## Tenofovir Disoproxil Fumarate (Viread, TDF)

Updated: January 31, 2023
Reviewed: January 31, 2023

Tenofovir disoproxil fumarate (TDF) is an orally bioavailable prodrug form of tenofovir (TFV). For information about tenofovir alafenamide (TAF), see the TAF section.

### *Summary*

- No dose adjustments are required for TDF during pregnancy.
- First-trimester exposure to TDF is not associated with increased risk of congenital anomalies.
- *In utero* exposure to TDF has been associated with an increased risk of preterm birth and fetal growth restriction in some but not all studies.

### *Human Studies in Pregnancy*

#### Pharmacokinetics

Plasma TFV exposures with TDF are lower during pregnancy without evidence of adverse impact on virologic efficacy; thus, standard dosing of TDF during pregnancy continues to be recommended.

*HIV Treatment*

In a prospective pharmacokinetic (PK) study of 37 women who received TDF-based combination therapy during pregnancy and postpartum, TFV trough levels and area under the concentration-time curve (AUC) were 17% lower during the third trimester than postpartum.[1] In another study of 34 women who received TDF plus emtricitabine (FTC) in the third trimester and postpartum, TFV AUC, peak concentration, and trough concentration were approximately 25% lower in pregnancy than postpartum but were not associated with virologic failure.[2] Population PK studies revealed that pregnant women receiving TDF had a 39% higher apparent oral clearance of TFV than nonpregnant women, and apparent clearance decreased slightly but significantly with increasing age.[3] In a separate population PK study, apparent oral clearance was 28% higher in pregnancy than postpartum, and weight and lower serum creatinine were independently associated with higher apparent oral clearance.[4]

The presence of a pharmacoenhancer also can affect TDF PK during pregnancy. TFV exposures in pregnant women receiving TDF with a ritonavir-boosted protease inhibitor (PI/r) are approximately 30% higher than in women receiving TDF without PI/r.[5] A separate analysis did not identify a difference in TFV exposures between pregnancy and postpartum among women receiving concomitant lopinavir/ritonavir (LPV/r), whereas TFV exposures were 27% lower in pregnant women who did not receive LPV/r.[6] TFV exposures were also higher in women receiving LPV/r than in those receiving atazanavir/ritonavir or other antiretroviral regimens during the third trimester, but no differences were identified among these groups in the postpartum period.

*HIV Pre-Exposure Prophylaxis (PrEP)*

In a study of women who did not have HIV and were using TDF as part of PrEP, intracellular concentrations of TFV diphosphate (TFV-DP) in dried blood spots (DBS) in pregnant women were approximately 70% of those in nonpregnant women, even after adjusting for adherence.[7] A separate study in pregnant and postpartum adolescent and young women receiving TDF/FTC under directly observed therapy identified a similar magnitude of difference between pregnancy and postpartum in DBS concentrations.[8] Baseline creatinine clearance was associated with TFV-DP in DBS, with every 1 mL/min increase associated with a decrease in TFV-DP by 0.96%.

**Placental and Breast Milk Passage**

*HIV Treatment*

In studies of pregnant women receiving chronic TDF, the cord blood–to–maternal plasma ratio of TFV ranged from 0.60 to 1.03, indicating high placental transfer.[1,2,9] Intracellular TFV concentrations were detected in peripheral blood mononuclear cells from cord blood in all infants after a single maternal dose of TDF 600 mg with FTC 400 mg, but intracellular TFV-DP was detectable in only 2 of 36 infants (5.5%) at birth.[10]

In study of 59 breastfeeding women with HIV in Uganda and Nigeria who received TDF/lamivudine (3TC)/efavirenz (EFV), no infant had detectable TFV in plasma after observed dosing.[11]

*HIV PrEP*

In a study of 50 breastfeeding women without HIV who received TDF/FTC for PrEP under directly observed therapy for 10 days, median peak and trough time–averaged TFV breast milk concentrations were similar at 3.2 ng/mL (interquartile range [IQR] 2.3–4.7) and 3.3 ng/mL (IQR 2.3–4.4), respectively. The infant plasma TFV concentration was below the limit of quantitation (<0.31 ng/mL) in 46 of 49 infants (94%); in the three infants with detectable TFV concentrations, the level was 0.9 ng/mL in two and 17.4 ng/mL in one. Based on this study's results, the median TFV dose ingested through breast milk was estimated to be 0.47 mcg/kg, or <0.01% of the proposed daily pediatric dose of TDF 6 mg/kg.[12]

