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ORIGINAL ARTICLE

Twelve-month effectiveness and safety of bictegravir/emtricitabine/tenofovir alafenamide in people with HIV: Real-world insights from BICSTaR cohorts

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Abstract

Background: Real-world evidence is an essential component of evidence-based medicine. The aim of the BICSTaR (BICtegravir Single Tablet Regimen) study is to assess effectiveness and safety of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in antiretroviral treatment-naïve (TN) and treatment-experienced (TE) people with HIV.

Methods: BICSTaR is a prospective, observational cohort study. Participants (≥18 years) are being followed for 24 months. A pooled analysis is presented at 12 months, with the primary endpoint of effectiveness (HIV-1 RNA <50 copies/mL) and secondary endpoints of safety and tolerability (as per protocol).

An exploration of patient-reported outcome measures using standardized questionnaires is included.

Results: Between June 2018 and May 2021, 1552 people with HIV were enrolled across 12 countries. The analysed population comprised 1509 individuals (279 TN, 1230 TE); most were white (76%), male (84%) and had one or more comorbid conditions (68%). Median age was 47 years. After 12 months of B/F/TAF treatment, HIV-1 RNA was <50 copies/mL in 94% (221/236) of TN participants and 97% (977/1008) of TE participants. Median CD4 cell count increased by 214 cells/μL ($p < 0.001$) in TN participants and 13 cells/μL ($p = 0.014$) in TE participants; median CD4/CD8 ratios increased by 0.30 and 0.03, respectively (both $p < 0.001$). Persistence was high at 12 months (TN, 97%; TE, 95%). No resistance to B/F/TAF emerged. Study drug-related adverse events occurred in 13% of participants through 12 months, leading to B/F/TAF discontinuation in 6%.

Conclusions: The findings of this study provide robust real-world evidence to support the broad use of B/F/TAF in both TN and TE people with HIV.

KEYWORDS

antiretroviral therapy, ART-experienced, ART-naïve, B/F/TAF, bictegravir, real-world evidence

INTRODUCTION

Improvements in antiretroviral treatment (ART) have led to an increase in life expectancy of people with HIV [1–5]. Older people often have more health challenges than younger individuals, including higher frequencies of comorbidity and polypharmacy [6–8]. As ART is taken for life, holistic patient-focused treatment goals are important. An optimal regimen should maintain viral suppression over the long-term with a low risk of emergent resistance, be well tolerated, have a low pill burden, few drug–drug interactions, and improve quality of life [1].

Current ART recommendations include two- and three-drug regimens for ART-naïve and ART-experienced people with HIV [9, 10]. Three-drug regimens are most commonly used (particularly in western countries), and usually consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus an integrase strand transfer inhibitor (INSTI) [1, 9, 10]. B/F/TAF is a three-drug coformulation consisting of bictegravir (B), emtricitabine (F) and tenofovir alafenamide (TAF). Bictegravir is a potent unboosted INSTI that is formulated for once-daily administration with a high barrier to resistance [11]. Emtricitabine in combination with either tenofovir disoproxil fumarate (TDF) or TAF is recommended as NRTI backbone therapy [10]. TAF is a prodrug of tenofovir and is associated with improved bone and renal safety profiles [12, 13]. Multiple clinical trials have shown B/F/TAF to be efficacious and a well-tolerated treatment in ART-naïve (TN) and ART-experienced (TE) people with HIV [4, 5, 14–20]. B/F/TAF has been approved in many countries around the world [21, 22] and is a recommended first-line treatment in international guidelines [1, 9, 10].

A growing number of real-world studies in a number of countries have evaluated B/F/TAF, providing evidence for its effectiveness, tolerability and safety in routine clinical practice [23–30]. Most of these data are from small and/or retrospective, country-specific studies.

Here, we report a pooled analysis on the 12-month effectiveness (primary endpoint), safety and tolerability of B/F/TAF in participants from 12 countries participating in the BICSTaR observational cohorts.

METHODS

Study design

The BICtegravir Single Tablet Regimen (BICSTaR) study is an ongoing, multi-regional programme composed of five observational cohorts that have enrolled 2379 TN and TE people with HIV (enrolment completed 16 December 2021) with a planned follow-up of 24 months. Data are being collected across the five cohorts using a common protocol: (1) France, Germany, Ireland, Italy, the Netherlands, Spain, Turkey, UK; (2) Canada; (3) Israel; (4) Singapore, South Korea and Taiwan; and (5) Japan. All cohorts are ongoing at the time of writing, apart from the

Israeli cohort (completed May 2022). The current analysis was conducted for the primary endpoint at 12 months.

Data were collected prospectively in all cohorts; however, for cohorts 4 and 5, the study protocols allowed for both prospective and retrospective data collection. Only prospective data are included in the current analysis. Data were retrieved from hospital files, clinical records, clinic visits, electronic medical records and patient-reported outcome questionnaires validated in the general population and/or people with HIV.

Follow-up visits occurred according to the standard practice of each site and as per the treating physician's judgement. No additional diagnostic or laboratory monitoring procedures were required by the study. Data were recorded on an Electronic Case Report Form using Medidata Rave Electronic Data Capture system (Medidata, New York, NY, USA) and accessed via a secure web portal. Adverse events (AEs) were recorded according to the Medical Dictionary for Regulatory Activities (MedDRA, V24.1; ICH, Geneva, Switzerland, 2021) system organ class and preferred terms.

Participants, treatment and study duration

Eligible participants were aged ≥18 years (≥21 and ≥20 years in cohorts 4 and 5, respectively) receiving B/F/TAF in routine clinical care. B/F/TAF (50/200/25 mg) was initiated based on country prescribing information, local treatment guidelines and/or consultation with the treating physician. Individuals participating in any interventional clinical trial with treatment involvement were not permitted to enter the study; those participating in non-ART interventional trials unrelated to study drug were allowed to continue in the study only with approval from the study sponsor. Data collection began with the first participant enrolled (28 June 2018) and ended for the current analysis (18 February 2022). The date of treatment start varied depending on the commercial availability of B/F/TAF in each country. Enrolment could only occur following the physician's independent decision to prescribe B/F/TAF and receipt of the participant's informed consent form. The index date was the day the participant started or switched to B/F/TAF (day 1/baseline).

