Tenofovir Disoproxil Fumarate (Viread, TDF)

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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 concentration (C_{trough}) levels and area under the 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 C_{trough} 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 (ARV) regimens during the third trimester, but no differences were identified among these groups in the postpartum period.

HIV Pre-exposure Prophylaxis

An *in silico* simulation of plasma TFV exposures in 1,000 pregnancies when the standard daily dose of TDF 300 mg/FTC 200 mg is prescribed demonstrated that plasma C_{trough} fell below the protective threshold of 35.5 ng/mL among 34.0%, 43.8%, and 65.1% of pregnancies in the first, second, and third trimesters, respectively.[7] Simulations were also performed with double dosing

(i.e., TDF 600 mg/FTC 400 mg), which suggested that lower proportions would fall below protective thresholds during pregnancy.

In a study of women who did not have HIV and were using TDF as part of pre-exposure prophylaxis (PrEP), intracellular concentrations of TFV diphosphate (TFV-DP) in dried blood spots (DBS) were approximately 30% lower in pregnant versus nonpregnant women after adjusting for adherence.[8] A separate study in pregnant and postpartum adolescents and young women receiving TDF/FTC under directly observed therapy identified a similar magnitude of difference in DBS concentrations between pregnancy and postpartum.[9] These differences were explained in part by renal function, as TFV-DP decreased by 0.96% for every 1 mL/min increase in baseline creatinine clearance. Another study of pregnant women without HIV randomized 1:1 to either TDF/FTC or TAF/FTC reported lower concentrations and magnitudes of difference for TFV-DP in DBS with TDF/FTC in comparison to the previously mentioned studies. TFV-DP in PBMC were also similar between pregnancy and postpartum[10] and comparable to concentrations associated with 67% to 100% adherence[11] in nonpregnant adults without HIV. Further studies are needed to better understand associations between the PK in plasma and cells, efficacy and safety in these populations.

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.[1,2,12] 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.[13]

In a 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.[14] A separate study in Ugandan women showed that breast milk composition among women with HIV who received TDF had higher calcium levels at 14 weeks postpartum, but then demonstrated greater declines through the first year of breastfeeding than in those without HIV.[15]

HIV Pre-exposure Prophylaxis

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.[16]

Reproduction/Fertility

In a retrospective analysis of 7,275 women with HIV receiving antiretroviral therapy (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.[17] In contrast, a trial involving Kenyan and Ugandan women without HIV but whose sexual partners had HIV (serodifferent 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.[18]

Teratogenicity

No associations have been identified between TDF use and the risk of overall birth defects. The Antiretroviral Pregnancy Registry (APR) provides updated birth defect data for TDF and other ARV drugs twice a year through an interim report released in June and December. The APR 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. In the APR interim report, Figure 1. Summary of Birth Defects Among First Trimester Exposures provides a summary of the number and prevalence of birth defects per live births among cases of first-trimester exposure to TDF and other ARV drugs reported to the APR where there are sufficient data to determine 95% confidence intervals (CIs). The data in Figure 1 can be compared with a total prevalence of birth defects in the U.S. population (2.72 birth defects per 100 live births), based on the Centers for Disease Control and Prevention surveillance system (The Metropolitan Atlanta Congenital Defects Program [MACDP]) and with the Texas Birth Defects Registry ([TBDR] 5.07 birth defects per 100 live births).

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)[19,20]; and Pediatric HIV/AIDS Cohort Study (PHACS) (n = 2,580, with 431 first-trimester TDF exposures).[21] 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).[22]

Adverse Pregnancy Outcomes

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

HIV Treatment

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 birth or very preterm birth, small for gestational age [SGA], or very SGA) was lower in women who received TDF/FTC/EFV compared with women who received regimens containing nevirapine (NVP), LPV/r, or zidovudine (ZDV)/3TC. 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.[23] However, there was a higher risk of preterm birth 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).[23]

Maternal TDF use was linked to an increased risk of low birth weight (LBW) (<2,500 g) in a Dutch study of 74 infants who were exposed to HIV (including 9 with *in utero* TDF exposure).[24] SGA at birth was more frequent in the dolutegravir (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 Virologic Efficacy and Safety of ART Combinations with TAF/TDF, EFV, and DTG (VESTED) trial, but this difference was not statistically significant.[25] 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.[23] 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[26-28] or very LBW, SGA,[26,27,29] and newborn length-for-age and

head circumference–for-age z-scores[26] or body size parameters at birth.[30] Duration of maternal TDF use also has not been infant length at birth.[31]

In the Promoting Maternal–Infant Survival Everywhere (PROMISE) trial, no significant differences were observed between the TDF- and ZDV-containing ART arms in the incidence of preterm birth (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 birth (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.[28] Subsequent analyses demonstrated persistence of this association even after adjustment for multiple well-established clinical, demographic, and obstetrical risk factors.[32] Potential explanations include a lower-than-expected very preterm birth 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, no relationship between maternal TFV-DP concentrations in DBS and very preterm birth/early neonatal death was identified.[33] A separate observational, multicenter Canadian study also showed a significantly higher rate of preterm birth 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.[34] Other studies have shown either no difference[25,27] or a lower risk[35] of these outcomes with TDF-containing therapy.

A systematic review of 15 cohort studies and 33,395 pregnant women with HIV, inclusive of some studies covered throughout this section, examined adverse pregnancy outcomes across multiple nucleos(t)ide reverse transcriptase inhibitor backbone options containing either TDF, abacavir, or ZDV with FTC or 3TC.[36] TDF-containing ART was associated with a lower risk of preterm birth, very preterm birth, SGA, very SGA, stillbirth, and neonatal death in comparison to non-TDF containing ART. However, the authors noted that all studies were observational and prone to biases, and the ability to adjust for potential confounders was limited.

