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

This document is in response to your request for information regarding the use of Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) in patients with baseline (BL) non-nucleos(t)ide reverse transcriptase inhibitor resistance (NNRTI-R).

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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 in adults and pediatric patients weighing ≥14 kg who have no ARV treatment history; or with an ARV treatment history and not virologically suppressed, 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 virologically suppressed (HIV-1 RNA <50 c/mL) on a stable ARV regimen with no known or suspected substitutions associated with resistance to BIC or TFV.

Clinical Data on BIC/FTC/TAF Use With BL NNRTI-R

In a pooled analysis of four studies that was conducted to determine the prevalence of preexisting NNRTI-R and associated risk factors in virologically suppressed participants who were switched to BIC/FTC/TAF, high rates (97–99%) of virologic suppression were observed in participants with BL NNRTI-R at various timepoints across clinical trials.[2-5]

In a pooled analysis of ARV-naive participants, BIC/FTC/TAF demonstrated non-inferior efficacy to DTG/ABC/3TC (Study 1489) and DTG + FTC/TAF (Study 1490) with 99% (81/82) of participants with preexisting NNRTI-R maintaining virological suppression at Week 144.[6]

Clinical Data on BIC/FTC/TAF Use With BL NNRTI-R

Pooled Prevalence of Preexisting NNRTI-R Mutations in Virologically Suppressed Participants

A pooled analysis of four studies (Studies 1844, 1878, 4030, and 4580) was conducted to determine the prevalence of preexisting NNRTI-R and associated risk factors in virologically suppressed participants (N=2200) who were switched to BIC/FTC/TAF (Table 1). BIC/FTC/TAF demonstrated non-inferior efficacy (HIV-1 RNA <50 c/mL) at the primary endpoints.[5]

Table 1. Summary of BIC/FTC/TAF Switch Studies in Virologically Suppressed Participants[5]

Study	Resistance Criteria	BL ARV Regimen	Participants, n	Study Phase and Treatment		
				Randomized Phase Through Week 48		OLE
1844	Excluded resistance to FTC or TFV	DTG + ABC/3TC (either STR or MTR)	282	BIC/FTC/TAF (DTG/ABC/3TC placebo)		BIC/FTC/TAF
			281	DTG/ABC/3TC (BIC/FTC/TAF placebo)		BIC/FTC/TAF
1878	Excluded resistance to FTC or TFV	Boosted DRV or ATV + either FTC/TDF or ABC/3TC	290	BIC/FTC/TAF		BIC/FTC/TAF
			287	SBR		BIC/FTC/TAF
4030	Allowed NRTI-R, NNRTI-R, and PI-R; excluded INSTI-R	DTG + either FTC/TAF or FTC/TDF	284	BIC/FTC/TAF (DTG + FTC/TAF placebo)		–
			281	DTG + FTC/TAF (BIC/FTC/TAF placebo)		–
4580	Allowed NNRTI-R or PI-R; excluded INSTI-R; NRTI-R: allowed M184V/I, <2 TAMs, K65R/E/N, T69 insertions, excluded ≥3 TAMs	Any third agent + 2 NRTIs	330	BIC/FTC/TAF		–
			165	SBR (through Week 24)	BIC/FTC/TAF (Weeks 24–48)	–

Abbreviations: ATV=atazanavir; DRV=darunavir; INSTI-R=integrase strand transfer inhibitor resistance; MTR=multi-tablet regimen; SBR=stay on BL regimen; STR=single-tablet regimen; TAM=thymidine analog mutations; TDF=tenofovir disoproxil fumarate.

Preexisting NNRTI-R was present in 22% of participants (448/1995) at BL, of which 14% (289/1995) were documented via proviral genotyping, making NNRTI-R the most frequently observed class of preexisting drug resistance. Participants who switched to BIC/FTC/TAF maintained high rates of virologic suppression regardless of preexisting NNRTI-R, with 99% of participants with NNRTI-R maintaining virologic suppression (HIV-1 RNA <50 c/mL) at last on-treatment visit.[5]

A univariate analysis showed that BL NNRTI-R was significantly associated with the presence of BL NRTI-R and PI-R. A multivariate logistic-regression model showed that history of BL NRTI-R, M184V/I, or PI-R; prior PI or raltegravir treatment, age <50 years, and Black race were all independently associated with preexisting NNRTI-R.[5]

Studies 1844 and 1878 OLE analysis and safety

In Study 1844, 86/88 participants with BL NNRTI-R who received BIC/FTC/TAF for a median duration of 96 weeks had HIV-1 RNA <50 c/mL at their last visit.[3] In Study 1878, 127/129 participants with BL NNRTI-R who received BIC/FTC/TAF for a median duration of 108 weeks had HIV-1 RNA <50 c/mL at their last visit.[2]

A safety analysis was not conducted in the subgroup of participants with NNRTI-R at BL. In Study 1844, the most common all-grade AEs reported in ≥10% of all participants who received ≥1 dose of BIC/FTC/TAF through a median exposure of 96 weeks were URTI, nasopharyngitis, and diarrhea.[3] In Study 1878, the most common all-grade AEs reported in ≥10% of all participants who received ≥1 dose of BIC/FTC/TAF through a median exposure of 101 weeks were headache, nasopharyngitis, upper respiratory infection, and diarrhea.[7]

Study 4030 safety results at Week 48[8]

A safety analysis was not conducted in the subgroup of participants with NNRTI-R at BL. In the overall safety analysis, the most commonly reported (≥10%) AEs in either group were nasopharyngitis, diarrhea, and URTI. Drug-related AEs that occurred in ≥2% in either group were diarrhea and headache. Six participants (2%) in each arm discontinued the study because of AEs.

