMARTT) of Pediatric HIV/AIDS Cohort Study (PHACS) | 143 singleton infants of HIV-infected women with DXA performed in first mo life | 74 TDF-ART exposed for 8 or more weeks in the third trimester (84% PI-based) | 69 non-TDF ART exposed at any point (62% PI based) | BMC (DXA), anthropometrics |
| Williams et al\(^{36}\) | Cohort | 03/2007 to 06/2012 | The Pediatric HIV/AIDS Cohort study’s Surveillance Monitoring of ART Toxicities (SMARTT) | 2580 children born to HIV-infected women receiving ART during pregnancy [175 (6.8%) had 242 birth defects] | 441 exposed to TDF-based ART (unspecified regimens) | 2139 exposed to non–TDF-based ART (unspecified regimens) | Congenital anomalies |
| Fowler et al\(^{34}\) | Randomized Controlled Trial | 04/2011 to 09/2014 | Promoting Maternal and Infant Survival Everywhere (PROMISE) trial | 1226 HIV-infected pregnant women with CD4 >350 cells/mm\(^3\) randomized to ZDV/3TC/LPVr, ZDV/3TC/LPVr and their parents received low birth weight, prematurity, neonatal mortality, maternal adverse outcomes |
| Floridia et al\(^{18}\) | Cohort | 2011 | Drug Resource Enhancement against AIDS, Malnutrition (DREAM) programme | 133 HIV-infected pregnant women receiving TDF-based ART and 40 HIV-infected pregnant women receiving non-TDF based ART | 136 infants born to 133 mothers received TDF/3TC/EFV | 40 infants born to mothers who received ZDV or d4T/3TC/NVP | Bone markers |
| Moodley et al\(^{28}\) | Cross-sectional | 2011–2014 | Large regional hospital | 2573 HIV-infected pregnant women | 1666 received EFV/TDF/FTC | 407 received AZT/NVP (907 received D4T/3TC/NVP) | Preterm, low birth weight, stillbirth, small for gestation age |
| Siberry et al\(^{17}\) | Randomized Controlled Trial | 2013–2014 | Substudy of Promoting Maternal and Infant Survival Everywhere (PROMISE) trial | 358 HIV-infected pregnant women with CD4\(^+\) >350 cells/mm\(^3\) randomized to ZDV/3TC/LPVr or TDF/FTC/LPVr and their 359 infants with DXA performed 0–21 d life | 113 randomized to receive TDF/FTC/LPVr | 127 randomized to receive ZDV/3TC/LPVr (118 randomized to ZDV/3TC/LPVr) | BMC (DXA) |

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TABLE 1. (Continued) Summary Characteristics of the Included Studies (TDF-ART Exposed Versus TDF ART Nonexposed)

| First Author | Study Design | Study Period | Study Setting | Study Population | TDF-ART Exposed | TDF-ART Nonexposed | Outcomes |
|--------------|--------------|--------------|---------------|------------------|-----------------|-------------------|----------|
| Zash et al38 | Cohort       | 2009–2011    | Two largest public maternity wards | 9445 HIV-infected pregnant women who delivered live or stillborn infant and had received ART during pregnancy or ZDV/sdNVP | 165 received TDF/FTC/EFV from before conception onward; 1054 received TDF/FTC/EFV during pregnancy | 2006 received non-TDF-based ART (ZDV/3TC-based different regimens, 19% PI based) from before conception onward; 243 received non-TDF-based ART started during pregnancy | Stillbirth, preterm, very preterm |
| Jacobson et al27 | Cohort       | 2007 to 2013 | The US-based Surveillance Monitoring of ART Toxicities (SMARTT) | HIV-exposed uninfected children | 127 infants exposed to TDF-based ART | 382 infants exposed to non-TDF-based ART | CDC Growth Z scores |

3TC, lamivudine; ABC, abacavir; ATVr, atazanavir-ritonavir; AZT, zidovudine; d4T, stavudine; EFV, efavirenz; FTC, emtricitabine; LPVr, lopinavir-ritonavir; NVP, nevirapine; sdNVP, single-dose nevirapine; ZDV, zidovudine.

