Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States

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Tenofovir Disoproxil Fumarate (Viread, TDF)

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Tenofovir disoproxil fumarate (TDF), an orally bioavailable form of tenofovir, is classified as Food and Drug Administration Pregnancy Category B.[1] For information about tenofovir alafenamide (TAF), see the TAF section.

Animal Studies

Carcinogenicity

Tenofovir is mutagenic in one of two *in vitro* assays and has no evidence of clastogenic activity. Long-term oral carcinogenicity studies of tenofovir were carried out at 16 times (in mice) and 5 times (in rats) the exposure in humans taking standard dosing. In female mice, liver adenomas were increased at exposures 16 times those observed in humans who received therapeutic doses. In rats, there was no evidence of carcinogenicity at exposures up to 5 times those observed in humans who received the therapeutic dose.[1]

Reproduction/Fertility

Reproduction studies have been performed in rats and rabbits at doses of tenofovir up to 14 times and 19 times the human dose, respectively, based on body surface area comparisons. These studies revealed no evidence of impaired fertility or harm to the fetus associated with tenofovir. There were also no effects on fertility, mating performance, or early embryonic development when tenofovir was administered to male rats (600 mg/kg/day; equivalent to 10 times the human dose based on body surface area) for 28 days before mating and to female rats from 15 days before mating through Day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats who were administered tenofovir 600 mg/kg/day.[1]

Teratogenicity/Adverse Pregnancy Outcomes

Fetal monkeys with chronic high-level exposure to tenofovir (exposure equivalent to 25 times the area under the curve [AUC] achieved with therapeutic dosing in humans) had lower fetal circulating insulin-like growth factor (IGF)-1, higher IGF binding protein-3 levels, and lower body weights compared to tenofovir-unexposed fetal monkeys. A slight reduction in fetal bone porosity was also observed. These effects were observed within 2 months of maternal treatment.[1]

Placental and Breast Milk Passage

Intravenous administration of tenofovir to pregnant cynomolgus monkeys resulted in a fetal/maternal plasma concentration of 17%, demonstrating that tenofovir crosses the placenta.[2]

Human Studies in Pregnancy

Pharmacokinetics

In a retrospective population pharmacokinetic study of 46 pregnant women and 156 nonpregnant women who were receiving combination regimens that included TDF, pregnant women had a 39% higher apparent clearance of tenofovir compared with nonpregnant women. Apparent clearance decreased slightly but significantly with increasing age.[3] In the P1026s study of 37 pregnant women who received TDF-based combination therapy at 30 to 36 weeks' gestation and 6 to 12 weeks postpartum, the percentage of women with tenofovir AUC exceeding the target of 1.99 μg•hour/mL (the 10th percentile in nonpregnant adults) was lower in the third trimester (73%, 27 of 37 women) than postpartum (84%, 27 of 32 women). Trough levels and AUCs were 17% to 20% lower during the third trimester compared to postpartum. The median weight of the women below the target exposure (97.9 kg) was significantly higher than the median weight of the women who met the target exposure (74.2 kg).[4] In another study of 34 women who received TDF plus emtricitabine in the third trimester and postpartum, tenofovir AUC, peak, and trough were all about 25% lower in pregnant women than in postpartum women, but these decreased exposures were not associated with virologic failure.[5] In a study of women who did not have HIV and who were using TDF as part of pre-exposure prophylaxis (PrEP), intracellular concentrations of tenofovir diphosphate (TFV-DP) in pregnant

women were about 70% of those in nonpregnant women, even after adjusting for adherence.[6]

Standard dosing of TDF during pregnancy continues to be recommended.