**Reproduction/Fertility**

*HIV Treatment*

In a retrospective analysis of 7,275 women with HIV receiving ART (1,199 of whom were receiving regimens that contained TDF), women who used TDF had a slightly lower pregnancy rate than women who did not use TDF.[13]

*HIV PrEP*

By contrast, in a trial involving Kenyan and Ugandan women without HIV but whose sexual partners had HIV (serodiscordant heterosexual couples), women randomized to receive daily TDF, TDF/FTC, or placebo for PrEP did not show a significant difference in pregnancy incidence among arms.[14]

## Teratogenicity

*HIV Treatment*

No association was seen between maternal TDF use and the occurrence of birth defects among offspring in three large U.S. cohorts of children born to women with HIV: the Pediatric AIDS Clinical Trials Group (PACTG) 219/219C (n = 2,202, with 214 first-trimester TDF exposures); P1025 protocol (n = 1,112, with 138 first-trimester TDF exposures)[15,16]; and Pediatric HIV/AIDS Cohort Study (PHACS) (n = 2,580, with 431 first-trimester TDF exposures).[17] In the French Perinatal Cohort, no association was found between birth defects and the use of TDF, with a power of 70% for an odds ratio (OR) of 1.5 (n = 13,124, with 823 first-trimester TDF exposures).[18]

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to TDF to detect at least a 1.5-fold increased risk of overall birth defects and at least a twofold increase in the risk of birth defects in the cardiovascular and genitourinary systems (the more common classes of birth defects in the general population). No such increase in the risk of birth defects has been observed with TDF. Among the cases of first-trimester TDF exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.5% (115 of 4,657 live births; 95% confidence interval [CI], 2.0% to 3.0%), compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[19]

*HIV PrEP*

No difference was observed in the risk of congenital anomalies in a study of 431 pregnancies that occurred during an HIV PrEP trial, in which women who did not have HIV were randomized to receive placebo, TDF, or TDF/FTC.[14]

## Adverse Pregnancy Outcomes

Available evidence is mixed regarding the relationship between TDF and adverse pregnancy outcomes, such as fetal growth effects and preterm birth. While the role of concomitant medications and other confounders requires further investigation, the data are reassuring overall.

An observational study in Botswana of >11,000 births among women with HIV who received ART during pregnancy found that the risk of any adverse birth outcome (i.e., stillbirth, neonatal death, preterm delivery or very preterm delivery, small for gestational age [SGA], or very small for gestational age) was lower in women who received TDF/FTC/EFV than in women who received any other regimen (TDF/FTC plus nevirapine [NVP], adjusted relative risk [ARR] 1.15; TDF/FTC plus LPV/r, ARR 1.31; zidovudine [ZDV]/3TC plus NVP, ARR 1.30; ZDV/3TC plus LPV/r, ARR 1.21). Furthermore, among infants who were exposed to ART from conception, TDF/FTC/EFV was associated with a lower risk for adverse birth outcomes than other ARV regimens.[20]

See the TAF section for a discussion of the findings of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT 2010)/Virologic Efficacy and Safety of ART Combinations with TAF/TDF, EFV, and DTG (VESTED) trial, which suggests that TDF, compared with TAF, may be associated with a higher rate of adverse pregnancy outcomes when dolutegravir (DTG) regimens are started in pregnancy.[21,22]

*Fetal Growth Effects*

Maternal TDF use was linked to an increased risk of low birth weight (LBW) (<2,500 g) in a Dutch study of 74 HIV-exposed infants (including 9 with *in utero* TDF exposure).[23] SGA at birth was more frequent in the DTG plus TDF/FTC arm (45 of 200 infants [23%]) than in the DTG plus TAF/FTC arm (33 of 202 infants [16%]) in the VESTED trial, but this difference was not statistically significant.[21] A separate large observational study in Botswana showed that TDF/FTC/EFV was associated with a lower risk of SGA infants than all other regimens.[20] Several other large cohort and randomized studies have not identified significant differences in infants exposed to HIV and TDF *in utero* when examining risk of LBW[24-26] or very LBW, SGA[24,25,27] and newborn length-for-age and head circumference–for–age z-scores (LAZ and HCAZ, respectively),[24] or body size parameters at birth.[28] Duration of maternal TDF use also has not been associated with long-bone (femur and humerus) growth in the infant[29] or infant length at birth.[30]