1.13, 1 study), miscarriage (RR = 1.09, 95% CI: 0.80 to 1.48, 1 study), or low birth weight (<2500 g) (pooled RR 0.91, 95% CI: 0.80 to 1.04, I² = 0%, 5 studies), in women receiving TDF-based ART compared with those receiving non–TDF-based ART. Two studies reported on very preterm (<34-week gestation) delivery34,38 (RR = 1.08, 95% CI: 0.72 to 1.02, 2 studies); the Promoting Maternal and Infant Survival Everywhere (PROMISE) trial which was conducted at 14 sites in 7 countries (India, Malawi, South Africa, Tanzania, Uganda, Zambia, and Zimbabwe), Fowler et al, found that exposure to TDF-based ART increased the risk of very preterm delivery (RR = 2.30, 95% CI: 1.06 to 4.97) whereas in another study conducted in Botswana by Zash et al found no significant difference in the rate of very preterm delivery (RR = 0.81, 95% CI: 0.50 to 1.30) between women who received TDF-based ART and those who received non–TDF-based ART.37 Also, the PROMISE trial reported on very low birth weight (<1500 g); although this was higher with TDF-based ART (2%) compared with non–TDF-based ART (0.6%), this was not statistically significant (P = 0.17).33

Five studies reported congenital anomalies as an outcome1,7,26,30,32,36 (Fig. 2). The reported congenital anomalies varied between the 5 studies with no pattern in types of anomalies observed. There was no statistically significant difference in the risk of congenital anomalies between infants born to HIV-infected pregnant women receiving first-trimester TDF-based vs non–TDF-based ART (pooled RR = 1.03, 95% CI: 0.83 to 1.28, I² = 0%, 5 studies); among 1883 HIV-infected pregnant women receiving first-trimester TDF-based ART, 94 gave birth to infants with congenital anomalies (5.0%, 95% CI: 4.1% to 6.1%) compared with 812 out of 17,067 (4.8%, 95% CI: 4.4% to 5.1%) who received non–TDF ART.

Risk of Infant Adverse Outcomes

The pooled RRs for the association of various outcomes for infants born to mothers who received TDF-based ART vs. non–TDF-based ART during pregnancy are provided in Figure 3. No significant differences in AEs were observed in infants born to mothers who received TDF-based ART vs. non–TDF-based ART in 2 studies.17,34 In one study, there was no significant difference in grades 1–4 levels of creatinine, phosphorus, alkaline phosphatase, hemoglobin, platelets, or neutrophils between infants exposed to TDF ART vs. non–TDF ART.17 In a randomized clinical trial, no significant differences in grade 3 or 4 signs/symptoms/diagnoses or hematologic or chemistry laboratory parameters were observed between TDF-based ART vs. non–TDF-based ART-exposed infants.34

Neonatal/Infant Mortality

Two studies reported on neonatal (<14 days) mortality17,34 (RR = 5.64, 95% CI: 1.70 to 18.79, 2 studies, Fig. 3). The PROMISE trial by Fowler et al,34 randomized HIV-infected pregnant women with CD4+ cell count >350 cells/mm³ starting at 14-week gestation to either tenofovir/emtricitabine/lopinavir–ritonavir (TDF-ART), zidovudine/lamivudine/lopinavir–ritonavir (non-TDF-ART), or zidovudine plus intrapartum single-dose nevirapine for prevention of mother-to-child transmission. Although this study found an increased risk in neonatal (age <14 days) mortality in infants exposed to TDF-based ART compared with those exposed to non–TDF-based ART (RR = 7.61, 95% CI: 1.75 to 33.03), there was no significant difference in neonatal mortality in infants exposed to TDF-based ART compared with those exposed to zidovudine/single-dose nevirapine (RR = 1.40, 95% CI: 0.65 to 2.99).34 The Development of Antiretroviral Therapy in Africa (DART) trial by Gibb et al,17 followed Ugandan and Zimbabwean women randomized to TDF-based ART or non–TDF-based ART who became pregnant and evaluated pregnancy outcomes. This study found no difference in neonatal mortality (age <14 days) (RR 3.06, 95% CI: 0.38 to 24.97) or infant mortality (age >14 days) (RR = 0.65, 95% CI: 0.23 to 1.85, 1 study; Fig. 3).
Growth

