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Biktarvy® (BIC/FTC/TAF) Use During Lactation

This document is in response to your request for information regarding the use of Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) or its components in women with HIV-1 who are breastfeeding.

Some data may be outside of the US FDA-approved Prescribing Information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA approved prescribing information.

The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi

Summary

Product Labeling[1]

Data from the published literature report the presence of BIC, FTC, TAF, and TFV in human milk. There are no data on the effects of BIC on the breastfed child. Data from the published literature have not reported adverse effects of FTC or TAF on a breastfed child. There are no data on the effects of BIC, FTC, or TAF on milk production.

Potential risks of breastfeeding include: (1) HIV-1 transmission to HIV-1–negative infants; (2) developing viral resistance in HIV-1–positive infants; and (3) adverse reactions in a breastfed infant similar to those seen in adults.

Clinical Data on the Use of BIC/FTC/TAF Components During Lactation

In an open-label, randomized study of pregnant women with HIV who were treated with various ARV regimens, including DTG + FTC/TAF, all infant plasma samples and all but 2 breast milk samples were <LLoQ for TAF, and the median relative infant dose of TAF from breastfeeding was estimated to be 0%.[2]

Intensive PK profiles were collected from maternal DBS, dried breast milk spots, and infant DBS of mother-infant pairs, of whom the mothers were treated with FTC-based regimens. Three infants (19%) had measurable FTC levels, and the relative infant dose was <1% of the treatment dose by weight in infants.[3]

In a PK study evaluating breast milk and plasma concentration of BIC in women without HIV after a single dose of BIC/FTC/TAF, exposure to BIC through breastmilk was very low, with a relative infant dose below 1%.[4]

In a short-term, open-label study of mothers without HIV who received FTC/TDF for PrEP, the mothers and their breastfed infants underwent PK sampling at steady state (infant plasma was collected once during the study). FTC was detected in 47 of 49 infant plasma samples, resulting in a relative infant dose 0.5% of the recommended therapeutic pediatric dose. No SAEs were reported during follow-up.[5]

Clinical Data on the Use of BIC/FTC/TAF Components During Lactation

IMPAACT 2010/VESTED Study[2]

An open-label, randomized trial in pregnant women with HIV from nine countries evaluated breast milk transfer and infant exposures to three ARV treatment regimens started between 14 and 28 weeks of gestation. Treatment regimens included the following: DTG + FTC/TAF, DTG + FTC/TDF, and EFV/FTC/TDF. Infants received non-study ARV prophylaxis per local standard of care. Drug concentrations of DTG, TAF, and TFV in plasma and breast milk were evaluated using time-matched samples from 192 mothers (plasma and breast milk) and their breastfeeding infants (plasma) collected at 6 weeks postpartum. The relative infant dose for each drug was estimated from the measured concentrations in whole breast milk using a standard target feeding volume of 150 mL/kg/day.

Mothers were enrolled from Zimbabwe (59%), Uganda (21%), South Africa (9%), Botswana (5%), Tanzania (5%), and India (1%). The mean age of all 192 enrolled mothers was 26 years, 99% were Black, and 1% were Asian. Approximately 55% of infants were female with a mean gestational age of 40 weeks, and the median weight of the infants at birth was 3089 g.

Concentrations of TAF were measured in breast milk and infant plasma from 98 mothers and their infants who were randomly assigned to the DTG + FTC/TAF arm of the study; of these, all infant plasma samples and all but 2 breast milk samples were <LLoQ, which was 3.9 ng/mL for plasma and 0.195 ng/mL for breast milk. The median (range) maternal plasma concentration of TAF was 0 (0–158) ng/mL, and the median (range) relative infant dose from breastfeeding was estimated to be 0% (0–0.03%).

