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Effectiveness, Safety and Patient-Reported Outcomes (Pros) of Once-Daily Single-Tablet Regimen of Bictegravir/Emtricitabine/Tenofovir Alafenamide for the Treatment of People with HIV in Routine Clinical Care in Italy: 24-Month Results from the Bicstar Cohort

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Abstract

Background: BICSTaR is a multi-national cohort study to evaluate effectiveness, safety, and patient-reported outcomes (PROs) in treatment-naïve (TN) and treatment-experienced (TE) people with HIV (PWH) receiving bictegravir/emtricitabine/tenofovir (B/F/TAF) in routine clinical care.

Methods: PWH initiating B/F/TAF were prospectively followed until month 24 (M24). Outcomes of interest included: virological effectiveness (HIV-1 RNA <50 copies/mL; missing/discontinuation/loss-to-follow-up=excluded [M=E] and discontinuation=failure [D=F] analyses), immunological changes, drug-related adverse events (DRAEs), Treatment persistence, body weight, and PROs (HIV-symptom index and treatment satisfaction).

Results: 205 PWH (29 TN, 176 TE) were eligible for M24-analysis (82% male, 96% white, median age 38 years in TN, 48 years in TE). Median CD4 cell count was 225/μL in TN, 724/μL in TE. At baseline, 94% of TE had HIV-1 <50 copies/mL, 92% switched to B/F/TAF to optimize therapy. In M=E analysis, 96% [24/25] of TN and 97% [144/148] of TE had <50 HIV-1 RNA copies/mL at M24. In D=F analysis, rates were 92% (24/26) in TN, 92% (144/156) in TE.

Median CD4 changes at M24 were +411/μL in TN, +47/μL in TE. DRAEs were reported for 6%, leading to discontinuation in 2%. HIV-symptom index decreased in TN (median (interquartile range, IQR) -3 (-5, 0)), and remained stable in TE. Median treatment satisfaction changes score (IQR) at M12 was +28 (21, 30) in TE.

Conclusions: B/F/TAF was well-tolerated and demonstrated high effectiveness and persistence over 24 months in this Italian routine clinical care cohort of PWH. B/F/TAF users reported a stable or decreased HIV-symptom burden and an increase in treatment satisfaction.

Keywords: Hiv-Infection; Antiretroviral Therapy; Bictegravir; Real-World Data; Patient-Reported Outcomes

Introduction

Antiretroviral therapy (ART) has significantly improved life expectancy and is associated with the maintenance of health in people with the human immunodeficiency virus (HIV). Due to these advantages, along with the reduction in transmission risk, it is recommended to initiate ART as soon as HIV infection is diagnosed, if feasible [1]. Considering that treatment is likely life-long, drug regimens should be effective with a low risk of resistance development, convenient to take, well tolerated, and with minimal potential for food and drug interactions [1]. As the population ages, interactions between ART and co-morbidities and their treatment, as well as polypharmacy, have become increasingly important [2–4].

Recommended initial ART regimens include one or two nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and either an integrase strand transfer inhibitor (INSTI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). The INSTI bictegravir (BIC; B) combined and co-formulated with the NRTIs tenofovir alafenamide (TAF) and emtricitabine (FTC; F) is among recommended regimens for initial ART [1]. Additionally, B/F/TAF has a role in switch strategies for virologically suppressed persons and in certain cases of virologic failure with only limited NRTI mutation(s) [1]. Non-inferiority, safety, and tolerability of B/F/TAF without development of resistance-associated mutations was demonstrated in phase 3 studies as initial treatment when compared to INSTI (dolutegravir)-based regimens and when switched from a boosted protease inhibitor in virally suppressed individuals [5–9]. Clinical trials have demonstrated the efficacy, tolerability, and high resistance barrier of B/F/TAF in both treatment-naïve (TN) and -experienced (TE) people living with HIV [10–13]. Long-term re-

al-world data, however, are limited [14–16].

The BICSTaR (Bictegravir Single Tablet Regimen) cohort study is a multinational, prospective, observational study with the aim to evaluate the effectiveness, safety, adherence, and self-reported quality of life in 2,379 TN and TE people with HIV-1 from Europe, Asia, Canada, Israel, and Japan receiving B/F/TAF in routine clinical care. Both twelve- and 24-month global data as well as the twelve--month Italian data have been published [17–19]. We present the final month 24 results from the Italian cohort of people living with HIV receiving B/F/TAF with additional emphasis on patient-reported outcomes (PROs).

Methods

Study Design and Study Population

BICSTaR (GS-EU-380-4472) is a prospective, two-year, multinational, observational, non-interventional cohort study in adult TN and TE people with HIV receiving B/F/TAF after June 2018 (extended to 5 years in Canada, France, and Germany). Participating countries are France, Germany, Ireland, Italy, the Netherlands, Spain, UK, Turkey, Taiwan, South Korea, Singapore, Japan, Canada, and Israel. Adult participants could be enrolled into this study after the physician had independently decided to treat with B/F/TAF in accordance with the approved indication label and with the participants' written informed consent. The detailed methodology has been previously published [18]. This month 24 analysis of the Italian BICSTaR cohort was a post-hoc subgroup analysis of all enrolled individuals with at least one follow-up visit.