We found no difference in mean birth weight (mean difference = −12.04 g, 95% CI: −172.17 to 148.09, I² = 0%, 3 studies, Fig. 4), mean weight-for-age Z-scores at birth (mean difference = −0.00, 95% CI: −0.11 to 0.11, I² = 39%, 3 studies), mean weight-for-age Z-scores at 1 year (mean difference = −0.04, 95% CI: −0.24 to 0.16, 1 study), mean length-for-age Z-scores at birth (mean difference = −0.09, 95% CI: −0.23 to 0.05, I² = 61%, 3 studies), or head circumference Z-scores at birth (mean difference = −0.10 to 0.15, I² = 0%, 2 studies) in infants born to mothers receiving TDF-based ART compared with those born to mothers receiving non–TDF-based ART during pregnancy (Fig. 5). However, one study reported that at 1 year of age, the mean length-for-age Z-scores (mean difference = −0.13 SD 95% CI: −0.57 to 0.31) were significantly smaller in infants born to mothers receiving TDF-based ART compared with those born to mothers receiving non–TDF-based ART during pregnancy.31

In one study from the United States, Jacobson et al27 reported growth measures at 2 years of age (Supplemental Digital Content, Figure 1 http://links.lww.com/QAI/A988). Among children born to women initiating ART in the first trimester, TDF-based ART-exposed children had slightly higher mean weight Z-scores (0.30 SD 95% CI: −0.18 to 0.78), length Z-scores (0.22 SD 95% CI: −0.19 to 0.63), weight-for-length Z-scores (0.21 SD 95% CI: −0.25 to 0.67), head circumference Z-scores (0.27 SD 95% CI: −1.08 to 1.62), and lower triceps skin fold Z-scores (−0.13 SD 95% CI: −0.57 to 0.31) compared with children exposed to non–TDF-based ART; however, none of these differences were statistically significant (Supplemental Digital Content, Figure 1 http://links.lww.com/QAI/A988). Similarly, among children born to women initiating ART in the second trimester, there were no differences in mean weight Z-scores (−0.09 SD 95% CI: 0.39 to 0.21), length Z-scores (−0.14, 95% CI: −0.41 to 0.13), weight-for-
length Z-scores (−0.01 SD 95% CI: −0.33 to 0.31), head circumference Z-scores (0.01 SD 95% CI: −0.29 to 0.31), and triceps skin fold Z-scores (−0.05 SD 95% CI: −0.41 to 0.31) in children born to mothers who received TDF-based ART vs. those who received non–TDF-based ART during pregnancy (Supplemental Digital Content, Figure 1 http://links.lww.com/QAI/A988). A second study from Africa similarly noted no significant difference in weight- and height-for-age Z scores from birth through age 5 years in 111 infants born to mothers receiving TDF-based ART compared with 62 born to mothers receiving non–TDF-based ART during pregnancy.17

Bone Health

In the studies we examined, the potential effects of in utero exposure to tenofovir on infant bone health were evaluated by different methods and this precluded our ability to combine the results in a meta-analysis.

