Poster: 1528848

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

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Key Findings

- Pre-existing primary resistance mutations (PRMs) were identified in 24% of virologically suppressed (VS) participants with available genotyping data at enrollment of this real-world study
  - M184V/I accounted for 37% of all PRMs
  - High levels of virologic suppression were maintained after switching to B/F/TAF irrespective of pre-existing PRMs, including those associated with NRTI resistance
  - No treatment-emergent PRMs to B/F/TAF were reported
- B/F/TAF was effective in achieving virologic suppression in a small number of participants with viremia and pre-existing PRMs at enrollment
- B/F/TAF was generally well tolerated and drug discontinuations for virologic reasons were rare

Conclusions

- After 12 months, treatment-experienced (TE) people with HIV initiating B/F/TAF in routine clinical practice maintained high rates of effectiveness despite the presence of PRMs (including M184V/I)

Introduction

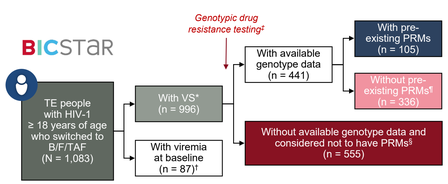
- B/F/TAF is a single tablet regimen recommended by U.S. and European guidelines for the treatment of HIV-1[1–3]
- BICSTaR is an ongoing, multinational, prospective, observational cohort study evaluating the real-world effectiveness and safety of B/F/TAF in ART treatment-naïve (TN) and TE people with HIV
- BICSTaR has reported high effectiveness and a favorable safety profile of B/F/TAF for up to 3 years in TE and TN people with HIV[4]

Objective

- To explore the effectiveness and tolerability of B/F/TAF after 12 months of treatment in TE people with HIV who were enrolled with pre-existing PRMs and who switched to B/F/TAF
  - While the primary analysis was in VS participants, we also explored effectiveness in a small number of people with viremia at the time of switch to B/F/TAF

Methods

Study Design



Cutoff date for analysis: February 2022

Study outcomes:

- HIV-1 RNA < 50 c/mL‖
- CD4 count
- CD4/CD8 ratio
- Treatment-emergent PRMs
- Discontinuations
- Drug-related adverse events (DRAEs)

Considered PRMs included the following:

NRTI	M41L, A62V, K65R, D67N, T69ins, K70R/E, L74V/I, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215Y/F, K219Q/E/N/R
NNRTI	L100I, K101E/P, K103N/S, V106M/A, E138K, Y181C/I/V, Y188L, G190A/S/E, M230L
PI	D30N, V32I, L33F, M46I/L, I47V/A, G48V, I50L/V, I54L/M/V, Q58E, T74P, L76V, V82F/I/A/T/S, I84V, N88S, L90M
INSTI	T66A/I/K, E92Q/G, T97A, G140S, Y143R/H/C, S147G, Q148R/H/K, N155H

*Virologic suppression defined as HIV-1 RNA < 50 c/mL; †Participants with HIV-1 RNA ≥ 50 c/mL were not included in the primary analysis; ‡Obtained either at the time of enrollment or from historic HIV-1 genotype tests; §For the purposes of the primary analysis, participants with missing or unavailable genotype data at enrollment were considered not to have PRMs; ¶A restricted population of those participants with available genotype data and no known PRMs was used in a sensitivity analysis to assess the robustness of the findings from the primary analysis; ‖Virologic failure was not predefined in the protocol, and participant management for virologic reasons was at the discretion of the investigator. A review of participants with HIV-1 RNA ≥ 50 c/mL was performed in the 12-month analysis window.

Results

Pre-existing PRMs at Enrollment in VS Participants

- At enrollment, genotypic drug resistance testing data were available for 441/996 participants (44%)
  - Most tests were historic, with only one test carried out within 2 weeks of starting B/F/TAF
    - 13 tests (1.3%) were performed > 60 months prior to starting B/F/TAF
    - Median (IQR) time from available genotype test to starting B/F/TAF was 32.2 (17.3–46.4) months
- Of 441 participants with available genotype data, 105 (24%) had evidence of pre-existing PRMs at the time of enrollment
  - 66 (15%) NRTI, 56 (13%) NNRTI, 28 (6%) PI, 1 (0.2%) INSTI*
  - 40 (9%) had existing PRMs to > 1 ARV drug class
- For 555/996 participants (56%), resistance data were either missing or not available; these participants were considered not to have PRMs for the purposes of this analysis

*INSTI PRM for n = 1 was the T97A accessory mutation.

