Tenofovir Alafenamide (Vemlidy, TAF)

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

Summary

- No dose adjustments are required for TAF during pregnancy.
- First-trimester exposure to TAF is not associated with increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

TAF pharmacokinetics (PK) can differ during pregnancy, depending on the concomitant antiretrovirals administered. However, TAF exposures appear to be adequate in the second and third trimesters based on comparisons with historical data in nonpregnant adults.

TAF PKs were evaluated as part of International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network P1026s in 31 women taking TAF 10 mg with cobicistat, 27 women taking TAF 25 mg without a pharmacoenhancer,[1] and 29 women taking TAF 25 mg with a pharmacoenhancer (cobicistat or ritonavir).[2] TAF area under the curve (AUC) did not differ between pregnancy and postpartum for women taking TAF 10 mg with cobicistat[1] or those taking TAF 25 mg with a pharmacoenhancer.[2] TAF AUC at a 25 mg dose without a pharmacoenhancer was 33% to 43% lower during pregnancy compared to postpartum but comparable to exposures in nonpregnant adults.[1] The Pharmacokinetics of Newly Developed Antiretroviral Agents in HIV-infected pregnant women (PANNA) Network also evaluated TAF and TFV PK in 20 pregnant and postpartum European women receiving TAF 10 mg with cobicistat or TAF 25 mg without a pharmacoenhancer.[3] PK results from both dosing combinations were pooled and showed that TAF and TFV AUCs were 46% and 33% lower during pregnancy, respectively, than postpartum. Despite these decreases, 94% of pregnant women remained above the predefined TAF AUC efficacy target of 53.1 ng•h/mL.

Placental and Breast Milk Passage

Limited data exist on TAF and TFV concentrations in placental blood and breast milk. TAF was below the assay limit of quantification (<3.9 ng/mL) in 43 of 44 cord blood samples tested and all infant washout samples in women receiving TAF 25 mg without a pharmacoenhancer[1] and in all cord blood and infant washout samples in women receiving TAF 25 mg with ritonavir or cobicistat. Maternal plasma TAF concentrations at delivery were measurable in only 4 of 45 paired samples in women receiving TAF 25 mg without a pharmacoenhancer[1] and in 2 of 25 paired samples in women receiving TAF 25 mg with ritonavir or cobicistat.[2] A separate study also did not detect TAF in any paired cord blood or maternal delivery samples, but it was able to quantify TFV and estimated a median placental transfer ratio of 0.81 from 13 paired samples.[3]

TAF breast milk transfer has been examined in smaller PK studies. One study examined TAF breast milk transfer in five breastfeeding women with HIV and identified a breast milk–to-plasma ratio of

4.09 for TAF[4] and a median estimated infant daily dose of 0.007 mg/kg. A separate PK study in eight breastfeeding women with hepatitis B virus (HBV) infection receiving TAF for at least 4 weeks estimated breast milk–to-plasma ratios for TAF and TFV to be 0.029 and 2.809, respectively.[5] The relative TAF dose was estimated at 0.005% of the maternal dose. TFV was detectable in the urine of three of seven infants at a median steady-state concentration of 5 ng/mL, which was 300 times less than urine concentrations measured in adults on TAF. TFV breast milk transfer was examined in 12 women receiving TAF 25 mg and 4 women receiving TDF 300 mg for HBV treatment.[6] TFV exposures in breast milk through 8 hours postdose were approximately fivefold higher at Day 3 postdelivery in women taking TAF than in women taking TDF. TFV concentrations with TAF decreased by 43% and 47% at 15 and 30 days postpartum, respectively, compared to Day 3. TFV has poor oral bioavailability, and TAF and infant plasma concentrations were not quantified, so the clinical relevance of higher TFV in breast milk with TAF is unclear.

Teratogenicity

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester TAF exposures to detect at least a twofold increase in the risk of overall birth defects; however, no such increase in the risk of birth defects has been observed with TAF. Among the cases of first-trimester TAF exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 3.9% (36 of 915 live births; 95% confidence interval [CI], 2.8% to 5.4%), not statistically significantly higher than the total prevalence in the U.S. population, according to the Centers for Disease Control and Prevention birth defects surveillance system Metropolitan Atlanta Congenital Defects Program (2.7%; 95% CI, 2.7–2.8) or the Texas Birth Defects Registry (4.2%; 95% CI, 4.15–4.19).[7]

Adverse Pregnancy Outcomes

Overall Adverse Pregnancy Outcomes

IMPAACT 2010/Virologic Efficacy and Safety of ART Combinations with TAF/TDF, EFV, and DTG (VESTED) was a randomized trial of dolutegravir (DTG)- and efavirenz (EFV)- containing ART regimens in pregnancy, which found lower composite adverse outcomes in the group receiving DTG and emtricitabine (FTC) with TAF (DTG+FTC/TAF) than in the group receiving DTG and FTC with TDF (DTG+FTC/TDF) or EFV and FTC with TDF (EFV+FTC/TDF) and a lower neonatal mortality than the arm receiving EFV+FTC/TDF (3.7% vs. 1.9%).[8] A post-hoc risk–benefit analysis of weighted infant outcomes showed a more favorable overall tradeoff for infants born to mothers in the DTG+TAF/FTC arm than in the DTG+TDF/FTC and EFV+TDF/FTC arms.[9,10]

Fetal Growth Effects

Length-for-age z-scores and weight-for-age z-scores among infants exposed to DTG+TAF/FTC *in utero* did not significantly differ from those exposed to DTG+TDF/FTC at 26 or 50 weeks of age but were higher than those measured in infants exposed to EFV+TDF/FTC.[11] There were no differences in weight-for-length z-scores between treatment regimens. All infants showed severely stunted growth through the first year of age.