One study evaluated bone health by tibial quantitative ultrasound, finding no significant difference between infants at 23 months (median age) born to mothers receiving TDF-based ART compared with non–TDF-based ART (mean difference in tibial speed of sound −0.20, 95% CI: −2.28 to 1.88, 1 study).20

In one study, tenofovir-unexposed and -exposed children had similar mean levels of bone markers (C-terminal telopeptide of type I collagen, CTX; and bone-specific alkaline phosphatase, BAP) at 6 months (CTX: 0.62 versus 0.55 ng/mL, \( P = 0.122 \); BAP: 384 versus 362 U/L, \( P = 0.631 \)).18

In a substudy of a prospectively followed observational US cohort (Pediatric HIV/AIDS Cohort Study, PHACS), bone mineral content (BMC) was measured by dual-energy x-ray absorptiometry (DXA) scan within 5 weeks of birth in HIV-exposed but uninfected singleton infants born at ≥36-week gestation. DXA scan results were compared between 74 infants born to mothers who received TDF-based ART for >8 weeks in the third trimester of pregnancy to results from 69 infants born to mothers who received non–TDF-based ART during pregnancy.35 Significantly lower mean BMC was reported in infants whose mothers received TDF-based

**FIGURE 3.** Forest plot of risk of child adverse outcomes (TDF exposed vs. TDF–nonexposed).

**FIGURE 4.** Forest plot of mean birth weight (TDF-exposed vs. TDF–nonexposed).
ART compared with non–TDF-based ART during pregnancy (12% difference, mean BMC 56 grams in infants whose mothers received TDF-based ART vs. 63.8 g in infants whose mothers received non–TDF-based ART, \( P = 0.002 \)). However, more recently, neonatal BMC measured by DXA scan at 0–21 days of age was evaluated in HIV-exposed infants in a substudy of a randomized clinical trial comparing different approaches to prevention of in utero perinatal HIV transmission in HIV-infected African women with CD4+ T-cell counts \( \geq 350 \) cells/mm\(^3\) (the PROMISE trial, described earlier). Whole-body BMC was significantly lower in infants whose mothers received either TDF-based ART compared with zidovudine/single-dose nevirapine (estimated mean difference 9.73 grams, 95% CI: 5.49 to 13.96, \( P < 0.001 \)) or non–TDF-based ART compared with zidovudine/single-dose nevirapine (estimated mean difference 7.97 g, 95% CI: 3.97 to 11.96, \( P < 0.001 \)). However, there was no significant difference between infants exposed to TDF-based ART vs. those on non–TDF-based ART (estimated mean difference 1.76 g, 95% CI: \(-2.43 \) to 5.95, \( P = 0.41 \)). No significant difference was seen between any of the study arms when lumbar spine BMC measurements were compared.

**Quality of the Evidence**

Our assessment of the quality of evidence using the GRADE approach is shown in Table 2. The quality of the evidence was judged low (low birth weight and congenital abnormalities) to very low (prematurity, birth weight, miscarriage, stillbirth, neonatal mortality, and infant mortality), and therefore further research is needed.

**DISCUSSION**

Reassuringly, we found no statistically significant differences between HIV-infected pregnant women receiving TDF-based vs those receiving non–TDF-based ART in the risks of maternal or infant grade 3 or 4 adverse outcomes, pregnancy loss or miscarriage, small for gestational age, low birth weight, congenital anomalies, or infant mortality at age \( > 14 \) days. Rates of preterm delivery (\(< 37\)-week gestation) and stillbirth were modestly lower in women receiving TDF-based compared with those receiving non–TDF-based ART. Also a recent study from Malawi on pregnancy outcomes with Option B+, in which women receive TDF-efavirenz-based ART, found that risk of very preterm birth was 2.3 times higher among women not receiving ART than...
TABLE 2. GRADE Summary of Finding

