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Biktarvy® (BIC/FTC/TAF) Use in Baseline INSTI 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 integrase strand transfer inhibitor resistance (INSTI-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 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.

Clinical Data on BIC/FTC/TAF Use in Participants With Baseline INSTI-R

In a pooled analysis of seven phase 3 studies that included ARV-naive and VS PWH who initiated or switched to BIC/FTC/TAF for 48 weeks, 20/1906 participants had preexisting primary INSTI-R substitutions, and 19 of these participants remained VS through Week 48 with no viral blips. The remaining participant with preexisting INSTI-R substitutions achieved virological suppression at Week 4 and maintained it through Week 216.[2,3]

Real-World Data on BIC/FTC/TAF Use in Patients With Baseline INSTI-R

In an analysis of patient data from the ARCA database, major and minor INSTI RAMs were detected in 3.3% and 8% of patients, respectively. Major INSTI RAMs (P=0.027), a history of virologic failure (P=0.027), and a history of INSTI virologic failure (P=0.003) were associated with an increased risk of virologic rebound.[4]

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Clinical Data on BIC/FTC/TAF Use in Participants With Baseline INSTI-R

Pooled Analysis of Virologic Outcomes After 48 Weeks

Study design and baseline demographics[2]

A pooled analysis of seven phase 3 studies was conducted to determine the virologic outcomes after 48 weeks of BIC/FTC/TAF treatment in ARV-naive participants who initiated BIC/FTC/TAF and in VS PWH who switched to BIC/FTC/TAF with preexisting INSTI-R (Table 1). Known INSTI-R was an exclusion criterion prior to study enrollment; however, participants with preexisting INSTI-R identified post enrollment were permitted to continue in the studies.

Table 1. Pooled Analysis: Overview of BIC/FTC/TAF Studies[2]

Study	BIC/FTC/TAF Participants, n	Study Design	Virologic Status	Age, Years
1489	315	Phase 3, randomized, active controlled, double blind	ARV naive	≥18
1490	320	Phase 3, randomized, active controlled, double blind	ARV naive	≥18
1844	282	Phase 3, randomized, double blind	VS[a]	≥18
1878	290	Phase 3, randomized, open label	VS	≥18
4580	330	Phase 3b, open label	VS[a]	≥18
4030	284	Phase 3, randomized, double blind	VS[a]	≥18
4449	86	Phase 3, single arm, open label	VS	≥65

[a]Prior INSTI use was allowed if there was no prior virological failure on the INSTI-based regimen.

Preexisting primary INSTI-R substitutions were observed in 1% of participants (20/1906) post enrollment. Of the 20 participants with preexisting primary INSTI-R, 75% were male, 55% were Black, and 85% had HIV-1 subtype B. The most frequent primary INSTI-R mutations identified were Y143C/H and Q148H/K/R (Table 2).[2]

Table 2. Pooled Analysis: Primary INSTI-R Mutations in BIC/FTC/TAF Studies[2]

Primary INSTI-R Mutations, n (%)	Participants Detected (n=20)
Y143C/H	6 (30)
Q148H/K/R	6 (30)
E92G	3 (15)
S147G	2 (10)
R263K	2 (10)
N155S	1 (5)

Efficacy results at Week 48

Of the 20 participants with primary preexisting INSTI-R substitutions, 19 were from studies that included VS participants, and 100% of these participants maintained HIV-1 RNA <50 c/mL at all study visits through Week 48 with no viral blips.[2]

One ARV-naive participant was retrospectively identified who had transmitted INSTI-R, NRTI-R, and NNRTI-R. The INSTI-R mutations G140S + Q148H were detected, with phenotypic sensitivity to BIC (<2.5-fold change) and partial sensitivity to DTG. After treatment with BIC/FTC/TAF, HIV-1 RNA <50 c/mL was achieved at Week 4 and maintained through Week 216.[2,3]

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Studies 1489 and 1490 OLE analysis in preexisting INSTI-R

BIC/FTC/TAF demonstrated noninferior 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.[5] Preexisting primary INSTI-R using a mutation frequency cutoff of ≥15% was discovered in 7 participants taking BIC/FTC/TAF; 100% of these participants were VS at Week 144.[6]

A safety analysis was not conducted in the subgroup of participants with INSTI-R at baseline. 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.[5]

Studies 1878 and 1844 OLE analysis in preexisting INSTI-R

At Week 48, 561/570 (98%) of the pooled BIC/FTC/TAF group, 280/285 (98%) of the PI + 2 NRTIs group, and 280/281 (>99%) of the DTG/ABC/3TC group were VS.[7] In Study 1878, 14/14 participants with baseline INSTI-R taking BIC/FTC/TAF for a median duration of 103 weeks had HIV-1 RNA <50 c/mL at their last visit.[8] In Study 1844, 16/16 participants with baseline INSTI-R taking BIC/FTC/TAF for a median duration of 96 weeks had HIV-1 RNA <50 c/mL at their last visit.[9]

