

# Biktarvy<sup>®</sup> (BIC/FTC/TAF) Coadministration With Rifamycins

This document is in response to your request for information regarding the coadministration of Biktarvy<sup>®</sup> (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) with rifamycins, including rifampin or rifampicin (RIF), rifabutin (RFB), and rifapentine (RPT).

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## Summary

### Product Labeling<sup>1</sup>

Coadministration of BIC/FTC/TAF with RIF is contraindicated due to the effect of RIF on the BIC component. Coadministration with RFB or RPT is not recommended.

BIC is a substrate of CYP3A and UGT1A1. A drug that is a strong inducer of CYP3A and also an inducer of UGT1A1 can substantially decrease the plasma concentrations of BIC which may lead to loss of therapeutic effect of BIC/FTC/TAF and development of resistance. TAF is a substrate of P-gp. Coadministration of drugs that inhibit P-gp activity may increase the absorption and plasma concentrations of TAF. Coadministration of drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF, which may lead to loss of therapeutic effect of BIC/FTC/TAF and development of resistance.

Coadministration of RIF, a strong inducer of CYP3A and P-gp and inducer of UGT1A1, with BIC/FTC/TAF is contraindicated due to decreased BIC plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to BIC/FTC/TAF. Coadministration of BIC/FTC/TAF with RFB or RPT is expected to decrease BIC and TAF concentrations.

### Clinical Studies of BIC/FTC/TAF With Rifamycins

In a phase 2b, open-label, randomized controlled study, adults with HIV and TB who received BIC/FTC/TAF twice daily concomitantly with a RIF-based treatment regimen for TB had a high rate (94%) of virologic suppression at Week 24. No SAEs were considered related to study drug.<sup>2</sup>

In a multicenter, retrospective cohort study in adults with HIV on RPT-based treatment regimens for LTBI, ≥96.5% of participants in the BIC/FTC/TAF groups maintained HIV-1 RNA <200 c/mL within 12 months of LTBI treatment. Most AEs were Grade 1 or 2.<sup>3</sup>

In three phase 1, open-label studies, decreases in BIC exposure were observed when BIC was coadministered with RIF or RFB; coadministration of BIC/FTC/TAF with RPT once weekly had less impact on the PK of BIC than coadministration with RIF or RFB.<sup>4</sup>

In a phase 1, open-label study, BIC/FTC/TAF twice daily in combination with daily RIF resulted in 60%, 14%, and 20% reductions in BIC, TAF, and TFV AUC<sub>0-24h</sub>, respectively, compared with BIC/FTC/TAF daily.<sup>5,6</sup>

In a phase 1, open-label study, coadministration of RIF with FTC/TAF decreased intracellular TFV-DP concentrations by 36% compared with FTC/TAF alone.<sup>7</sup>

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## Clinical Studies of BIC/FTC/TAF Use With Rifamycins

### CAPRISA 093 INSIGHT: BIC/FTC/TAF Twice Daily With RIF

#### Study design<sup>2</sup>

A phase 2b, open-label, non-comparative, randomized controlled study evaluated the efficacy, safety, and PK of BIC/FTC/TAF 50/200/25 mg twice daily in adults (n=80) with HIV and TB who received a RIF-based treatment regimen for TB. In the non-comparative control arm, participants received treatment with DTG/3TC/TDF once daily + DTG 50 mg at night (n=42). Participants in both arms received concomitant RIF-based TB treatment for 24 weeks, remained on their respective ARV regimen for an additional 2 weeks after TB treatment was stopped, then continued the once-daily dosing of their ARV regimen (BIC/FTC/TAF or DTG/3TC/TDF) until Week 48.

#### Results<sup>2</sup>

Virologic suppression (HIV-1 RNA <50 c/mL) at Week 24 (primary endpoint) was similar between the BIC/FTC/TAF (94%; 95% CI: 86–98%) and DTG/3TC/TDF (95%; 95% CI: 84–99%) arms. At Week 48, rates of virologic suppression were 95% (95% CI: 88–99%) in the BIC/FTC/TAF arm and 93% (95% CI: 81–99%) in the DTG/3TC/TDF arm. No treatment failures (HIV-1 RNA >400 c/mL) at Week 24 or Week 48 were reported.