Placental and Breast Milk Passage

In studies of pregnant women on chronic TDF, the cord-to-maternal-blood ratio of tenofovir ranged from 0.60 to 1.03, indicating high placental transfer.[4,5,7,8] In studies of pregnant women who received single-dose TDF (with and without emtricitabine) during labor, the median tenofovir cord-to-maternal-blood ratio at delivery ranged from 0.55 to 0.73.[9,10] Intracellular tenofovir concentrations were detected in the peripheral blood mononuclear cells from cord blood in all infants after a single maternal dose of TDF 600 mg with emtricitabine 400 mg, but intracellular TFV-DP was detectable in only two of 36 infants (5.5%).[11]

In a study of 50 breastfeeding women without HIV infection who received TDF/emtricitabine (under directly observed therapy for 10 days) as PrEP, median peak and trough time-averaged tenofovir 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 tenofovir concentration was unquantifiable (<0.31 ng/mL) in 94% of infants (46 of 49 infants); in the three infants with detectable tenofovir, the level was 0.9 ng/mL in two and 17.4 ng/mL in one. Based on this study's results, the median tenofovir dose ingested through breast milk was estimated to be 0.47 mcg/kg, or <0.01% of the proposed daily 6 mg/kg pediatric TDF dose.[12] In a study of 59 breastfeeding women who received TDF/lamivudine/efavirenz in Uganda and Nigeria, no infant had detectable tenofovir in plasma.[13]

Reproduction/Fertility

In a retrospective analysis of 7,275 women (1,199 of whom were receiving TDF-based antiretroviral therapy) women who used TDF had a slightly lower pregnancy rate than women who did not use TDF, but the findings were limited by the observational nature of the data, and additional studies are needed for confirmation.[14]

Teratogenicity/Adverse Pregnancy Outcomes

In a study of 431 pregnancies that occurred during an HIV PrEP trial in which women who did not have HIV infection were randomized to receive placebo, TDF, or TDF plus emtricitabine, there was no difference in risk of congenital anomalies between the TDF-containing arms and placebo arms.[15] 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: PACTG 219/219C (n = 2,202, with 214 first-trimester TDF exposures), P1025 (n = 1,112, with 138 first-trimester TDF exposures),[16,17] and PHACS (n = 2,580, with 431 first-trimester TDF exposures).[18] In the French Perinatal Cohort, no association was found between birth defects and use of TDF with a power of 70% for an odds ratio of 1.5 (n = 13,124, with 823 first-trimester TDF exposures).[19] Among 382 pregnancies that occurred in 302 women in Uganda and Zimbabwe who participated in the DART trial—approximately two-thirds of whom received TDF during >90% of their pregnancies—TDF use was not associated with birth defect risk.[20] Finally, in the Antiretroviral Pregnancy Registry, sufficient numbers of first-trimester exposures to TDF have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a two-fold increase in risk of birth defects in the cardiovascular and genitourinary systems. No increase in birth defects has been observed with TDF. Among the cases of first-trimester TDF exposure reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.3% (82 of 3,535 births; 95% CI, 1.9% to 2.9%), compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[21]

In the PHACS study from the United States, 449 of the 2,029 infants (21%) who were exposed to HIV but who were uninfected had *in utero* exposure to TDF. TDF-exposed infants and infants without exposure to TDF had similar rates of low birthweight (LBW), small-for-gestational-age (SGA), and newborn length-for-age and head circumference-for-age z-scores (LAZ and HCAZ, respectively).[22] In a different U.S. cohort study, P1025, maternal TDF use was similarly not associated with differences in body size parameters at birth.[23] A fetal ultrasound study in South Africa demonstrated no association between duration of maternal

TDF use and long-bone (femur and humerus) growth.[24] This same research group also demonstrated that the duration of *in utero* tenofovir exposure was not related to infant length at birth.[25] However, in a Dutch study of 74 HIV-exposed infants (including nine with *in utero* TDF exposure), maternal TDF use was linked to an increased risk of LBW (<2,500 g).[26]