PK Profiles of FTC, TDF, and 3TC in Mother-Infant Pairs[3]

Mother-infant pairs recruited from Uganda (n=30) and Nigeria (n=29) who were receiving first-line ARV regimens underwent PK sampling using maternal DBS, dried breast milk spots, and infant DBS. FTC, TDF, and 3TC levels were evaluated within this study population; all mothers (overall) were receiving regimens containing those ARV agents prior to or during their pregnancy.

Only mothers recruited from the Nigeria study site (mean [range] age, 30 [20–38] years; median [IQR] baseline CD4 count, 689 [552–938] cells/mm^3) received FTC-containing regimens. The FTC dose was 200 mg as part of a once-daily FDC tablet (eg, EFV/TDF/FTC once daily [n=13] and nevirapine twice daily + TDF/FTC once daily [n=7]). Of infants in the Nigerian cohort, the mean (range) infant age and weight were 143 (80–215) days and 6.2 (3–10) kg, respectively, and 80% of infants were exclusively breastfed as reported by the mothers. Sixteen mother-infant pairs contributed to the FTC PK analysis. FTC sampling of these pairs occurred at the following time points: maternal DBS and dried breast milk spot sampling occurred pre-dose and at 0.5-, 1-, 2-, 4-, 8-, and 12-hours post-dose; infant DBS sampling occurred at 2 and 8 hours post-dose.

Using a correction factor to correlate maternal DBS levels with maternal plasma levels, the estimated median (IQR) FTC $AUC_{0–12\ h}$ from maternal plasma and dried breast milk spots were 2371 (1276–3344) ng·h/mL and 4991 (4094–7179) ng·h/mL, respectively, which resulted in a median (IQR) $AUC_{0–12\ h}$ milk to plasma ratio of 3.01 (2.06–3.38). The estimated

median (IQR) FTC T_{max} and C_{max} levels in maternal plasma were 2 (0.5–4) h and 384 (269–530) ng/mL, respectively. In dried breast milk spots, the estimated median (IQR) FTC T_{max} and C_{max} levels were 4 (2–8) h and 843 (702–1132) ng/mL, respectively. Measurable FTC levels were obtained in 3 infants (19%): 17.5, 18.8, and 19.4 ng/mL. The relative infant dose was <1% of the treatment dose by weight in infants. No safety data were reported.

PK Study of BIC concentrations in breast milk of lactating women without HIV after a single dose of BIC/FTC/TAF[4]

Twelve healthy lactating women without HIV received a single dose of BIC/FTC/TAF and samples of blood and breast milk were collected at regular intervals up to 24 hours post ingestion. Eligible participants had a median age of 33 (32 - 33.8) years, median BMI of 24.8 (23.9 – 28.4) kg/m², and were a median of 10 (5.3 – 15.3) months postpartum, with infants weighing a median of 8.8 (7.2 – 10) kg at the time of evaluation. Plasma and breastmilk drug concentrations were measured via a validated LC-MS/MS assay and PK parameters were calculated using non-compartmental analysis. A total of 132 plasma and 72 breastmilk samples were collected. All concentrations fell within the quantifiable range.

The geometric mean (CV%) AUC_{last} was 52.17 (22.6) mg*h/L in plasma and 0.44 (32.0) mg*h/L in breastmilk, resulting in a geometric mean (CV%) breastmilk to maternal plasma ratio of 0.009 (26.6). Additional BIC PK parameters for plasma and breastmilk are listed in Table 1.

Table 1. BIC PK concentrations in plasma and breastmilk

Pharmacokinetic parameters	Plasma [GM CV%]	Breastmilk [GM CV%]
AUC_{inf} (mg*h/L)	79.03 (28.8)	0.75 (40.5)
AUC_{last} (mg*h/L)	52.17 (22.6)	0.44 (32.0)
C_{max} (mg/L)	4.634 (17.4)	0.030 (25.8)
T_{max} (hours)	1.19 (45.2)	3.13 (52.2)
$T_{1/2}$ (hours)	15.5 (18.5)	17.2 (28.5)

The authors reported exposure to BIC through breastmilk was very low, with a relative infant dose below 1%. No SAEs were reported. All reported AEs were grade 1-2, including one possibly drug-related lab change in bilirubin. The study limitations were only single-dose of BIC/FTC/TAF was evaluated and transmission of HIV or clinical outcomes were not assessed.