There were no treatment discontinuations or drug switches due to AEs. SAEs were reported in 11 participants (14%) in the BIC/FTC/TAF arm and 3 (7%) in the DTG/3TC/TDF arm; no SAEs were deemed related to study drug. Grade 3 and 4 AEs were reported in 33 participants (41%) and 7 (9%), respectively, in the BIC/FTC/TAF arm and in 21 participants (50%) and 6 (14%) in the DTG/3TC/TDF arm. One death due to massive hemoptysis was reported in the DTG/3TC/TDF arm.

BIC C<sub>T</sub> levels were lower with twice-daily BIC/FTC/TAF administration during TB treatment than once-daily BIC/FTC/TAF administration after TB treatment completed (0.397 mg/L [71%] vs 1.88 mg/L [57%], respectively; GMR, 0.217; 90% CI: 0.179–0.263). Most C<sub>T</sub> levels remained above the inhibitory quotient of 0.162 mg/L, with none of the observed doses and 11.8% of unobserved twice-daily BIC/FTC/TAF plus TB treatment and 3.8% of unobserved once-daily BIC/FTC/TAF doses falling below the inhibitory quotient.

#### PK substudy<sup>8</sup>

A nested PK substudy was conducted in adults who received BIC/FTC/TAF (N=43) with and without RIF. Plasma and DBS were collected pre-dose and through 12 hours post-dose at Weeks 4 and 12 (during RIF-based TB treatment) and through 24 to 25 hours post-dose at Week 32 (after TB treatment had been completed).

During the BIC/FTC/TAF twice-daily + RIF dosing period, exposure values for plasma TFV and TFV-DP exposures were higher than when BIC/FTC/TAF was administered once daily (Table 1).

**Table 1. CAPRISA 093 INSIGHT PK Substudy:  
Plasma TFV and Intracellular TFV-DP PK Parameters<sup>§</sup>**

PK Parameters		Geometric Mean (CV%)			GMR (90% CI)	
		BIC/FTC/TAF Twice Daily + RIF Week 4	BIC/FTC/TAF Twice Daily + RIF Week 12	BIC/FTC/TAF Once Daily Week 32	Week 4 vs Week 32	Week 12 vs Week 32
TFV	AUC <sub>0-24h</sub> (ng·h/mL)	370 (59) <sup>a</sup>	356 (66) <sup>a</sup>	305 (47) <sup>b</sup>	1.28 (1.1–1.5)	1.24 (1.06–1.45)
	C <sub>max</sub> (ng/mL)	23 (55) <sup>a</sup>	22 (60) <sup>a</sup>	19 (40) <sup>b</sup>	1.21 (1.05–1.4)	1.23 (1.07–1.41)
TFV-DP	AUC <sub>0-24h</sub> (fmol·h/punch)	5116 (84) <sup>a</sup>	5889 (73) <sup>c</sup>	4685 (61) <sup>c</sup>	1.08 (0.93–1.26)	1.32 (1.13–1.53)
	C <sub>max</sub> (fmol/punch)	300 (80) <sup>a</sup>	341 (69) <sup>c</sup>	222 (56) <sup>c</sup>	1.37 (1.19–1.57)	1.63 (1.42–1.87)

<sup>a</sup>n=40. <sup>b</sup>n=39. <sup>c</sup>n=41

Note: AUC<sub>0-24h</sub> for BIC/FTC/TAF twice daily + RIF was calculated by multiplying the extrapolated AUC<sub>0-12h</sub> by 2.

## BIC/FTC/TAF With RPT-Based Regimens for LTBI<sup>3</sup>

A multicenter, retrospective cohort study was conducted in 479 PWH who were given 3 months of weekly RPT plus isoniazid (3HP) or 1 month of daily RPT plus isoniazid (1HP) in combination with ART. The primary outcome was the virologic response (HIV-1 RNA <200 c/mL) rate in the ITT and PP populations. A total of 142 patients received 1HP and BIC/FTC/TAF (1HP/BIC group) and 38 received 3HP and BIC/FTC/TAF (3HP/BIC group). Overall, 97.9% of patients achieved HIV-1 RNA <200 c/mL before LTBI treatment.