Study Endpoints

The primary endpoint of BICSTaR was the proportion of participants in the overall cohort with viral suppression 12 months after initiating B/F/TAF. Secondary endpoints of the study included viral suppression at month 24, change in CD4 cell count and CD4/CD8 cell ratio from baseline to month 24, resistance post baseline, and the cumulative incidence of drug-related adverse events (DRAEs) and drug-related serious adverse events (DRSAEs) at month 24.

Patient-reported outcomes focused on physical and mental health status (SF-36, not part of evaluation), symptom distress (i.e. HIV Symptom Index, HIV-SI), and treatment satisfaction (using the HIV treatment satisfaction questionnaire, HIVTSQ; only applied at month 12).

Additional factors for evaluation were reasons for switching to B/F/TAF (TE participants), self-reported adherence to prior ART as determined by visual analogue scale (VAS) at baseline, persistence on B/F/TAF and reasons for any discontinuations, metabolic assessment (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL] and triglycerides), renal assessment (creatinine and estimated glomerular filtration rate [eGFR]), weight and body mass index (BMI).

Outcome Measures

HIV-1 RNA suppression was defined as plasma HIV-1 RNA level <50 copies/mL Analyses used missing=excluded (M=E) and discontinuation=failure (D=F) approaches (using only HIV-1 RNA data collected during the observation period while On study treatment). The M=E analysis only included participants with at least one HIV-1 RNA value within the 24-month visit window. The D=F analysis also considered those who had discontinued B/F/TAF before the 24-month visit window and imputed these with an HIV-1 RNA value of ≥50 copies/mL. Data from participants who discontinued B/F/TAF during the 24-month visit window were not imputed for the D=F analysis.

Safety outcomes included frequency of reported adverse events or serious adverse events related or potentially related to B/F/TAF as well as changes in body weight and change in laboratory parameters. All medical events were coded using MedDRA (Medical Dictionary for Regulatory Activities) SOC (systems organ classes) and preferred terms (PT).

Standardized questionnaires were used to evaluate self-reported HIV symptom burden and treatment satisfaction. Twenty dichotomized items of HIV-SI (HIV Symptom Index) were used to rank symptoms associated with HIV infection into "not bothersome" (includes "I do not have this symptom") and "bothersome" within a recall period of the past four weeks. The total score ranged from 0 to 20, with higher scores indicating more bothersome symptoms [20].

The HIV Treatment Satisfaction Questionnaire encompassed both a status (HIVTSQs) as well as a change (HIVTSQc) version with ten items each. HIVTSQs scores ranged from 0 to 60 with higher scores indicating greater treatment satisfaction. During study follow-up the HIVTSQc score, ranging from -30 to +30, provided insight into how treatment satisfaction changed from baseline. A positive score indicates an improvement in treatment satisfaction [21-22].

The eGFR was calculated using the Cockcroft--Gault formula [23].

Statistical Analysis

All analyses were carried out for the full analysis set and stratified by TN or TE participants. Numbers and percentages of participants were reported for categorical variables. Data of continuous variables are expressed as median (with an interquartile range [IQR] of Q1 and Q3) if not otherwise specified. Testing for statistical significance using two-sided p-values and/or 95% confidence intervals (CIs) was only performed for explorative reasons, i.e. when considered relevant (andonly in case of ≥20 observations). To account for multiple testing, Bonferroni correction was applied. The alpha level for statistical testing was <0.05. The analyses were performed in a descriptive manner based on observed data using the software package SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Regulatory Requirements, Ethics and Quality Control

Approval of the ethics committees and competent authorities was obtained prior to study initiation according to the local regulations in Italy. All participants provided written informed consent prior to study enrolment and following the physician's independent decision to treat with B/F/TAF. Quality control of data entries in the electronic case report forms involved programmed plausibility checks, electronic queries and remote monitoring.

Results

Study Population

Between December 2019 and July 2021, 213 people with HIV were enrolled in ten HIV-specialized centers in Italy. Of these, eight were excluded due to missing follow- up data after enrolment, leaving a study population of 205 (29 TN, 176 TE participants). Baseline characteristics are shown in Table 1. The cohort was predominantly male (n=169 [82%]) and white (n=196 [96%]). TE participants were older than TN participants (median [Q1, Q3] 48 years [38, 56]) vs. 38 years [33, 56] and with a greater proportion being at least 50 years of age (81 [46%] TE vs. 9 [31%] TN). CDC stage C (clinical acquired immunodeficiency syndrome, AIDS) was documented for 9 (31%) TN and 32 (19%) TE participants.

At baseline, 138 (94%) TE participants presented with viral suppression. In the TN group, median (Q1, Q3) HIV-1 RNA level was 5.3 log10 copies/mL (4.9, 5.8). Median (Q1, Q3) CD4 cell counts at baseline were 225 (49, 452) cells/µl for TN and 724 (542, 927) cells/µL for TE participants; CD4/CD8 ratios were 0.27 (0.08, 0.60) and 0.90 (0.60, 1.30), respectively (Table 1).

Antiretroviral Treatment History and Reason for B/F/TAF Initiation

All TN participants-initiated B/F/TAF according to guidelines. Three (10%) additionally had used treatment as prevention.