| Outcomes                                      | Illustrative Comparative Risks (95% CI)* | Assumed Risk       | Corresponding Risk TDF-Exposed Versus TDF-Non-Exposed | Relative Effect (95% CI) | No. of Participants (Studies) | Quality of the Evidence (GRADE) | Comments |
|-----------------------------------------------|-----------------------------------------|--------------------|------------------------------------------------------|--------------------------|-------------------------------|--------------------------------|----------|
| Prematurity: defined as babies born alive before 37 weeks of pregnancy are completed | RR 0.910 (0.81–0.99) | 243 per 1000       | 219 per 1000 (197–248)                               | 7924 (4 studies)         |                                | Low quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. |
| Low birth weight: defined as birth weight less than 2500 grams | RR 0.91 (0.80–1.04) | 178 per 1000       | 162 per 1000 (142–185)                               | 5042 (5 studies)         |                                | Low quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. |
| Still birth: defined as baby born with no signs of life at or after 28 weeks’ gestation or miscarriage | RR 0.60 (0.43–0.84) | 56 per 1000        | 34 per 1000 (24–47)                                 | 5584 (3 studies)         |                                | Very low: Further research is very unlikely to change our confidence in the estimate of effect. |
| Congenital anomalies                          | RR 1.02 (0.83–1.28) | 46 per 1000        | 47 per 1000 (38–58)                                 | 21,205 (6 studies)       |                                | Low quality: Further research is very unlikely to change our confidence in the estimate of effect. |
| Birth weight, g                               | The mean birth weight (g) in the intervention group was 12.04 lower | 2092 (3 studies)   | 2092 (3 studies)                                   | 2092 (3 studies)         |                                | Very low: Further research is very unlikely to change our confidence in the estimate of effect. |

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

*The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

†Inconsistency rated serious as there was considerable heterogeneity in treatment effect estimates ($I^2 > 50\%$).

‡Imprecision rated serious as small number of studies, smaller than the optimal information size.

**RR, Risk Ratio.**

those receiving TDF-based ART;39; furthermore, in a study from Botswana, TDF-based ART initiated during pregnancy was associated with lower rates small for gestational age infants than those on non–TDF ART, but similar rates of preterm delivery and stillbirth.38 However, outside congenital anomalies, available data on the effects of TDF-containing ART in pregnancy remain relatively limited.

Our data on congenital anomalies are consistent with data from the Antiretroviral Pregnancy Registry. The registry has recorded sufficient numbers of first-trimester TDF exposures to confidently rule out 1.5-fold increased risk of overall birth defects, with a prevalence of birth defects with first-trimester TDF exposure of 2.3% as compared to 2.7% total prevalence in the US population.9 To date, available human data suggest that the use of TDF-based ART during pregnancy does not increase the risk of major congenital anomalies.

One study, the PROMISE trial, reported elevated rates of neonatal (age <14 days) mortality in infants born to mothers receiving TDF-based ART compared with those born to mothers receiving non–TDF-based ART.34 This study enrolled HIV-infected pregnant women with CD4+ counts >350 cells/mm3 and randomized them to receive zidovudine alone plus intrapartum single-dose nevirapine, TDF-based ART (TDF/emtricitabine/lapinavir–ritonavir), or non–TDF-based ART (zidovudine/lamivudine/lapinavir–ritonavir). In the initial 1½ years of enrollment (during which 65% of participants enrolled), only women with hepatitis B virus coinfection were allowed to be randomized to the TDF ART arm, but after a protocol modification, in the second 1½ years of enrollment (accounting for 35% of enrollment), all HIV-infected women regardless of hepatitis B status were randomized among all 3 arms. TDF ART comparisons were limited to the second part of the study with concomitant randomization to all arms. There were no significant differences between the TDF ART and non–TDF ART arms in maternal grade ≥2 AEs, spontaneous abortion, stillbirth, preterm delivery <37 weeks, low birth weight <2500 grams, very low birth weight <1500 grams, or grade ≥3 infant AEs between infants born to mothers in the TDF ART and non–TDF ART arms. However, there was a lower rate of very preterm delivery (<34 weeks) in the non–TDF ART compared with TDF ART arm (2.6% vs. 6.0%, respectively, $P = 0.04$), which led to a difference in neonatal mortality (age <14 days) (0.6% with non–TDF ART vs. 4.4% with TDF ART, $P = 0.001$), as most deaths were among very preterm infants. It is important to note, however, that there was not a significant difference between the TDF ART arm and zidovudine/single-dose nevirapine arm in very preterm delivery (6.0% vs. 3.2%, respectively, $P = 0.10$) or neonatal mortality (4.4% vs. 3.2%, $P = 0.43$). In addition, of the 17 neonatal deaths in the non–TDF ART arm, 88% (N = 15) occurred during the initial period of the trial and only 12% (N = 2) during the period of comparison with TDF ART. This suggests that the non–TDF ART arm may have had artificially low rates of very preterm delivery and infant mortality during the 3-arm comparative period of the study, and not that the TDF-ART arm had elevated risk of these events.