Study endpoints and assessments

The primary endpoint of effectiveness was the proportion of participants with HIV-1 RNA suppression (HIV-1 RNA <50 copies/mL) at month 12.

Secondary endpoints included the proportion of participants with HIV-1 RNA <50 copies/mL (months 3 and 6); change from baseline in CD4 count and CD4/CD8 ratio (month 12) and the cumulative incidence of investigator-assessed AEs, serious AEs (SAEs), drug-related AEs (DRAEs) and drug-related SAEs (month 12).

Exploratory endpoints included: reasons for initiating B/F/TAF in TN participants and for switching to B/F/TAF in TE participants; treatment persistence and reasons for treatment discontinuation; laboratory analyses including metabolic assessments [total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides], estimated glomerular filtration rate (eGFR), weight and body mass index (BMI) at month 12.

Treatment satisfaction was assessed using the HIV Treatment Satisfaction status (HIVTSQs) and change (HIVTSQc) questionnaires. The HIVTSQs is a validated, 10-item questionnaire using an ordinal scale (version 2006), where a score of 6 represents high satisfaction and 0 represents low satisfaction [31]. Responses to all questions are summed to produce a 'total treatment satisfaction' score ranging from 0 to 60, with higher scores indicating greater satisfaction. The HIVTSQc is a 10-item measure of relative satisfaction. All items are rated on a scale where +3 represents 'much more satisfied' now and −3 represents 'much less satisfied now'. Responses to all questions are summed to produce a total treatment satisfaction (change) score, ranging from +30 (improvement) to −30 (deterioration).

Further analyses explored effectiveness (HIV-1 RNA <50 copies/mL; month 12) and safety (AE frequency; month 12) in specific populations of people with HIV. Virological failure was not specifically defined within the study protocol and was assessed at the discretion of the study investigators based on local clinical practice guidelines. Investigators could discontinue treatment at their discretion for virological reasons.

Statistical analysis

Sample size calculation

Details of sample size calculations are outlined in the Online Supplementary Information (page 16).

Analyses

The analysis population included all participants with a visit within the 12-month visit window (defined as ≥275 days or 9 months to ≤548 days or 18 months) and those who discontinued the study having initiated B/F/TAF ≥275 days (the lower bound of the 12-month visit window) prior to the data cut-off date.

Demographics and outcomes were assessed using summary statistics. Numbers and percentages of participants,

including 95% confidence interval (CI), were reported for categorical variables. Median and first and third quartiles (Q1, Q3) were calculated for continuous variables, alongside the total number of observations and the number of missing values.

For the main analysis of effectiveness (primary endpoint), a missing-equals-excluded (M=E) analysis was performed, including participants with one or more HIV-1 RNA value within the 12-month visit window. Only values available within this window were analysed. Participants who discontinued the study and/or B/F/TAF before the 12-month visit window and participants still in the study and taking B/F/TAF but without an HIV-1 RNA value available within the visit window were not considered (no imputation) for the M=E analysis. For participants who discontinued B/F/TAF during study follow-up and remained in the study (as allowed by study protocols), results collected after discontinuation of B/F/TAF were not considered for analysis.

A treatment discontinuation-equals-failure (D=F) analysis was conducted for effectiveness at months 3, 6 and 12. The 12-month D=F analysis included participants with ≥1 HIV-1 RNA value within the 12-month visit window and those participants who discontinued B/F/TAF before the lower bound of the 12-month visit window (i.e. ≥275 days or 9 months from baseline); in the latter case, HIV-1 RNA was imputed as ≥50 copies/mL. Results from participants who discontinued B/F/TAF during the 12-month visit window were not imputed for the D=F analysis.

Persistence with B/F/TAF at month 12 was defined as still being in the study and having received B/F/TAF for ≥275 days (i.e. the lower bound of the 12-month visit window). Participants who discontinued the study before the 12-month visit window, and where it could not be ascertained as to whether they also discontinued B/F/TAF, were not included in the denominator in the persistence analysis. The calculation for persistence involved dividing the number of participants who remained on B/F/TAF within the visit window by the total number of participants in the study, after excluding those who discontinued the study without any indication of stopping B/F/TAF.

Median changes in CD4 cell count, CD4/CD8 ratio, weight, BMI, lipids and eGFR from baseline to month 12 were assessed using 95% two-sided *p*-values and/or CIs and Sign tests. eGFR was calculated using the Cockcroft–Gault formula [32].

Analyses in specific populations

Analyses were performed to explore the effectiveness and safety of B/F/TAF within specific groups of participants at 12 months (M=E analysis). Groups of participants were categorized according to whether they had received prior treatment (TN vs. TE), sex (male vs. female), older age (<50 vs. ≥50 years and <65 vs. ≥65 years), race/ethnicity (black vs. other), those with late HIV diagnosis (CD4 count <350 cells/μL and/or ≥1 AIDS-defining event vs. ≥350 cells/μL) or late diagnosis with advanced HIV disease (CD4 count <200 cells/μL and/or ≥1 AIDS-defining event vs. ≥200 cells/μL), those with/without present or past evidence of primary HIV drug-resistance mutations (PRMs) at baseline (including those with/without M184V/I) and people with comorbidities at baseline (including those with neuropsychiatric symptoms).

Analyses were conducted using SAS software, version 9.4 (SAS Institute Inc, Cary, NC, USA).

RESULTS

Participants

Between 28 June 2018 and 17 May 2021, 1552 people with HIV were enrolled in BICSTaR cohorts across 12 countries. Of these, 43 people were excluded from this analysis, mostly because no follow-up form was completed ($n = 40$). Thus, the analysis population consisted of 1509 individuals (prospective data), comprising 279 TN and 1230 TE participants (Figure S1). A small number of enrolled participants ($n = 15$) participating in non-ART interventional clinical trials unrelated to the use of study drug were allowed to continue in the study only with approval of the study sponsor. Baseline demographic and clinical characteristics are shown in Table 1 and country enrolment is shown in Table S1.