Antiretroviral treatment history was available for 174 out of the 176 TE participants. Prior to switching to B/F/TAF, TE participants were treated with a median (Q1, Q3) of 3 (2, 5) ART regimens. Twenty-six (15%) TE participants had one previous regimen, 52 (30%) had two, and 35 (20%) three previous regimens. Among the 174 TE with a known ART history, 119 (69%) TE participants had been exposed to INSTIs, 97 (56%) to PIs, 66 (38%) to NNRTIs, and 170 (98%) to NRTI. More than three-quarters (n=138, 79%) had received a regimen in the past which included TDF; 142 (81%) were on F/TAF at the time of switch. A history of virological failure on any regimen was documented for 24 (14%) TE participants. The most common regimen immediately prior to B/F/TAF was elvitegravir/cobicistat/F/TAF (n=83 [47%]), followed by darunavir+F/TAF (n=18 [10%]) and dolutegravir/F/TAF (n=16 [9%]) (Figure 1).

Table 1: Baseline Characteristics and Comorbidities/Comedications

	All (N=205)	TN (N=29)	TE (N=176)
Demographics			
Male sex, n (%)	169 (82)	24 (83)	145 (82)
Female sex, n (%)	36 (18)	5 (17)	31 (18)
Age, years, median (Q1, Q3)	47 (37, 56)	38 (33, 56)	48 (38, 56)
Age ≥50 years, n (%)	90 (44)	9 (31)	81 (46)
Weight, kg, median (Q1, Q3)	75 (66, 85)	75 (65, 85)	75 (66, 85)
White, n (%)	196 (96)	28 (97)	168 (95)
HIV-related characteristics			
Number of previous ART regimens, median (Q1, Q3)		—	3 (2, 5)
Time from HIV diagnosis to B/F/TAF start, days, median (Q1, Q3)		22 (15, 38)	—
HIV-1 RNA, log10 cp/mL, median (Q1,Q3)	1.3 (1.3,1.3)	5.3 (4.9,5.8)	1.3 (1.3,1.3)
HIV-1 RNA >100,000 cp/mL, n/N (%)		19/29 (66)	1/147 (1)
HIV-1 RNA <50 cp/mL, n/N (%)		0	138/147 (94)
CD4 count, cells/μL, median (Q1, Q3)	655 (425,874)	225 (49,452)	724 (542927)
CD4/CD8 ratio, median (Q1, Q3)	0.78 (0.5, 1.2)	0.27 (0.1, 0.6)	0.9 (0.6, 1.3)
CDC Stage C (AIDS), n/N (%)	41/197 (21)	9/29 (31)	32/168 (19)
History of virological failure, n/N (%)	41/197 (21)	—	24/168 (14)
Ongoing comorbidities/comedication, n (%)			
Any comorbidity	147 (72)	17 (59)	130 (74)
None	58 (28)	12 (41)	46 (26)
1–2	80 (39)	10 (34)	70 (40)
≥3	67 (33)	7 (24)	60 (34)
Category (in ≥10% participants)			
Hyperlipidemia	58 (28)	1 (3)	57 (32)
Hypertension	37 (18)	3 (10)	34 (19)
Osteopathic disorder	29 (14)	1 (3)	28 (16)
Neuropsychiatric disorder	25 (12)	0	25 (14)
Cardiovascular illness	20 (10)	1 (3)	19 (11)
Any comedication, n/N (%)	106/191 (55)	16/28 (57)	90/163 (55)

Percentages are reported as n over the total TN or TE population (data as observed), unless specifically reported as n/N. cp/mL, copies/mL; Q1, quartile 1; Q3, quartile 3; TE, treatment experienced; TN, treatment-naïve

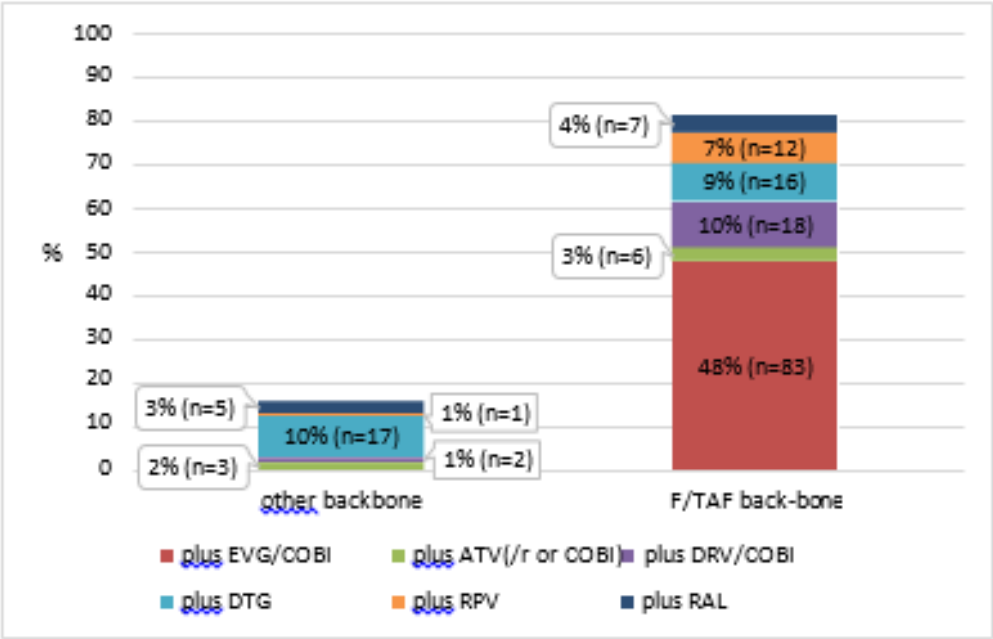

Figure 1: ART regimens immediately prior to B/F/TAF (n=175)