*Preterm Delivery*

In the Promoting Maternal–Infant Survival Everywhere (PROMISE) trial, no significant differences were observed between the TDF-containing ART arm and the ZDV-containing ART arms in the incidence of preterm delivery (delivery at <37 weeks; 18.5% vs. 19.7%, respectively, $P = 0.77$). However, TDF-containing ART was associated with higher rates of very preterm delivery (delivery before 34 weeks; 6.0% vs. 2.6%, $P = 0.04$) and early infant death (4.4% vs. 0.6%, $P = 0.001$) than ZDV-containing ART.[26] Subsequent analyses demonstrated persistence of this association even after adjustment for multiple well-established clinical, demographic, and obstetrical risk factors.[31] Potential explanations include a lower than expected very preterm delivery rate in the ZDV-containing ART arm or increased TFV exposure due to coadministration with LPV/r (LPV/r doses were increased in late pregnancy). However, investigators were unable to demonstrate a relationship between maternal TFV-DP concentrations in DBS and very preterm delivery/early neonatal death.[32] A separate observational, multicenter Canadian study also showed a significantly higher rate of preterm delivery in mothers who received TDF-containing ART compared to regimens without TDF (19.4% vs. 15.2%, $P = 0.024$), and no associations with the concomitant anchor drug class were identified.[33]

Other studies have shown either no difference[21,25] or a lower risk[34,35] of these outcomes with TDF-containing therapy. However, in the Botswana study that showed a lower overall risk, there was a higher risk of preterm delivery among women who started treatment with TDF/FTC/EFV in the year prior to conception than those who started the same regimen late in the second trimester (adjusted risk ratio 1.33; 95% CI, 1.04–1.7).[20]

## *Other Safety Data*

### Maternal Safety Outcomes

TDF has not been associated with an increased risk of renal side effects in pregnancy but has shown variable effects on maternal bone mineral density (BMD), with more notable declines in women with HIV.

Retrospective analyses in pregnant women with HIV receiving TDF have not identified significant differences between pregnancy and postpartum for changes in serum creatinine and estimated glomerular filtration rate,[36] nor when comparing TDF- to TAF-containing ART regarding renal

function changes, toxicity, or treatment discontinuations due to renal toxicity.[37] A separate retrospective analysis did identify lower creatinine clearance and maternal phosphate levels, in addition to higher rates of hypophosphatemia, in women randomized to TDF-containing ART than to ZDV alone or ZDV in combination with other antiretrovirals. However, these differences were not deemed to be clinically relevant, and no significant differences were seen in these measures among infants.[38]

Significant decreases in lumbar spine and total hip BMD were identified in pregnant women receiving TDF-containing regimens compared with pregnant women receiving non-TDF-containing regimens,[39] and in total hip BMD compared with pregnant women without HIV.[40] Areal BMD did not return to baseline values in women with HIV but did in the reference group for total hip (−3.1% vs. +0.1%, $P = 0.0008$) and for whole body (less head) (−2.4% vs. −0.1%, $P = 0.002$).[40]

### Infant Safety Outcomes

Maternal TDF has not been associated with an increase in the likelihood of adverse infant metabolic, growth and developmental, cardiac, neurological, or neurodevelopmental outcomes after adjusting for birth cohort and other factors[41] or in infant mortality.[42]

### Infant Growth Effects

Evidence is inconsistent regarding the association between maternal TDF use during pregnancy and transient, small growth delays during the first year of life. These delays are of uncertain clinical significance.[43] Available evidence is further detailed throughout the rest of this section.

#### *HIV Treatment*

Multiple studies have shown varying effects of TDF exposure on infant growth measures despite no differences being identified at birth. In the U.S. PHACS study, infants exposed to combination regimens with TDF had a slightly but significantly lower adjusted mean LAZ and HCAZ than those without TDF exposure at 1 year of age (LAZ: -0.17 vs. -0.03, $P = 0.04$; HCAZ: 0.17 vs. 0.42, $P = 0.02$). No difference was observed in weight-for-age z-score (WAZ) or when defining low LAZ or HCAZ as ≤1.5 z-score. Thus, these slightly lower mean LAZ and HCAZ scores are of uncertain significance.[24] In the U.S. P1025 study, TDF exposure after the first trimester was associated with being underweight (WAZ <5%) at age 6 months (OR 2.06; 95% CI, 1.01–3.95; $P = 0.04$) when compared to no exposure.[28] A Kenyan cohort study also found an association between maternal TDF use (compared to ART without TDF) and lower infant 6-week WAZ; however, TDF exposure was not associated with infant WAZ differences at age 9 months or any other infant anthropometric measures at the 6-week or 9-month time points.[44] Maternal TDF use was also linked to lower 6-month HAZ and WAZ after adjusting for differences in birth weight and prematurity in the Dutch study of 74 HIV-exposed infants.[23]

Conversely, other studies have not identified an effect of TDF on infant growth rates.[30,42] In IMPAACT 2010/VESTED, growth as measured by LAZ and WAZ among infants exposed to DTG+TDF/FTC *in utero* did not significantly differ from those exposed to DTG+TAF/FTC at 26 and 50 weeks of age. LAZ and WAZ in the DTG+TDF/FTC arm were higher than those measured in infants exposed to EFV+TDF/FTC at both these time points.[45] There were no differences in weight-for-length Z scores between treatment regimens, but all infants showed severely stunted growth through the first year of age.

