



**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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## ***Tenofovir Disoproxil Fumarate (Viread, TDF)***

**(Last updated October 19, 2017; last reviewed October 19, 2017)**

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

#### *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.<sup>1</sup>

#### *Teratogenicity/Adverse Pregnancy Outcomes*

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.<sup>1</sup>

#### *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.<sup>2</sup>

### **Human Studies in Pregnancy**

#### *Pharmacokinetics*

In a retrospective population pharmacokinetic study of 46 pregnant women and 156 non-pregnant women receiving combination regimens including TDF, pregnant women had a 39% higher apparent clearance of tenofovir compared with non-pregnant women, which decreased slightly but significantly with increasing age.<sup>3</sup> In the 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).<sup>4</sup> 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.<sup>5</sup>

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.<sup>4,7</sup> In studies of pregnant women receiving single-dose TDF (with and without emtricitabine) in labor, the median tenofovir cord-to-maternal-blood ratio at delivery ranged from 0.55 to 0.73.<sup>8,9</sup> 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.<sup>10</sup>

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; infant plasma levels were not directly measured in this study.<sup>11</sup> In a study of 50 breastfeeding women without HIV infection who received TDF/emtricitabine (under directly observed therapy for 10 days) as pre-exposure prophylaxis (PrEP), median (IQR) peak and trough time-averaged tenofovir breastmilk concentrations were similar at 3.2 ng/mL (2.3-4.7) and 3.3 ng/mL (2.3-4.4), respectively. The infant plasma tenofovir concentration was unquantifiable (<0.31 ng/mL) in 94% (46/49) of infants; in the 3 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 breastmilk was estimated at 0.47 mcg/kg or <0.01% of the proposed 6 mg/kg pediatric daily TDF dose.<sup>12</sup>

### *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.<sup>13</sup>

### *Teratogenicity/Adverse Pregnancy Outcomes*

In a study of 431 pregnancies occurring during an HIV pre-exposure prophylaxis trial in which women who did not have HIV infection 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.<sup>14</sup> No association was seen between maternal TDF and offspring birth defects in three large U.S. cohorts of children born to women living with HIV: PACTG 219/219C (n = 2,202 with 214 first-trimester TDF exposures), P1025 (n = 1,112 with 138 first-trimester TDF exposures),<sup>15,16</sup> and PHACS (n = 2,580 with 431 first-trimester TDF exposures).<sup>17</sup> 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).<sup>18</sup> 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 birth defects.<sup>19</sup> 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% (75 of 3,229 births; 95% confidence interval [CI], 1.8% to 2.9%), compared with a 2.7% total prevalence in the U.S. population, based on Centers for Disease Control and Prevention surveillance.<sup>20</sup>

In the PHACS study from the United States, 449 (21%) of the 2,029 infants exposed to HIV who were uninfected 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 (LBW), small-for-gestational-age (SGA), and newborn length-for-age and head circumference-for-age z-scores (LAZ and HCAZ, respectively).<sup>21</sup> In a different U.S. cohort study, P1025, maternal TDF use was similarly not associated with differences in body size parameters at birth.<sup>22</sup> A fetal ultrasound study in South Africa demonstrated no association between duration of maternal TDF use and long-bone (femur and humerus) growth.<sup>23</sup> However, in a Dutch study of 74 HIV-exposed infants (including 9 with *in utero* TDF exposure), maternal TDF use was linked to an increased risk of LBW <2500g.<sup>24</sup>

In the largely Africa-based PROMISE trial, in which pregnant women living with HIV but without advanced disease or immunosuppression (CD4 counts  $\geq 350$ ) were randomized at  $\geq 14$  weeks' (median 26 weeks') gestation to receive zidovudine alone, zidovudine/lamivudine/lopinavir/ritonavir (zidovudine-based ART), or TDF/emtricitabine/lopinavir/ritonavir (tenofovir-based ART), there was no significant difference between tenofovir-based ART and zidovudine-based ART arms in LBW  $< 2,500$ g (16.9% vs. 20.4%,  $P = 0.3$ ) or preterm delivery  $< 37$  weeks (18.5% vs 19.7%,  $P = 0.77$ ) but tenofovir-based ART was associated with higher rates than zidovudine-based ART of very preterm delivery before 34 weeks (6.0% vs. 2.6%,  $P = 0.04$ ) and early infant death (4.4% vs. 0.6%,  $P = 0.001$ ).<sup>25</sup> The greater number of early infant deaths were likely attributable to poor outcomes of very preterm infants in 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 lopinavir/ritonavir (lopinavir/ritonavir doses were increased in trial participants in late pregnancy).