Most common pre-existing PRMs (in > 1% of participants)	Participants with any pre-existing PRMs, n (%) N = 105
NRTI	
M184V/I	39 (37)
M184V/I + 1–2 TAMs	14 (13)
M184V/I + ≥ 3 TAMs	4 (4)
T215Y/F	15 (14)
D67N	13 (12)
M41L	13 (12)
K70R/E	9 (9)
K219Q/E/N/R	8 (8)
L210W	4 (4)
> 1 TAM	40 (38)
NNRTI	
K103N/S	23 (22)
K101E/P	9 (9)
Y181C/I/V	10 (10)
PI	
M46I/L	13 (12)

Baseline Characteristics of VS Participants With or Without Evidence of Pre-existing PRMs

Characteristic	Total N = 996*	With any pre-existing PRMs n = 105	Without pre-existing PRMs n = 891†	With available genotype data and no known PRMs n = 336
Female sex at birth, n (%)	163 (16)	27 (26)	136 (15)	39 (12)
Age at B/F/TAF initiation				
Median (IQR), years	49 (39–56)	52 (46–58)	48 (39–56)	45 (37–54)
≥ 50 years, n (%)	470 (47)	63 (60)	407 (46)	132 (39)
Race , %				
White	79	77	79	82
Black	12	15	12	9
Other	9	8	10	10
Time from HIV diagnosis to B/F/TAF initiation, years, median (IQR)	11 (5–18)	17 (7–24)	10 (5–17)	7 (3–13)
CD4 count, cells/μL, median (IQR)	680 (480–884)	619.5 (420–865)	683 (482–886)	702 (507–880)
CD4/CD8 ratio, median (IQR)	0.9 (0.6–1.3)	0.9 (0.6–1.1)	0.9 (0.6–1.3)	0.9 (0.6–1.3)
Number of previous regimens, median (IQR)	2 (2–4)	4 (2–7)	2 (1–4)	2 (1–3)
Prior virologic failure, n (%)	97 (10)	41 (39)	56 (6)	18 (5)
Reasons for switching to B/F/TAF,‡ n (%)				
Simplification of ART regimen	604 (61)	73 (70)	531 (60)	224 (67)
Participant preference	227 (23)	20 (19)	207 (23)	77 (23)
Side effects of current ART	222 (22)	27 (26)	195 (22)	72 (21)
Other reasons‡	197 (20)	19 (18)	178 (20)	59 (18)

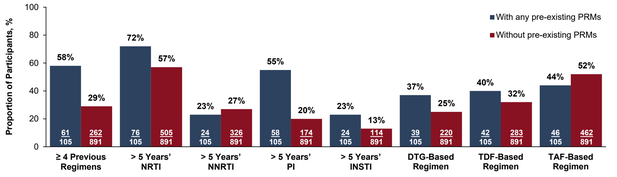
*Includes n = 441 (336 + 105) who had genotype test data available and n = 555 with either missing or unavailable genotype data; †Includes n = 336 who had genotype test data available and n = 555 with either missing or unavailable genotype data and who were considered not to have pre-existing PRMs; ‡Other reasons included safety (e.g., cardiovascular, renal and bone health), which was selected by 58 (6%) of the total number of participants (with PRMs at enrollment: n = 7 [7%], without PRMs at enrollment: n = 51 [6%], with genotype data and no known PRMs: n = 15 [4%]), and drug–drug interaction, which was selected by 56 (6%) of the total number of participants (with PRMs at enrollment: n = 7 [7%]), without PRMs at enrollment: n = 49 [6%], with genotype data and no known PRMs: n = 21 [6%]).

- Compared with participants without PRMs, those with pre-existing PRMs tended to be older (aged ≥ 50 years), with a longer time between HIV diagnosis and starting B/F/TAF, more prior ARTs and a greater likelihood of prior virologic failure (no statistical testing performed)

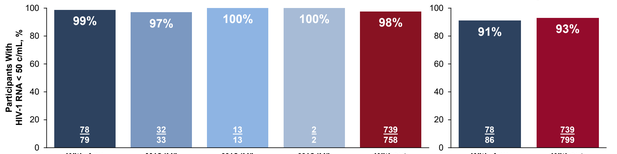
Prior ART History in VS Participants

- Overall, in all 996 participants, the most common ART regimens taken immediately before B/F/TAF were E/C/F/TAF (27%), DTG + F/TAF (9%) and ABC/DTG/3TC (8%)
- Compared with participants without PRMs, more participants with pre-existing PRMs had received ≥ 4 prior ART regimens, > 5 years' NRTI use, > 5 years' PI use, > 5 years' INSTI use and a regimen containing DTG or TDF (no statistical testing performed)

Prior ART History in VS Participants (Continued)



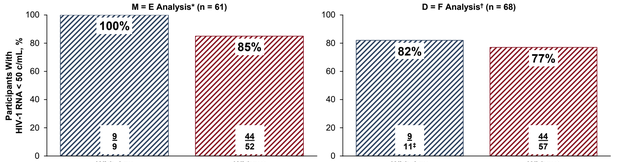
Virologic Suppression at Month 12 in VS Participants (M = E and D = F)



*Denominators represent number of participants with available HIV-1 RNA data at Month 12. n = 837/996 had available HIV-1 RNA data at Month 12. For n = 159 with missing HIV-1 RNA data at Month 12, n = 48 had discontinued B/F/TAF or had a treatment interruption > 30 days before the 12-month analysis window, and n = 111 were still on B/F/TAF and had no HIV-1 RNA data in the Month 12 analysis window; †Participants who discontinued B/F/TAF or had a treatment interruption > 30 days before the beginning of the 12-month analysis window were imputed as > 50 c/mL.