### Infant Bone Effects

The impact of maternal TDF use on infant bone mineral status remains uncertain and requires further longitudinal evaluation. Available evidence is further summarized throughout this section.

*HIV Treatment*

A study examining whole-body, dual-energy X-ray absorptiometry scans performed within 4 weeks of birth among infants exposed to >8 weeks of TDF *in utero* (n = 74) versus those with no TDF exposure (n = 69) identified a significantly lower adjusted mean whole-body bone mineral content (BMC) in the TDF group (-6.5 g; $P = 0.004$) in addition to whole-body-less-head BMC (-2.6 g; $P = 0.056$).[46] A separate analysis in breastfed infants exposed to maternal TDF-based ART also showed lower lumbar spine BMC than infants receiving NVP prophylaxis at week 26 (mean difference -0.13 g, $P = 0.007$), although the clinical relevance of this finding is unclear.[47] There were also no significant differences in creatinine clearance between treatment groups. A separate study of 136 infants in Malawi whose mothers received TDF/FTC/EFV during pregnancy (with no control group for comparison) documented low-grade, transient abnormalities of serum phosphate and serum creatinine at ages 6 and 12 months.[48]

Other studies have not identified any effects of TDF exposure on infant bone development. In a cross-sectional study of 68 children aged 1 to 6 years who were exposed to HIV (but not infected) and had *in utero* exposure to combination regimens that contained TDF (n = 33) or did not contain TDF (n = 35), quantitative bone ultrasound measures and bone metabolism marker levels were similar for both groups.[49] A separate small, randomized trial among pregnant women in China with HBV/HIV coinfection showed that BMD and BMC at age 6 months were not significantly lower in TDF-exposed infants (n = 14) than those not exposed to TDF (n = 13).[50] In the randomized PROMISE trial, no difference was observed in BMC between infants whose mothers received LPV/r-based ART with TDF and those whose mothers received LPV/r-based ART with ZDV.[51]

## *Animal Studies*

### Carcinogenicity

TDF was mutagenic in one of two *in vitro* assays and has shown no evidence of clastogenic activity. Long-term oral carcinogenicity studies of oral TDF were carried out at 16 times the exposure in humans and showed increased incidence of liver adenomas in mice, but no effects were seen in rats at 5 times the exposure.[52]

### Reproduction/Fertility

TDF was not associated with impaired fertility or harm to the fetus in reproductive toxicity studies at exposures up to 14 times (in rats) and 19 times (in rabbits) the human dose. No effects were observed on fertility, mating performance, or early embryonic development when TDF was administered producing TFV exposures equivalent to 10 times the human dose based on body surface area in male or female rats, but an alteration of the estrous cycle in female rats was observed.[52]

### Teratogenicity/Adverse Pregnancy Outcomes

Fetal monkeys with chronic, high-level TFV exposure equivalent to 25 times the AUC achieved with therapeutic dosing in humans had lower fetal circulating insulin-like growth factor (IGF)-1, higher

IGF binding protein-3 levels, lower body weights, and slightly reduced fetal bone porosity compared with TFV-unexposed fetal monkeys.[52]

### Placental and Breast Milk Passage

Intravenous administration of TFV to pregnant cynomolgus monkeys resulted in a cord blood–to–maternal plasma ratio of 0.17, demonstrating that TFV crosses the placenta.[53]

**Excerpt from Table 14**

**Note:** When using fixed-dose combination (FDC) tablets, refer to other sections in Appendix B and Table 14 in the Perinatal Guidelines for information about the dosing and safety of individual drug components of the FDC tablet during pregnancy.