In the largely Africa-based PROMISE trial, pregnant women with HIV but without advanced disease or immunosuppression (defined as CD4 counts ≥350 cells/mm^3) were randomized at ≥14 weeks' (median 26 weeks') gestation to receive zidovudine alone, zidovudine/lamivudine plus lopinavir/ritonavir (LPV/r) (zidovudine-based ART), or TDF/emtricitabine plus LPV/r (tenofovir-based ART). The tenofovir-based ART arm and zidovudine-based ART arms showed no significant differences in the incidence of LBW infants (<2,500 g; 16.9% vs. 20.4%, $P = 0.3$) or the incidence of preterm delivery (delivery at <37 weeks; 18.5% vs 19.7%, $P = 0.77$). However, tenofovir-based 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 zidovudine-based ART.[27] The greater number of early infant deaths was likely attributable to poor outcomes of very preterm infants in the settings where the trial took place, but the higher rate of very preterm delivery in the tenofovir-based ART arm remains unexplained. Potential explanations include a lower than expected severe preterm delivery rate in the zidovudine-based ART arm or increased tenofovir exposure due to coadministration with LPV/r (LPV/r doses were increased in late pregnancy).

In contrast to the PROMISE trial results, in a large observational study in Botswana of >11,000 births among women with HIV who received ART during pregnancy and gave birth between August 2014 and August 2016, the risk of any adverse birth outcome was lower in those who received TDF/emtricitabine/efavirenz than in those who received any other regimen (TDF/emtricitabine plus nevirapine, adjusted relative risk [ARR], 1.15; TDF/emtricitabine plus lopinavir/ritonavir, ARR 1.31; zidovudine/lamivudine plus nevirapine, ARR 1.30; zidovudine/lamivudine plus LPV/r, ARR 1.21) Furthermore, TDF/emtricitabine/efavirenz was associated with a lower risk of SGA than all other regimens, and zidovudine/lamivudine plus lopinavir/ritonavir was associated with higher risk of preterm birth, very preterm birth, and neonatal death than TDF/emtricitabine/efavirenz. Finally, among infants exposed to ART from conception, TDF/emtricitabine/efavirenz was associated with lower risk for adverse birth outcomes than other ART regimens.[28]

In a combined analysis of data from 4,646 births that occurred during the PHACS and P1025 studies, women who received TDF/lamivudine plus lopinavir/ritonavir and those who received zidovudine/lamivudine plus lopinavir/ritonavir during pregnancy had no significant differences in the risks of preterm delivery overall (defined as a gestational age of <37 weeks), very preterm delivery (<34 weeks), LBW infants (<2,500 g), and very LBW infants (<1,500 g).[29]

Additionally, a placebo-controlled trial of TDF 300 mg that was initiated at 28 weeks' gestation in Thai women with hepatitis B (but not HIV infection) permits an assessment of the potential impact of TDF on birth outcomes when TDF is used in pregnancy without other antiviral drugs and outside the context of maternal HIV infection. In this study, 322 deliveries resulted in 323 live births (including two twin pairs and one stillbirth in the TDF arm). No difference was observed in birthweights (median birth weight was 3,028 g in the TDF arm and 3,061 g in the placebo arm) or frequency of preterm delivery (8 of 162 infants [5%] in TDF arm, with none at <35 weeks; 13 of 160 infants [8%] in the placebo arm, including 3 of 160 infants [2%] delivered at 32–34 weeks) between the TDF and placebo arms.[30]

Finally, in an observational, multicenter Canadian study of 2,787 mother-infant pairs in which the mothers received ART during pregnancy, the rate of preterm delivery (defined as delivery at <37 weeks) was significantly higher in mothers who received TDF-containing ART than in mothers who received ART that did not contain TDF (19.4% vs. 15.2%, $P = 0.024$). This difference was not associated with whether the regimen also included a protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or integrase strand transfer inhibitor.[31]

In all, there remains some concern for a link between maternal TDF use and preterm birth or LBW, but the evidence is mixed; the role of potential cofactors and/or confounders requires further investigation.