In contrast to the PROMISE trial results, in a large observational study in Botswana of more than 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/nevirapine, adjusted relative risk [ARR], 1.15; TDF/emtricitabine/lopinavir/ritonavir, ARR, 1.31; zidovudine/lamivudine/nevirapine, ARR, 1.30; zidovudine-lamivudine-lopinavir-ritonavir, ARR, 1.21) Furthermore, TDF/emtricitabine/efavirenz was associated with a lower risk of SGA compared with all other regimens, and zidovudine/lamivudine/lopinavir/ritonavir was associated with higher risk of preterm birth, very preterm birth and neonatal death compared with TDF/emtricitabine/efavirenz. Finally, among infants exposed to ART from conception, tenofovir/emtricitabine/efavirenz was associated with lower risk for adverse birth outcomes than other ART regimens.<sup>26</sup>

Additionally, the placebo-controlled trial of 300 mg TDF initiated at 28 weeks' gestation in Thai women with hepatitis B (but not HIV infection) permits an assessment of potential TDF impact 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 2 twin pairs and 1 stillbirth in the TDF arm) and no difference in birthweight (median birth weight 3,028 g in TDF arm and 3,061 g in placebo arm) or preterm delivery (8/162 [5%] in TDF arm including none  $< 35$  weeks and 13/160 [8%] in the placebo arm including 3/160 [2%] at 32–34 weeks) between TDF and placebo arms.<sup>27</sup>

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

### *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) 6 weeks postpartum (1 woman's postpartum eGFR was 60 mL/min).<sup>28</sup>

#### **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.<sup>29</sup>

In the DART trial (described above), there were no differences noted in infant mortality or growth.<sup>19</sup> In the U.S. PHACS Study, while there was no difference at birth between those exposed to combination drug regimens with or without TDF in **LBW, SGA or newborn LAZ and HCAZ**, 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.<sup>21</sup> 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 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],  $P = 0.04$ ).<sup>22</sup> A Kenyan cohort study also found an association between maternal TDF-ART 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 there were no associations with all other anthropometric measures at the 6-week or 9-month time points.<sup>30</sup> In the Dutch study of 74 HIV-exposed infants, maternal TDF use was linked to lower 6-month HAZ and WAZ, adjusted for differences in birthweight and adjusted for prematurity.<sup>24</sup> Finally, in the placebo-controlled trial of TDF initiated at 28 weeks' gestation in Thai women with hepatitis B (but not HIV) infection, there was no difference in growth outcomes at age 6 months between infants in the maternal TDF and placebo arms.<sup>27</sup>

In all, there is inconsistent evidence that maternal TDF use during pregnancy may be associated with transient, small growth delays in the first year of life that are of uncertain clinical significance.<sup>31</sup>

In a cross-sectional study of 68 children ages 1 to 6 years who were exposed to but not infected with HIV and who had *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.<sup>32</sup> In contrast, a study evaluating whole body dual-energy X-ray absorptiometry (DXA) scans within 4 weeks of birth among 74 infants exposed to more than 8 weeks of TDF *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.<sup>33</sup>

A study of 136 infants in Malawi whose mothers received TDF/emtricitabine/efavirenz in pregnancy (and no control group for comparison) documented low-grade, transient abnormalities of serum phosphate and serum creatinine at ages 6 and 12 months.<sup>34</sup>

## Excerpt from Table 9<sup>a</sup>

Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations	Use in Pregnancy
<b>Tenofovir Disoproxil Fumarate</b> (TDF) <i>Viread</i>  (TDF/FTC) <i>Truvada</i>  (TDF/FTC/EFV) <i>Atripla</i>  (TDF/FTC/RPV) <i>Complera</i>  (TDF/FTC/EVG/COBI) <i>Stribild</i>	<u>TDF (Viread)</u>  <i>Tablet:</i> • 300 mg  <i>Powder:</i> • 40 mg/1 g oral powder  <u>Truvada:</u> • TDF 300 mg plus FTC 200-mg tablet  <u>Atripla:</u> • TDF 300 mg plus FTC 200 mg plus EFV <sup>c</sup> 600-mg tablet  <u>Complera:</u> • TDF 300 mg plus FTC 200 mg plus RPV 25-mg tablet  <u>Stribild:</u> • TDF 300 mg plus FTC 200 mg plus EVG 150 mg plus COBI 150-mg tablet	<u>Standard Adult Dose</u>  <i>TDF (Viread)</i>  <u>Tablet:</u> • 300 mg once daily without regard to food  <u>Powder:</u> • 8 mg/kg (up to maximum 300 mg), take with food  <i>Truvada:</i> • 1 tablet once daily without regard to food  <i>Atripla:</i> • 1 tablet once daily at or before bedtime. Take on an empty stomach to reduce side effects.  <i>Complera:</i> • 1 tablet once daily with food  <i>Stribild:</i> • 1 tablet once daily with food  <u>PK in Pregnancy:</u> • AUC lower in third trimester than postpartum but trough levels adequate  <u>Dosing in Pregnancy:</u> • No change in dose indicated.	High placental transfer to fetus. <sup>b</sup>  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 <b>consistent link to low birth weight</b> , but data are conflicting about potential effects on growth outcomes later in infancy.  If HBV-coinfected, it is possible that an HBV flare may occur if TDF is stopped; see <a href="#">HIV/Hepatitis B Virus Coinfection</a> .  Renal function should be monitored because of potential for renal toxicity.

<sup>a</sup> Individual ARV drug dosages may need to be adjusted in renal or hepatic insufficiency (for details, see [Adult Guidelines, Appendix B, Table 7](#)).

<sup>b</sup> Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:

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

<sup>c</sup> 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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