Tenofovir Disoproxil Fumarate (Viread, TDF)

(Last updated June 7, 2016; last reviewed June 7, 2016)

Tenofovir disoproxil fumarate (TDF), an orally bioavailable form of tenofovir, is classified as Food and Drug Administration Pregnancy Category B.1

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 in mice and rats were carried out at 16 times (mice) and 5 times (rats) human exposure. In female mice, liver adenomas were increased at exposures 16 times that observed in humans at therapeutic doses. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose.1

Reproduction/Fertility

Reproduction studies have been performed in rats and rabbits at doses up to 14 and 19 times the human dose, respectively, based on body surface area comparisons and 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 for 15 days before mating through Day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats administered 600 mg/kg/day.1

Teratogenicity/Developmental Toxicity

Chronic exposure of fetal monkeys to tenofovir at high doses (exposure equivalent to 25 times the area under the curve (AUC) achieved with therapeutic dosing in humans) resulted in lower fetal circulating insulin-like growth factor (IGF)-1, higher IGF binding protein-3 levels, and lower body weights. A slight reduction in fetal bone porosity was also observed. Effects on these parameters 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 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 non-pregnant women receiving combination regimens including tenofovir, pregnant women had a 39% higher apparent clearance of tenofovir compared with non-pregnant women, which decreased slightly but significantly with increasing age.3 In a P1026s study of 37 pregnant women receiving 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 non-pregnant 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 receiving TDF plus emtricitabine in the third trimester and postpartum, tenofovir AUC, peak, and trough were all about 25% lower in pregnant women compared to postpartum women, but these decreased exposures were not associated with virologic failure.5 Standard dosing 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. In studies of pregnant women receiving single-dose TDF (with and without emtricitabine) in labor, the drugs were well tolerated and the median tenofovir cord-to-maternal-blood ratio at delivery ranged from 0.55 to 0.73. Intracellular tenofovir concentrations were detected in the peripheral blood mononuclear cells from cord blood in all infants after a single maternal dose of 600 mg TDF with 400 mg emtricitabine, but intracellular tenofovir-diphosphate was detectable in only 2 (5.5%) of 36 infants.

Sixteen breast milk samples were obtained from 5 women who received 600 mg TDF at the start of labor followed by 300 mg daily for 7 days. Tenofovir levels in breast milk ranged from 5.8 to 16.3 ng/mL, resulting in nursing infants ingesting an estimated daily amount of tenofovir that corresponds to 0.03% of the proposed oral dose of TDF for neonates. Because the form of tenofovir in breastmilk is expected to have lower bioavailability than TDF, these exposures are likely overestimates. No studies have measured tenofovir blood levels in infants breastfed by women taking TDF.

Reproduction/Fertility

A retrospective analysis of 7,275 women (1,199 receiving TDF-based antiretroviral therapy) demonstrated a slight reduction in pregnancy rates, but the findings were limited by the observational nature of the data and additional studies are needed for confirmation.

Teratogenicity/Developmental Toxicity

In a study of 431 pregnancies occurring during an HIV pre-exposure prophylaxis trial in which HIV-uninfected women were randomized to placebo, TDF, or TDF plus emtricitabine, there was no difference in risk of congenital anomalies between the TDF-containing and placebo arms. No association was seen between maternal TDF and offspring birth defects in three large U.S. cohorts: PACT 219/219C (n = 2,202 with 214 first-trimester TDF exposures), P1025 (n = 1,112 with 138 first-trimester TDF exposures), and Pediatric HIV AIDS Cohort Study (n = 2,580 with 431 first-trimester TDF exposures). In the French Perinatal Cohort, no association was found between birth defects and TDF with a power of 70% for an odds ratio of 1.5 (n = 13,124 with 823 first-trimester TDF exposures). Finally, in the Antiretroviral Pregnancy Registry (APR), sufficient numbers of first-trimester exposures to TDF in humans have been monitored to be able to detect at least a 1.5-fold increased risk of overall birth defects and a 2-fold increase in risk of birth defects in the cardiovascular and genitourinary systems. No increase in birth defects has been observed with TDF. Among cases of first-trimester TDF exposure reported to the APR, the prevalence of birth defects was 2.3% (60 of 2,608 births; 95% confidence interval [CI], 1.8% to 3.0%), compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.