| Generic Name (Abbreviation) *Trade Name* | Formulation | Dosing Recommendations[a] | Use in Pregnancy |
|---|---|---|---|
| Tenofovir Disoproxil Fumarate (TDF) *Viread*<br><br>(TDF/EFV/FTC) *Atripla*<br><br>(TDF/3TC) *Cimduo*<br><br>(TDF/FTC/RPV) *Complera*<br><br>(TDF/DOR/3TC) *Delstrigo*<br><br>(TDF/EVG/c/FTC) *Stribild*<br><br>(TDF/EFV/3TC) *Symfi*<br><br>(TDF/EFV/3TC) *Symfi Lo*<br><br>(TDF/3TC) *Temixys*<br><br>(TDF/FTC) *Truvada*<br><br>Note: Generic products are available for some formulations. | TDF (Viread)<br><br>*Tablet[d]*<br>• 300 mg<br><br>*Powder*<br>• 40-mg/1-g oral powder<br><br>TDF/EFV/FTC (Atripla)<br>• TDF 300-mg/EFV 600-mg/ FTC 200-mg tablet<br><br>TDF/3TC (Cimduo)<br>• TDF 300-mg/3TC 300-mg tablet<br><br>TDF/FTC/RPV (Complera)<br>• TDF 300-mg/FTC 200-mg/ RPV 25-mg tablet<br><br>TDF/DOR/3TC (Delstrigo)<br>• TDF 300-mg/DOR 100-mg/ 3TC 300-mg tablet<br><br>TDF/EVG/c/FTC (Stribild)<br>• TDF 300-mg/EVG 150-mg/ COBI 150-mgFTC 200-mg tablet<br><br>TDF/EFV/3TC (Symfi)<br>• TDF 300-mg/EFV 600-mg/ 3TC 300-mg tablet<br><br>TDF/EFV/3TC (Symfi Lo)<br>• TDF 300-mg/EFV 400-mg/ 3TC 300-mg tablet<br><br>TDF/3TC (Temixys)<br>• TDF 300-mg/3TC 300-mg tablet | Pregnancy<br><br>*PKs in Pregnancy*<br>• AUC is lower in third trimester than postpartum, but trough levels are adequate.<br><br>*Dosing in Pregnancy*<br>• No change in dose is indicated.<br><br>For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., Lamivudine (Epivir, 3TC), Cobicistat (Tybost, COBI), Doravirine (Pifeltro, DOR), Efavirenz (Sustiva, EFV), Elvitegravir (EVG), Emtricitabine (Emtriva, FTC), Rilpivirine (Edurant, RPV)).<br><br>Standard Adult Doses<br><br>*TDF (Viread)*<br>• Tablet<br>o TDF 300 mg once daily without regard to food<br>• Powder<br>o TDF 8 mg/kg daily (up to a maximum of TDF 300 mg). Take with food.<br><br>*TDF/EFV/FTC (Atripla)*<br>• One tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. | High placental transfer to fetus[b]<br><br>No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects)<br><br>Human studies demonstrate no consistent link to low birth weight, but data are conflicting about potential effects on growth outcomes later in infancy.<br><br>If patient has HBV/HIV coinfection, an HBV flare may occur if TDF is stopped; see Hepatitis B Virus/HIV Coinfection.<br><br>Renal function should be monitored because of potential for renal toxicity. |

## Excerpt from Table 14

| Generic Name (Abbreviation) *Trade Name* | Formulation | Dosing Recommendations[a] | Use in Pregnancy |
|---|---|---|---|
| | TDF/FTC (Truvada)<br>• TDF 300-mg/FTC 200-mg tablet | *TDF/3TC (Cimduo)*<br>• One tablet once daily without regard to food<br>*TDF/FTC/RPV (Complera)*<br>• One tablet once daily with food<br>*TDF/DOR/3TC (Delstrigo)*<br>• One tablet once daily without regard to food<br>*TDF/EVG/c/FTC (Stribild)*<br>• One tablet once daily with food<br>*TDF/EFV/3TC (Symfi or Symfi Lo)*<br>• One tablet once daily on an empty stomach and preferably at bedtime<br>*TDF/3TC (Temixys)*<br>• One tablet once daily without regard to food<br>*TDF/FTC (Truvada)*<br>• One tablet once daily without regard to food | |

[a] Individual ARV drug doses may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Antiretroviral Guidelines, Appendix B, Table 11).

[b] Placental transfer categories are determined by mean or median cord blood/maternal delivery plasma drug ratio:

High: >0.6
Moderate: 0.3–0.6
Low: <0.3

[d] Generic product is available.

Key: 3TC = lamivudine; ARV = antiretroviral; AUC = area under the curve; COBI = cobicistat; DOR = doravirine; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HBV = hepatitis B virus; PK = pharmacokinetic; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

## References


1. Best BM, Burchett S, Li H, et al. Pharmacokinetics of tenofovir during pregnancy and postpartum. *HIV Med*. 2015;16(8):502-511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25959631.