Most TN and TE participants were male (90% and 83%, respectively) and white (69% and 77%, respectively). TN participants were younger than TE participants (median 38 vs. 49 years) and had lower body weight (median 70.0 vs. 76.0 kg) and BMI (median 22.8 vs. 24.8 kg/m^2) at baseline. The majority of participants had one or more comorbid condition at baseline; the median (Q1, Q3) number of comorbidities per participant was 1 (0, 3). The proportion of individuals with three or more comorbidities was twice as high in TE as in TN participants. Over half of the cohort were receiving one or more concomitant non-ART medication at baseline; the most common (WHO ATC Class) of these were vitamins (15%), analgesics (12%), lipid-modifying agents (11%), psycholeptics (11%) and blood pressure medications (11%).

The most common reason for TN participants starting B/F/TAF was related to local treatment guidelines (82%) (Table S2). Among the TN group, the median (Q1, Q3) time from HIV diagnosis to B/F/TAF initiation was

TABLE 1 Baseline demographics of study participants.

	All ($N = 1509$)	TN ($N = 279$)	TE ($N = 1230$)
Sex[a] [*n* (%)]			
Male	1268 (84.0)	251 (90.0)	1017 (82.7)
Female	241 (16.0)	28 (10.0)	213 (17.3)
Age			
Median (Q1, Q3) (years)	47 (37, 55)	38 (30, 47)	49 (39, 56)
≥50 years [*n* (%)]	635 (42.1)	62 (22.2)	573 (46.6)
≥65 years [*n* (%)]	103 (6.8)	11 (3.9)	92 (7.5)
Median (Q1, Q3) weight (kg)	75.0 (65.0, 85.1)	70.0 (62.0, 81.0)	76.0 (66.0, 86.0)
Median (Q1, Q3) BMI (kg/m^2)	24.4 (22.0, 27.3)	22.8 (20.3, 25.4)	24.8 (22.4, 27.7)
Race/ethnicity [*n* (%)]			
White	1140 (75.5)	193 (69.2)	947 (77.0)
Black	196 (13.0)	23 (8.2)	173 (14.1)
Asian	93 (6.2)	44 (15.8)	49 (4.0)
American Indian/Alaska native	4 (0.3)	1 (0.4)	3 (0.2)
Other	55 (3.6)	11 (3.9)	44 (3.6)
Comorbidities[b] [*n* (%)]			
None	481 (31.9)	133 (48.0)	348 (28.3)
1	360 (23.9)	66 (23.8)	294 (23.9)
2	230 (15.3)	34 (12.3)	196 (15.9)
≥3	436 (28.9)	44 (15.9)	392 (31.9)
Most common			
Neuropsychiatric	324 (21.5)	33 (11.8)	291 (23.7)
Hyperlipidaemia	282 (18.7)	17 (6.1)	265 (21.5)
Hypertension	241 (16.0)	21 (7.5)	220 (17.9)
Musculoskeletal	161 (10.7)	7 (2.5)	154 (12.5)
Cardiovascular	115 (7.6)	13 (4.7)	102 (8.3)
HIV-1 RNA viral load			
Median (Q1, Q3) ($\log_{10}$ copies/mL)	1.59 (1.28, 1.90)	4.79 (4.07, 5.29)	1.59 (1.28, 1.59)
<50 copies/mL [*n* (%)]	999 (73.6)	3 (1.1)	996 (92.0)
>100 000 copies/mL [*n* (%)]	110 (8.1)	102 (37.1)	8 (0.7)
Median (Q1, Q3) CD4 count (cells/μL)[c]	598.5 (381.0, 816.0)	377.0 (194.0, 534.0)	667.0 (450.0, 876.0)
Median (Q1, Q3) CD4/CD8 ratio[d]	0.76 (0.46, 1.10)	0.36 (0.20, 0.60)	0.87 (0.59, 1.22)
Late HIV diagnosis [*n* (%)][e]			
CD4 <350 cells/μL[f]	-	128 (47.4)	-
CD4 <200 cells/μL[f]	-	74 (27.4)	-
Concomitant non-ART medications at baseline [*n* (%)][g]			
None	650 (45.1)	153 (58.4)	497 (42.2)
1	299 (20.8)	54 (20.6)	245 (20.8)
2	157 (10.9)	25 (9.5)	132 (11.2)
≥3	334 (23.2)	30 (11.5)	304 (25.8)
Median (Q1, Q3) number of previous ART regimens	-	-	2.0 (1.0, 4.0)

(Continues)

TABLE 1 (Continued)

	All ($N = 1509$)	TN ($N = 279$)	TE ($N = 1230$)
Prior ART regimens (taken just prior to B/F/TAF) (%)[h]			
INSTI	-	-	815 (66.3)
NNRTI	-	-	232 (18.9)
PI	-	-	193 (15.7)
TDF	-	-	397 (32.3)
TAF	-	-	621 (50.5)
History of prior virological failure [n (%)]	-	-	141 (11.5)
Time from HIV diagnosis to B/F/TAF initiation (days) [median (Q1, Q3)]	-	20.0 (9.0, 45.0)	-

Abbreviations: ART, antiretroviral treatment; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BMI, body mass index; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TE, treatment-experienced; TN, treatment-naïve.

[a]Sex was defined by the individual.

[b]Missing or unknown in two TN participants.

[c]Sample size: TN, $n = 267$; TE, $n = 1015$.

[d]Sample size: TN, 216; TE, 898.

[e]Missing in nine participants.

[f]And/or ≥1 AIDS-defining event at baseline.

[g]Missing in 17 TN and 52 TE participants.

[h]Sample size: 1230.

20 (9, 45) days. Three TN participants had HIV-1 RNA <50 copies/mL and 37% had a viral load of >100 000 copies/mL at baseline. A total of 47% of TN participants presented with a late diagnosis (CD4 count <350 cells/μL and/or ≥1 AIDS-defining event) and 27% presented with a CD4 count <200 cells/μL and/or one or more AIDS-defining event at baseline.