In contrast to the PROMISE trial results, rates of very preterm delivery were similar to TDF ART (combined with efavirenz) compared with non–TDF ART exposure in a Botswana study by Zash et al,38 and no differences in
neonatal mortality were observed with TDF ART exposure (primarily combined with nevirapine) compared with non-TDF ART exposure in a study in Uganda/Zimbabwe. It is important to note that the PROMISE trial used lopinavir, a protease inhibitor (PI) that is coformulated with ritonavir (LPV/r)-based ART regimens, whereas the Botswana and Uganda/Zimbabwe studies use non-PI-based ART regimens. In addition, in the PROMISE trial, the LPV/r dose was increased during the third trimester, based on studies showing decreased lopinavir–ritonavir levels with standard doses in pregnancy. A pharmacokinetic interaction has been reported with concurrent administration of tenofovir and lopinavir–ritonavir, which could result in increased plasma and intracellular tenofovir levels. Of note, the WHO-recommended first-line ART regimen for HIV-infected pregnant women [TDF + FTC (or 3 TC) + EFV] is distinct from the LPV/r-based ART regimen used in the PROMISE study. The results from other studies have not suggested that TDF is associated with excess adverse outcomes. By contrast, PIs, including LPV/r, have been reported to be associated with prematurity and low birth weight. As LPV/r-based regimen is recommended for second-line ART regimen, toxicity associated with such ART regimens needs further research. The PROMISE team is evaluating this further.

Data on the effects of in utero tenofovir exposure on bone and long-term growth are inadequate and therefore we cannot draw any conclusions at this time. One study that evaluated bone density using tibial quantitative ultrasound at a median age of 23 months found no significant differences between BMC when comparing infants exposed to TDF ART during pregnancy and those whose mothers received non–TDF ART. However, DXA scan is considered the gold standard for bone mineral status assessments. In a substudy within the observational PHACS cohort which assessed BMC by DXA scan in HIV-exposed uninfected children born to mothers who received TDF-based ART during pregnancy and those whose mothers received non–TDF ART. In this study that should be considered. First, some of the studies had small sample sizes. Second, the review was limited by the small number of studies reporting most of the outcomes of interest. Most of the pooled estimates should be interpreted with caution, and more research with larger sample sizes is needed to confirm these findings. We applied the I² value to assess heterogeneity. It is worth considering that I² values are typically high, and potentially exaggerated, when combining observational studies; therefore, interpreting the I² values should be performed with caution. Finally, inclusion of observational studies may lead to bias because unknown confounding that were not adjusted for, other than ART, might be responsible for maternal or infant AEs.

In summary, although the available data suggest that use of a TDF-containing ART regimen seems to be safe for HIV-infected pregnant women and their infants, the data remain limited and few studies addressed maternal toxicity or infant growth and bone effects. In consideration of these data, the good safety and efficacy data of TDF-containing first-line therapy overall, and the programmatic advantages of harmonizing ART across populations, the latest WHO guidelines continue to recommend TDF + FTC (or 3 TC) + EFV as first-line ART for adults, including pregnant women. Nevertheless, given the expected global increase in TDF use with implementation of WHO guidelines for universal treatment for all HIV-infected individuals, including pregnant and nonpregnant women, additional research on the safety of TDF in pregnancy is needed, particularly prospective longitudinal data on growth and maternal/infant bone density measurements.

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