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Biktarvy® (BIC/FTC/TAF) Use in Baseline M184V/I Resistance

This document is in response to your request for information regarding Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) and its use in people with HIV (PWH) with baseline M184V/I resistance mutations.

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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]

BIC/FTC/TAF is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing ≥14 kg with no ARV treatment history; or with an ARV treatment history and not VS, with no known or suspected substitutions associated with resistance to the INSTI class, FTC, or TFV; or to replace the current ARV regimen in those who are VS (HIV-1 RNA <50 c/mL) on a stable ARV regimen with no known or suspected substitutions associated with resistance to BIC or TFV.

HIV-1 isolates with reduced susceptibility to FTC were selected in cell culture and in participants treated with FTC. Reduced susceptibility to FTC was associated with M184V or I substitutions in HIV-1 RT.

Cross-resistance has been observed among NRTIs. FTC-resistant viruses with an M184V/I substitution in HIV-1 RT were cross-resistant to 3TC.

Clinical Data on BIC/FTC/TAF Use in Participants With Baseline M184V/I Mutations

In a pooled analysis of participants in Studies 4030, 4580, 1844, 1878, 4449, and 1474, participants with baseline M184V/I maintained high rates (97–100%) of virologic suppression (HIV-1 RNA <50 c/mL) with BIC/FTC/TAF treatment.[2]

In an analysis of ARV-naive participants with low-frequency variants in the phase 3 Studies 1489 and 1490, all 6 participants on BIC/FTC/TAF with baseline M184V/I at a 2% to 15% frequency achieved virologic suppression (HIV-1 RNA <50 c/mL) at 96 weeks.[3]

Real-World Data on BIC/FTC/TAF Use in PWH With Baseline M184V/I Mutations

Real-world studies summarizing outcomes of PWH with baseline M184V/I mutations treated with BIC/FTC/TAF are summarized below.[4-8]

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Clinical Data on BIC/FTC/TAF Use in Participants With Baseline M184V/I Mutations

Pooled Analysis: M184V/I in VS Participants[2]

Study design and baseline resistance

A pooled analysis was conducted in participants (N=2034) from Studies 4030, 4580 (BRAAVE 2020), 1844, 1878, 4449, and 1474 to evaluate the prevalence of preexisting M184V/I resistance mutation and its effect on virologic outcomes in VS (ie, HIV-1 RNA <50 c/mL for 3 or 6 months) participants who switched to BIC/FTC/TAF. In Studies 4030 and 4580, participants with baseline M184V/I mutations were allowed, but other studies included in the analysis excluded participants if an M184V/I mutation was detected prior to the switch in therapy. Historical genotype reports were collected during enrollment, if available, and HIV-1 proviral DNA genotype testing was conducted retrospectively on any available baseline samples.

Across all six studies in the pooled analysis, 10% of participants with PR/RT data had preexisting M184V/I (182/1825; Table 1). Most M184V/I mutations were identified by baseline proviral DNA genotyping (167/182; 92%). Eighty-one percent of participants with M184V/I mutations (147/182) had ≥1 other resistance substitution.

Table 1. Pooled Analysis: Frequency of Baseline M184V/I in Participants Treated With BIC/FTC/TAF[2]

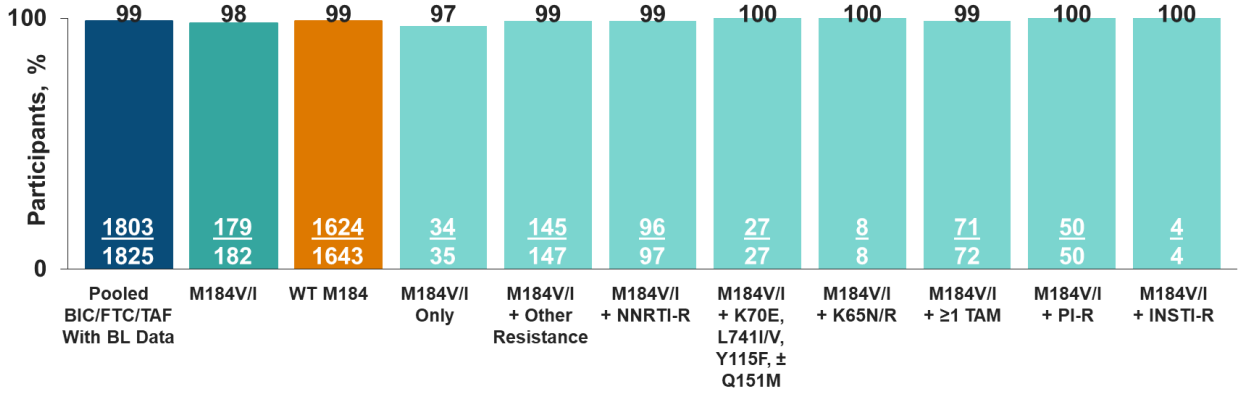
Baseline Substitution, n/N (%)	Pooled BIC/FTC/TAF (N=2034)
PR/RT data available (historical and/or proviral)	1825/2034 (90)
NRTI-R	288/1825 (16)
M184V/I	182/1825 (10)
M184V only	161/182 (88)
M184I only	11/182 (6)
M184V and M184I mixture	10/182 (5)

