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ORIGINAL RESEARCH

Bictegravir/Emtricitabine/Tenofovir Alafenamide Treatment: Efficacy and Tolerability in Clinical Practice

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Objective: Analysis of bictegravir/emtricitabine/tenofovir alafenamide (BFTAF) efficacy and safety in virologically suppressed people living with HIV (PLWH) in clinical practice.

Patients and methods: The retrospective cohort study, which included adult treatment-experienced and virologically suppressed PLWH, switched to BFTAF from June 2019 to June 2021. Efficacy and safety were evaluated as virological failure (VF=2 consecutive HIV-RNA>50 copies/mL or a single HIV-RNA>400 copies/mL) and treatment failure (TF=VF or discontinuation for any reason) until data freezing (August 2022).

Results: Of the 1040 PLWH included, 67.8% switched from elvitegravir/cobicistat/FTAF. VF occurred in 4.2% (n=44), with incidence rate of 1.63 per 1000 person-months of follow-up (PMFU) and probability at 24–30 months of 3.8%–4.0%, respectively. Out of the 44 VF, in 75% virological re-suppression was achieved while maintaining BFTAF. Discontinuation occurred in 15% after a median time of 13.5 months of follow-up, with an incidence rate of 5.67 per 1000 PMFU, and a probability at 24–30 months of 11.9%–15.3%, respectively. Main discontinuation reasons were simplification (51.3%) and toxicity (21.8%, involving CNS in half of cases). TF occurred in 18.6% with an incidence rate of 7.01 per 1000 PMFU after a median time of 13.6 observation months; probability at 24–30 months was 14.8%–18.4%, respectively.

Conclusion: BFTAF has proven effective and well tolerated in clinical practice.

Plain Language Summary: In Clinical Randomized Trials, BFTAF proved to have a high genetic barrier regimen.
In this context of clinical practice:

- BFTAF proved effective and well tolerated
- It showed a low rate of virological failure
- Discontinuation was largely influenced by simplification with 2-drug regimens.

Keywords: bictegravir, people living with HIV, PLWH, efficacy, safety, clinical practice

Introduction

A fixed combination of bictegravir/emtricitabine/tenofovir alafenamide (BFTAF, Biktarvy®), an HIV integrase strand transfer inhibitor (InSTI) associated with two nucleoside reverse transcriptase inhibitors, has been available in Italy since June 2019 for the treatment of people living with HIV infection (PLWH).[1]

It represents a complete single-tablet antiretroviral therapy (ART) to be taken every 24 hr, both with food and on an empty stomach, which presents very few drug interactions and a high barrier to the selection of drug-resistant viral variants.[2]

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BFTAF has proven to be very effective and well tolerated, both in antiretroviral-naive PLWH[3–5] and in treatment-experienced ones,[6–8] even in conditions of frailty due to co-morbidities.[9]

Based on these features, BFTAF appears as an attractive oral therapeutic regimen in terms of efficacy, tolerability, and ease of use.

Since its availability in our hospital pharmacy, it was planned to replace all regimens consisting of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (ECFTAF) with BFTAF, depending upon several advantages in terms of safety, pharmacokinetics, antiviral activity, and pharmacoeconomics.[10] In addition, BFTAF was prescribed according to a case-by-case clinical opinion, in other PLWH with a current regimen other than ECFTAF.

The aim of this study is to describe the efficacy and tolerability of BFTAF in PLWH virologically suppressed, while exposed to other antiretroviral regimens, in a context of clinical practice.

Methods

A retrospective cohort study was conducted in adult PLWH on antiretroviral therapy and HIV-RNA <50 copies/mL, who switched to BFTAF to replace the current regimen, from June 2019 to June 2021. To be included in the analysis, they had to have at least an HIV-RNA determination (PCR Cobas® HIV-1 test 6800 Systems, Roche Diagnostics) after the introduction of BFTAF. A validated in-house method was used to identify resistance-associated mutations (RAMs), as previously described by our group.[11] GRT on plasma HIV-RNA and PBMC HIV-DNA was interpreted according to the Stanford University HIV Drug Resistance Database version 9.0 (hivdb.stanford.edu/hivdb/by-sequences/, last updated on 22 June 2023).