2. Colbers AP, Hawkins DA, Gingelmaier A, et al. The pharmacokinetics, safety and efficacy of tenofovir and emtricitabine in HIV-1-infected pregnant women. *AIDS*. 2013;27(5):739-748. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23169329.

3. Benaboud S, Hirt D, Launay O, et al. Pregnancy-related effects on tenofovir pharmacokinetics: a population study with 186 women. *Antimicrob Agents Chemother*. 2012;56(2):857-862. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22123690.

4. Eke AC, Shoji K, Best BM, et al. Population pharmacokinetics of tenofovir in pregnant and postpartum women using tenofovir disoproxil fumarate. *Antimicrob Agents Chemother*. 2021;65(3). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33318014.

5. Bukkems VE, Smolders EJ, Jourdain G, et al. Effect of pregnancy and concomitant antiretrovirals on the pharmacokinetics of tenofovir in women with HIV receiving tenofovir disoproxil fumarate-based antiretroviral therapy versus women with HBV receiving tenofovir disoproxil fumarate monotherapy. *J Clin Pharmacol*. 2021;61(3):388-393. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32960984.

6. Mulligan N, Salama E, Momper JD, et al. Lopinavir and tenofovir interaction observed in non-pregnant adults altered during pregnancy. *J Clin Pharm Ther*. 2021;46(5):1459-1464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34254323.

7. Pyra M, Anderson PL, Hendrix CW, et al. Tenofovir and tenofovir-diphosphate concentrations during pregnancy among HIV-uninfected women using oral preexposure prophylaxis. *AIDS*. 2018;32(13):1891-1898. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29894385.

8. Stranix-Chibanda L, Anderson PL, Kacanek D, et al. Tenofovir diphosphate concentrations in dried blood spots from pregnant and postpartum adolescent and young women receiving daily observed pre-exposure prophylaxis in Sub-Saharan Africa. *Clin Infect Dis*. 2021;73(7):e1893-e1900. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33341883.

9. Hirt D, Urien S, Ekouevi DK, et al. Population pharmacokinetics of tenofovir in HIV-1-infected pregnant women and their neonates (ANRS 12109). *Clin Pharmacol Ther*. 2009;85(2):182-189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18987623.

10. Hirt D, Ekouevi DK, Pruvost A, et al. Plasma and intracellular tenofovir pharmacokinetics in the neonate (ANRS 12109 trial, step 2). *Antimicrob Agents Chemother*. 2011;55(6):2961-2967. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21464249.

11. Waitt C, Olagunju A, Nakalema S, et al. Plasma and breast milk pharmacokinetics of emtricitabine, tenofovir and lamivudine using dried blood and breast milk spots in nursing African mother-infant pairs. *J Antimicrob Chemother*. 2018;73(4):1013-1019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29309634.

12. Mugwanya KK, Hendrix CW, Mugo NR, et al. Pre-exposure prophylaxis use by breastfeeding HIV-uninfected women: a prospective short-term study of antiretroviral excretion in breast milk and infant absorption. *PLoS Med*. 2016;13(9):e1002132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27676257.

13. Maskew M, Westreich D, Firnhaber C, Sanne I. Tenofovir use and pregnancy among women initiating HAART. *AIDS*. 2012;26(18):2393-2397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22951630.

14. Mugo NR, Hong T, Celum C, et al. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. *JAMA*. 2014;312(4):362-371. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25038355.

15. Brogly SB, Abzug MJ, Watts DH, et al. Birth defects among children born to human immunodeficiency virus-infected women: pediatric AIDS clinical trials protocols 219 and 219C. *Pediatr Infect Dis J*. 2010;29(8):721-727. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20539252.

16. Knapp KM, Brogly SB, Muenz DG, et al. Prevalence of congenital anomalies in infants with in utero exposure to antiretrovirals. *Pediatr Infect Dis J*. 2012;31(2):164-170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21983213.

17. Williams PL, Crain M, Yildirim C, et al. Congenital anomalies and in utero antiretroviral exposure in human immunodeficiency virus-exposed uninfected infants. *JAMA Pediatr*. 2015;169(1):45-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25383770.

18. Sibiude J, Mandelbrot L, Blanche S, et al. Association between prenatal exposure to antiretroviral therapy and birth defects: an analysis of the French Perinatal Cohort Study (ANRS CO1/CO11). *PLoS Med*. 2014;11(4):e1001635. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4004531.

19. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 January 2022. Wilmington, NC: Registry Coordinating Center; 2022. Available at: http://www.apregistry.com/forms/interim_report.pdf.

20. Zash R, Rough K, Jacobson DL, et al. Effect of gestational age at tenofovir-emtricitabine-efavirenz initiation on adverse birth outcomes in Botswana. *J Pediatric Infect Dis Soc*. 2018;7(3):e148-e151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29688554.

21. Lockman S, Brummel SS, Ziemba L, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet*. 2021;397(10281):1276-1292. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33812487.

22. Brummel S, Ziemba L, Coletti A, et al. Risk-benefit trade-off for pregnancy and infant outcomes: DTG, EFV, TAF, and TDF. Presented at: The Conference on Retroviruses and Opportunistic Infections. 12–16 February, 2022; Virtual. Available at:

https://www.impaactnetwork.org/sites/default/files/inline-files/IMPAACT2010_Brummel_DOOR_CROI2022_poster_0.pdf.

23. Denneman L, Cohen S, Godfried MH, et al. In-utero exposure to tenofovir is associated with impaired fetal and infant growth: need for follow-up studies in combination antiretroviral therapy/HIV-exposed infants. *AIDS*. 2016;30(13):2135-2137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27465280.

24. Siberry GK, Williams PL, Mendez H, et al. Safety of tenofovir use during pregnancy: early growth outcomes in HIV-exposed uninfected infants. *AIDS*. 2012;26(9):1151-1159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22382151.

25. Rough K, Seage GR, 3rd, Williams PL, et al. Birth outcomes for pregnant women with HIV using tenofovir-emtricitabine. *N Engl J Med*. 2018;378(17):1593-1603. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29694825.

26. Fowler MG, Qin M, Fiscus SA, et al. Benefits and risks of antiretroviral therapy for perinatal HIV prevention. *N Engl J Med*. 2016;375(18):1726-1737. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27806243.

27. European Pregnancy Paediatric HIV Cohort Collaboration Study Group. Nucleoside reverse transcriptase inhibitor backbones and pregnancy outcomes. *AIDS*. 2019;33(2):295-304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30562172.

28. Ransom CE, Huo Y, Patel K, et al. Infant growth outcomes after maternal tenofovir disoproxil fumarate use during pregnancy. *J Acquir Immune Defic Syndr*. 2013;64(4):374-381. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24169122.

29. Jao J, Abrams EJ, Phillips T, Petro G, Zerbe A, Myer L. In utero tenofovir exposure is not associated with fetal long bone growth. *Clin Infect Dis*. 2016;62(12):1604-1609. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27009251.

30. le Roux SM, Jao J, Brittain K, et al. Tenofovir exposure in utero and linear growth in HIV-exposed, uninfected infants. *AIDS*. 2017;31(1):97-104. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27898591.

31. Sebikari D, Farhad M, Fenton T, et al. Risk factors for adverse birth outcomes in the PROMISE 1077BF/1077FF trial. *J Acquir Immune Defic Syndr*. 2019;81(5):521-532. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31295174.

32. Aizire J, Brooks KM, Mirochnick M, et al. Antenatal intracellular concentrations of tenofovir diphosphate and emtricitabine triphosphate and associations between tenofovir diphosphate and severe adverse pregnancy outcomes: IMPAACT-PROMISE (1077BF) trial. *J Acquir Immune Defic Syndr*. 2020;83(2):173-180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31929405.

33. Brophy J, Lee T, Bitnun A, Kakkar F, et al. . Is tenofovir use in pregnancy associated with preterm delivery? A Canadian perinatal HIV surveillance program analysis. Presented at: 9th IAS Conference on HIV Science 2017. Paris, France. Available at: http://programme.ias2017.org/Abstract/Abstract/3898.

34. Zash R, Jacobson DL, Diseko M, et al. Comparative safety of antiretroviral treatment regimens in pregnancy. *JAMA Pediatr*. 2017;171(10):e172222. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28783807.

35. Pintye J, Baeten JM, Celum C, et al. Maternal tenofovir disoproxil fumarate use during pregnancy is not associated with adverse perinatal outcomes among HIV-infected East African women: a prospective study. *J Infect Dis*. 2017;216(12):1561-1568. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29040666.

36. Flanagan S, Barnes L, Anderson J, Barber T. The effect of tenofovir on renal function in HIV-positive pregnant women. *J Int AIDS Soc*. 2014;17(4 Suppl 3):19694. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25397444.

37. Thimm MA, Eke AC. Tenofovir, pregnancy and renal function changes in pregnant women living with HIV. *Aids*. 2021;35(8):1319-1320. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8172469.

