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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

In BICSTaR, a prospective study of the effectiveness and safety of BIC/FTC/TAF in PWH in clinical practice, high rates (97–100%) of virologic suppression (HIV-1 RNA <50 c/mL) were observed at Month 12 among VS participants with preexisting M184V/I.[4]

In a subanalysis of the retrospective BICTARG study, high rates (94–97%) of virologic suppression (HIV-1 RNA <50 c/mL) were observed at Weeks 24 and 48 of BIC/FTC/TAF treatment among PWH with a history of virologic failure and preexisting M184V/I ± TAMs.[5]

In a case series that assessed the effectiveness of BIC/FTC/TAF in PWH with archived M184V/I, 91% of patients were VS (HIV RNA <200 c/mL) at Month 12.[6]

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.

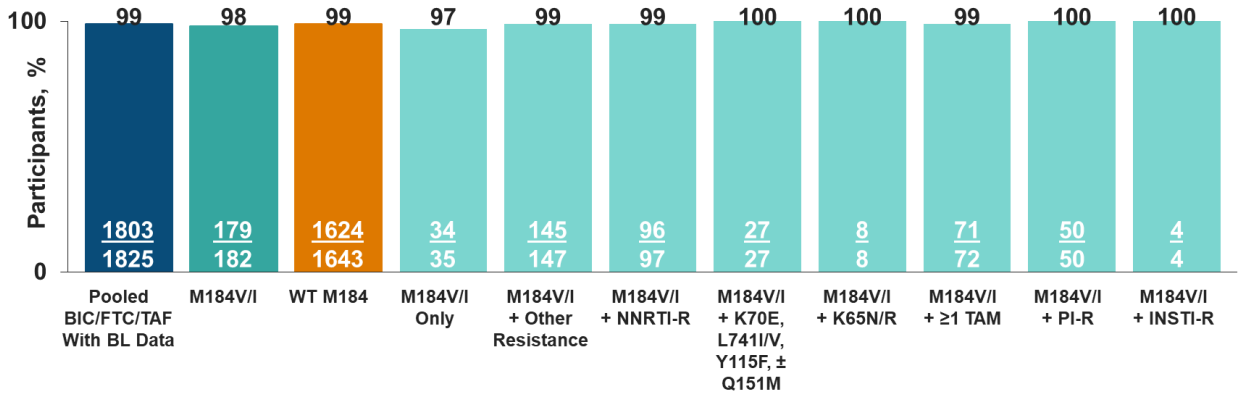
Table 1. Pooled Analysis: Frequency of Baseline M184V/I in Participants Treated With BIC/FTC/TAF[2]

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).

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

BICSTaR Study[4]

Study design and baseline resistance

BICSTaR is an ongoing, multinational, prospective, observational cohort study evaluating the effectiveness, safety, and tolerability of BIC/FTC/TAF in PWH in clinical practice, including 1083 TE PWH. Of the 996 VS (HIV-1 RNA <50 c/mL) PWH, 105/441 with available genotype data at baseline had preexisting PRMs (Table 2). The effectiveness and tolerability of 12 months of BIC/FTC/TAF in TE VS PWH with baseline PRMs were assessed.

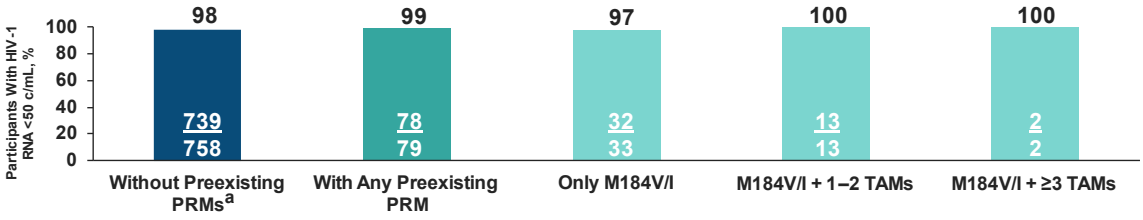
Table 2. BICSTaR: Preexisting M184V/I Resistance Mutations[4]

n (%)	Preexisting PRMs (n=105)
M184V/I	39 (37)
M184V/I + 1–2 TAMs	14 (13)
M184V/I + ≥3 TAMs	4 (4)

Results

High rates (97–100%) of virologic suppression (HIV-1 RNA <50 c/mL) were observed among VS participants with preexisting M184V/I who had available data at Month 12 (M=E analysis; Figure 2). No treatment-emergent PRMs were detected.

Figure 2. BICSTaR: Virologic Suppression in VS Participants at Month 12[4]



[a]Participants without resistance data (n=555) were considered to not have PRMs.