Virological failure (VF) was defined as two consecutive HIV-RNA values >50 copies/mL or a single HIV-RNA value >400 copies/mL. Treatment failure (TF) is defined as the occurrence of virological failure or discontinuation of BFTAF for any reason.

Follow-up accrued from the start of BFTAF (baseline) up to the stop of any drug in the regimen or lost to follow-up or data freezing (31 August 2022).

Data are reported as medians (first-third quartile). The incidence rate of VF or TF was calculated as number of VF or TF events per 1000 person-months of follow-up (PMFU). The cumulative probabilities (95% confidence interval, CI) of VF or TF were estimated using Kaplan–Meier curves; the Log rank test was used to compare survival curves. Univariate mixed linear models (MLM) with random slope and intercept for each patient were fitted to estimate mean changes in laboratory parameters (CD4+ lymphocytes, CD4+/CD8+ ratio, haemoglobin, neutrophil granulocytes, creatinine and estimated glomerular filtration rate, glucose, total cholesterol, HDL, LDL, FIB-4) since baseline. Slopes were reported with the corresponding 95% confidence interval. All analyses were conducted using SAS statistical software version 9.4 (Statistical Analyses System Inc, Cary, NC, USA).

Individuals provided written informed consent on the use of their data in scientific analyses and to be included in the Centro San Luigi (CSL) HIV Cohort. The CSL-HIV Cohort was approved by the Ethics Committee of the IRCCS San Raffaele Scientific Institute (Milan, Italy; date of approval 4 December 2017, protocol n. 34).

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration.

Results

Overall, 1040 patients who met the above-mentioned inclusion criteria were considered in the analysis (flowchart of data extraction in Figure 1).

Males represented 82.1% of the study population. At the beginning of BFTAF treatment, the median age (Q1-Q3) was 51.1 (42–57.1) years; patients had a known HIV infection lasting 13.8 (6.8–23.4) years and were on ART for 10.2 (5.1–19.7) years; nadir CD4+ lymphocyte count was 291 (166–447) cells/μL, while their current CD4+ count was 718 (535–941) cells/μL; an AIDS diagnosis was present in 181 subjects (17.4%) and a history of HCV co-infection in 212 (20.4%).

Of these 1040, 705 (67.8%) were taking ECFTAF, while 335 (32.2%) were on a different regimen. Of those on a regimen other than ECFTAF, 194 (59.9%) were on a three-drug integrase inhibitor-based regimen other than elvitegravir, 56 (16.7%) on a protease inhibitor-based regimen, 38 (11.7%) on a non-nucleoside reverse transcriptase inhibitor-based regimen, and 47 (14%) were taking a regimen that cannot be classified among the previous ones, including mono-and dual-therapies and study-protocol regimens. Among 335 patients not treated with ECFTAF, the

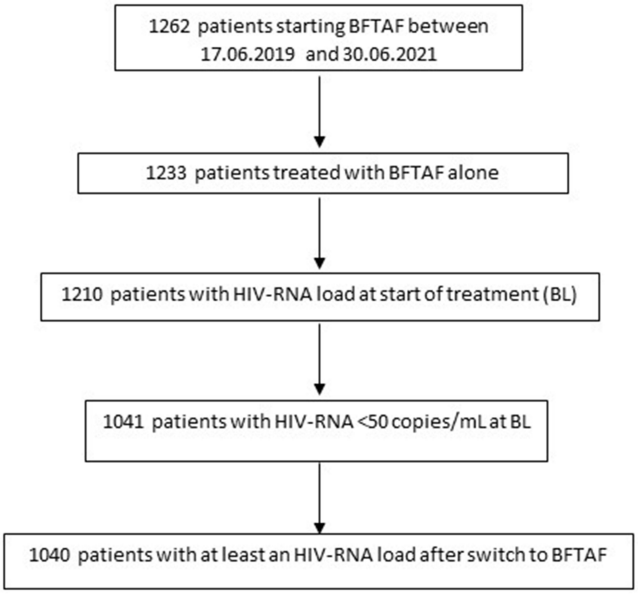

Figure 1 Flowchart of data extraction.

switch to BFTAF was motivated by simplification (lower drug burden, lower pill burden, no food requirement, fewer potential adverse effects, and/or potential drug–drug interactions) in 236 cases (70.4%), toxicity in 26 (7.8%), and by a miscellany of different reasons in 73 cases (21.8%), such as presence of drug–drug interactions, concern of co-morbidities, exit from clinical studies, patient's request.