Prospective, Open-Label Study of FTC/TDF for PrEP in Mother-Infant Pairs Without HIV[5]

Fifty mother-infant pairs were enrolled into this prospective, short-term, open-label study at two clinical research sites in Kenya and Uganda. Eligible mothers were HIV seronegative, breastfeeding their singleton healthy infant and were not co-infected with HBV. Eligible infants were HIV seronegative, were 1 to 24 weeks of age, and did not have any serious infections or other active clinically significant medical conditions. Mothers were administered an FDC of FTC/TDF (200 mg/300 mg) daily as directly observed PrEP for 10 days. The primary study outcome was the proportion of infants with detectable FTC and TDF in plasma at steady state in the overall study group and stratified by infant age (ie, aged ≤12 weeks

and 13–24 weeks;). The median age at enrollment was 25 (22-28) years for the mothers and for infants the median age was 13 (9–19) weeks. The median frequency of breastfeeding was generally similar at baseline and during follow up at a median of 15 (12–18) times a day.

Maternal blood and breast milk samples were collected within 30 minutes of each other at the following time points regardless of food ingestion on Days 7 and 10: C_{max}, 1 to 2 hours after FTC/TDF administration; C_{trough}, 23 to 24 hours after FTC/TDF administration. One infant blood sample was collected after the maternal dose on Day 7. At each study visit, mothers completed an interview to collect maternal and infant safety data, breastfeeding patterns, and concomitant medications. All except 1 daily PrEP dose (499/500 doses; >99%) were received by mothers, and 98% of the expected PK samples (439/450) were collected.

Ninety-six percent of infant plasma samples (47/49) detected FTC, with a median (IQR) concentration of 13.2 (9.3–16.7) ng/mL and higher levels observed among the younger subgroup of infants (Table). The resulting median (IQR) estimated FTC dose ingested by the infant was 31.9 (21–60.8) mcg/kg, which was 200-fold lower than the recommended daily pediatric dose of FTC (6 mg/kg).

Table 2. FTC Concentrations in Mothers and Infants Overall and by Age Subgroup (Mugwanya et al)[5]

PK Levels, Median (IQR)		All Mother-Infant Pairs (N=50)	Mother-Infant Pairs: Infants Aged ≤12 Weeks (n=24)	Mother-Infant Pairs: Infants Aged 13–24 Weeks (n=26)
C_{max} time point	Samples available, n	98	49	49
	Maternal plasma level, ng/mL	267.5 (103–1370)	236.5 (93.6–1380)	533 (115–1370)
	Breast milk level, ng/mL	212.5 (140–405)	208 (139.5–377.5)	215 (149–431)
	Milk:plasma ratio	0.63 (0.31–1.43)	0.7 (0.31–1.76)	0.59 (0.31–1.14)
	Infant plasma level,[a] ng/mL	13.2 (9.3–16.7)	16.6 (13.2–20.9)	10.5 (7.1–13.2)[b]
	Infant plasma:milk ratio	0.05 (0.03–0.08)	0.07 (0.04–0.1)	0.05 (0.02–0.06)[c]
	Infant daily dose from breastmilk, mcg/kg	31.9 (21–60.8)	31.2 (20.9–56.6)	32.3 (22.4–64.7)[d]
	Infant dose fraction,[e] %	0.5 (0.3–1)	0.5 (0.3–0.9)	0.5 (0.4–1.1)[d]
C_{trough} time point	Samples available, n	97	48	49
	Maternal plasma level, ng/mL	84.4 (68.5–99.7)	82.8 (69.3–101)	84.8 (68.2–97.5)
	Breast milk level, ng/mL	183 (113–250)	187.5 (95.6–256)	183 (125–250)
	Milk:plasma ratio	2.1 (1.67–2.81)	2.36 (1.48–2.83)	2.08 (1.69–2.81)
	Infant daily dose from breastmilk, mcg/kg	27.5 (17–37.5)	28.1 (14.3–38.4)	27.5 (18.9–37.5)[f]
	Infant dose fraction,[e] %	0.5 (0.3–0.6)	0.5 (0.2–0.6)	0.5 (0.3–0.6)[f]