ATV, atazanavir; B, bictegravir; COBI, cobicistat; DTG, dolutegravir; DRV, darunavir; EVG, elvitegravir; F, emtricitabine; r, ritonavir as booster; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; 5 participants not assignable (e.g. DRV/RTV), 1 missing data

Most TE participants stated simplification to optimize therapy of ART as a reason for switching to B/F/TAF (n=162 [92%]); side effects on the previous ART were documented as a reason for 6 (3%) TE participants. Using a visual analogue scale as a measure of adherence to the ART regimen just prior to B/F/TAF, 118/139 (85%) self-reported >95% adherence, while 133/139 (96%) reported >80% adherence.

HIV Drug Resistance at Baseline and During Follow-Up

At baseline, results from historical resistance testing was available for 21 TN and 118 TE participants. Primary resistance mutations were detected in 29 participants: 4 TN (4 associated with NNRTIs) and 25 TE (14 associated with NNRTI, 10 with protease inhibitors [PIs], 16 with NRTI, 1 with INSTIs). Eleven (6%) TE participants carried the M184V mutation; the INSTI mutation was T97A.

During follow up, resistance testing was performed in four participants (without discontinuation due to virological failure) with no emergent B/F/TAF-specific resistance-associated mutations.

Comorbidities and Comedication

At baseline, 147 (72%) participants had comorbidities or co-infections (17 [59%] TN, 130 [74%] TE) (Table 1). Most common comorbidities were hyperlipidemia (n=58 [28%]), hypertension (n=37 [18%]), bone disorder (n=29 [14%]) and neuropsychiatric disorders (n=25 [12%]) (Table 1). Co-infections included 11 cases of chronic hepatitis B and 18 of chronic hepatitis C.

More than half of participants (106/191 [55%]; 16/28 [57%] TN, 90/163 [55%] TE) were receiving concomitant medication/supplements at baseline. Most common were vitamins (n=42 [20%]). Use of concomitant medications by >10% of the following drug classes was observed: 30 (15%) participants used agents acting on the renin-angiotensin system, 27 (13%) analgesics, and 27 (13%) lipid--modifying agents. These rates were primarily driven by the TE group (28 [16%] agents acting on the renin-angiotensin system, 25 [14%] analgesics, and 27 [15%] lipid-modifying agents).

Treatment Persistence and Discontinuations

In 14 cases (1 TN, 13 TE), B/F/TAF was discontinued after a median (Q1, Q3) time of treatment of 17.8 (7.3, 18.7) months (Figures 2a, 2b). Reasons (one was missing) were participant's decision (2), investigator's decision (3), new treatment available (2), death (1) and drug-related adverse events (5). There was no treatment discontinuation due to virological failure.

Virologic Outcomes

At month 24, 97% of participants remaining on B/F/TAF and in the study (M=E analysis; n=168/173) had an HIV-1 RNA of <50 copies/mL (96% [24/25] TN, 97% [144/148] TE) (Figure 2). According to the D=F analysis at month 24, 92% (24/26) of TN and 92% (144/156) of TE participants had an HIV-1 RNA of <50 copies/ml (3 TN and 20 TE participants had missing data at month 24). (Figures 2a, 2b) Of note, all TE participants with data available (8/8) with detectable viral load at baseline had reached viral suppression after 6 months of B/F/TAF; viral suppression was maintained in 5/6 (83%) after 24 months.