In the ITT analysis, 96.5% of patients (137/142) in the 1HP/BIC group and 100% (38/38) in the 3HP/BIC group maintained HIV-1 RNA <200 c/mL within 12 months after completing LTBI treatment. Completion rates were 95.8% and 97.4% in the 1HP/BIC and 3HP/BIC groups, respectively. In the PP analysis, 131/131 patients in the 1HP/BIC group and 37/37 in the 3HP/BIC group maintained HIV-1 RNA <200 c/mL within 12 months after LTBI treatment completion.

Most AEs were Grade 1 or 2. Grade 3 AEs were reported in 16 patients (7.8%) and 7 (2.6%) in the 1HP and 3HP groups, respectively. One Grade 4 hepatotoxicity event related to acute HCV was reported in the 1HP group. Discontinuations due to AEs occurred in 13/205 patients (6.3%) and 21/274 (7.7%) in the 1HP and 3HP groups, respectively.

## PK of BIC or BIC/FTC/TAF With RIF, RFB, or RPT<sup>4</sup>

### Study design

Three phase 1, open-label, multiple-dose studies were conducted in healthy volunteers to determine how RIF, RFB, and RPT affect the PK, safety, and tolerability of BIC/FTC/TAF. In Study 1/Cohort 2, participants received BIC 75 mg on Days 1 and 15, with a washout period from Days 2 to 4, then received RIF 600 mg once daily on Days 5 through 18; PK sampling was performed on Days 1 and 15. In Study 1/Cohort 5, BIC 75 mg was administered once daily for 6 days, followed by BIC coadministration with RFB 300 mg once daily on Days 7 through 20, with PK sampling on Days 6 and 20. In Study 2/Cohort 2, BIC/FTC/TAF was coadministered twice daily with RIF 600 mg once daily on Days 1 through 28, followed by

RIF 600 mg administered once daily alone on Days 29 through 35, with PK sampling on Days 1 and 28. In Study 3, BIC/FTC/TAF was given once daily on Days 1 through 8 and Days 15 through 30, with a washout period on Days 9 through 14; RPT was dosed once weekly starting on Day 15 and 22, in the evening of Day 29, followed by BIC/FTC/TAF 12 hours later on Day 30.

## Results

Decreases in BIC exposure were observed when BIC was coadministered with RIF or RFB; coadministration of BIC/FTC/TAF with RPT once weekly had less impact on the PK of BIC than coadministration with RIF or RFB (Table 2).

**Table 2. Comparison of BIC Plasma PK Parameters Between Studies and Coadministration With RIF, RFB, or RPT (Arora et al)<sup>4</sup>**

Study and PK Parameters		Test GLSM	Reference GLSM of BIC Alone	% GLSM Ratio (90% CI)
Study 1/Cohort 2 (BIC + RIF) <sup>a</sup>	AUC <sub>last</sub> , h mcg/mL	35.3	141.3	25 (22.7–27.6)
	AUC <sub>inf</sub> , h mcg/mL	35.7	145.8	24.5 (22–27.3)
	C <sub>max</sub> , mcg/mL	5.07	7.02	72.2 (67.1–77.8)
Study 1/Cohort 5 (BIC + RFB) <sup>b</sup>	AUC <sub>T</sub> , h mcg/mL	61	98.4	62 (53.1–72.5)
	C <sub>max</sub> , mcg/mL	5.72	7.12	80.4 (66.9–96.5)
	C <sub>T</sub> , mcg/mL	1.09	2.48	44 (37.1–52.1)
Study 2/Cohort 2 (BIC/FTC/TAF twice daily + RIF once daily) <sup>c</sup>	AUC <sub>0–24</sub> , h mcg/mL	44.5	112.6	39.5 (35.7–43.7)
	C <sub>max</sub> , mcg/mL	4.48	8.43	53.2 (49.1–57.6)
	C <sub>T</sub> , mcg/mL	0.58	2.95	19.7 (17.2–22.7)
Study 3 (BIC/FTC/TAF once daily + RPT once weekly) <sup>d</sup>	AUC <sub>T</sub> , h mcg/mL	80.3	93.9	85.5 (81.3–89.8)
	C <sub>max</sub> , mcg/mL	6.79	6.78	100.1 (95.5–104.9)
	C <sub>T</sub> , mcg/mL	1.47	2.44	60.4 (56.3–64.7)
Study 3 (BIC/FTC/TAF 12 hours after RPT) <sup>e</sup>	AUC <sub>T</sub> , h mcg/mL	69.6	93.9	74.1 (70.2–78.3)
	C <sub>max</sub> , mcg/mL	6.5	6.78	95.9 (91.8–100.1)
	C <sub>T</sub> , mcg/mL	1.04	2.44	42.5 (39.1–46.2)

