Bictegravir (BIC)

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Summary

- No dose adjustment for bictegravir (BIC) is recommended in pregnancy.
- First-trimester exposure to BIC has not been associated with an increased risk of congenital anomalies.

Human Studies in Pregnancy

Pharmacokinetics

BIC pharmacokinetics (PK) during pregnancy have been reported in two clinical studies and a case series. Preliminary PK results among 27 pregnant women showed that BIC area under the curve (AUC) and concentrations at 24 hours postdose (C_{24h}) were decreased by 56% and 71%, respectively, at the third trimester compared to postpartum (n = 11 with paired data).[1] Thirteen of 21 (62%) women with PK results also fell below the 10th percentile AUC for nonpregnant adults during the third trimester, but none of these women had a detectable viral load. Additionally, all C_{24h} values across the second and third trimesters were above the BIC protein-adjusted 95% maximal effective concentration (EC_{95}) of 0.162 ug/mL, with median values 4.4- and 5.9-fold above the EC_{95}.[1] Virologic suppression (<20 copies/mL) was maintained in 76% to 88% of participants across pregnancy and postpartum, and only one participant had a viral load above 200 copies/mL. Additionally, 90% of participants were suppressed at delivery and no infant HIV infections occurred.

A separate study[2] in 33 pregnant women showed that total BIC AUC was approximately 56% to 59% lower, and BIC trough concentrations (C_{trough}) were approximately 71% lower during the second or third trimester compared to 6 or 12 weeks postpartum. Total BIC AUC in the pregnant women was 41% lower during the third trimester compared with historical data in nonpregnant adults with HIV. Because BIC is highly protein bound and pregnancy can be associated with decreased plasma protein binding, unbound drug concentrations were also assessed. The AUC for unbound BIC was approximately 38% to 41% lower during pregnancy than postpartum. The mean unbound fractions were higher during pregnancy than postpartum (0.351% and 0.365% during the second and third trimester, respectively, compared with 0.261% and 0.252% at 6 and 12 weeks postpartum, respectively). Mean C_{trough} values during the second and third trimesters were about 6.5-fold above the BIC protein-adjusted EC_{95}, and all but one individual C_{trough} value was above this threshold. All women maintained virologic suppression (<50 copies/mL) through week 18 postpartum, including at delivery, and no infant HIV infections occurred.

A case series describing two pregnant women, one of whom had paired PK data during pregnancy and postpartum, has also been detailed.[3,4] This patient's AUC, trough concentration, and maximum plasma concentration were 35%, 49%, and 19% lower, respectively, at 33 weeks gestation than at 6 weeks postpartum. The patient remained virologically suppressed through delivery.

Collectively, these findings demonstrate that despite lower AUC and C_{24h} or C_{trough} values during pregnancy, drug exposures were still above those needed to maintain virologic suppression when using standard BIC doses.

Placental and Breast Milk Passage

Placental transfer of BIC is high, with a mean umbilical cord blood–to–maternal plasma ratio of 1.4 (coefficient of variance percentage 35%) at delivery.[2] The estimated median half-life in neonates was 43 hours (interquartile range 38 – 58). These umbilical cord blood–to–maternal plasma ratios are comparable to a previous case series where ratios of 1.49 were measured in one patient 20 hours after BIC dosing and 1.42 in another patient 7 hours after BIC dosing.[3] A separate case report conveyed an umbilical cord blood–to–maternal plasma ratio of 0.68 approximately 16 hours after BIC dosing.[4] The concentration of BIC was 2,826 ng/mL in cord blood at delivery, 2,097 ng/mL in the infant on Day 3 after birth, and undetectable (<5 ng/mL) in the infant by Day 22.

Data on the passage of BIC in human breast milk are very limited. BIC milk–to–plasma ratios have only been reported in one individual, which revealed a ratio of 0.01 and subsequent estimated infant daily dose of 0.01 mg/kg.[5] Additional data are needed to refine our understanding of the breast milk passage of BIC.

Teratogenicity/Adverse Pregnancy Outcomes

The Antiretroviral Pregnancy Registry has monitored sufficient numbers of first-trimester exposures to BIC to detect at least a twofold increase in the risk of overall birth defects. No such increase in the risk of birth defects has been observed with BIC. Among the cases of first-trimester BIC exposure that had been reported to the Antiretroviral Pregnancy Registry as of January 31, 2023, the prevalence of birth defects was 4.32% (14 of 324 live births; 95% confidence interval, 2.38–7.14).[6]

Animal Studies

Carcinogenicity

BIC has not been shown to be genotoxic or mutagenic *in vitro*.[7]

Reproduction/Fertility

BIC did not affect fertility, reproductive performance, or embryonic viability in male or female rats at exposures (based on AUC) that were 29 times higher than those observed in humans who received the recommended dose.[7]

Teratogenicity/Adverse Pregnancy Outcomes

No adverse embryo-fetal effects were observed in rats and rabbits at BIC exposures (based on AUC) of up to about 36 times (in rats) and 0.6 times (in rabbits) the exposures observed in humans who received the recommended dose. Spontaneous abortion, increased clinical signs (e.g., fecal changes, thin body, cold to touch), and decreased body weight were observed in rabbits at a maternally toxic dose (i.e., 1,000 mg/kg per day, which produced an exposure approximately 1.4 times higher than the exposure observed in humans who received the recommended dose).[7]

Placental and Breast Milk Passage

No data are available on placental passage of BIC in animals. In a prenatal and postnatal development study conducted in rats, BIC was detected in the plasma of nursing rat pups on postnatal Day 10, likely due to the presence of BIC in milk.[7]

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
Bictegravir/Emtricitabine/ Tenofovir Alafenamide (BIC/FTC/TAF) *Biktarvy* Note: BIC is available only as part of an FDC tablet.	BIC/FTC/TAF (Biktarvy) • BIC 50-mg/FTC 200 mg/TAF 25-mg tablet • BIC 30-mg/FTC 120-mg/TAF 15-mg tablet	Pregnancy *PK in Pregnancy* • AUC and C_{24h}/C_{trough} are decreased during the third trimester compared with postpartum, but exposures during pregnancy are well above those needed to inhibit viral replication. *Dosing in Pregnancy* • No change in dose indicated For guidance about use of combination products in pregnancy, please see the specific sections on other components (i.e., FTC, TAF). Standard Adult Doses • One tablet of BIC 50 mg/FTC 200 mg/TAF 25 mg once daily with or without food	High placental transfer to fetus[b] No evidence of human teratogenicity (can rule out twofold increase in overall birth defects) BIC can be taken with food at the same time as any preparation containing iron or calcium—including prenatal vitamins—but should not be administered within 2 hours of these preparations when taken on an empty stomach. BIC can be taken at least 2 hours before or 6 hours after antacids containing aluminum or magnesium.

[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; AUC = area under the curve; BIC = bictegravir; C_{24h} = concentrations at 24 hours postdose; FDC = fixed-dose combination; FTC = emtricitabine; PK = pharmacokinetics; TAF = tenofovir alafenamide

References

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