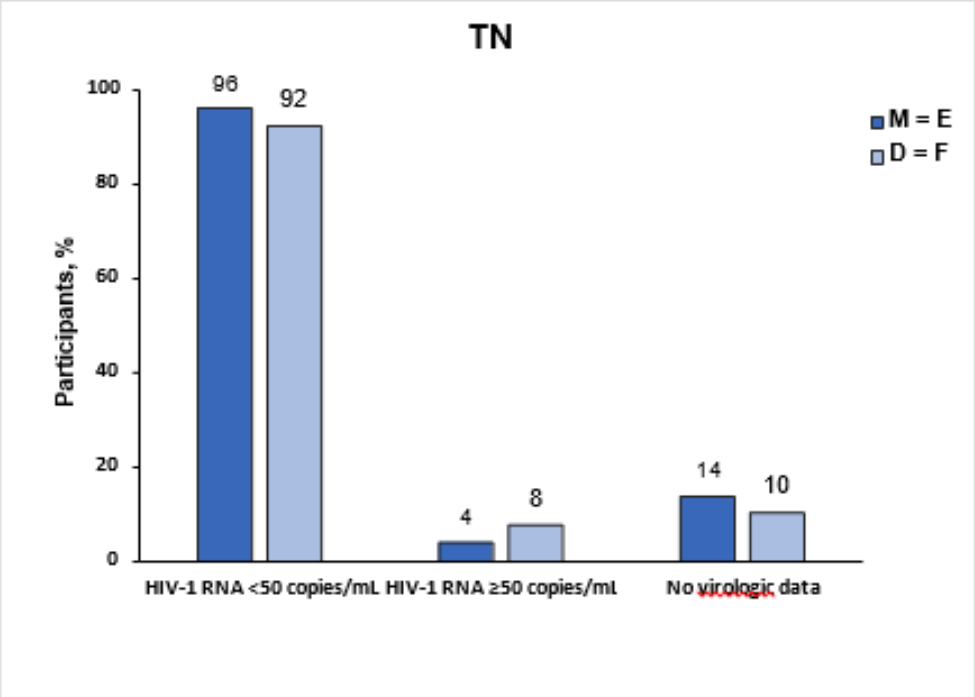

Figure 2a: Virologic outcomes in TN participants (N=29); M=E and D=F analyses

TN, treatment-naïve; M=E (missing=excluded) analysis: only values available within the time window of month 24 (M24) were included in the analysis. In the D=F (discontinuation=failure) analysis, B/F/TAF discontinuations before start of M24 window were imputed as HIV-1 RNA ≥50 copies/mL (M24 window: 18 to 30 months)

Immunologic Outcomes

After 24 months, median (Q1, Q3) absolute CD4 cell counts had increased to 748 cells/µl (568, 935) (n=163) (TN [n=20]: 671 cells/µl [519, 899]; TE [n=142]: 758 cells/µl [568, 948]). The median (Q1, Q3) absolute CD4 change from baseline in participants remaining on B/F/TAF with baseline and month 24 data available (n=135) was +71 cells/µl (-53, +187) (TN [n=20]: +411 cells/µl [202, 589]; TE [n=115]: +47 cells/µl [-98, +135]). The median (Q1, Q3) relative CD4 changes were +9% overall (-7, +42) (TN: +120% [+64, +774]; TE: +6% [-13, +23]).

After 24 months, the median (Q1, Q3) CD4/CD8 ratio had increased to +0.4 (+0.2, +0.9) in TN (n=19) and remained stable by +0.2 (-0.1, +0.2) in TE (n=110).

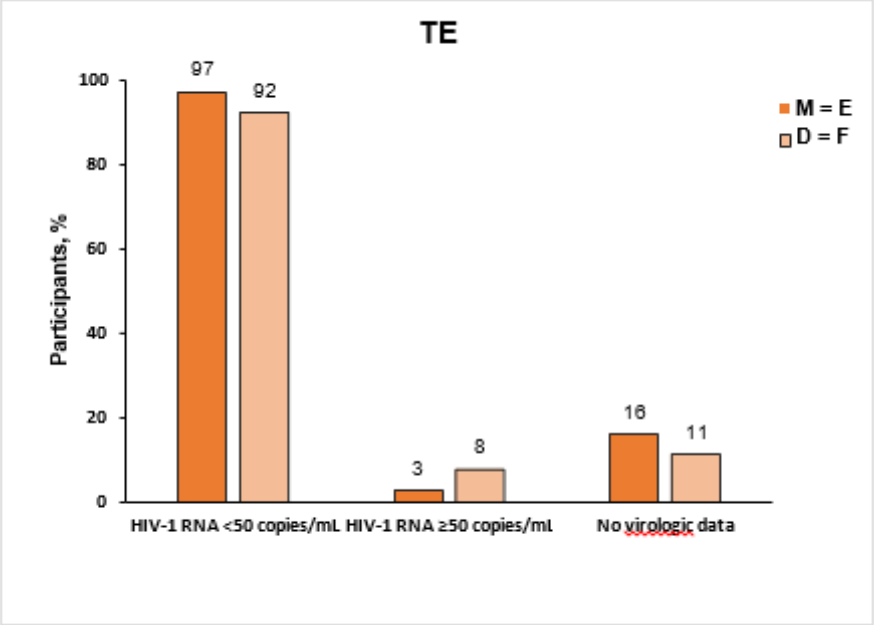

Figure 2b: Virologic outcomes in TE participants (N=176); M=E and D=F analyses

TE, treatment experienced; M=E (missing=excluded) analysis: only values available within the time window of month 24 (M24) were included in the analysis. In the D=F (discontinuation=failure) analysis, B/F/TAF discontinuations before start of M24 window were imputed as HIV-1 RNA ≥50 copies/mL (M24 window: 18 to 30 months)

Safety

Within the 24-month observation period, AEs were reported by 106/205 (52%) of participants. Thirteen individuals (6%) had AEs related to B/F/TAF, primarily gastrointestinal and psychiatric/neurologic, one of which was defined as severe.

DRAEs are outlined in Table 2. B/F/TAF-related AEs led to 5 (2.4%) drug discontinuations. All these were in the TE group aside from a hypersensitivity reaction in one TN person. Most common reactions leading to discontinuation were psychiatric disorders (5 events in 3 participants). There were no discontinuations due to renal adverse events related to B/F/TAF.