Other Safety Data

Maternal Safety Outcomes

In a United Kingdom cohort of 71 pregnant women receiving TDF, retrospective analysis of serum creatinine and estimated glomerular filtration rate (eGFR) measured throughout pregnancy and 6 weeks after delivery revealed no decline in renal function during pregnancy and normal renal function (>90 mL/min) at 6 weeks postpartum (one woman's postpartum eGFR was 60 mL/min).[32]

Infant Safety Outcomes

In the U.S. PHACS/SMARTT cohort study, after adjusting for birth cohort and other factors, maternal use of TDF led to no increase in the likelihood of adverse metabolic, growth/development, cardiac, neurological, or neurodevelopmental outcomes.[33]

In the DART trial described above, there were no differences in infant growth rates or infant mortality between infants born to mothers who received TDF during pregnancy and those born to mothers who received other ARV drugs.[20] In the U.S. PHACS Study, there was no difference at birth in rates of LBW, SGA, or newborn LAZ and HCAZ between infants who were exposed to combination drug regimens that contained TDF and those who were exposed to regimens that did not contain TDF. However, at age 1 year, infants exposed to combination regimens with TDF had a slight but significantly lower adjusted mean LAZ and HCAZ than those without TDF exposure (LAZ: -0.17 vs. -0.03, $P = 0.04$; HCAZ: 0.17 vs. 0.42, $P = 0.02$) but no difference in weight-for-age z-score (WAZ). There were no significant differences between infants with and without TDF exposure at age 1 year when defining low LAZ or HCAZ as ≤1.5 z-score. Thus, these slightly lower mean LAZ and HCAZ scores are of uncertain significance.[22] In the U.S. P1025 study, maternal TDF use was similarly not associated with differences in body size parameters at birth; however, among the 1,496 infants that were followed for 6 months, TDF exposure after the first trimester was associated with being underweight (WAZ <5%) at age 6 months (OR [95% CI]: 2.06 [1.01, 3.95], $P = 0.04$) when compared to no exposure.[23]

A Kenyan cohort study also found an association between maternal TDF use (compared to ART without TDF) and lower 6-week WAZ despite no difference in weight at birth; however, TDF exposure was not associated with WAZ differences at age 9 months, and no associations were found with any other anthropometric measures at the 6-week or 9-month time points.[34] In the Dutch study of 74 HIV-exposed infants, maternal TDF use was linked to lower 6-month HAZ and WAZ after adjusting for differences in birthweight and prematurity.[26]

On the other hand, results from a South African study demonstrated that the duration of *in utero* tenofovir exposure was not related to infant length at birth or to linear growth through the first 48 weeks of life.[25]

Finally, in the placebo-controlled trial that involved Thai women with hepatitis B infection (but not HIV infection) who initiated TDF at 28 weeks' gestation, there was no difference in growth outcomes at age 6 months between infants in the maternal TDF and placebo arms.[30]

In all, there is inconsistent evidence that maternal TDF use during pregnancy may be associated with transient, small growth delays during the first year of life. These delays are of uncertain clinical significance.[35]

In a cross-sectional study of 68 children aged 1 to 6 years who were exposed to HIV (but uninfected) and who had *in utero* exposure to combination regimens with (n = 33) or without (n = 35) TDF, quantitative bone ultrasound measures and bone metabolism marker levels were similar for both groups.[36] Another study evaluated whole body dual-energy X-ray absorptiometry (DXA) scans performed within 4 weeks of birth among 74 infants who were exposed to >8 weeks of TDF *in utero* and 69 infants with no TDF exposure. The adjusted mean whole-body bone mineral content (BMC) was significantly lower in the TDF group by 6.3 g ($P = 0.004$), as was the whole-body-less-head BMC (-2.6 g, $P = 0.056$). The duration and clinical significance of these findings require further longitudinal evaluation.[37]