Further details on the characteristics of the individuals included in the analysis are shown in Table 1.

Table 1 Characteristics of Patients Included in the Analysis at the Time of BFTAF Treatment Initiation

Variable	Overall (n=1040)	Switch FROM ECFTAF (n=705)	Switch from Other Regimens (n=335)
Age (years)	51.1 (42–57.1)	49.5 (40.5–56.2)	53.5 (44.8–58.5)
Male gender	854 (82.1%)	596 (84.5%)	258 (77%)
HIV risk factor			
MSM	532 (51.2%)	392 (55.6%)	140 (41.8%)
PWID	120 (11.5%)	58 (8.2%)	62 (18.5%)
Heterosexual	201 (19.3%)	122 (17.3%)	79 (23.6%)
Other (blood transfusion, MTCT, unknown)	187 (18.0%)	133 (18.9%)	54 (16.1%)
Years since HIV diagnosis	13.8 (6.8–23.4)	12.7 (6.7–20.5)	19.3 (7–27.9)
Years of ART	10.2 (5.1–19.7)	9.2 (5.1–17.2)	13.9 (5.1–22.7)
Nadir CD4+ lymphocytes (cells/μL)	291 (166–447)	308 (173–460)	258 (133–419)
HCV IgG positive test	212 (20.4%)	120 (17%)	92 (27.5%)
HBsAg positive test	82 (7.9%)	52 (7.4%)	30 (9%)
AIDS diagnosis	181 (17.4%)	99 (14%)	82 (24.5%)

(*Continued*)

Table 1 (Continued).

Variable	Overall (n=1040)	Switch FROM ECFTAF (n=705)	Switch from Other Regimens (n=335)
Type of previous ART			
3-drug PI-based	56 (5.4%)	0 (0%)	56 (16.7%)
3-drug NNRTI-based	38 (3.7%)	0 (0%)	38 (11.7%)
3-drug InSTI-based	899 (87.4%)	705 (100%)	194 (59.9%)
Other regimens	47 (4.5%)	0 (0%)	47 (14%)
CD4+ (cells/μL)	718 (535–941)	732 (535–955)	697 (532–904)
CD8+ (cells/μL)	827 (605–1128)	834 (614–1142)	807 (580–1088)
CD4+ (%)	32.4 (26.5–39.3)	32.7 (26.7–39.3)	32 (25.5–39.3)
CD8+ (%)	36.3 (29.9–44.1)	37 (30.2–44.2)	35.2 (29.5–43.6)
CD4+/CD8+ ratio	0.91 (0.62–1.24)	0.91 (0.63–1.22)	0.93 (0.61–1.27)
Platelets (10^9/L)	227 (192–269)	227 (196–270)	224 (189–264)
Haemoglobin (g/dL)	15.1 (14.2–16)	15.2 (14.3–16)	14.9 (14–16)
White blood cells (10^9/L)	6.4 (5.3–7.6)	6.4 (5.3–7.7)	6.2 (5.4–7.4)
Total lymphocytes (10^9/L)	2.2 (1.8–2.8)	2.3 (1.8–2.8)	2.2 (1.8–2.7)
Total neutrophils (10^9/L)	3.3 (2.5–4.1)	3.2 (2.4–4.2)	3.3 (2.5–4)
Creatinine (mg/dL)	1.04 (0.91–1.16)	1.04 (0.91–1.16)	1.04 (0.91–1.18)
eGFR (mL/min/1.73m2)	81 (69–94)	82 (72–95)	78 (65–91)
Glucose (mg/dL)	94 (87–102)	93 (86–100)	95 (88–106)
Triglycerides (mg/dL)	116 (85–160)	116 (86–163)	114 (82–157)
Total cholesterol (mg/dL)	186 (165–213)	189 (169–215)	184 (158–209)
HDL cholesterol (mg/dL)	50 (43–59)	51 (43–59)	49 (42–59)
LDL cholesterol (mg/dL)	124 (103–147)	126 (105–149)	120 (99.5–144.5)
ALT (U/L)	24 (19–34)	24 (18–33)	26 (19–35)
AST (U/L)	25 (21–30)	24 (20–29)	26 (21–32)
Fib-4 index	1.07 (0.78–1.47)	1.01 (0.77–1.39)	1.19 (0.83–1.62)

Abbreviations: MSM, Men who have Sex with Men; PWID, People Who Inject Drugs; MTCT, Mother-To-Child Transmission; PI, Protease Inhibitor; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor; InSTI, Integrase Strand Transfer Inhibitor; eGFR, estimated Glomerular Filtration Rate; Fib-4, Fibrosis-4 index for liver fibrosis.

