Emtricitabine (Emtriva, FTC)

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Summary

- No dose adjustments are required for emtricitabine (FTC) during pregnancy.
- First-trimester exposure to FTC is not associated with increased risk of congenital anomalies.
- FTC use during pregnancy has not been associated with adverse maternal, obstetric, or infant outcomes.

Human Studies in Pregnancy

Pharmacokinetics

In the International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) P1026s study, FTC exposure was modestly lower during the third trimester (geometric mean, 8.0 mcg•h/mL; 90% confidence interval [CI], 7.1–8.9 mcg•h/mL) than during the postpartum period (9.7 mcg•/mL; 90% CI, 8.6–10.9 mcg•h/mL). Fifty-eight percent of pregnant women (15 of 26 women) met the area under the curve (AUC) target (≤30% reduction from typical exposure for nonpregnant historical controls) compared to 95% of postpartum women (21 of 22 women). Trough FTC levels also were lower during pregnancy (C_{24h} geometric mean concentration [GMC] 58 ng/mL; 90% CI, 37–63 ng/mL) than during the postpartum period (C_{24h} GMC 85 ng/mL; 90% CI, 70–100 ng/mL).[1] Similar differences in pharmacokinetic parameters of FTC were found during pregnancy or after delivery in the Pediatric AIDS Clinical Trials Group (PACTG) 394 study[2] and in a European study.[3,4] The increase in FTC clearance during pregnancy correlated with the normal pregnancy-related increase in glomerular filtration rate.[4] These changes are not believed to be large enough to warrant a dose adjustment during pregnancy.

Placental and Breast Milk Passage

FTC has high placental transfer in pregnant women. In a study of 15 women who received FTC during pregnancy, the mean cord blood–to–maternal plasma ratio was 1.2 (90% CI, 1.0–1.5).[1] In eight women who were given a single dose of FTC 600 mg with tenofovir disoproxil fumarate (TDF) 900 mg, the median cord blood FTC concentration was 717 ng/mL (range, 21–1,072 ng/mL), and the median cord blood–to–maternal plasma ratio was 0.85 (range, 0.46–1.07).[2]

FTC is excreted into human milk. Among women in Uganda and Nigeria who were taking antiretroviral therapy (ART) that contained FTC 200 mg, FTC concentrations in breast milk peaked later than they did in maternal plasma (at 4–8 hours, compared with 2–4 hours) and were threefold higher than maternal plasma concentrations. FTC was detectable in three infants (19%).[5] In a study in Ivory Coast, five women with HIV who exclusively breastfed their newborn infants were given FTC 400 mg, TDF 600 mg, and nevirapine 200 mg at onset of labor, followed by FTC 200 mg and TDF 300 mg once daily for 7 days postpartum. The median minimal and maximal concentrations of FTC in breast milk were 177 ng/mL and 679 ng/mL, respectively (interquartile ranges [IQR], 105–254 ng/mL and 658–743 ng/mL, respectively), well above the estimated FTC 50% inhibitory concentration for HIV-1.[6] In a study of 50 women without HIV who received daily oral FTC 200 mg

and TDF 300 mg as pre-exposure prophylaxis (PrEP), median peak and trough breast milk concentrations of FTC were 212.5 ng/mL (IQR 140.0–405.0 ng/mL) and 183.0 ng/mL (IQR 113.0–250.0 ng/mL), respectively. FTC was detectable in 47 of 49 infants at a median concentration of 13.2 ng/mL (IQR 9.3–16.7 ng/mL), corresponding to estimated daily infant ingestion of a 31.9-mcg/kg dose (IQR 21.0–60.8 mcg/kg) of FTC or 0.5% of the daily dose for treating infants.[7]

Teratogenicity/Adverse Pregnancy Outcomes

In pregnancies that occurred in women without HIV in an HIV PrEP trial that randomized participants to receive placebo, TDF, or TDF plus FTC, no increase in the incidence of congenital anomalies was observed in the TDF plus FTC arm.[8] No overall difference was observed between the rate of pregnancy loss in the TDF plus FTC arm and the rate of pregnancy loss in the TDF arm of this PrEP study.

In the U.S. Pediatric HIV/AIDS Cohort Study (PHACS) Surveillance Monitoring for ART Toxicities (SMARTT) cohort study, FTC exposure was not associated with an increase in specific or overall birth defect risk.[9] In a large French cohort, FTC exposure in the first trimester was associated with lower risk of birth defects.[10] The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to FTC to detect at least a 1.5-fold increased risk of overall birth defects and at least a twofold increase in cardiovascular and genitourinary defects (the most common classes of birth defects in the general population). No such increase in the risk of birth defects has been observed with FTC. Among the cases of first-trimester FTC exposure that have been reported to the Antiretroviral Pregnancy Registry, the prevalence of birth defects was 2.7% (113 of 4,226 live births; 95% CI, 2.2% to 3.2%) compared with a total prevalence of 2.7% in the U.S. population, based on Centers for Disease Control and Prevention surveillance.[11]