In TE participants, the main reasons for switching to B/F/TAF from previous regimens were to simplify ART (58%) and to avoid side effects of current ART (23%) (Table S2). Participants had received a median (Q1, Q3) of 2 (1, 4) prior ART regimens, and most (70%) had a history of prior TDF use. The most common ART regimens taken immediately before B/F/TAF were elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF; 27%), dolutegravir plus emtricitabine/tenofovir alafenamide (DTG + F/TAF; 8%) and abacavir/dolutegravir/lamivudine (ABC/DTG/3TC; 8%). In total, 92% of TE participants had undetectable viraemia at baseline and 12% ($n = 141$) had a history of prior virological failure. Of these, 41% (58/141) had a history of PRMs most commonly related to NRTI (33%; 47/141).

At baseline, 158/1509 (10%) participants [8% (21/279) TN, 11% (137/1230) TE] had evidence of one or more pre-existing PRM [NRTI, 6%; non-nucleoside reverse transcriptase inhibitor (NNRTI), 6%; protease inhibitor, 3%; INSTI, <1%] (Table S3). Of these, 49/158 (31%) had evidence of PRMs to two drug classes [19% (4/21) TN; 33% (45/137) TE]. The most frequently reported PRMs at baseline were M184V/I (TN 0%, TE 4%), K103N/S (TN 2%, TE 3%) and M46I/L (TN 0%, TE 1%).

Effectiveness at 12 months

At 12 months, high levels of effectiveness were observed in 94% (221/236; TN) and 97% (977/1008; TE) of participants with HIV-1 RNA <50 copies/mL (M=E analysis; Figure 1). Results were similar in the D=F analysis (TN, 90%; TE, 91%; Table S4). Among the 46 participants with HIV-1 RNA ≥50 copies/mL at 12 months (15 TN, 31 TE), 43 had low-level viraemia (14 TN, 29 TE), ranging from 50 to 400 copies/mL. In 33/43 (77%) participants with low-level viraemia, one or more viral load was <50 copies/mL prior to the 12-month time point. Post-baseline genotyping based on local clinical practice was reported for 20 participants at 12 months. There was no evidence of treatment-emergent resistance mutations to the components of B/F/TAF.

Rates of viral suppression were high (≥78%) across all the specific groups analysed at 12 months (M=E analysis; Table 2), including those with present or past evidence of PRMs at baseline (including M184V/I). However, there were small but statistically significant differences in rates of viral suppression in some groups, most notably in TN participants with very advanced HIV (CD4 <200 cells/μL