Other Safety Data

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) 6 weeks postpartum (one woman’s postpartum eGFR was 60 mL/min).

Among 382 pregnancies occurring in 302 women in Uganda and Zimbabwe participating in the DART trial—approximately two-thirds of whom received TDF through more than 90% of their pregnancies—there were no differences noted in mortality, birth defects, or growth. In the Pediatric HIV/AIDS Cohort Study from the United States, 449 (21%) of the 2,029 HIV-exposed but uninfected infants had in utero exposure to TDF, and there was no difference at birth between those exposed to combination drug regimens with or without TDF in low birthweight, small-for-gestational-age, and newborn length-for-age and head circumference-for-age z-scores (LAZ and HCAZ, respectively). 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 those with and
without TDF exposure at age 1 year when defining low LAZ or HCAZ as \( \leq 1.5 \) z-score. Thus, these slightly lower mean LAZ and HCAZ scores are of uncertain significance.\(^{21} \) In a different U.S. study (P1025), maternal TDF use was similarly not associated with differences in body size parameters at birth; however, among the 1,496 infants followed for 6 months, TDF exposure after the first trimester, relative to no exposure, was associated with being underweight (WAZ \(< 5\%\) at age 6 months (OR [95% CI]: 2.06 [1.01, 3.95], \( P = 0.04 \)).\(^{22} \)

In a cross-sectional study of 68 HIV-exposed uninfected children enrolled at ages 1 to 6 years who had \textit{in utero} exposure to combination regimens with (\( N = 33 \)) or without (\( N = 35 \)) TDF, evaluation of quantitative bone ultrasound and parameters of bone metabolism gave similar measures between groups.\(^{23} \) In contrast, a study evaluating whole body dual-energy X-ray absorptiometry scans within 4 weeks of birth among 74 infants exposed to more than 8 weeks of TDF \textit{in utero} and 69 infants with no TDF exposures, 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.\(^{24} \)

**Excerpt from Table 8**

<table>
<thead>
<tr>
<th>Generic Name (Abbreviation) Trade Name</th>
<th>Formulation</th>
<th>Dosing Recommendations</th>
<th>Use in Pregnancy</th>
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| Tenofovir Disoproxil Fumarate (TDF) Viread (TDF/FTC) Truvada (TDF/FTC/EFV) Atripla (TDF/FTC/RPV) Complera (TDF/FTC/EVG/COBI) Stribild | TDF (Viread) Tablet: • 300 mg Powder: • 40 mg/1 g oral powder Truvada: • TDF 300 mg plus FTC 200 mg tablet Atripla: • TDF 300 mg plus FTC 200 mg plus EFV\(^{c} \) 600 mg tablet Complera: • TDF 300 mg plus FTC 200 mg plus RPV 25 mg tablet Stribild: • TDF 300 mg plus FTC 200 mg plus EVG 150 mg plus COBI 150 mg tablet | Standard Adult Dose TDF (Viread) Tablet: • 300 mg once daily without regard to food Powder: • 8 mg/kg (up to maximum 300 mg), take with food Truvada: • 1 tablet once daily without regard to food Atripla: • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects. Complera: • 1 tablet once daily with food Stribild: • 1 tablet once daily with food PK in Pregnancy: • AUC lower in third trimester than postpartum but trough levels adequate Dosing in Pregnancy: • No change in dose indicated. | 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 that 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 effect on intrauterine growth, but data are conflicting about potential effects on growth outcomes later in infancy.
If HBV-cointected, 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 antiretroviral drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see Adult Guidelines, Appendix B, Table 7).

\(^{b} \) Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:
High: >0.6 Moderate: 0.3–0.6 Low: <0.3

\(^{c} \) See Teratogenicity for discussion of EFV and risks in pregnancy.

**Key to Acronyms:** AUC = area under the curve; COBI = cobicistat; EFV = efavirenz; FTC = emtricitabine; HBV = hepatitis B virus; PK = pharmacokinetic; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate

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**Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States**

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References