Efficacy results

High rates (97–100%; M=E analyses) of virologic suppression (HIV-1 RNA <50 c/mL) were maintained up to 180 weeks after switching to BIC/FTC/TAF, and no treatment-emergent resistance was detected. In participants with preexisting M184V/I who received BIC/FTC/TAF (median duration, 69 weeks), rates of virologic suppression were high (Figure 1). Rates of virologic suppression were similar between participants with and without M184V/I resistance mutations (98% vs 99%, respectively; *P*=0.48).

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Figure 1. Pooled Analysis: Virologic Suppression by Preexisting M184V/I in the Pooled BIC/FTC/TAF Group (LOCF)[2]



Abbreviations: BL=baseline; INSTI-R=integrase strand transfer inhibitor resistance; NNRTI-R=non-nucleos(t)ide reverse transcriptase inhibitor resistance; PI-R=protease inhibitor resistance; WT=wild-type allele.

Safety outcomes were not provided for this pooled analysis. Please see product labeling for BIC/FTC/TAF safety information.

Low-Frequency M184V/I in ARV-Naive Participants[3]

Study design and baseline resistance

An analysis of participants in the phase 3 Studies 1489 and 1490 was conducted to assess the impact of low-frequency variants on treatment outcomes of ARV-naive participants treated with BIC/FTC/TAF, DTG/ABC/3TC, or DTG + FTC/TAF. All participants were screened using HIV-1 genotype data, with PR and RT population sequencing data obtained from the GenoSure MG assay; a report showing sensitivity to FTC and TAF was required, and participants with M184V/I or K65R were excluded. After enrollment, a retrospective deep sequencing analysis of PR, RT, and integrase was conducted using the deepType HIV assay, and results were compared to population sequencing. Virologic outcomes were assessed at Week 96 using the LOCF method.

Results

In the overall population, high rates (97–98%) of virologic suppression (HIV-1 RNA <50 c/mL) were achieved at Week 96 across all treatment arms, regardless of baseline resistance. Primary NRTI-R substitutions occurred in 26/1274 participants (2%) at baseline per population sequencing methods. Using deep sequencing analysis (2–15% cutoff), 47/1270 participants (3.7%) had low-frequency primary NRTI-R substitutions at baseline; of these, 11 had M184V/I (BIC/FTC/TAF, 6/632 [0.9%]; DTG/ABC/3TC, 4/314 [1.3%]; DTG + FTC/TAF, 1/324 [0.3%]). All 11 participants were VS (HIV RNA <50 c/mL) at Week 96. Safety data were not reported in this subgroup analysis.

Real-World Data on BIC/FTC/TAF Use in PWH With Baseline M184V/I Mutations

Table 2 summarizes real-world studies that report outcomes in PWH with baseline M184V/I resistance who received BIC/FTC/TAF.

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Table 2. Real-World Data on PWH With Baseline M184V/I Resistance Who Received BIC/FTC/TAF[4-8]