A safety analysis was not conducted in the subgroup of participants with INSTI-R at baseline. In Study 1878, the most common all-grade adverse reactions reported in ≥10% of all participants taking ≥1 dose of BIC/FTC/TAF through a median exposure of 101 weeks were headache, nasopharyngitis, URTI, and diarrhea.[10] AEs led to study drug discontinuation in 6 participants (1%) in the pooled BIC/FTC/TAF group. In Study 1844, the most common all-grade adverse reactions reported in ≥10% of all participants taking ≥1 dose of BIC/FTC/TAF through a median exposure of 96 weeks were URTI, nasopharyngitis, and diarrhea. AEs led to study drug discontinuation in 7 participants (1%) in the pooled BIC/FTC/TAF group.[9]

Study 4030 safety through Week 48[11]

A safety analysis was not conducted in the subgroup of participants with INSTI-R at baseline. In the overall safety analysis, the most commonly reported AEs reported by ≥10% in either group were nasopharyngitis, diarrhea, and URTI. Drug-related AEs occurring 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 in preexisting INSTI-R

Switching to BIC/FTC/TAF was noninferior to continuing the baseline regimen of 2 NRTIs plus a third agent by FDA Snapshot analysis at the Week 24 primary endpoint.[12] High rates of virologic suppression were maintained through Week 72 in the BIC/FTC/TAF and delayed-switch arms (99% and 100%, respectively, in a missing=excluded analysis).[13]

Preexisting primary INSTI-R was discovered in 2% of participants (Table 3). Through Week 72, 99% (486/489) of the pooled BIC/FTC/TAF group and 100% (11/11) of participants with preexisting INSTI-R were VS at their last study visit.[14]

Table 3. BRAAVE 2020: Prevalence of Preexisting INSTI-R Substitutions[14]

Resistance Category, n (%)	Cumulative Baseline Genotype (n=468)
Primary INSTI-R	11 (2)
Y143C/H	4 (1)[a]
E92G[b]	3 (1)
Q148H/K/R	3 (1)[a]
T66A[b]	1 (<1)
Secondary INSTI-R	227 (50)
M50I	107 (24)
S119P/R/T	101 (22)
E157K/Q	42 (9)
T97A	11 (2)

[a]Y143C and Q148K were detected by historical genotype in 1 participant each; both participants were excluded from efficacy analyses but maintained virologic suppression at all study visits through Week 24.
[b]Resistance category corrected per author communication.

A safety analysis was not conducted in the subgroup of participants with INSTI-R at baseline. In the overall safety analysis, switching to BIC/FTC/TAF was well tolerated, and reported AEs were comparable between the two treatment arms at Week 24.[12] All-grade AEs that occurred in ≥5% of participants receiving 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 baseline and Week 24, 3 discontinuations between Weeks 24 and 48, and 3 discontinuations after Week 48.[13]

Real-World Data on BIC/FTC/TAF Use in Patients With Baseline INSTI-R

BIC-Barrier Study[4]

A real-world, observational, retrospective study used data from the ARCA database to assess the prevalence of preexisting RAMs, including INSTI RAMs, and to evaluate the association between RAMs and the risk of virologic rebound (two consecutive HIV-1 RNA levels >50 c/mL) in PWH who were VS (HIV-1 RNA <50 c/mL) when they were switched to BIC/FTC/TAF. The study included BIC-naive adults with ≥1 genotypic resistance test after ARV therapy initiation and before switching to an exclusive BIC/FTC/TAF regimen for any reason (N=1414). At baseline, 1028 patients (72.7%) were male, the median age was 53 years, 924 (65.3%) were White race, and 960 (67.9%) had HIV-1 subtype B.

Of the 727 patients with available INSTI genotypic resistance test results, 193 (26.5%) had a cumulative GSS for BIC/FTC/TAF of <3. Major INSTI RAMs were detected in 24 patients (3.3%), including in 4 (0.6%) with INSTI-R that affected susceptibility to BIC, and 58 patients (8%) had minor INSTI RAMs. The most prevalent INSTI RAMs were T97A (2.8%), G163R (1.8%), and E157Q (1.7%).

A Cox regression analysis was used to assess the association of various factors linked to resistance or a history of virologic failure and risk of virologic rebound in a subset of patients with virologic follow-up (n=973). The analysis included 13 patients with major INSTI RAMs; 3 of these patients had major BIC mutations, and none experienced virologic rebound. After controlling for confounding factors, major INSTI RAMs (aHR, 4.21; 95% CI: 1.18–15.02; *P*=0.027), a history of virologic failure (aHR, 1.96; 95% CI: 1.08–3.55; *P*=0.027), and a

history of INSTI virologic failure (aHR, 2.68; 95% CI: 1.4–5.12; *P*=0.003) were associated with an increased risk of virologic rebound.

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Abbreviations

3TC=lamivudine
ABC=abacavir
AE=adverse event
aHR=adjusted hazard ratio
ARCA=Antiviral Response Cohort Analysis
ARV=antiretroviral
BIC=bictegravir
c/mL=copies/mL
DTG=dolutegravir
FTC=emtricitabine
GSS=genotypic susceptibility score
INSTI=integrase strand transfer inhibitor
INSTI-R=integrase strand transfer inhibitor resistance
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
PWH=people with HIV-1
RAM=resistance-associated mutation
TAF=tenofovir alafenamide
TFV=tenofovir
URTI=upper respiratory infection
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

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