Through Month 12, 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%]).

BICTARG Study[5]

A subanalysis of a retrospective, observational study in Argentina examined virologic suppression rates (plasma HIV-1 RNA <50 c/mL) in PWH with a history of virologic failure treated with BIC/FTC/TAF from October 2019 to December 2021. Of 2356 TE PWH, 185 (7.8%) had a history of virologic failure, including 28 with ongoing virologic failure. Of these 185 patients, 174 had RAMs at baseline, with NRTI mutations present in 111 patients at baseline.

A total of 92 patients had M184V/I mutations, and 31 had M184V/I + TAMs. The virologic suppression rates among patients with M184V/I mutations were 74% at baseline, 94% at Week 24, and 97% at Week 48. Among patients with M184V/I + TAMs, the rates were 75%, 96%, and 95%, respectively. No cases of virologic failure occurred with BIC/FTC/TAF treatment, and no new RAMs emerged during follow-up. No safety data were reported.

Case Series of PWH With M184V/I

There are limitations in the interpretation of case reports. Case reports cannot be generalized. Unlike controlled clinical trials, causality cannot be inferred based on uncontrolled observational data. In addition, incidence or prevalence cannot be estimated due to the lack of a representative population sample. Other limitations of case reports include the retrospective design and publication bias.[7] This is not exhaustive of all cases found in literature, and additional cases can be found by conducting a literature search in PubMed or other databases.

A case series assessed the effectiveness of BIC/FTC/TAF in achieving and maintaining virologic suppression among TE PWH with recorded M184V/I mutations. All patients included in the study (N=33) had either failed a prior regimen or were placed on BIC/FTC/TAF as a switch strategy. The primary outcome was sustained virologic suppression (HIV RNA <200 c/mL) after 12 months of BIC/FTC/TAF treatment.[6]

After 12 months of BIC/FTC/TAF treatment, the proportion of VS PWH increased from 27/33 (82%) at baseline to 30/33 (91%). Two of the 3 patients who were not VS at Month 12 were not suppressed for the entire course of treatment; 1 of these patients was ARV naive at baseline, had poor adherence to treatment, and developed an R263K mutation that conferred resistance to BIC. The third patient who was not VS at Month 12 was suppressed at baseline and at Month 3 of BIC/FTC/TAF, with missing data thereafter until Month 12. Safety data were not reported.[6]

References

1. Enclosed, Gilead Sciences Inc. BIKTARVY® (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Sax PE, Andreatta K, Molina JM, et al. High efficacy of switching to bictegravir/emtricitabine/tenofovir alafenamide in people with suppressed HIV and preexisting M184V/I. *AIDS.* 2022;36(11):1511-1520. https://www.ncbi.nlm.nih.gov/pubmed/35466963
3. Acosta R, Willkom M, Martin R, et al. Low-Frequency Resistance Variants in ART-Naive Participants Do Not Affect Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) Triple Therapy Outcome [Poster MOPEB242]. Paper presented at: 10th IAS Conference on HIV Science; July 21-24, 2019; Mexico City, Mexico.
4. Trottier B, Bonnet F, García-Deltoro MG, et al. Real World Effectiveness and Tolerability of Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) in Treatment Experienced People With HIV and a History of Antiretroviral Drug Resistance Mutations [Poster 1628848]. Paper presented at: ID Week 2023; October 11-15, 2023; Boston, MA.
5. Lamaizon C, Cecchini D, Bottaro E, et al. Effectiveness of bictegravir / emtricitabine/tenofovir alafenamide fixed-dose combination in experienced people living with HIV with a history of virologic failure, M184V /I, and other resistance-associated mutations in clinical practice [Poster PN097]. Paper presented at: 25th International AIDS Conference; July 22-26, 2024; Munich, Germany.
6. Chamberlain N, Mena L, Brock JB. BIC/FTC/TAF Maintains Viral Suppression In Patients With Documented M184V/I Mutations: A Real World Experience [Poster 1003]. Paper presented at: ID Week Virtual; 21-25 October, 2020.

7. Nissen T, Wynn R. The Clinical Case Report: A Review of Its Merits and Limitations. *BMC Res Notes.* 2014;7:264. https://www.ncbi.nlm.nih.gov/pubmed/24758689

Abbreviations

3TC=lamivudine
ABC=abacavir
AE=adverse event
ARV=antiretroviral
BIC=bictegravir
BICSTaR=BIC Single Tablet Regimen
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
PRM=primary resistance mutation
PWH=people with HIV
RAM=resistance-associated mutation
RT=reverse transcriptase
TAF=tenofovir alafenamide
TAM=thymidine analog mutation
TE=treatment-experienced
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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Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
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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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