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Biktarvy® (BIC/FTC/TAF) Coadministration With Rifamycins

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

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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]

Coadministration of BIC/FTC/TAF with RIF is contraindicated due to the effect of RIF on the BIC component. Coadministration with rifabutin 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. TAF is a substrate of P-gp. Coadministration of drugs that induce P-gp activity is expected to decrease the absorption of TAF, resulting in decreased plasma concentration of TAF. A decrease in the plasma concentrations of BIC or TAF 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 rifabutin 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 (95%) of viral load suppression at Week 24. Most AEs were Grade 1 or 2.[2]

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.[3]

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 $AUC_{0\text{-}24h}$, respectively, compared with BIC/FTC/TAF daily.[4,5]

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.[6]

In a phase 1, open-label study, C_T of BIC decreased up to 83% after weekly RPT administration versus BIC/FTC/TAF alone, and the C_T never returned to steady state between RPT doses. The effects of weekly RPT on the PK of FTC, TAF, TFV, and TFV-DP compared with BIC/FTC/TAF alone were not considered clinically significant.[7]

Clinical Studies of BIC/FTC/TAF Use With Rifamycins

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

Study design[2,8]

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 (n=42) received treatment with DTG/3TC/TDF once daily + DTG 50 mg at night. Participants in both arms received concomitant treatment with a 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[2]

Virologic suppression (HIV-1 RNA <50 c/mL) at Week 24 (primary endpoint) was similar between the BIC/FTC/TAF (95%; 95% CI: 87–98%) and DTG/3TC/TDF (95%; 95% CI: 81–99%) arms. No treatment failures (VL >400 c/mL at Week 24 or Week 48) were reported.

All participants reported an AE. The majority were Grade 1 or 2. There were no treatment discontinuations, withdrawals, or drug switches due to AEs. SAEs were reported in 9 participants (11%) in the BIC/FTC/TAF arm and 3 (7%) in the DTG/3TC/TDF arm. Grade 3 and 4 AEs were reported in 30 participants (38%) and 6 (8%), respectively, in the BIC/FTC/TAF arm and in 15 participants (36%) and 6 (14%) in the DTG/3TC/TDF arm.

BIC C_T levels were reduced during TB treatment (Weeks 4 and 12 geometric mean [CV%], 0.397 mg/L [73.4%]) compared with after TB treatment (Week 32 geometric mean [CV%], 2.29 mg/L [45.1%]) but mostly remained above the inhibitory quotient of 0.162 mg/L.

PK substudy[9]

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[9]

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	$AUC_{0–24h}$ (ng·h/mL)	370 (59)[a]	356 (66)[a]	305 (47)[b]	1.28 (1.1–1.5)	1.24 (1.06–1.45)
	C_{max} (ng/mL)	23 (55)[a]	22 (60)[a]	19 (40)[b]	1.21 (1.05–1.4)	1.23 (1.07–1.41)
TFV-DP	$AUC_{0–24h}$ (fmol·h/punch)	5116 (84)[a]	5889 (73)[c]	4685 (61)[c]	1.08 (0.93–1.26)	1.32 (1.13–1.53)
	C_{max} (fmol/punch)	300 (80)[a]	341 (69)[c]	222 (56)[c]	1.37 (1.19–1.57)	1.63 (1.42–1.87)

[a]n=40. [b]n=39. [c]n=41

Note: $AUC_{0–24h}$ for BIC/FTC/TAF twice daily + RIF was calculated by multiplying the extrapolated $AUC_{0–12h}$ by 2.

BIC/FTC/TAF With RPT-Based Regimens for LTBI[3]

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 and TAF Twice Daily in Combination With RIF[4,5]

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 $AUC_{0–24h}$ was expected to be 60% lower in Cohort 2 than in Cohort 1 (Table 2). Mean BIC C_T 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 $paEC_{95}$ of BIC (162 ng/mL).[4] In Cohort 2, $AUC_{0–24h}$ was expected to be reduced by <15% for TAF, ~20% for TFV, and ~24% for intracellular PBMC-associated TFV-DP vs Cohort 1.[5] The study authors concluded that BIC/FTC/TAF STR should not be used in combination with RIF.

