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# Biktarvy® (BIC/FTC/TAF) Treatment-Emergent RAMs

This document is in response to your request for information regarding the use of Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]) and treatment-emergent, resistance-associated mutations (RAMs).

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## Summary

Available Data on BIC/FTC/TAF Use and Treatment-Emergent RAMs

No treatment-emergent RAMs were detected in >3000 PWH receiving BIC/FTC/TAF in Gilead-sponsored phase 3 clinical trials.[1-10]

In BICSTaR, an ongoing, multicountry, prospective, observational cohort study in PWH that is evaluating the effectiveness and safety of BIC/FTC/TAF in clinical practice, no treatment-emergent RAMs to the components of BIC/FTC/TAF were detected at 24 months (ARV-naive, n=483; TE, n=1591), 36 months (ARV-naive, n=67; TE, n=382), or 5 years (ARV-naive, n=132; TE, n=691).[11-13]

In most reported cases there were several risk factors for resistance.[14-24]

## Available Data on BIC/FTC/TAF Use and Treatment-Emergent RAMs

### Phase 3 Clinical Trials

No treatment-emergent RAMs were detected in >3000 PWH treated with BIC/FTC/TAF in Gilead-sponsored phase 3 clinical trials (Table 1).[1-10,25-29]

**Table 1. Treatment-Emergent RAMs in BIC/FTC/TAF Phase 3 Clinical Trials (BIC/FTC/TAF-Treated Participants)[1-10,25-29]**

| Trial | Population | N[a] | Drugs With Excluded Resistance[b] | Treatment-Emergent RAMs[c] |
|---|---|---|---|---|
| GS-US-380-1489[1] | ARV-naive adults | 314/254 | FTC, TFV, ABC, and 3TC[26] | No |
| GS-US-380-1490[1] | ARV-naive adults | 320/265 | FTC and TFV[27] | No |
| GS-US-380-1878[2] | VS adults | 290/244 | FTC, TFV, ABC, and 3TC | No |
| GS-US-380-1844[3] | VS adults | 284/265 | FTC, TFV, DTG, ABC, and 3TC[30] | No |
| GS-US-380-4030[4] | VS adults | 284 | INSTI | No |

| Trial | Population | N[a] | Drugs With Excluded Resistance[b] | Treatment-Emergent RAMs[c] |
|---|---|---|---|---|
| GS-US-380-1961[5] | VS adult women | 234/228 | FTC, TFV, ATV, and EVG[28] | No |
| BRAAVE 2020[6] GS-US-380-4580 | VS adults self-identifying as Black or African American | 330/163 | INSTI and specific NRTI RAMs (ie, K65R/E/N, T69 insertions, ≥3 TAMs) | No |
| GS-US-380-1474[7,8] | VS adolescents and children | 122 | FTC, TFV, and INSTI[29] | No |
| GS-US-380-4449[9] | VS adults ≥65 years of age | 86 | FTC, TFV, and BIC[29] | No |
| ALLIANCE GS-US-380-4458[10] | ARV-naive adults with HIV/HBV co-infection | 119/89 | FTC and TFV[25] | No |

Abbreviations: 3TC=lamivudine; ATV=atazanavir; EVG=elvitegravir; TAM=thymidine analog mutation; TFV=tenofovir; VS=virologically suppressed.

[a]Total number of participants includes those randomly assigned to receive BIC/FTC/TAF at baseline/those who later switched to BIC/FTC/TAF if the study included an extension phase.

[b]The trial excluded participants with resistance to the drugs listed.

[c]Resistance testing performed for participants with confirmed viremia with second HIV-1 RNA ≥200 c/mL or ≥200 c/mL at last visit, with no resuppression of HIV-1 RNA to <50 c/mL while on study drug.

