

Biktarvy[®] (BIC/FTC/TAF) CNS Penetration

This document is in response to your request for information regarding the penetration of Biktarvy[®] (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) into the central nervous system (CNS). This response was developed according to principles of evidence-based medicine and contains clinical trial and real-world data (N≥5).

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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

PK Data on the CNS Penetration of BIC/FTC/TAF

A real-world study assessed the CSF diffusion of BIC/FTC/TAF in 24 participants with HIV-related CNS impairment. Unbound levels of FTC and TFV were undetectable in CSF and plasma. Lower concentrations in the CSF for BIC (total and unbound), FTC, and TFV compared with plasma concentration were reported.^{1,2}

An open-label study evaluated the PK of BIC in the CSF of 15 VS PWH. BIC concentrations in plasma and CSF of 14 participants were above the EC₅₀ of 1.1 ng/mL.³

Detectable concentrations of FTC in the CSF were reported in two PK studies of PWH treated with FTC/TDF along with other ARVs.^{4,5}

TAF concentrations were undetectable in plasma and CSF at 6 hours after dosing in 9 VS PWH who switched from E/C/F/TDF to E/C/F/TAF.⁶

Available CPE scores for the individual components of BIC/FTC/TAF are presented below.

PK Data on the CNS Penetration of BIC/FTC/TAF

Real-World Observational Study

Study design and demographics

An open-label, prospective, single-center, observational study was conducted in France to assess the CSF diffusion of BIC/FTC/TAF in participants with HIV-related CNS impairment. Participants with ≥1 HIV-related CNS impairment and ≥1 month of treatment with optimized ART containing BIC/FTC/TAF were included. Blood and CSF samples were collected during routine care.^{1,2}

Table 1. Baseline Demographics and Disease Characteristics (Gele et al)²

Key Demographics and Characteristics		BIC/FTC/TAF (N=24)
Age, median (range), years		45 (26–68)
Male/female, n		15/9
CD4 count, median (range), cells/mcL		229 (55–707)
Plasma HIV-RNA >40 c/mL, n (%)		8 (33)
CSF HIV-RNA >40 c/mL, n (%)		2 (8)
HIV-related CNS impairment, %	Progressive multifocal leukoencephalopathy	46
	Cerebral toxoplasmosis	25
	HIV encephalitis	13
	Acute disseminated encephalomyelitis	4
	Cerebral toxoplasmosis with HIV encephalitis	4
	Meningitis associated with primary HIV infection	4
	Varicella-zoster virus meningoencephalitis	4
ART, %	BIC/FTC/TAF	71
	BIC/FTC/TAF + MVC	25
	BIC/FTC/TAF + DRV/r	4
Duration of current ART, median (range), days		33 (27–365)

Abbreviations: DRV/r=ritonavir-boosted darunavir; MVC=maraviroc.

Results

Concentrations of BIC (total and unbound), FTC, and TFV were lower in the CSF than in plasma (Table 2).²

Table 2. PK Concentrations of BIC, FTC, and TAF in Plasma and CSF (Gele et al)²

PK Parameters, Median (Range)		BIC	FTC	TFV
Plasma concentration	Total, ng/mL	2610 (107–5707)	158 (41–1252)	19.7 (5.7–43.4)
	Unbound, ng/mL	9.3 (0.5–46.9)	Not detected	Not detected
CSF concentration	Total, ng/mL	11.8 (0.5–44.9)	84.4 (28.6–337.4)	1.6 (0.7–4.3)
	Unbound, ng/mL	4.4 (1.6–9.6)	Not detected	Not detected

The median (range) unbound BIC CSF fraction was 34% (15–82%), and the median (range) unbound BIC plasma concentration was 0.33% (0.11–0.92%). The unbound BIC plasma concentration remained stable and did not correlate with the total BIC plasma concentration ($P=0.96$).²

Participants aged >51 years had significantly higher CSF concentrations of the individual components of BIC/FTC/TAF than those aged ≤51 years of age (unbound BIC, $P=0.0356$; total FTC, $P=0.0082$; and total TFV, $P=0.0413$).²

Significant correlations were observed between the plasma and CSF concentrations for BIC ($r=0.7429$; $P=0.0002$) and FTC ($r=0.7654$; $P<0.0001$). The authors noted a limited effect of TAF in the CSF based on low concentrations in the CSF.¹

Blood-brain barrier damage was reported in 3 participants: 2 had progressive multifocal leukoencephalopathy, and 1 had HIV encephalitis.¹

PK of BIC in CSF³

Study design and demographics

An open-label, single-center study was conducted to evaluate the PK of BIC in the CSF of 15 VS PWH (Table 3). All participants switched from stable ART to BIC/FTC/TAF. PK parameters were assessed 24 hours after dosing at Week 4.