Patient-Reported Outcomes (Pros)

HIV-Symptom burden: HIV-SI

Of the 29 TN and 176 TE, a respective 17 (59%) and 117 (66%) people with HIV responded to the HIV-SI questionnaire both at baseline and at month 24. At baseline, median (Q1, Q3) bothersome counts were 6 (4, 7) in TN and 3 (1, 5) in TE participants. At month 24, the median (Q1, Q3) change in bothersome symptoms was -3 (-5, 0) for TN and 0.0 (-2, +1, p=0.560 signed rank test) for TE participants.

Treatment satisfaction: HIVTSQ in TE

Response rates of TE to the HIVTSQs were 162/176 (92%) at baseline and 118/176 (67%) at month 24. The median (Q1, Q3) treatment satisfaction status score (HIVTSQs, range 0 to 60) for TE was 57.5 (51.0, 60.0) at baseline and 58.0 (54.0, 60.0) at month 24. The median treatment satisfaction change score (HIVTSQc, range-30 to 30) at M12 was 28 (21.0, 30.0), with a range of -24 to +30 (in 124/176 TE); HIVTSQc data were not collected at month 24.

In a sub-analysis of TE participants with an ongoing neuropsychiatric disorder at baseline (n=25) compared to those TE without such a disorder (n=151) and who had responded to the HIVTSQs questionnaire (20/25 vs. 144/151), it was found that those with the disorder were statistically significantly less satisfied with their current treatment (median score [IQR] 5 [4, 6] vs.6 [5, 6], p=0.005) and felt their HIV infection was less controlled (5 [5, 6] vs. 6 [6,

6], p<0,001). There were no significant differences in the other eight items.

Laboratory Parameters

Small but statistically significant changes from baseline in the lipid profile and renal function were detected at month 24. While total cholesterol increased in TN, it decreased in TE along with LDL and triglycerides, however TC/HDL ratio remained unchanged (Table 3).

Table 2: B/F/TAF-related adverse events (DRAEs)

DRAE, SOC: PT (n>1)	**Participants**[a] **(N=205)**	**Events (n=21)**
Psychiatric disorders	**5 (2.4%)**	**7**
Anxiety	2 (1.0%)	2
Insomnia	2 (1.0%)	2
Affect lability	1 (0.5%)	1
Depression	1 (0.5%)	1
Loss of libido	1 (0.5%)	1
Gastrointestinal disorders	**5 (2.4%)**	**5**
Abdominal distension	1 (0.5%)	1
Diarrhoea	1 (0.5%)	1
Nausea	1 (0.5%)	1
Tongue disorder	1 (0.5%)	1
Vomiting	1 (0.5%)	1
Nervous system disorders	**4 (2.0%)**	**5**
Amnesia	1 (0.5%)	1
Headache	1 (0.5%)	1
Hypersomnia	1 (0.5%)	1
Paraesthesia	1 (0.5%)	1
Somnolence	1 (0.5%)	1
Skin and subcutaneous tissue disorders	**2 (1.0%)**	**2**
Alopecia	1 (0.5%)	1
Hyperhidrosis	1 (0.5%)	1
General disorders	**1 (0.5%)**	**1**
Fatigue	1 (0.5%)	1
Immune system disorders	**1 (0.5%)**	**1**
Hypersensitivity	1 (0.5%)	1
Investigations	**1 (0.5%)**	**1**
Weight increased	1 (0.5%)	1

[a] if several events with the same preferred term were reported for the same participant, s/he is counted once for that term; the same rule applies for results by system organ class. All events experienced within 913 days (= upper bound of the 24-month time window) after B/F/TAF initiation and up to 30 days after B/F/TAF discontinuation were considered. B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DRAE, drug-related adverse events; PT, preferred term; SOC, system organ class

Table 3: Change in laboratory parameters from baseline to month 24

	TN				TE			
	na	**baseline median (Q1, Q3)**	**change at M24 median (Q1, Q3)**	**p- value[b]**	**na**	**baseline median (Q1, Q3)**	**change at M24 median (Q1, Q3)**	**p- value[b]**
Total cholesterol (TC) (mmol/L)	21	3.91 (3.16, 4.35)	0.28 (+0.08, +1.04)	p=0.007	121	5.02 (4.40, 5.44)	-0.26 (-0.75, +0.28)	p=0.002
LDL (mmol/L)	15	2.23 (1.81, 2.82)	0.34 (+0.03, +1.01)	n/a	78	3.12 (2.69, 3.81)	-0.12 (-0.54, +0.36)	p=0.040
HDL (mmol/L)	19	0.91 (0.73, 1.19)	0.18 (+0.08, +0.36)	n/a	111	1.19 (1.01, 1.48)	-0.05 (-0.18, +0.08)	p=0.064
Triglycerides (mmol/L)	21	0.86 (0.72, 1.50)	0.06 (-0.44, +0.18)	p=0.933	116	1.27 (0.97, 1.73)	-0.11 (-0.42, +0.19)	p=0.016
TC/HDL ratio	19	4.08 (3.41, 4.71)	-0.26 (-1.05, -0.00)	n/a	111	4 (3.32, 4.83)	-0.02 (-0.46, +0.40)	p=0.793
Creatinine (µmol/L)	25	76.02 (61.88, 81.33)	11.49 (+2.65, +15.91)	p<0.001	124	79.56 (70.72, 91.94)	3.54 (-2.65, +9.72)	p<0.001
eGFR (ml/min/1.73 m^2)	21	123.24 (103.61, 162.01)	-15.17 (-24.47, -5.79)	p=0.007	93	106.05 (85.08, 127.16)	-5.78 (-16.68, +1.90)	p=0.002