Other Safety Information

In the U.S. PHACS/SMARTT cohort study, after adjusting for birth cohort and other factors, maternal use of FTC did not increase the likelihood of adverse metabolic, growth and development, cardiac, neurologic, or neurodevelopmental infant outcomes.[12]

Animal Studies

Carcinogenicity

FTC was neither mutagenic nor clastogenic in a series of *in vitro* and animal *in vivo* screening tests. In long-term carcinogenicity studies of oral FTC, no drug-related increases in tumor incidence were found at doses up to 26 times in mice or 31 times in rats than the exposures seen in humans who received the therapeutic dose.[13]

Reproduction/Fertility

FTC had no observable effect on reproduction or fertility at doses that produced systemic drug exposures (as measured by AUC) that were approximately 60-fold higher in female and male mice and 140-fold higher in male rats than human exposure at the recommended therapeutic dose.[13]

Teratogenicity/Adverse Pregnancy Outcomes

No fetal variations or malformations were observed following maternal FTC doses that produced systemic drug exposures that were 60-fold higher in mice or 120-fold higher in rabbits than those observed in humans who received the recommended dose.[13]

Placental and Breast Milk Passage

FTC crosses the placenta in mice and rabbits; the average fetal-to-maternal drug concentration ratio was 0.4 in mice and 0.5 in rabbits.[14]

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
Emtricitabine (FTC) *Emtriva* (FTC/EFV/TDF) *Atripla* (FTC/BIC/TAF) *Biktarvy* (FTC/RPV/TDF) *Complera* (FTC/TAF) *Descovy* (FTC/EVG/c/TAF) *Genvoya* (FTC/RPV/TAF) *Odefsey* (FTC/EVG/c/TDF) *Stribild* (FTC/DRV/c/TAF) *Symtuza* (FTC/TDF) *Truvada* Note: Generic products are available for some formulations.	FTC (Emtriva) *Capsule*[c] • 200 mg *Oral Solution* • 10 mg/mL FTC/EFV/TDF (Atripla)[c] • FTC 200-mg/EFV 60-mg/TDF 300-mg tablet FTC/BIC/TAF (Biktarvy) • FTC 200-mg/BIC 50-mg/TAF 25-mg tablet FTC/RPV/TDF (Complera) • FTC 200-mg/RPV 25-mg/TDF 300-mg tablet FTC/TAF (Descovy) • FTC 200-mg/TAF 25-mg tablet FTC/EVG/c/TAF (Genvoya) • FTC 200-mg/EVG 150-mg/COBI 150-mg/TAF 10-mg tablet FTC/RPV/TAF (Odefsey) • FTC 200-mg/RPV 25-mg/TAF 25-mg tablet	Pregnancy *PKs in Pregnancy* • PKs of FTC are not significantly altered in pregnancy. *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., TDF, TAF, EFV, RPV, DRV, EVG, BIC, COBI). Standard Adult Doses *FTC (Emtriva)* • Capsule o FTC 200 mg once daily without regard to food • Oral Solution o FTC 240mg (24 mL) once daily without regard to food *FTC/EFV/TDF (Atripla)* • One tablet once daily at or before bedtime • Take on an empty stomach to reduce or mitigate side effects. *FTC/BIC/TAF (Biktarvy)* • One tablet once daily with or without food *FTC/RPV/TDF (Complera)* • One tablet once daily with food *FTC/TAF (Descovy)*	High placental transfer to fetus[b] No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects) If patient has HBV/HIV coinfection, it is possible that an HBV flare may occur if the drug is stopped; see Hepatitis B Virus/HIV Coinfection.

Generic Name (Abbreviation) *Trade Name*	Formulation	Dosing Recommendations[a]	Use in Pregnancy
	FTC/EVG/c/TDF (Stribild) • FTC 200-mg/EVG 150-mg/COBI 150-mg/TDF 300-mg tablet FTC/DRV/c/TAF (Symtuza) • FTC 200-mg/DRV 800-mg/COBI 150-mg/TAF 10-mg tablet FTC/TDF (Truvada)[c] • FTC 200-mg/TDF 300-mg tablet	• One tablet once daily with or without food *FTC/EVG/c/TAF (Genvoya)* • One tablet once daily with food *FTC/RPV/TAF (Odefsey)* • One tablet once daily with food *FTC/EVG/c/TDF (Stribild)* • One tablet once daily with food *FTC/DRV/c/TAF (Symtuza)* • One tablet once daily with food *FTC/TDF (Truvada)* • One tablet once daily without regard to food	

[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 11).

[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.

Key: BIC = bictegravir; COBI = cobicistat; DRV = darunavir; DRV/c = darunavir/cobicistat; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HBV = hepatitis B virus; PK = pharmacokinetic; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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