Abbreviations: AUC<sub>T</sub>=area under the concentration-time curve over the dosing interval; AUC<sub>inf</sub>=area under the concentration-time curve from Time 0 to infinity; AUC<sub>last</sub>=area under the concentration-time curve up to the last measurable concentration.

<sup>a</sup>n=15. <sup>b</sup>n=13. <sup>c</sup>n=26. <sup>d</sup>n=29. <sup>e</sup>n=28.

No SAEs related to the coadministration of BIC or BIC/FTC/TAF with RIF, RFB, or RPT were reported. One participant in Study 2 reported SAEs following a physical assault that were not related to study drug.

## PK of BIC and TAF Twice Daily in Combination With RIF<sup>5,6</sup>

### Study design

A phase 1, open-label, parallel-design, single-center study evaluated the safety, tolerability, and PK of BIC/FTC/TAF 50/200/25 mg once daily (Cohort 1; n=26) vs BIC/FTC/TAF 50/200/25 mg twice daily plus RIF 600 mg once daily (Cohort 2; n=26) in healthy volunteers.

### Results

Daily BIC exposure measured by AUC<sub>0–24h</sub> was expected to be 60% lower in Cohort 2 than in Cohort 1 (Table 3). Mean BIC C<sub>T</sub> was reduced by 80% in Cohort 2 vs Cohort 1. After this ~80% reduction is accounted for, individuals who receive BIC/FTC/TAF twice daily in combination with RIF once daily may fall below the paEC<sub>95</sub> of BIC (162 ng/mL). In Cohort 2,

AUC<sub>0–24h</sub> was expected to be reduced by <15% for TAF, ~20% for TFV, and ~24% for intracellular PBMC-associated TFV-DP vs Cohort 1. The study authors concluded that BIC/FTC/TAF STR should not be used in combination with RIF.

**Table 3. PK of BIC, TAF, and TFV (Custodio et al)<sup>5,6</sup>**

Parameter		Cohort 1: BIC/FTC/TAF Once Daily (n=26)	Cohort 2: BIC/FTC/TAF Twice Daily + RIF Once Daily (n=26)	%GLSM Ratio (90% CI)
BIC, mean (CV)	AUC <sub>0–24h</sub> , ng·h/mL	115,000 (21)	45,600 (23)	39.5 (35.7–43.7)
	C <sub>max</sub> , ng/mL	8530 (16)	4560 (19)	53.2 (49.1–57.6)
	C <sub>T</sub> , ng/mL	3070 (28)	608 (30)	19.7 (17.2–22.7)
TAF, mean (CV)	AUC <sub>0–24h</sub> , ng·h/mL	345 (52)	290 (48)	85.8 (69.7–106)
TFV, mean (CV)	AUC <sub>0–24h</sub> , ng·h/mL	348 (20)	277 (19)	79.9 (73.1–87.3)
TFV-DP	AUC <sub>0–24h</sub> , fmol·h/10 <sup>6</sup> cells	–	–	76.3 (58.7–99.2)

All healthy volunteers completed the study. Treatment-emergent AEs occurred in 31% in Cohort 1 and 39% in Cohort 2. All AEs were mild or moderate and resolved during the study. No Grade 3 or 4 AEs and no laboratory abnormalities were observed.