- Twenty participants had detectable viral load (VL) at Month 12 (HIV-1 RNA ≥ 50 c/mL)
  - 19/20 participants were without pre-existing PRMs; of these, 10 had isolated blips (VL between 52 and 229 c/mL) and re-suppressed at the next visit, seven had confirmed (×2) episodes of HIV-1 RNA > 50 c/mL (VL between 51 and 118 c/mL) and two had virologic rebound (VL 24,672 c/mL and 174 c/mL)
  - One participant with pre-existing PRMs had an isolated blip (VL 78 c/mL) and re-suppressed at the next visit
- No treatment-emergent PRMs to B/F/TAF were reported
- The predefined category of "lack of efficacy" was selected by the investigator as the reason for B/F/TAF discontinuation in only two participants through Month 12 (n = 1 with, and n = 1 without, pre-existing PRMs) (see Table to the right)

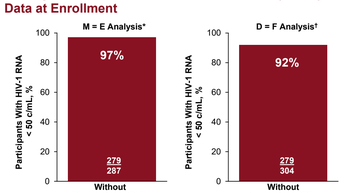
Virologic Suppression at Month 12 in Participants With Viremia at Enrollment (M = E and D = F)



*Denominators represent number of participants with available HIV-1 RNA data at Month 12. For n = 26 with missing HIV-1 RNA data at Month 12, n = 7 had discontinued B/F/TAF or had a treatment interruption > 30 days before the 12-month analysis window, and n = 19 were still on B/F/TAF and had no HIV-1 RNA data in the Month 12 analysis window; †Participants who discontinued B/F/TAF or had a treatment interruption > 30 days before the beginning of the 12-month analysis window were imputed as > 50 c/mL; ‡Of the 11 participants with viremia at enrollment who had pre-existing PRMs: n = 7 had a history of prior virologic failure and n = 5 had ≥ 1 pre-existing PRM related to NRTI resistance (M184V/I in n = 3, M184V/I plus T215Y/F in n = 1, and M184V/I plus D67N, K70R/E, K219Q/E/N/R in n = 1).

- Eight of the 52 participants with viremia at enrollment and without pre-existing PRMs had a detectable VL at Month 12 (HIV-1 RNA ≥ 50 c/mL)
  - VLs at enrollment ranged from 95 c/mL to 560,000 c/mL
  - All eight participants continued to have viremia at Month 12, ranging from 129 c/mL to 6,120 c/mL

Virologic Suppression at Month 12: Sensitivity Analysis in VS Participants With Available Genotypic Data at Enrollment



- A high level of effectiveness was observed in the sensitivity analysis of participants with available genotype data and no PRMs (n = 336), and was consistent with the findings from the primary analysis

*Denominators represent number of participants with available HIV-1 RNA data at Month 12.
†Participants who discontinued B/F/TAF before the beginning of the 12-month analysis window were imputed as > 50 c/mL.

Immunologic Outcomes at Month 12 in VS Participants

Change from baseline, median (IQR)	Total N = 996	With any pre-existing PRMs n = 105	Without pre-existing PRMs n = 891
CD4 count, cells/μL	9 (-94, 109)	26 (-53, 100)	8 (-98, 110)
CD4/CD8 ratio	0 (-0.1, 0.1)	0 (-0.1, 0.1)	0 (-0.1, 0.1)

Study Drug Discontinuations Through 12 Months in VS Participants

Details of B/F/TAF discontinuations	Total N = 996	With any pre-existing PRMs n = 105	Without pre-existing PRMs n = 891
Discontinued B/F/TAF, n (%)	115 (12)	17 (16)	98 (11)
Due to AE	71 (7)	12 (11)	59 (7)
Due to DRAE	56 (6)	9 (9)	47 (5)
Due to "lack of efficacy"*	2 (< 1)	1 (1)	1 (< 1)
Duration of B/F/TAF among those who discontinued, months, median (IQR)	10.5 (5.5–16.3)	9.4 (3.6–14.0)	10.7 (5.7–16.8)
Switched from B/F/TAF to another ART, n (%)	98 (10)	15 (14)	83 (9)
Most common regimen switched to†			
DOR/3TC/TDF	17 (18)	0	17 (21)
DTG/3TC	14 (15)	2 (14)	12 (15)
E/C/F/TAF	12 (13)	3 (21)	9 (11)
DTG/RPV	5 (< 1)	3 (3)	2 (< 1)

*A predefined category in the electronic case report form; †> 10% of participants in any group.