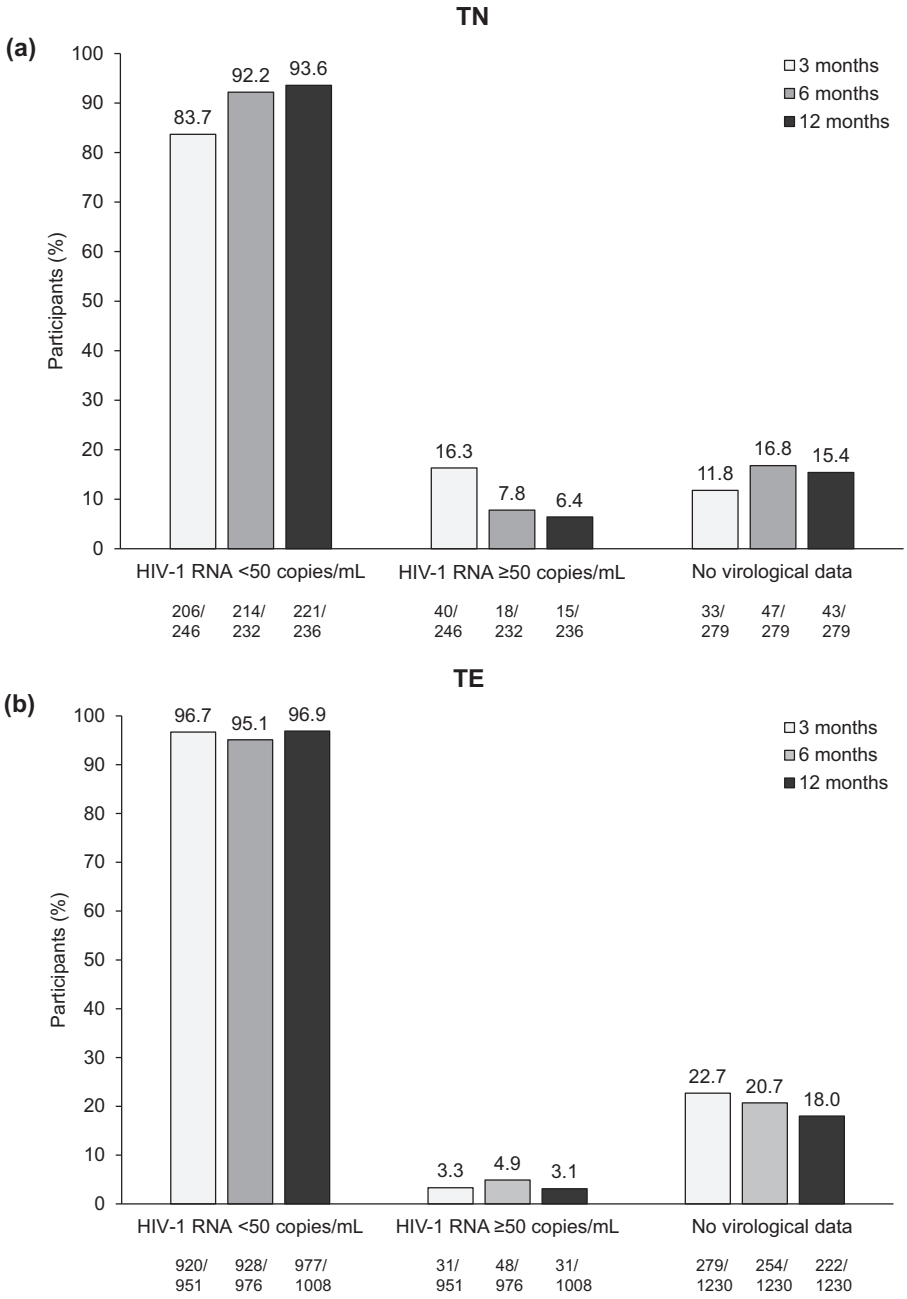

FIGURE 1 Effectiveness at 3, 6, and 12 months [missing-equals-excluded (M=E) analysis] in treatment-naïve (TN) participants (a) and treatment-experienced (TE) participants (b). Data were missing for 33 TN participants and 279 TE participants at 3 months, 47 TN participants and 254 TE participants at 6 months, and 43 TN participants and 222 TE participants at 12 months. Of the 15 TN participants with viral load ≥50 copies/mL at 12 months, nine had HIV-1 RNA >100 000 copies/mL at baseline and no participants had HIV-1 RNA >1000 copies/mL at 12 months. Of the 31 TE participants with viral load ≥50 copies/mL at 12 months, 8/28 had HIV-1 RNA ≥50 copies/mL at baseline (data were missing for three participants) and two participants had HIV-1 RNA >1000 copies/mL at 12 months.

and/or ≥1 AIDS-defining event at baseline), as compared with those without (86% vs. 96%; $p = 0.006$). Median baseline viral load in these participants was 5.29 (4.83, 5.90) and 4.59 (3.92, 5.09) $\log_{10}$ copies/mL, respectively, with baseline HIV-1 RNA >100 000 copies/mL in 67% of participants with very advanced HIV, compared with 27% without. Differences in rates of viral suppression were also seen between TE participants with a history of neuropsychiatric symptoms versus those without (95% vs. 98%; $p = 0.008$) and in TN participants with comorbidities versus those without (90% vs. 99% $p = 0.017$) (Table 2).

TABLE 2 Effectiveness (HIV-1 RNA <50 copies/mL) in specific populations at 12 months [missing-equals-excluded (M=E) analysis].

	TN ($N = 236$)	TE ($N = 1008$)
Sex [n/N (%)]		
Male	198/213 (93.0)	814/840 (96.9)
Female	23/23 (100)	163/168 (97.0)
p-value	0.373[a]	0.935[b]
Age [n/N (%)]		
<50 years	179/189 (94.7)	523/535 (97.8)
≥50 years	42/47 (89.4)	454/473 (96.0)
p-value	0.187[a]	0.104[b]
<65 years	213/228 (93.4)	908/934 (97.2)
≥65 years	8/8 (100)	69/74 (93.2)
p-value	1.000[a]	0.070[a]
Race [n/N (%)][c]		
Black	21/21 (100)	132/137 (96.4)
Other	196/210 (93.3)	833/859 (97.0)
p-value	0.623[a]	0.603[a]
Late HIV diagnosis [n/N (%)]		
CD4 <350 cells/μL[d]	97/107 (90.7)	-
CD4 ≥350 cells/μL	115/120 (95.8)	-
p-value	0.117[b]	-
CD4 <200 cells/μL[d]	53/62 (85.5)	-
CD4 ≥200 cells/μL	159/165 (96.4)	-
p-value	0.006[a]	-
History of neuropsychiatric symptoms at baseline [n/N (%)]		
Yes	29/32 (90.6)	262/277 (94.6)
No	192/204 (94.1)	715/731 (97.8)
p-value	0. 436[a]	0.008[b]
Any primary resistance mutations at baseline [n/N (%)]		
Yes	14/18 (77.8)	103/104 (99.0)
No	119/126 (94.4)	326/339 (96.2)
p-value	NA[e]	0.143[b]
M184V/I mutation at baseline [n/N (%)]		
Yes	-	46/47 (97.8)
No	-	446/461 (96.7)
p-value	-	1.00[a]
Comorbidities at baseline [n/N (%)][f]		
Yes	123/137 (89.8)	763/791 (96.5)
No	96/97 (99.0)	214/217 (98.6)
p-value	0.017[b]	0.103[b]

Note: Numbers correspond to those participants with available HIV-1 RNA data.
Abbreviations: ART, antiretroviral treatment; NA, not applicable; TE, treatment-experienced; TN, treatment-naïve.
[a]Calculated by Fisher's exact test for the null hypothesis of equal proportions in the two subgroups.
[b]Calculated by χ^2 test for the null hypothesis of equal proportions in the two subgroups.
[c]Race not available for five participants in the TN group and 12 participants in the TE group.
[d]And/or ≥1 AIDS-defining event at baseline.
[e]Not calculated because N <20 for one group.
[f]Medical history unknown for two participants in the TN group.

Immunological outcomes

Median CD4 counts increased by 214 cells/μL in TN and 13 cells/μL in TE participants ($p < 0.001$ and $p = 0.014$, respectively). Median CD4/CD8 ratios increased by 0.30 and 0.03 in TN and TE participants, respectively (both $p < 0.001$) (Table 3).

Persistence and study drug discontinuations

Persistence at 12 months was high, with 258/265 (97%) of TN participants and 1137/1201 (95%) of TE participants still receiving B/F/TAF. Discontinuation of B/F/TAF occurred in 9% (TN, 5%; TE, 10%) with the most frequent reason being an AE, affecting 88 (6%) participants (Table S5). For six TE participants, the reason given for discontinuing B/F/TAF prior to month 12 was 'lack of efficacy' (i.e. HIV-1 RNA ≥50 copies/mL; see Table S5 for details). None of these participants had evidence of emergent drug-resistance mutations.

Safety and tolerability

Overall, AEs occurred in 862/1509 (57%) of participants through 12 months (56% TN, 57% TE; Table 4). The most common AEs were body weight increase (5% of participants), nasopharyngitis (4%), diarrhoea (4%), arthralgia (3%), headache (3%), depression (2%) and fatigue (2%). In most participants (93% TN, 95% TE), these AEs were mild to moderate. Overall, 8% (9% TN, 7% TE) experienced SAEs.