[a]Overall, n=49 infant samples; ≤12-week infant subgroup, n=24; 13- to 24-week infant subgroup, n=25. FTC was not detected in 2 samples.
[b]$P<0.01$, [c]$P=0.12$, [d]$P=0.94$ for comparison between the two infant subgroups.
[e]Daily amount of FTC an infant ingests from breast milk, calculated as a percentage of the therapeutic pediatric dose (6 mg/kg).
[f]$P=0.58$ for comparison between the two infant subgroups.

No SAEs were reported. AEs that occurred in ≥2 mothers included abdominal pain (n=3, 6%), nausea (n=3, 6%), and diarrhea (n=2, 4%), with abdominal pain and nausea occurring at the same time in 2 mothers. Diarrhea occurred in 2 infants (4%) at 2 study visits. All AEs

were mild and were limited in duration to 2 to 3 days. CrCl was >90 mL/min at baseline and study end among all mothers who had CrCl assessed at study end (n/N=48/50).

References

1. Enclosed, Gilead Sciences Inc. BIKTARVY® (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Nguyen T, Chae J, Ziemba L, et al. Breast Milk Transfer and Infant Exposures to DTG, TAF, and TFV: Results From IMPAACT 2010/VESTED [Poster 925]. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); March 3-6, 2024; Denver, CO.
3. Waitt C, Olagunju A, Nakalema S, et al. Plasma and breast milk pharmacokinetics of emtricitabine, tenofovir and lamivudine using dried blood and breast milk spots in nursing African mother–infant pairs. *Journal of Antimicrobial Chemotherapy.* 2018;73. https://academic.oup.com/jac/article-abstract/73/4/1013/4788788
4. van der Wekken-Pas LC, van Leeuwen E, van Ewijk-Beneken Kolmer EWJ, Burger DM, Colbers AC. Bictegravir concentrations in breastmilk of healthy, lactating women without HIV. *J Antimicrob Chemother.* 2026;81(3).
5. Mugwanya KK, Hendrix CW, Mugo NR, et al. Pre-exposure Prophylaxis Use by Breastfeeding HIV-Uninfected Women: A Prospective Short-Term Study of Antiretroviral Excretion in Breast Milk and Infant Absorption. *PLoS Med.* 2016;13(9):e1002132. http://www.ncbi.nlm.nih.gov/pubmed/27676257

Abbreviations

3TC=lamivudine
AE=adverse event
ARV=antiretroviral
$AUC_{0–12h}$=area under the concentration-time curve from time 0 to 12 hours
AUC_{inf}=area under the concentration–time curve from time 0 to infinity
AUC_{last}= area under the concentration–time curve from time 0 to the last measurable drug concentration
BIC=bictegravir
BMI=body mass index
CD4=cluster of differentiation 4
C_{max}=maximum plasma concentration
C_{trough}=trough plasma concentration
DBS=dried blood spot(s)
DTG=dolutegravir
EFV=efavirenz
FDC=fixed-dose combination
FTC=emtricitabine
LLoQ=lower limit of quantitation
PK=pharmacokinetic(s)
PrEP=pre-exposure prophylaxis
SAE=serious adverse event
$T_{1/2}$=the time for the drug concentration in plasma to decrease by 50%
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TFV=tenofovir
T_{max}=time to maximum plasma concentration

Product Label

For the full indication, important safety information, and boxed warning, please refer to the Biktarvy US Prescribing Information available at:
www.gilead.com/~/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

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🖱 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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