A study of 136 infants in Malawi whose mothers received TDF/emtricitabine/efavirenz 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.[38]

Excerpt from Table 10[a]

Note: When using FDCs, refer to other sections in Appendix B and Table 10 for information about the dosing and safety of individual drug components of the FDC during pregnancy.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations	Use in Pregnancy
Tenofovir Disoproxil Fumarate (TDF) *Viread* (TDF/EFV/FTC) *Atripla* (TDF/3TC) *Cimduo* (TDF/FTC/RPV) *Complera* (TDF/DOR/3TC) *Delstrigo* (TDF/EVG/COBI /FTC) *Stribild* (TDF/EFV/3TC) *Symfi* (TDF/EFV/3TC) *Symfi Lo* (TDF/3TC) *Temixys* (TDF/FTC) *Truvada* **Note:** Generic available for some formulations	TDF (Viread) *Tablet:*[d] • 300 mg *Powder:* • 40 mg/1 g oral powder TDF/EFV/FTC (Atripla): • TDF 300 mg plus EFV 600 mg plus FTC 200 mg tablet TDF/3TC (Cimduo): • TDF 300 mg plus 3TC 300 mg tablet TDF/FTC/RPV (Complera): • TDF 300 mg plus FTC 200 mg plus RPV 25 mg tablet TDF/DOR/3TC (Delstrigo): • TDF 300 mg plus DOR 100 mg plus 3TC 300 mg tablet TDF/EVG/COBI /FTC (Stribild): • TDF 300 mg plus EVG 150 mg plus COBI 150 mg plus FTC 200 mg tablet TDF/EFV/3TC (Symfi): • TDF 300 mg plus EFV 600 mg plus 3TC 300 mg tablet TDF/EFV/3TC (Symfi Lo): • TDF 300 mg plus EFV 400 mg plus 3TC 300 mg tablet TDF/3TC (Temixys): • TDF 300 mg plus 3TC 300 mg tablet TDF/FTC (Truvada): • TDF 300 mg plus FTC 200 mg tablet	Standard Adult Doses *TDF (Viread)* *Tablet:* • TDF 300 mg once daily without regard to food *Powder:* • TDF 8 mg/kg (up to a maximum of TDF 300 mg). Take with food. *TDF/EFV/FTC (Atripla):* • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. *TDF/3TC (Cimduo):* • 1 tablet once daily without regard to food *TDF/FTC/RPV (Complera):* • 1 tablet once daily with food *TDF/DOR/3TC (Delstrigo):* • 1 tablet once daily without regard to food. *TDF/EVG/COBI/FTC (Stribild):* • 1 tablet once daily with food *TDF/EFV/3TC (Symfi or Symfi Lo):* • 1 tablet once daily on an empty stomach and preferably at bedtime *TDF/3TC (Temixys):* • 1 tablet once daily without regard to food *TDF/FTC (Truvada):* • 1 tablet once daily without regard to food 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 use of combination products in pregnancy, please see the specific sections on other components (i.e., 3TC, COBI, DOR, EFV, EVG, FTC, RPV)	High placental transfer to fetus.[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects). Studies in monkeys (at doses approximately 2-fold higher than those for human therapeutic use) show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy. Human studies demonstrate no consistent link to low birth weight, but data are conflicting about potential effects on growth outcomes later in infancy. If patient is HBV coinfected, it is possible that an HBV flare may occur if TDF is stopped; see HIV/Hepatitis B Virus Coinfection. Renal function should be monitored because of potential for renal toxicity.

[a] Individual ARV drug dosages may need to be adjusted in patients with renal or hepatic insufficiency (for details, see the Adult and Adolescent Guidelines, Appendix B, Table 8).

[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 formulation available.

Key to Acronyms: AUC = area under the curve; 3TC = lamivudine; COBI = cobicistat; DOR = doravirine; EFV = efavirenz; EVG = elvitegravir; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; PK = pharmacokinetic; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

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