Drug-related AEs occurred in 13% (195/1509) of participants through 12 months (13% TN; 13% TE). The majority (94%) of DRAEs were mild to moderate. The most common were body weight increase (3% of participants), headache (1%), depression (1%), nausea (1%) and fatigue (1%). DRAEs led to B/F/TAF discontinuation in 84 (6%) participants, most commonly weight gain, headache, depression and fatigue (2%, 1%, 1%, and 1% of participants, respectively). Two participants discontinued B/F/TAF due to drug-related renal impairment (TN, $n = 1$; TE, $n = 1$) and were switched to alternative ART (see Online Supplementary Information, page 17). Among 42 TE participants who reported a weight increase DRAE, 21 (50%) had been on either TDF or efavirenz immediately before initiating B/F/TAF, 9 (21%) had either a CD4 count <350 cells/μL or HIV-RNA >50 copies/mL at baseline, 9 (21%) were taking a co-medication known to be associated with weight gain, and 15 (36%) had a 12-month visit during the COVID-19 pandemic (Figure S2). Of the 12 drug-related cases of depression reported, 6 (50%) had an ongoing neuropsychiatric condition at B/F/TAF initiation.

TABLE 3 CD4 cell count and CD4/CD8 ratio (and categories) at 12 months.

	TN ($N = 279$)	TE ($N = 1230$)
CD4 cell count		
n	215	815
Baseline (cells/μL) [median (Q1, Q3)]	377.0 (179.0, 534.0)	670.0 (467.0, 870.0)
Change (cells/μL) [median (Q1, Q3)]	+214.0 (120.0, 380.0)	+13.0 (−84.0, 114.0)
p-value	<0.001	0.014
CD4/CD8 ratio		
n	179	720
Baseline, median (Q1, Q3)	0.39 (0.19, 0.60)	0.89 (0.60, 1.24)
Change, median (Q1, Q3)	+0.30 (0.16, 0.50)	+0.03 (−0.06, 0.15)
p-value	<0.001	<0.001
CD4/CD8 ratio (category)		
n	216	898
Baseline <0.9 [*n* (%)]	194 (89.8)	469 (52.2)
Baseline <0.9–1.9 [*n* (%)]	22 (10.2)	382 (42.5)
Baseline >1.9 [*n* (%)]	0	47 (5.2)
n	191	856
12 months, <0.9 [*n* (%)]	118 (61.8)	420 (49.1)
12 months, <0.9–1.9 [*n* (%)]	61 (31.9)	389 (45.4)
12 months, >1.9 [*n* (%)]	12 (6.3)	47 (5.5)

Note: *p*-values were calculated using the Sign test: to test for the null hypothesis that the median is equal to zero.
Abbreviations: Q, quartile; TE, treatment-experienced; TN, treatment-naïve.

There were no discontinuations due to hepatic or bone DRAEs. Two TE participants experienced a drug-related SAE. Both were episodes of depression (one severe and one life-threatening). Of these, one participant had ongoing depression at baseline and B/F/TAF was continued, while in the other participant, who had no evidence of neuropsychiatric symptoms at baseline, B/F/TAF was discontinued; both events resolved. By month 12, there had been 10 deaths, none of which were considered related to B/F/TAF (Table 4).

Statistically significant increases from baseline in body weight were seen in both TN and TE groups at month 12 (Table 5), with more weight gain observed in TN than in TE participants: median (Q1, Q3) of 3.0 (0.5, 8.0) kg and 1.0 (−1.0, 3.0) kg, respectively (both $p < 0.001$). Extreme weight gain (>10%) was observed in 27% of TN participants, compared with 5% in TE participants. Statistically significant increases in BMI were also observed in TN and TE participants.

Small but statistically significant increases from baseline were observed in some lipid parameters in the TN group (total cholesterol, LDL and HDL cholesterol; all $p \leq 0.001$) alongside significant reductions (total cholesterol, LDL and triglycerides) in the TE group (all $p < 0.05$) (Figure S3). However, changes in total cholesterol/HDL ratio were negligible and not statistically significant. Only 26 participants started lipid-lowering agents after B/F/TAF initiation. Small reductions in eGFR were observed from baseline to 12 months in both the TN and TE groups ($p < 0.001$) (Figure S4).

Statistically significant differences in the frequency of AEs were also observed according to sex and race (TE participants only), and presence of comorbidities at baseline and history of neuropsychiatric symptoms (both TN and TE participants) (Table S6).

Patient-reported outcomes: treatment satisfaction

Satisfaction with current ART was high among TE participants at baseline, with a median (Q1, Q3) total score of 56 (50, 60) out of 60 using the HIVTSQs, based on 1134 (92%) completed questionnaires (Table S7). Following the switch to B/F/TAF, further improvements in treatment satisfaction were observed at months 6 and 12 as indicated by the HIVTSQc, with a median (Q1, Q3) total change score of +24 (13, 29) at month 6 ($n = 628$), and +25 (12, 29) at month 12 ($n = 842$).

DISCUSSION

We report on the 12-month real-world effectiveness, persistence, safety and tolerability of B/F/TAF in routine clinical practice from an analysis of BICSTaR, an ongoing, multi-country, observational cohort programme in people with HIV.

The B/F/TAF regimen achieved high levels of viral suppression across all groups of people investigated (78–100% with HIV-1 RNA <50 copies/mL; M=E analysis). This supports previously published data from both randomized controlled trials (RCTs) and other real-world studies of B/F/TAF [23, 25, 28]. Baseline viral load was >100 000 copies/mL in two-thirds of TN participants with advanced HIV, which may have contributed to the observed difference in effectiveness in this group of people. Further, the high burden of other comorbidities, potentially leading to more co-medications, polypharmacy and drug–drug interactions, may have affected the

TABLE 4 Adverse events (AEs) reported through 12 months.