38. Baltrusaitis K, Makanani B, Tierney C, et al. Maternal and infant renal safety following tenofovir disoproxil fumarate exposure during pregnancy in a randomized control trial. *BMC Infect Dis*. 2022;22(1):634. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35858874.

39. Stranix-Chibanda L, Tierney C, Sebikari D, et al. Impact of postpartum tenofovir-based antiretroviral therapy on bone mineral density in breastfeeding women with HIV enrolled in a randomized clinical trial. *PLoS One*. 2021;16(2):e0246272. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33544759.

40. Nabwire F, Prentice A, Hamill MM, et al. Changes in bone mineral density during and after lactation in Ugandan women with HIV on tenofovir-based antiretroviral therapy. *J Bone Miner Res*. 2020;35(11):2091-2102. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32573842.

41. Williams PL, Hazra R, Van Dyke RB, et al. Antiretroviral exposure during pregnancy and adverse outcomes in HIV-exposed uninfected infants and children using a trigger-based design. *AIDS*. 2016;30(1):133-144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26731758.

42. Gibb DM, Kizito H, Russell EC, et al. Pregnancy and infant outcomes among HIV-infected women taking long-term ART with and without tenofovir in the DART trial. *PLoS Med*. 2012;9(5):e1001217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22615543.

43. Liotta G, Floridia M, Andreotti M, et al. Growth indices in breastfed infants pre and postnatally exposed to tenofovir compared with tenofovir-unexposed infants. *AIDS*. 2016;30(3):525-527. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26765942.

44. Pintye J, Langat A, Singa B, et al. Maternal tenofovir disoproxil fumarate use in pregnancy and growth outcomes among HIV-exposed uninfected infants in Kenya. *Infect Dis Obstet Gynecol*. 2015;2015:276851. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26823647.

45. Stranix-Chibanda L, Ziemba L, Brummel S, et al. Growth of infants with perinatal exposure to maternal DTG vs EFV and TDF vs TAF: the randomized IMPAACT 2010 trial. Presented

at: Conference on Retroviruses and Opportunistic Infections. 2022. Virtual. Available at: https://www.hivandmore.de/kongresse/croi2022/slides/gilead/Stranix-Chibanda_Perinatal-exposure-DTG--EFV--TDF--TAF_CROI2022_Oral-30.pdf.

46. Siberry GK, Jacobson DL, Kalkwarf HJ, et al. Lower newborn bone mineral content associated with maternal use of tenofovir disoproxil fumarate during pregnancy. *Clin Infect Dis*. 2015;61(6):996-1003. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26060285.

47. Vhembo T, Baltrusaitis K, Tierney C, et al. Association of maternal TDF-based ART with bone mineral content in breastfed infants. Presented at: Conference on Retroviruses and Opportunistic Infections. 2022. Virtual. Available at: https://www.impaactnetwork.org/sites/default/files/inline-files/PROMISE-P1084s_Vhembo_MaternalTDF-InfantBMC_CROI2022_poster_0.pdf.

48. Floridia M, Liotta G, Andreotti M, et al. Serum phosphate and creatinine levels in the first year of life in infants born to HIV-positive mothers receiving tenofovir-based combination regimens during pregnancy and prolonged breastfeeding in an option B+ program in Malawi. *J Acquir Immune Defic Syndr*. 2016;73(5):e90-e91. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27559686.

49. Vigano A, Mora S, Giacomet V, et al. In utero exposure to tenofovir disoproxil fumarate does not impair growth and bone health in HIV-uninfected children born to HIV-infected mothers. *Antivir Ther*. 2011;16(8):1259-1266. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22155907.

50. Kourtis AP, Wiener J, Wang L, et al. Tenofovir disoproxil fumarate use during pregnancy and infant bone health: the tenofovir in pregnancy pilot study. *Pediatr Infect Dis J*. 2018;37(11):e264-e268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30067600.

51. Siberry G, Tierney C, Stanix-Chibanda L. Impact of maternal tenofovir disoproxil fumarate (TDF) use on HIV-exposed newborn bone mineral content. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA.

52. Tenofovir disproxil fumarate (Viread) [package insert]. Food and Drug Administration. 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021356s058,022577s014lbl.pdf.

53. Tarantal AF, Marthas ML, Shaw JP, Cundy K, Bischofberger N. Administration of 9-[2-(R)-(phosphonomethoxy)propyl]adenine (PMPA) to gravid and infant rhesus macaques (Macaca mulatta): safety and efficacy studies. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1999;20(4):323-333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10096575.