# Real-World Data

## BICSTaR study

BICSTaR is a Gilead-sponsored, ongoing, multicountry, prospective, observational cohort study in PWH that is evaluating the effectiveness, safety, and tolerability of BIC/FTC/TAF in clinical practice. ARV-naive (n=483) and TE (n=1591) PWH were evaluated in a 24-month pooled analysis of data from clinical sites in Europe, Canada, Israel, Asia, and Japan (June 27, 2018–December 20, 2023). Pooled analyses of data collected through 36 months (data cutoff date, August 12, 2022; ARV-naive, n=67; TE, n=382) and 5 years (data cutoff date, June 24, 2024; ARV-naive, n=132; TE, n=691) from clinical sites in Germany, France, and Canada were also conducted. No treatment-emergent RAMs to the components of BIC/FTC/TAF were detected at 24 months, 36 months, or 5 years.[11-13]

## Case reports

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.[31]

Six case reports describe treatment-emergent INSTI RAMs (with or without NRTI RAMs) in PWH on BIC/FTC/TAF (Table 2). Isolated instances of the NRTI RAM M184V/I have been reported in individuals with documented poor or intermittent adherence or prior history of ART failures.[20,22,23]

**Table 2. Case Reports: BIC/FTC/TAF Treatment-Emergent INSTI RAMs[14-16,18,19,24]**

| ART History; VL; CD4[a] | Baseline Mutations | Treatment-Emergent RAMs | Comments |
|---|---|---|---|
| ARV-naive and INSTI-naive; 2,000,000 c/mL; 57 cells/mcL[16] | IN polymorphism: M50I + S119P | IN: R263K + H51Y(M7) RT: M184V/I(M4) | • PML with aphasia; worsening clinical condition<br>• Erratic adherence |
| ARV-naive and INSTI-naive; 3,700,000 c/mL; 16 cells/mcL[18] | RT: L74I | IN: R263K(M9) RT: M184V/I(M4) | • Poor adherence<br>• VL not suppressed over 12 months of follow-up<br>• Cryptococcal meningitis (recurrent), mental illness, substance abuse |
| ARV-naive and INSTI-naive; 932 c/mL; Not reported[19] | None | IN: 263KR(M12) RT: M184V(M12) | • Complex HIV subtype CRF06-cpx<br>• One viral blip (182 c/mL) was reported prior to loss of virologic suppression<br>• Virologic failure (VL 836 c/mL) was reported at Week 48<br>• Patient from an observational cohort study with unknown adherence |
| TE and INSTI-experienced; 467,000 c/mL; 8 cells/mcL[14] | IN: M50I + N155H RT: M184V | IN: R138K + S147G + R263K(M3) | • E/C/F/TDF first-line failure due to poor adherence related to GI side effects |
| TE and INSTI-experienced; 1,023,293 c/mL; 37 cells/mcL[15] | IN: L74I | IN: R263K(M3) RT: M184V(M3) | • RAL + ABC + FTC second-line failure due to frequent treatment interruptions<br>• Unknown ARV levels (due to NG tube administration)<br>• Cerebral toxoplasmosis with dysphagia; acute neurologic deterioration due to PML-IRIS |
| TE and INSTI-experienced; 626,000 c/mL; 2 cells/mcL[24] | RT: K219KE, V179E, Y181C | IN: R263K, E157Q NRTI: K70KE, Y115YF, M184V, K219KE NNRTI: V179E, Y181C | • Poor adherence to ART since HIV diagnosis in 1998<br>• History of multiple opportunistic infections, history of IV drug use<br>• Switched to DTG + DRV/c under parental supervision and achieved VL <100 c/mL for the first time in 25 years |

Abbreviations: CD4=cluster of differentiation 4; DRV/c=cobicistat-boosted darunavir; E/C/F/TDF=elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; GI=gastrointestinal; IN=integrase; IRIS=immune reconstitution Inflammatory syndrome; M=month; NG=nasogastric; NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor; PML=progressive multifocal leukoencephalopathy; RAL=raltegravir; RT=reverse transcriptase; VL=viral load.

[a]Describes VL and CD4 count at baseline in ARV-naive patients and at switch to BIC/FTC/TAF in TE patients.

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# Abbreviations

ABC=abacavir
ART=antiretroviral therapy
ARV=antiretroviral
BIC=bictegravir
BICSTaR=BIC Single Tablet Regimen
c/mL=copies/mL
DTG=dolutegravir
FTC=emtricitabine
INSTI=integrase strand transfer inhibitor
NRTI=nucleos(t)ide reverse transcriptase inhibitor
PWH=people with HIV
RAM=resistance-associated mutation
TAF=tenofovir alafenamide
TE=treatment experienced

## 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.

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