Summary of AEs [*n* (%)]	All (*N* = 1509)	TN (*N* = 279)	TE (*N* = 1230)
Any AE	862 (57.1)	156 (55.9)	706 (57.4)
Drug-related AEs	195 (12.9)	35 (12.5)	160 (13.0)
Any SAE[a]	117 (7.8)	26 (9.3)	91 (7.4)
Any drug-related SAE	2 (0.1)	0	2 (0.2)
Discontinued B/F/TAF due to drug-related AEs[b]	84 (5.6)	11 (3.9)	73 (5.9)
Deaths[c]	10 (0.7)	1 (0.4)	9 (0.7)
Most common drug-related AEs			
Weight increased	52 (3.4)[d,e]	10 (3.6)	42 (3.4)
Headache	18 (1.2)	4 (1.4)	14 (1.1)
Depression	12 (0.8)	1 (0.4)	11 (0.9)
Nausea	12 (0.8)	3 (1.1)	9 (0.7)
Fatigue	10 (0.7)	1 (0.4)	9 (0.7)

Abbreviations: BMI, body mass index; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; Q, quartile; SAE, serious adverse event; TE, treatment-experienced; TN, treatment-naïve.
[a]Seriousness criteria were: led to death, life threatening, initial/prolonged hospitalization, persistent or significant disability, or other significant medical event.
[b]Most common reasons for discontinuation (≥0.5% of all participants) include weight increased (1.7%), headache, (0.6%), depression (0.5%), fatigue (0.5%).
[c]Causes of death were: sepsis with multiorgan failure ($n = 1$), pulmonary insufficiency following trauma ($n = 1$), metastasis of the brain ($n = 1$), meningeosis carcinomatosa ($n = 1$), cardiorespiratory arrest ($n = 1$), heart failure ($n = 1$), pancreatic cancer ($n = 1$), and unknown ($n = 3$).
[d]Median (Q1, Q3) [min, max] baseline weight, 75.0 kg (64.9, 85.8) [45.0, 107.8]; and change in weight, +6.5 kg (5.0, 8.6) [−0.4, 33.0].
[e]Median (Q1, Q3) [min, max] baseline BMI, 24.0 kg/m^2 (22.2, 26.6) [17.6, 38.7]; and change in BMI, +1.9 kg/m^2 (1.6, 3.0) [−0.1, 11.0].

TABLE 5 Weight and BMI analyses at 12 months.[a]

	TN (*N* = 147)	TE (*N* = 685)
Weight		
Median baseline (Q1, Q3) (kg)	69.0 (61.0, 80.4)	75.3 (66.0, 86.0)
Min, max	41.7, 126.0	39.0, 153.0
Change from baseline		
Median (Q1, Q3) (kg)	3.0 (0.5, 8.0)	1.0 (−1.0, 3.0)
Min, max	−10.3, 42.0	−29.3, 26.0
p-value for change from baseline	<0.001	<0.001
>10% weight gain [*n* (%)]	39 (26.5)[b]	36 (5.3)[c]
>10% weight loss [*n* (%)]	1 (0.7)	16 (2.3)
BMI		
Median baseline (Q1, Q3) (kg)	22.4 (20.1, 25.4)	24.9 (22.5, 27.7)
Min, max	15.7, 46.1	16.4, 44.4
Change from baseline		
Median (Q1, Q3) (kg)	1.1 (0.1, 2.5)	0.3 (−0.4, 1.1)
Min, max	−3.6, 13.7	−10.0, 8.3
p-value for change from baseline	<0.001	<0.001

Note: *p*-values were calculated using the Sign test: to test for the null hypothesis that the median is equal to zero.
Abbreviations: BMI, body mass index; Q, quartile; TE, treatment-experienced; TN, treatment-naïve.
[a]Participants with weight and BMI available at baseline and 12 months.
[b]The majority of these participants were male (85%) and white (69%). Median age was 44 years. In total, 10% had diabetes mellitus at baseline and 5% were taking at least one concomitant medication related to weight increase at the time of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) initiation. Overall, 67% had CD4 count <350 cells/μL and ≥1 AIDS-defining event. Median HIV-1 RNA viral load was 4.98 $\log_{10}$ copies/mL and 54% had HIV-1 RNA >100 000 copies/mL at baseline. Median (Q1, Q3) [min, max] baseline weight: 65.4 kg (60.0, 71.3) [43.0, 98.0]; baseline BMI: 21.7 kg/m^2 (19.8, 23.5) [16.4, 29.9].
[c]Median (Q1, Q3) [min, max] baseline weight: 67.5 kg (58.0, 78.5) [50.0, 110.0]; baseline BMI: 23.0 kg/m^2 (20.7, 25.5) [17.5, 35.1].

ability of some people to take their medication, resulting in lower rates of viral suppression. A previous pooled analysis of the BICSTaR study suggested that people who have neuropsychiatric symptoms when starting treatment were less likely to have an undetectable viral load at 12 months [33]. Overall, our current findings add to the data supporting B/F/TAF as an effective option for a broad range of people, including those with late HIV diagnosis [27], women [34], older individuals [15, 28, 34, 35], people of black race [36], and those with evidence of pre-existing viral resistance (mainly M184V/I) [30, 37].

CD4 cell count and CD4/CD8 ratio were statistically significantly improved in TN participants and, to a lesser extent, in TE participants, consistent with the known benefits of ART [4, 11, 18, 20], indicating a shift towards restoration of immunological function.

Persistence with B/F/TAF was high in both TN and TE participants at 12 months. While interpretation of these findings is limited by only 12 months' follow-up, the results support findings from the US OPERA cohort, in which TN participants initiating B/F/TAF were less likely to discontinue or modify their regimen compared with other regimens [27]. There was no evidence of treatment-emergent resistance mutations to the components of B/F/TAF through 12 months. Also, people discontinuing treatment due to lack of efficacy was uncommon and only observed in TE participants.