- Two participants discontinued B/F/TAF due to "lack of efficacy"
  - One participant without pre-existing PRMs had viral rebound (VL 740 c/mL) at Month 3 and and re-suppressed after switch to DTG + DRV/r
  - One participant with a pre-existing PRM (K103N) had viral rebound (VL 445 c/mL) at Month 6 and re-suppressed after switch to ABC/DTG/3TC

Other Safety Outcomes Through 12 Months in VS Participants

DRAE type, n (%)	Total N = 996	With any pre-existing PRMs n = 105	Without pre-existing PRMs n = 891
≥ 1 DRAE	130 (13)	17 (16)	113 (13)
≥ 1 serious DRAE	2 (< 1)	0	2 (< 1)
Depression	1 (< 1)	0	1 (< 1)
Depression episode	1 (< 1)	0	1 (< 1)
≥ 1 DRAE leading to discontinuation of B/F/TAF	56 (6)	9 (9)	47 (5)
Most common DRAEs leading to discontinuation*			
Weight increased	18 (32)	3 (33)	15 (32)
Headache	6 (11)	2 (22)	4 (9)
Fatigue	5 (9)	2 (22)	3 (6)

DRAEs occurring by the end of the Month 12 visit window are included. The DRAEs were not mutually exclusive. *> 12% of participants in any group.

References: **1.** Gandhi RT, et al. JAMA 2023;329:63-84. **2.** Department of Health and Human Services. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv (accessed July 31, 2023). **3.** European AIDS Clinical Society. https://www.eacsociety.org/guidelines/eacs-guidelines/ (accessed July 31, 2023). **4.** Schellberg S, et al. DÖAK 2023, Poster 80874.

Acknowledgments: We thank all study participants and all participating study investigators and staff. This study was sponsored by Gilead Sciences. Medical writing support was provided by Joanna Nikitorowicz-Buniak, PhD (Aspire Scientific Ltd, U.K.), and was funded by Gilead.

Disclosures: **BT:** advisor/consultant for and honoraria from Gilead, Merck and ViiV. **FB:** grant/research support, honoraria and educational support from Gilead. **MG-D:** advisor/consultant for and grant/research support from AbbVie, Gilead, MSD and ViiV; board member for and grant/research support from Janssen. **MA:** advisor/consultant for Gilead, Moderna and MSD. **MB:** honoraria from AstraZeneca; advisor/consultant for and honoraria from ATEA; advisor/consultant for and grant/research support and honoraria from Gilead, GSK, MSD and Pfizer; advisor/consultant and speakers bureau for and grant/research support and honoraria from ViiV; grant/research support from Moderna, Novavax, Roche and Valneva. **BJvW:** advisor/consultant for and grant/research support from Gilead; advisor/consultant for ViiV. **DTu:** advisor/consultant for and honoraria from Gilead and GSK. **SM** and **P-LL:** nothing to disclose. **DW:** honoraria from Gilead K.K., Janssen K.K., MSD K.K. and ViiV K.K. **AG:** advisor/consultant for and honoraria from Gilead, GSK and MSD. **DTh**, **MLD**, **TC**, **AM**, **ARW** and **RH:** employed by and hold stocks/bonds in Gilead. **SS:** advisor/consultant for and honoraria from AbbVie; grant/research support and honoraria from Cepheid; advisor/consultant for and grant/research support, honoraria and congress/travel support from Gilead and ViiV; grant/research support from GSK; advisor/consultant for and honoraria and congress support from Janssen.

Abbreviations: 3TC, lamivudine; ABC, abacavir; AE, adverse event; ART, antiretroviral therapy; ARV, antiretroviral; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BICSTaR, BICtegravir Single Tablet Regimen; c, copies; C, cobicistat; CD, cluster of differentiation; D = F, discontinued = failure; DOR, doravirine; DRAE, drug-related adverse event; DRV/r, darunavir/ritonavir; DTG, dolutegravir; E, elvitegravir; F, emtricitabine; HIV, human immunodeficiency virus; INSTI, integrase strand-transfer inhibitor; IQR, interquartile range; M = E, missing = excluded; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; PRM, primary resistance mutation; RPV, rilpivirine; TAF, tenofovir alafenamide; TAM, thymidine analog mutation; TDF, tenofovir disoproxil fumarate; TE, treatment experienced; TN, treatment naïve; VL, viral load; VS, virologically suppressed.