Table 3. Baseline Demographics and Disease Characteristics (Tiraboschi et al)³

Key Demographics and Characteristics	BIC/FTC/TAF (N=15)
Age, median (IQR), years	42 (37–56)
Male, %	86
BMI, median (IQR), kg/m ²	24.7 (23.3–29.7)
CD4 count, median (IQR), cells/mm ³	801 (628–1011)
HIV-1 RNA at diagnosis, median (IQR), c/mL	60,000 (30,094–410,304)
HIV-1 RNA <40 c/mL for >6 months, n (%)	15 (100)
History of AIDS-defining disease, n	4

Results

All participants maintained virologic suppression (HIV-1 RNA <40 c/mL) in plasma and CSF (Table 4). BIC concentrations in plasma and CSF (total and unbound) for 14 of the 15 participants were above the EC₅₀ of 1.1 ng/mL. Low concentrations of BIC in plasma (97.9 ng/mL) and CSF (below the lower limit of quantification for both total and unbound) were observed in 1 individual who was taking magnesium supplements. The plasma concentration of BIC increased after magnesium supplements were discontinued.

Table 4. Summary of BIC PK Parameters (Tiraboschi et al)³

PK Parameters		BIC (N=15)
Total plasma concentration, median (IQR), ng/mL		1837.1 (1237.2–2586.7)
CSF concentration	Total, median (IQR), ng/mL	6.9 (4.8–10.9)
	Unbound, median (IQR), ng/mL	2.48 (1.6–3.7)
CSF to plasma ratio, median (IQR)		0.003 (0.002–0.004)

Overall, BIC/FTC/TAF was well tolerated, and no significant adverse events were reported.

PK of FTC in the CSF

Two studies that evaluated the PK of FTC in PWH who received FTC/TDF along with other ARVs demonstrated detectable concentrations of FTC in the CSF, suggesting a strong association between plasma and CSF FTC concentrations.^{4,5} In a study of 30 PWH, plasma FTC concentration was reported as one of the significant predictors of CSF FTC concentration based on a univariate analysis ($P<0.0001$).⁴ In a study of 21 participants, the median (range) FTC concentrations in plasma and CSF were 212 (86.5–445.5) ng/mL and 68 (2.5–98) ng/mL, respectively, with a significant correlation observed between CSF and plasma FTC concentrations ($P=0.02$). The FTC CSF-to-plasma ratio (range) was 0.26 (0.05–0.41).⁵

PK of TAF in CSF

Study design⁶

In a single-arm, open-label study, CSF PK and antiviral activity were measured in 9 VS PWH who switched from E/C/F/TDF to E/C/F/TAF. Participants initially continued E/C/F/TDF, switched to E/C/F/TAF at Week 12, and were followed for an additional 12 weeks. Neurocognitive performance was evaluated by the Montreal Cognitive Assessment.

PK results

TFV concentrations declined over time from baseline to Week 24 in both the CSF (3 ng/mL and 0.481 ng/mL; $P=0.004$) and plasma (174 ng/mL and 14.1 ng/mL; $P=0.004$), consistent with the lower effective dose of TAF 10 mg compared with TDF 300 mg.^{6,7} Although the switch was associated with reduced TFV concentrations in CSF and plasma, TFV CSF-to-plasma ratio increased from 1.76% at baseline to 3.38% at Week 24 ($P=0.004$).⁶

There was a significant correlation of TFV concentrations in CSF and plasma ($P<0.0001$). At Week 24, median (range) TAF concentrations in plasma peaked 2 hours after dosing at 11.05 (2.84–147.11) ng/mL but were below the lower limit of quantification at 6 hours. TAF was not detected in CSF or plasma at 6 hours.⁶

There were no changes in blood-brain barrier permeability, with a mean CSF-to-serum albumin ratio of 3.86 before switching and 4.86 at Week 24.⁶

Safety⁶

No clinically significant trends in neurocognitive performance or post-dose laboratory abnormalities were observed.

Efficacy⁶

Switching from E/C/F/TDF to E/C/F/TAF maintained virologic suppression in the CSF and plasma. All participants had CSF HIV-1 RNA ≤ 20 c/mL at Week 24. Eight of 9 participants (89%) had plasma HIV-1 RNA ≤ 20 c/mL at Week 24. One individual, who had an HIV-1 RNA level of 40 c/mL at Week 24, had a CSF HIV-1 RNA level < 20 c/mL.

CPE Score

The CPE ranking system analyzes differences in estimated distribution of ARV drugs into the CNS, with a larger number reflecting estimates of better penetration or effectiveness in the CNS.⁸ The relationship between CPE score and neurocognitive or clinical outcomes has not yet been established.⁹⁻¹¹ A CPE score of 3 has been reported for FTC and a score of 1 for TAF.^{8,12-14} The CPE score for BIC has not been determined.

References

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Abbreviations

ART=antiretroviral therapy
ARV=antiretroviral
BIC=bicitegravir
c/mL=copies per mL
CD4=cluster of
differentiation 4
CNS=central nervous
system
CPE=central nervous
system penetration
effectiveness

CSF=cerebrospinal fluid
EC₅₀=half-maximal effective
concentration
E/C/F/TAF=elvitegravir/
cobicistat/emtricitabine/
tenofovir alafenamide
E/C/F/TDF=elvitegravir/
cobicistat/emtricitabine/
tenofovir disoproxil fumarate
FTC=emtricitabine
PK=pharmacokinetic(s)

PWH=people with HIV-1
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil
fumarate
TFV=tenofovir
VS=virologically suppressed

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

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