[a] participants with data available at baseline and M24; [b] student's t-test or signed rank test as appropriate, bold and italic font: p<0.05; Abbreviations: HDL, high- density lipoprotein; LDL, low-density lipoprotein; M24, month 24; Q1, quartile 1; Q3 quartile 3; TE, treatment experienced; TN, treatment-naïve

Other laboratory parameters, including glucose, alanine and aspartate aminotransferase, bilirubin, albumin, and phosphorus, did not show statistically or clinically significant changes (data not shown).

Body Weight and BMI Changes

Body weight and BMI change throughout the course of the observation period were assessed for 131/205 (21/29 TN, 110/176 TE) participants remaining on B/F/TAF and with data available at baseline and at month 24. At baseline, the median (Q1, Q3) weight was 76 kg (70, 85) in the TN, and 76 kg (66, 82) in the TE groups. At month 24, the median absolute weight change among TN participants was +4.0 kg (-0.5, +7.0), while the absolute BMI change was +1.4% (-0.1, +2.1; p=0.115). The median absolute weight change in the TE group was +0.3 kg (-3.0, +3.0), while absolute BMI change was +0.1% (-0,9, +1,0; p=0.426).

By month 24, 11/21 (52%) TN compared to 22/110 (20%) TE participants gained >5% of their baseline weight. A >10% weight gain was documented for 5/21 (24%) TN and 6/110 (6%) TE participants. One TE participant discontinued B/F/TAF due to weight gain.

On the other end of the spectrum, 3/21 (14%) TN and 19/110 (17%) TE participants experienced a >5% relative weight loss. One person in each group lost >10%.

Discussion

In the Italian BICStaR cohort, reflecting routine clinical care, B/F/TAF showed high durable effectiveness over 24 months with respect to its primary endpoint of viral suppression. After 24 months, HIV-1 RNA was <50 copies/ml in 97% of people with HIV remaining on B/F/TAF and in the study (96% of TN and 97% of TE) and in 92% (92% of TN and 92% of TE) using the more conservative discontinuation-equals- failure approach. This compares to the international results of 94% (TN) to 96% (TE) in missing-equals-excluded and 88% (TN) to 86% (TE) in discontinuation-equals-failure approach [18]. A high level of persistence was also detected in this cohort, and only 2% discontinued B/F/TAF due to side effects. The likelihood of discontinuing B/F/TAF has been shown to be lower when compared to other three-drug regimens in treatment-naïve individuals [16].

The cohort was mostly antiretroviral treatment (ART)-experienced (86%), of which 94% were virologically suppressed at baseline, switching primarily to simplify treatment (92%). In total, 85% had self-reported at least 95% adherence to the previous ART and 14% had experienced virologic failure in the past.

In TE, the CD4/CD8 ratio remained stable throughout the observation period in this mostly successfully pre-treated cohort. As expected, it increased in TN.

Although this national cohort is not designed to evaluate the incidence of relatively rare ART-related adverse events, the ones seen in this cohort are consistent with those known for INSTIs and B/F/TAF [24]. Adverse events considered related to B/F/TAF were experienced by 6% of participants. These were primarily psychiatric in nature and led to discontinuation only in five participants (2%). This is in line with a retrospective cohort study by Hoffmann et al., where B/F/TAF was discontinued by 3% of participants after approx. six months due to (partly neuropsychiatric) side effects, which was higher than rates observed in clinical trials [25]. Statistically significant reductions in the lipid profile (total cholesterol, LDL, and triglycerides) were detected in the TE arm. Since the majority of TE participants (81%) were already on F/TAF-based ART prior to treatment with B/F/TAF, the observed decreases can likely be explained by the change in the previous third combination agent, which may have had an effect on the lipid profile (including boosted EVG or boosted PI in 48% and 13%, respectively). Similarly, small but statistically significant changes were observed in the BICSTaR global cohort, and deemed not to be clinically significant [18]. A decrease in LDL and TC after 48 weeks on B/F/TAF was also observed by Lazzaro, et al. in a treatment-experienced population [15].

Mild but significant increases in creatinine levels with subsequent decreases in eGFR in the TE group is also in accordance with the known inhibition of tubular secretion of creatinine via OCT-2 by bictegravir and dolutegravir [24-26]. This is without clinical significance, because detected changes remained within the normal ranges. Weight gain has been reported in people with HIV receiving antiretrovirals and is of additional importance in the ART switching population [18, 27]. There are several publications on antiretrovirals and weight change in the literature, reviewed in a recent 2024 publication in Clinical Infectious Diseases reviews [27]. The authors reviewed 63 articles of clinical trial and real-world evidence studies (including PrEP use in people without HIV, TN and TE people with HIV), as well as clinical HIV treatment guidelines [27]. They emphasized that tenofovir (TDF) and efavirenz (EFV) demonstrate variable and reversible weight suppression, and that a comprehensive data review of major clinical trials provides strong evidence for the weight neutrality of BIC and TAF, as well as DTG. This underscores the importance of considering weight change in people with HIV as a multifactorial phenomenon and the importance of understanding differences in demographics and in pre-switch regimens at baseline when interpreting weight data in switch trials. Our observed weight increase of four kilograms in the TN group may in part reflect a return to better health.