Study Design and Population	Outcomes
BICTARG, a retrospective, observational cohort study of PWH in Argentina treated with BIC/FTC/TAF: a subanalysis in PWH with a history of virologic failure[4] • Of the 111 patients with NRTI-R at baseline, 92 had M184V/I mutations, and 31 had M184V/I + TAMs	• Rates of virologic suppression (HIV-1 RNA <50 c/mL) among patients with M184V/I and M184V/I + TAMs were as follows: ○ Baseline: 74% and 75%, respectively ○ Week 24: 94% and 96% ○ Week 48: 97% and 95% • No cases of virologic failure with BIC/FTC/TAF were reported, and no treatment-emergent RAMs developed • No safety data were reported
BICTARG: a subanalysis in PWH with baseline NTRI-R who were treated with BIC/FTC/TAF[5] • Of the 117 patients with ≥1 NRTI RAM, 50 had a single M184V/I mutation, 32 had M184V/I + TAMs, and 13 had M184V/I + L74V	• At 36 months, virologic suppression (HIV-1 RNA <50 c/mL) was maintained or achieved by the following subgroups of patients: ○ NRTI-R (n=117): 92% ○ Single M184V/I mutation (n=50): 83% ○ M184V/I + TAMs (n=32): 95% ○ M184V/I + L74V (n=13): 100% • At 48 months, rates of virologic suppression were as follows: ○ Single M184V/I mutation (n=18): 100% ○ M184V/I + L74V (n=6): 100% ○ M184V/I + TAMs (n=15): 100% • Safety data were not reported
In BICSTaR, an ongoing, multinational, prospective, observational cohort study in PWH treated with BIC/FTC/TAF, an analysis of TE VS PWH with preexisting PRMs was conducted[6] • 39/105 patients (37%) with genotypic resistance testing with pre-existing PRMs had preexisting M184V/I, including 14 patients (13%) with M184V/I + 1–2 TAMs and 4 (4%) with M184V/I + ≥3 TAMs	• At Month 12, virologic suppression (HIV-1 RNA <50 c/mL) was maintained in the following subgroups (M=E analysis): ○ Without preexisting PRMs: 739/758 (98%) ○ With any preexisting PRM: 78/79 (99%) ○ With M184V/I only: 32/33 (97%) ○ With M184V/I + 1–2 TAMs: 13/13 (100%) ○ With M184V/I + ≥3 TAMs: 2/2 (100%) • Through Month 12, a total of 17 participants (16%) with any preexisting PRMs and 98 participants (11%) without preexisting PRMs discontinued BIC/FTC/TAF due to AEs (12 [11%] and 59 [7%], respectively), drug-related AEs (9 [9%] and 47 [5%]), and lack of efficacy (1 [1%] and 1 [<1%])
Retrospective, single-center study in PWH who switched from a DRV-based ARV regimen to BIC/FTC/TAF[7] • Of the 54 patients with NRTI-R, 27 had M184V/I only, 19 had 1–2 TAMs ± M184V/I, 5 had 3–4 TAMs ± M184V/I, and 3 had M184V/I + K65R	• After a median (IQR) follow-up of 2.4 (1.3–3.3) years, outcomes were as follows: ○ M184V/I only: 20 (74%) maintained virologic suppression, 7 (26%) had virologic failure, and 1 patient each had NRTI and INSTI emergent resistance ○ 1–2 TAMs ± TAMs: 14 (78%) maintained virologic suppression, 1 (6%) had HIV-1 RNA ≥200 c/mL, and 3 (17%) had virologic failure ○ 3–4 TAMs ± M184V/I: 5 (100%) maintained virologic suppression ○ M184V/I + K65R: 2 (67%) maintained virologic suppression, and 1 (33%) had virologic failure • Safety data were not reported

Study Design and Population	Outcomes
Retrospective, multicenter, observational study in adult PWH with viremia (HIV-1 RNA ≥400 c/mL) and documented M184V/I at time of viremia treated with BIC/FTC/TAF (N=8)[8]	• At 3 months, 100% of participants (5/5) with available data achieved virologic suppression (HIV-1 RNA <50 c/mL) • At 6 months, 88% (7/8) were VS; the 1 patient who was not VS had 75–84% adherence with an HIV-1 RNA of 328 c/mL at 6 months. This participant discontinued BIC/FTC/TAF and achieved virologic suppression on DRV + DTG • Safety data were not reported

Abbreviations: AE=adverse event; BICSTaR=BIC Single Tablet Regimen; DRV=darunavir; PRM=primary resistance mutation; RAM=resistance-associated mutation; TAM=thymidine analog mutation.

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Abbreviations

3TC=lamivudine
ABC=abacavir
ARV=antiretroviral
BIC=bictegravir
c/mL=copies/mL
DTG=dolutegravir
FTC=emtricitabine
INSTI=integrase strand transfer inhibitor
LOCF=last observation carried forward
M=E=missing=excluded
NRTI=nucleos(t)ide reverse transcriptase inhibitor
NRTI-R=nucleos(t)ide reverse transcriptase inhibitor resistance
PR=protease
PWH=people with HIV
RT=reverse transcriptase
TAF=tenofovir alafenamide
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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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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