## PK of FTC/TAF Administered in Combination With RIF<sup>7</sup>

### Study design

A phase 1, open-label, single-center study was conducted in 23 HIV-negative, healthy volunteers to assess the PK, safety, and tolerability of FTC/TAF, FTC/TAF + RIF, and TDF. Healthy volunteers received FTC/TAF 200/25 mg once daily for 28 days, given with a standard meal containing 20 g of fat content. For the next 28 days (Days 29–56), participants received RIF 600 mg daily, given 30 minutes before a standard meal, followed by FTC/TAF 200/25 mg. On Day 57, participants discontinued FTC/TAF + RIF and began receiving TDF 300 mg monotherapy daily, given with a standard meal on Days 57 to 84.

### Results

Compared with FTC/TAF, FTC/TAF + RIF decreased the plasma TAF C<sub>max</sub> by 50% and the TAF AUC<sub>0–24h</sub> by 55%; intracellular TFV-DP C<sub>max</sub> decreased by 38%, and AUC<sub>0–24h</sub> decreased by 36%. However, intracellular TFV-DP concentrations were 4-fold higher with FTC/TAF + RIF than with TDF monotherapy (Table 4). RIF coadministration did not alter plasma FTC or intracellular FTC-triphosphate concentrations.

**Table 4. Summary of PK Parameters (Cerrone et al)<sup>7</sup>**

Parameter, GMR (90% CI)	FTC/TAF + RIF vs FTC/TAF	FTC/TAF + RIF vs TDF Monotherapy
TAF C <sub>max</sub>	0.5 (0.42–0.61)	–
TAF AUC <sub>0–24h</sub>	0.45 (0.33–0.6)	–
TFV-DP C <sub>max</sub>	0.62 (0.52–0.74)	4.4 (3.09–6.27)
TFV-DP AUC <sub>0–24h</sub>	0.64 (0.54–0.75)	4.21 (2.98–5.95)

FTC/TAF, FTC/TAF + RIF, and TDF monotherapy were well tolerated. Two AEs (both Grade 3) were reported, and no Grade 4 AEs were observed. There were 2 discontinuations: 1 case of transient ALT increase, deemed unlikely to be TAF-related by the study investigators, and 1 case of Grade 2 gastrointestinal symptoms, deemed RIF-related by the study investigators.

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## Abbreviations

3TC=lamivudine  
AE=adverse event  
ARV=antiretroviral  
ART=antiretroviral therapy  
AUC<sub>0-12/24h</sub>=area under the concentration-time curve from Time 0 to 12/24 hours  
BIC=bictegravir  
c/mL=copies/mL  
CAPRISA=Centre for the AIDS Programme of Research in South Africa  
CD4=cluster of differentiation 4  
C<sub>T</sub>=trough concentration

C<sub>max</sub>=maximum concentration  
CV=coefficient of variation  
DBS=dried blood spots  
DTG=dolutegravir  
FTC=emtricitabine  
GLSM=geometric least squares mean  
GMR=geometric mean ratio  
LTBI=latent tuberculosis infection  
paEC<sub>95</sub>=protein-adjusted 95% effective concentration  
PBMC=peripheral blood mononuclear cells

P-gp=permeability glycoprotein  
PK=pharmacokinetic(s)  
PP=per protocol  
RFB=rifabutin  
RIF=rifampin or rifampicin  
RPT=rifapentine  
SAE=serious adverse event  
STR=single-tablet regimen  
TAF=tenofovir alafenamide  
TB=tuberculosis  
TDF=tenofovir disoproxil fumarate  
TFV=tenofovir  
TFV-DP=tenofovir diphosphate

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## Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Biktarvy US Prescribing Information available at:

[www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy\\_pi](http://www.gilead.com/-/media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi).

## Follow-Up

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🌐 [www.gilead.com/utility/contact/report-an-adverse-event](http://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](http://www.accessdata.fda.gov/scripts/medwatch)

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