Table 2. PK of BIC, TAF, and TFV (Custudio et al)[4,5]

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)	$AUC_{0–24h}$, ng·h/mL	115,000 (21)	45,600 (23)	39.5 (35.7–43.7)
	C_{max}, ng/mL	8530 (16)	4560 (19)	53.2 (49.1–57.6)
	C_T, ng/mL	3070 (28)	608 (30)	19.7 (17.2–22.7)
TAF, mean (CV)	$AUC_{0–24h}$, ng·h/mL	345 (52)	290 (48)	85.8 (69.7–106)
TFV, mean (CV)	$AUC_{0–24h}$, ng·h/mL	348 (20)	277 (19)	79.9 (73.1–87.3)
TFV-DP	$AUC_{0–24h}$, fmol·h/10^6 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 Daily BIC/FTC/TAF With Weekly RPT[7]

Study design

A phase 1, open-label, multiple-dose study was conducted in 30 HIV-negative, healthy volunteers to determine how RPT affects the PK, safety, and tolerability of BIC/FTC/TAF. BIC/FTC/TAF was given 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; it was given with BIC/FTC/TAF on Days 15 and 22 (co-dosed) and 12 hours before BIC/FTC/TAF on Day 29 (staggered).

Results

Compared with BIC/FTC/TAF alone, RPT given with BIC/FTC/TAF reduced the C_T of BIC by 35% to 83%. C_T did not return to steady state between RPT doses. After the ~83% reduction in BIC C_T was accounted for, individuals who receive BIC/FTC/TAF daily + RPT once weekly may fall below the $paEC_{95}$ of BIC (162 ng/mL). Thus, study investigators did not recommend BIC/FTC/TAF to be used in combination with once-weekly dosing of RPT.

There was a greater decline in BIC C_T with staggered dosing in comparison to that observed when co-dosed (Table 3). The effects of RPT on the PK of FTC, TAF, TFV, and TFV-DP compared with BIC/FTC/TAF given alone were not considered to be clinically significant.

Table 3. BIC Plasma PK Parameter Estimates (Arora et al)[7]

Parameter	BIC/FTC/TAF (n=29)	BIC/FTC/TAF + RPT; Co-Dosed (n=29)	BIC/FTC/TAF + RPT; 12 h Stagger (n=28)	%GLSM (90% CI)	
				Co-Dosed vs Alone	12 h Stagger vs Alone
C_T, mean (CV), ng/mL	2510 (28.1)	1520 (26.6)	1080 (27.2)	60.4 (56.3–64.7)	42.5 (39.1–46.2)

Most AEs were Grade 1. One Grade 3 AE of neck pain considered unrelated to study drugs was reported. Treatment-emergent AEs occurred at a higher frequency in those who received BIC/FTC/TAF + RPT (48%) vs BIC/FTC/TAF alone (27%). No SAEs and no clinically significant or Grade ≥3 laboratory abnormalities were reported.

PK of FTC/TAF Administered in Combination With RIF[6]

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_{max} by 50% and the TAF $AUC_{0–24h}$ by 55%; intracellular TFV-DP C_{max} decreased by 38%, and $AUC_{0–24h}$ 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)[6]

Parameter, GMR (90% CI)	FTC/TAF + RIF vs FTC/TAF	FTC/TAF + RIF vs TDF Monotherapy
TAF C_{max}	0.5 (0.42–0.61)	–
TAF $AUC_{0–24h}$	0.45 (0.33–0.6)	–
TFV-DP C_{max}	0.62 (0.52–0.74)	4.4 (3.09–6.27)
TFV-DP $AUC_{0–24h}$	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
$AUC_{0–12/24h}$=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_{max}=maximum concentration
C_T=trough 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
P-gp=permeability glycoprotein
$paEC_{95}$=protein-adjusted 95% effective concentration
PBMC=peripheral blood mononuclear cells
PK=pharmacokinetic(s)
PP=per protocol
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

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.

Follow-Up

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

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

Adverse Event Reporting

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Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 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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