See the Tenofovir Alafenamide section for a discussion of the findings of the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT 2010)/VESTED trial, which suggests that TDF, compared with TAF, may be associated with a higher rate of adverse pregnancy outcomes when DTG regimens are started in pregnancy.[25,37]

HIV Pre-exposure Prophylaxis

A systematic analysis of 13 studies among 8,712 pregnant women in Africa either did not identify or showed a reduced risk of preterm birth among women on oral PrEP in comparison to no oral PrEP.[38] There were also no associations identified with LBW and very LBW, SGA, or neonatal death.

Other Safety Data

Maternal Safety Outcomes

TDF has not been associated with an increased risk of renal side effects in pregnancy. In contrast, TDF use has been associated with variable effects on maternal bone mineral density, with more notable declines in women with HIV.[39-41]

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,[42] nor when comparing TDF- to TAF-containing ART regarding renal function changes, toxicity, or treatment discontinuations due to renal toxicity.[43] 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 compared with ZDV alone or ZDV in combination with other ARVs. However, these differences were

not deemed to be clinically relevant, and no significant differences were seen in these measures among infants.[44]

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[45] or in infant mortality.[46]

Evidence is inconsistent regarding the association between maternal TDF use during pregnancy and transient, small growth delays during the first year of life. Some studies have shown that TDF exposure negatively impacts infant growth measures despite no differences being identified at birth,[24,26,30,47] whereas others have not identified an effect of TDF on infant growth rates[31,46,48] In cases where infantile growth delays were identified, differences are of uncertain clinical significance.[49]

The impact of maternal TDF use on infant bone mineral status also remains uncertain and requires further longitudinal evaluation. Some studies have shown lower mean whole-body bone mineral content (BMC), whole-body-less-head BMC,[50] and lumbar spine BMC[51] among those exposed to TDF either *in utero* or through breastmilk, whereas others have not identified any effects on these measures or other bone metabolism markers.[52-54]

The impact of TDF exposure on renal function has also been examined in multiple studies. One study among mothers who 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.[55] However, a separate study identified no differences in creatinine clearance between those exposed to maternal TDF compared with those on NVP prophylaxis.[56]

See Long-Term Follow-Up of Infants Exposed to Antiretroviral Drugs for additional information.

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.[57]

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.[57]

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.[57]

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.[58]

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* (TDF/EFV/FTC) (TDF/3TC) *Cimduo* (TDF/FTC/RPV) *Complera* (TDF/DOR/3TC) *Delstrigo* (TDF/EVG/c/FTC) *Stribild* (TDF/EFV/3TC) *Symfi* (TDF/EFV/3TC) *Symfi Lo*[c,d] (TDF/FTC) *Truvada* **Note:** Generic products are available for some formulations.	**TDF (Viread)** *Tablet*[c] • 300 mg *Powder* • 40-mg/1-g oral powder **TDF/EFV/FTC** • TDF 300-mg/EFV 600-mg/ FTC 200-mg tablet **TDF/3TC (Cimduo)** • TDF 300-mg/3TC 300-mg tablet **TDF/FTC/RPV (Complera)** • TDF 300-mg/FTC 200-mg/ RPV 25-mg tablet **TDF/DOR/3TC (Delstrigo)** • TDF 300-mg/DOR 100-mg/ 3TC 300-mg tablet **TDF/EVG/c/FTC (Stribild)** • TDF 300-mg/EVG 150-mg/ COBI 150-mg/FTC 200-mg tablet **TDF/EFV/3TC (Symfi)** • TDF 300-mg/EFV 600-mg/ 3TC 300-mg tablet **TDF/EFV/3TC (Symfi Lo[c,d])** • TDF 300-mg/EFV 400-mg/ 3TC 300-mg tablet **TDF/FTC (Truvada)[c]** • TDF 300-mg/FTC 200-mg tablet	**Pregnancy** *PK in Pregnancy* • AUC is lower in third trimester than postpartum, but trough levels are adequate. *Dosing in Pregnancy* • No change in dose is indicated. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, COBI, DOR, EFV, EVG, FTC, RPV). **Standard Adult Doses** *TDF (Viread)* • Tablet o TDF 300 mg once daily without regard to food • Powder o TDF 8 mg/kg daily (up to a maximum of TDF 300 mg). Take with food. *TDF/EFV/FTC* • One tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects.	High placental transfer to fetus[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects) Human studies demonstrate no consistent link to LBW, but data are conflicting about potential effects on growth outcomes later in infancy. If patient has HBV/HIV coinfection, an HBV flare may occur if TDF is stopped; see Hepatitis B Virus/HIV Coinfection. Renal function should be monitored because of potential for renal toxicity. **Note:** Please see FDA label for full list of drugs with potential interactions and drugs for which administration with TDF is contraindicated.

Excerpt From Table 14

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

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

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

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

[c] Generic product is available.

[d] As of May 2025, Symfi Lo brand products are no longer available.

Key: 3TC = lamivudine; ARV = antiretroviral; AUC = area under the curve; COBI = cobicistat; DOR = doravirine; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FDA = U.S. Food and Drug Administration; FTC = emtricitabine; HBV = hepatitis B virus; LBW = low birth weight; PK = pharmacokinetic; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

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