The proportion of participants who experienced DRAEs was low (13%) and drug-related SAEs were rare (0.1%). The discontinuation rate due to DRAEs was 6% through 12 months, which was similar to rates reported from other real-world studies (2–5%) [26, 28, 38]. No people discontinued due to drug-related hepatic or bone AEs in this study, in line with previous clinical studies [15, 20]. The renal tolerability of B/F/TAF in the current study is consistent with other real-world data [25]. The observed reduction in eGFR at month 12, primarily in TN participants, was as expected, consistent with the known inhibitory effect of bictegravir (and other ARTs) on renal tubular secretion of creatinine, without affecting actual glomerular filtration rate [20].

Statistically significant changes from baseline in body weight and BMI were seen in both TN and TE participants. ART is associated with weight gain in TN individuals, which may, in part, reflect a return to health with weight returning to pre-HIV infection levels [39]. Typical average weight gains of 0.5–1 kg/year have been reported in western adult populations [40], and the median weight gain for TE participants in this study was similar. In TE individuals, switching from drugs that are associated with a weight-suppressant effect, such as TDF and efavirenz, may be associated with a higher risk of weight gain [41] and it is noteworthy that 70% of TE participants in this study switched from a TDF-containing regimen at baseline. Changes in physical activity and eating behaviour during the COVID-19 pandemic may also have led to greater weight gain [42]. Weight gain was the most common reason for people discontinuing treatment due to DRAEs, but only in <2% of the participants during the first 12-month observation period. As the study showed statistically significant increases in body weight and BMI in TN and TE participants, clinicians should monitor and counsel people on healthy lifestyle choices to manage potential weight gain during treatment. Finally, some small but statistically significant changes in lipid parameters were observed in TN and TE participants, with few participants initiating lipid-lowering agents. Overall, our safety and tolerability findings support the use of B/F/TAF in a broad population of people with HIV.

As with all observational cohort studies, there are limitations to our analyses, such as unmeasured confounding and bias due to the non-randomized nature of the study. The number of TN participants was relatively small, which could affect the generalizability of results for this group. Notably, the COVID-19 pandemic may have led to missing in-person visits, although no specific method was used to record these. In particular, there were missing data for some outcome measures in approximately 50% of participants. For the primary endpoint, there was a relatively small (8%) decrease in participants with available viral load data at 12 months. The observation period for evaluation of persistence, safety and tolerability was relatively short; however, the BICSTaR study is ongoing and will eventually provide longer-term data through 5 years of follow-up. The study has several strengths. For example, it is a large, multicentre cohort that is representative of the current population of people with HIV in routine clinical care across multiple countries. The prospective study design with standardized data collection through use of a common protocol enabled data to be pooled across a more diverse population than those studied in RCTs.

CONCLUSION

The B/F/TAF regimen demonstrated high levels of effectiveness and was generally well tolerated in a broad population of people with HIV in routine clinical care. Data were consistent with the known safety profile of B/F/TAF established through RCTs and observed in other cohort studies, with no new or unexpected safety findings. The study will continue through 24 months for the full BICSTaR cohort with an additional 36-month extension in Canada, France and Germany.

AUTHOR CONTRIBUTIONS

SE, JB, IL, AD'AM, JSL, BvW, KT, AI, MB, C-EL, OAA and OR contributed to participant accrual, clinical care and data recording; DT, MH, MB, TC, LD and RH contributed to trial management, data collection, data analysis or interpretation; MH and RH contributed to study design. All authors reviewed and critically revised the manuscript, approved the final draft and agree to be accountable for the manuscript's accuracy and integrity.

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CONFLICT OF INTEREST STATEMENT

SE participated in advisory boards for Gilead, GSK, Janssen, MSD, ViiV Healthcare, and Theratechnologies; received honoraria from AbbVie, Gilead, Janssen, MSD and ViiV; received research funding from Gilead, Janssen, MSD and ViiV; and travel expenses from Gilead, Janssen, MSD and ViiV Healthcare. JB has acted as consultant/advisor for, and is a recipient of conference sponsorship and speaker fees from, Gilead Canada; as advisor for ViiV Healthcare Canada and Merck Canada. AI received research funding from Gilead, Janssen and GSK, and participated on advisory boards for Almirall, Pfizer, AbbVie and Bayer. All fees were paid to the institution. IL has acted as consultant/advisor for Gilead, GSK and MSD; offered expert testimony for GSK; and received grants from Gilead and payment for lectures from GSK, Gilead, MSD and Pfizer. AD'AM participated in advisory boards for Gilead, Janssen, MSD, Pfizer, ViiV; received honoraria from Gilead, ViiV; and received research funding from Gilead, Janssen, MSD and ViiV. JSL has received an honorarium for a presentation/workshop supported by ViiV GSK. BvW participated in advisory boards for Gilead and ViiV Healthcare; received honoraria from Gilead and ViiV Healthcare; and received research funding from Gilead. All fees were paid to the institution. KT received payment for lectures from Shionogi Pharmaceuticals. MB has received speaker and advisor fees and/or research grants (to her organization) from GSK, ViiV Healthcare, Pfizer, Roche, Novavax, Valneva, Moderna, Gilead, Mylan, Cipla, Janssen and MSD. C-EL has nothing to disclose. OAA participated in advisory boards for Gilead and GSK; received conference sponsorship and speaker fees from AbbVie, Gilead, MSD and GSK; and received research funding from Gilead and GSK. All fees were paid to the institution. OR has acted as consultant/advisor for Gilead Sciences, MSD and ViiV Healthcare. DT is an employee of Gilead and owns shares in Gilead. MH is a employee of Gilead and owns shares in Gilead. AM is an employee of Gilead and owns shares in Gilead. TC is an employee of Gilead and owns shares in Gilead. RH is an employee of Gilead and owns shares in Gilead. LD'A is an employee of Gilead and owns shares in Gilead.

DATA AVAILABILITY STATEMENT

Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non-conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Sciences' discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

ETHICS STATEMENT

The protocol was approved by the independent ethics committee at each centre, and the study was conducted following Ethical Guidelines for Medical and Health Research Involving Human Subjects. Participants provided signed informed consent.

STUDY REGISTRATION

Canada cohort: NCT03580668. Israel cohort: NCT04009057. European cohort: EUPAS22185. Japan cohort: none. Asia cohort: none.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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