Other Safety Data

Maternal Safety Outcomes

The DTG+FTC/TAF arm of IMPAACT 2010/VESTED had higher maternal weight gain than the other two arms.[8] Although greater weight gain was seen in mothers receiving DTG+FTC/TAF, the extent of average weekly weight gain that occurred was still below the recommended amount by the Institute of Medicine. Follow-up analyses did not identify significant differences in metabolic issues between study arms as measured by hemoglobin A1C or random glucose levels among pregnant women or infants,[12] and they also showed that lower antepartum weight gain was associated with a higher risk of adverse pregnancy outcomes.[13] However, a separate analysis of weight gain patterns within the United States did show a 1.7-fold higher relative risk of excessive gestational weight gain among pregnant women on TAF with an integrase strand transfer inhibitor (INSTI) than among those not exposed to these drugs.[14] Although INSTI use alone was not associated with excessive weight gain, all women on TAF were also on an INSTI, so the effect of TAF alone could not be examined. No differences in pregnancy outcomes or gestational diabetes were identified, but there was a higher risk of hypertensive disorders in the INSTI group than in those not on INSTIs or on TDF.

Renal safety also has been examined in a separate retrospective cohort of 100 pregnant women with HIV receiving TAF- or TDF-containing ART, and no significant differences in renal function, toxicity, or treatment discontinuations due to renal toxicity among regimens were identified.[15]

Animal Studies

Carcinogenicity

Carcinogenicity studies for TFV have only been performed with TDF, but given the lower TFV exposure with TAF, the associated carcinogenicity is assumed to be commensurate or lower. Refer to the TDF section for more information.

Reproduction/Fertility

There is no evidence of impaired fertility or mating performance with TAF administration in rats or rabbits at exposures up to 53 times those seen in humans.[16]

Teratogenicity/Adverse Pregnancy Outcomes

No effects on early embryonic development were seen in rats at TAF doses that produced exposures that were 62 times those seen in humans who received the therapeutic dose.[16]

Placental and Breast Milk Passage

Rat studies demonstrated secretion of TFV in breast milk after administration of TDF, but secretion of TAF or TFV in animal milk after administration of TAF has not been evaluated.[16]

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 Alafenamide (TAF) *Vemlidy* (TAF/BIC/FTC) *Biktarvy* (TAF/FTC) *Descovy* (TAF/EVG/c/FTC) *Genvoya* (TAF/FTC/RPV) *Odefsey* (TAF/DRV/c/FTC) *Symtuza*	TAF (Vemlidy) • 25-mg tablet TAF/BIC/FTC (Biktarvy) • TAF 25-mg/ BIC 50-mg/FTC 200-mg tablet TAF/FTC (Descovy) • TAF 25-mg/FTC 200-mg tablet TAF/EVG/c/FTC (Genvoya) • TAF 10-mg/EVG-150-mg/ COBI 150-mg/FTC 200-mg tablet TAF/FTC/RPV (Odefsey) • TAF 25-mg/FTC 200-mg/ RPV 25-mg tablet TAF/DRV/c/FTC (Symtuza) • TAF 10-mg/DRV 800-mg/ COBI 150-mg/FTC 200-mg tablet	Pregnancy *PKs in Pregnancy* • AUC is lower in pregnancy, depending on the dose and concomitant ARV, but overall exposures are adequate. *Dosing in Pregnancy* • No change in dose indicated. For guidance about the use of combination products in pregnancy, please see the specific sections on other components (i.e., BIC, COBI, DRV, EVG, FTC, RPV). Standard Adult Doses *TAF (Vemlidy)* • One tablet once daily with food *TAF/BIC/FTC (Biktarvy)* • One tablet once daily with or without food *TAF/FTC (Descovy)* • One tablet once daily with or without food • Same dose (TAF 25 mg) can be used with or without PK enhancers. *TAF/EVG/c/FTC (Genvoya)* • One tablet once daily with food *TAF/FTC/RPV (Odefsey)* • One tablet once daily with food *TAF/DRV/c/FTC (Symtuza)* • One tablet once daily with food	TAF: low placental transfer to fetus[b] TFV: high placental transfer to fetus; plasma and cord blood concentrations lower than TDF[b] No evidence of human teratogenicity (can rule out twofold increase in overall birth defects) Renal function should be monitored because of the potential for renal toxicity.

Excerpt from Table 14

[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 12).

[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

Key: ARV = antiretroviral; BIC = bictegravir; COBI = cobicistat; DRV/c = darunavir/cobicistat; EVG/c = elvitegravir/cobicistat; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide

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