Study 4580 (BRAAVE) OLE analysis and safety

Preexisting BL NNRTI mutations were detected in 22% (n=101) of participants (K103N/S, n=52 [11%]; rilpivirine-associated [ie, L100I, K101E/P, E138A/G/K/R, V179L, Y181C/I, Y188L, H221Y, F227C, and M230I/L in RT], n=41 [9%]). Virologic suppression was maintained through Week 72 at a rate of 99% in both the overall pooled BIC/FTC/TAF group (486/489) and in participants with preexisting NNRTI-R (100/101).[4]

A safety analysis was not conducted in the subgroup of participants with NNRTI-R at BL. In the overall safety analysis, switching to BIC/FTC/TAF was well tolerated, and AEs were comparable between the two treatment arms at Week 24.[9] All-grade AEs that occurred in ≥5% of participants who received BIC/FTC/TAF at any time (n=493) included URTI, syphilis, headache, pain in extremity, arthralgia, hypertension, and nasopharyngitis. AEs led to 6 study drug discontinuations between BL and Week 24, 3 discontinuations between Weeks 24 and 48, and 3 discontinuations after Week 48.[10]

Pooled Efficacy and BL Resistance in ARV-Naive Participants

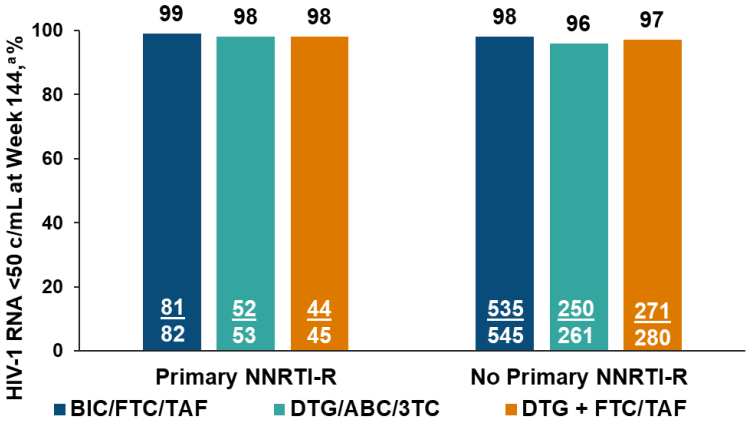
Study design

An integrated viral resistance analysis of two phase 3 BIC/FTC/TAF clinical trials in ARV-naive participants (Studies 1489 and 1490) was conducted. All participants were screened using HIV-1 genotypic data with PR and RT population sequencing data obtained from the GenoSure MG assay.[11,12] Exclusion criteria included FTC or TFV resistance (Studies 1489 and 1490), in addition to ABC or 3TC resistance (Study 1489). Screened participants with mutations conferring resistance to the NRTIs studied (eg, M184V/I, K65R/E/N) were excluded from study participation as well.[11]

Efficacy results

BIC/FTC/TAF demonstrated non-inferior efficacy (HIV-1 RNA <50 c/mL) to DTG/ABC/3TC (Study 1489) and DTG + FTC/TAF (Study 1490) by FDA Snapshot analysis at the Week 48 primary endpoint and the secondary endpoints at Weeks 96 and 144.[13] Preexisting NNRTI-R (mutation frequency cut-off: ≥15%) was noted in 82 participants who received BIC/FTC/TAF; 99% of these participants were virologically suppressed at Week 144 (Figure 1).[6]

Figure 1. Studies 1489 and 1490: Virologic Outcomes With BL NNRTI-R at Week 144[14]



[a]Last observation carried forward outcome analysis did not include 7 BIC/FTC/TAF-treated participants and 1 DTG/ABC/3TC-treated participant who had no on-treatment, postbaseline HIV-1 RNA data; 1 of these BIC/FTC/TAF-treated participants had a primary PI-associated resistance substitution.

Retrospective next-generation sequencing/deep sequencing techniques were used to analyze low-frequency viral variants in PR, RT, and integrase. Primary NNRTI-R mutations were detected at low frequencies (2–15%) using deep sequencing in an additional 4.2% of participants (53/1270); all participants with BL primary NNRTI-R were virologically suppressed at Week 96.[12]

Safety results at Week 144

A safety analysis was not conducted in the subgroup of participants with NNRTI-R at BL. The most common all-grade adverse reactions reported in ≥10% of all participants in the BIC/FTC/TAF arms in either study through Week 144 were nausea, diarrhea, URTI, headache, nasopharyngitis, back pain, fatigue, cough, and syphilis. AEs led to study drug discontinuation in no participants in the BIC/FTC/TAF arm in Study 1489 and in 6 participants (2%) in the BIC/FTC/TAF arm in Study 1490, compared with 5 discontinuations (2%) in the DTG/ABC/3TC arm and 6 discontinuations (2%) in the DTG + FTC/TAF arm.[13]

References

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Abbreviations

3TC=lamivudine
ABC=abacavir
AE=adverse event
ARV=antiretroviral
BIC=bictegravir
BL=baseline
c/mL=copies/mL
DTG=dolutegravir
FTC=emtricitabine
INSTI=integrase strand transfer inhibitor
NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor
NNRTI-R=non-nucleos(t)ide reverse transcriptase inhibitor resistance
NRTI=nucleos(t)ide reverse transcriptase inhibitor
NRTI-R=nucleos(t)ide reverse transcriptase inhibitor resistance
OLE=open-label extension
PI=protease inhibitor
PI-R=protease inhibitor resistance
PR=protease
RT=reverse transcriptase
TAF=tenofovir alafenamide
TFV=tenofovir
URTI=upper respiratory tract infection

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
🖱 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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