COVID-19 may also have had an influence [28]. On the other hand, a smaller weight gain of 0.3 kg without any statistical and clinical significance was detected in the experienced cohort, which is in accordance with previously reported data [24]. This is supported by the PRO HIV-SI, where TE indicated no significant effect on "changes in the way your body looks such as fat deposits or weight gain" as bothersome vs. not bothersome at 24 months (data not shown).

Though numbers are small, the HIV symptom burden improved significantly in previously treatment-naïve participants over the course of 24 months on B/F/TAF, which correlates with an earlier study [29]. It remained stable for those previously on antiretroviral therapy, which is not surprising, considering that this latter group was almost exclusively being successfully treated.

Treatment satisfaction improved in the TE group after 12 months, which could be expected given that the primary reasons for switching to B/F/TAF had been reported as treatment simplification and side effects of the previous regimen. Similar results have been reported elsewhere [30-31]. However, participants with a neuropsychiatric disorder were significantly less satisfied with their current treatment and felt their HIV infection was less controlled.

The study has several limitations due to its observational nature. First and foremost, the TN group is too small for statistical analysis. In addition, questionnaires on PROs were completed by only two-thirds of participants, which may be related to some kind of selection bias during the course of the study. However, as persistence in the study was high, non-response to the questionnaires or other missing data may have been Random. Also, this predominantly male and almost exclusively white cohort is not representative of the HIV population as a whole. Of note, more than one-quarter (28%) of people with HIV-1 in Italy are women [32].

Conclusions

In conclusion, B/F/TAF was well-tolerated and demonstrated high effectiveness and persistence over 24 months in this Italian routine clinical care cohort. Therapy with B/F/TAF had a positive effect on patient-reported outcomes. Treatment with B/F/TAF was associated with a decreased HIV-symptom burden and increased treatment satisfaction.

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Declarations

Ethics Approval and Consent to Participate

Approval was obtained from the Comitato Etico Regionale Marche (CERM), Comitato Etico Interregionale (Policlinico di Bari), Comitato Etico Di Brescia, Comitato Etico Milano Area 1, Comitato Etico Dell'Ospedale San Raffaele – Milano, Comitato Etico Milano Area 1, Comitato Etico Dell'Istituto Nazionale Per Le Malattie Infettive Lazzaro Spallanzani, Comitato Etico Indipendente Roma Fondazione PTV - Policlinico Tor Vergata, Comitato Etico Interaziendale Aou Città Della Salute e Della Scienza Di Torino, and Comitato Etico Campania 2.

All participants provided written informed consent prior to study enrolment and following the physician's independent decision to treat with B/F/TAF.

Consent for Publication

Not applicable

Availability of Data and Materials

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.

Competing Interests

GM received honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from ViiV, MSD, Gilead, Janssen, Angelini.

AA received grants/contracts from Astra Zeneca, Gilead Sciences and ViV Healthcare; honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Astra Zeneca, Gilead Sciences, GSK, Janssen- Cilag, Merck, Moderna, Pfizer, Viatris, and ViiV Healthcare.

VE received grants/contracts from Gilead; honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from ViiV, MSD, Abbvie, Angelini, Astrazeneca, Teratechnologies, Gilead.

SR received grants/contracts from Gilead Sciences, Janssen, and ViiV Healthcare; honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from MSD, Gilead Sciences, Janssen, Menarini, and ViiV Healthcare; support for attending meetings and/or travel from Janssen, Gilead.

DC received grants/contracts from Gilead, GSK; honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from ViiV, MSD, Gilead.

EQR received grants/contracts from Gilead Sciences. BC had no conflict of interest.

AS received honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from ViiV, MSD, Gilead, Janssen, Abbivie, Pfizer, GSK, Shinogi, Angelini, Menarini.

MA received grants/contracts, honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events and support for attending meetings and/or travel from Gilead Sciences, Janssen-Cilag, Viiv Healthcare, Merck Sharp and Dohme, Abbvie, Angelini, Pfizer, GSK, Menarini, Astra Zeneca, Moderna.

AM, TC, DT, LA, RC, GF are employees of Gilead and own shares in Gilead.

GDP received grants/contracts, consulting fees and honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events from Abbvie, MSD, Janssen, ViiV, Pfizer, Novartis, Astellas, Basilea, Zambon, Correvio, Angelini.

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Authors' Contributions

GM, AA, VE, SR, DC, EQR, BC, AS, MA and GDP contributed to participant accrual, clinical care, and data recording. All authors reviewed and critically revised the manuscript, approved the final draft, and agree to be accountable for the manuscript's accuracy and integrity.

Clinical Trial Registration

European cohort: EUPAS22185

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