The overall median follow-up was of 29.7 (24.4–32.3) months, for a total of 27,536 PMFU. The median follow-up was of 30.5 (26.7–32.7) months with 19,352 PMFU among people who switched from an ECFTAF regimen and of 27.8 (19.1–30.8) months with 8,183 PMFU among people from another regimens.

Overall, VF occurred in 44 (4.2%) patients, with an incidence rate of 1.63 (95% CI 1.16–2.11) per 1000 PMFU; this event occurred after a median of 12.8 (5.8–22.8) months of observation. Median HIV-RNA values at failure were 246 (68–12,025) copies/mL, with 23 cases satisfying the finding of two consecutive HIV-RNA values >50 copies/mL, and 21 corresponding to the criterion of a single HIV-RNA value >400 copies/mL.

The probability of VF at 12, 24 and 30 months was 2.1% (95% CI 1.4–3.3%), 3.8% (95% CI 2.7–5.2%), and 4.0% (95% CI 2.9–5.5%), respectively. The estimate up to 30 months of the probability of VF is illustrated in Figure 2.

No statistically significant differences were observed in the probability of VF between patients whose prior regimen was ECFTAF and those who were on a regimen other than ECFTAF at the time of initiating BFTAF.

Mainly due to the low values of viremia at VF, genotypic resistance tests (GRTs) were able to evaluate the drug resistance at VF only in five patients: none selected variants resistant to integrase inhibitors and no new mutations emerged in any case (Table 2).

Out of the 44 documented VF, in 33 cases (75%) BFTAF was successfully maintained with spontaneous virological re-suppression in at least two subsequent HIV-RNA determinations (data not shown). In a case-by-case revision, those HIV-RNA blips were attributable to self-reported transient non adherence (13/33 cases), intercurrent illnesses such as high or low respiratory tract infections, diarrhoea and vomiting, urinary tract infection and others (5/33 cases), drug–drug interactions (2/33 cases), recent vaccine administration (1/33 cases), and no evident explanation in the remaining 12 cases. Five patients who developed VF were switched to another regimen: darunavir/cobicistat/FTAF (DcFTAF) in two cases, dolutegravir (DTG) plus FTAF, DTG plus DcFTAF and rilpivirine (RPV)/FTAF in the other three cases, with virological suppression (3/5) or recurrent blips/low-level viremia (2/5). GRTs were fully amplifiable only in one case and resulted in susceptibility to all NRTIs, InSTIs, and PIs; in another case, switched to DcFTAF, GRTs were performed but analysis was feasible only for PIs, with full susceptibility. Finally, 6 PLWH with evidence of VF were lost at follow-up. Finally, 6 PLWH with evidence of VF were lost at follow-up.

BFTAF discontinuation occurred in 156 (15%) of patients after a median of 13.5 (6.8–23.4) months of follow-up; the incidence rate of regimen discontinuation was 5.67 (95% CI 4.78–6.55) per 1000 PMFU. The probability of discontinuation at 12, 24 and 30 months was 6.4% (95% CI 5.1–8.1%), 11.9% (95% CI 10–14%), and 15.3% (95% CI 13.2%-17.8), respectively. The estimate of the probability of discontinuation up to 30 months is illustrated in Figure 3.

No statistically significant differences were observed in the likelihood of discontinuing BFTAF between patients whose prior regimen was ECFTAF and those who were on a regimen other than ECFTAF at the time of initiating BFTAF.

The discontinuation of BFTAF occurred due to simplification to a regimen with a lower drug burden in 70 (44.9%) patients, due to simplification for other reasons in 10 patients (6.4%), due to central nervous system toxicity in 14 (9%) and due to other types of toxicity in 20 (12.8%), due to enrolment in clinical trials in 8 (5.1%), due to switch during pregnancy in 3 cases (1.9%), due to suspected weight gain in 2 (1.3%) and to drug–drug interactions in 2 cases (1.3%);

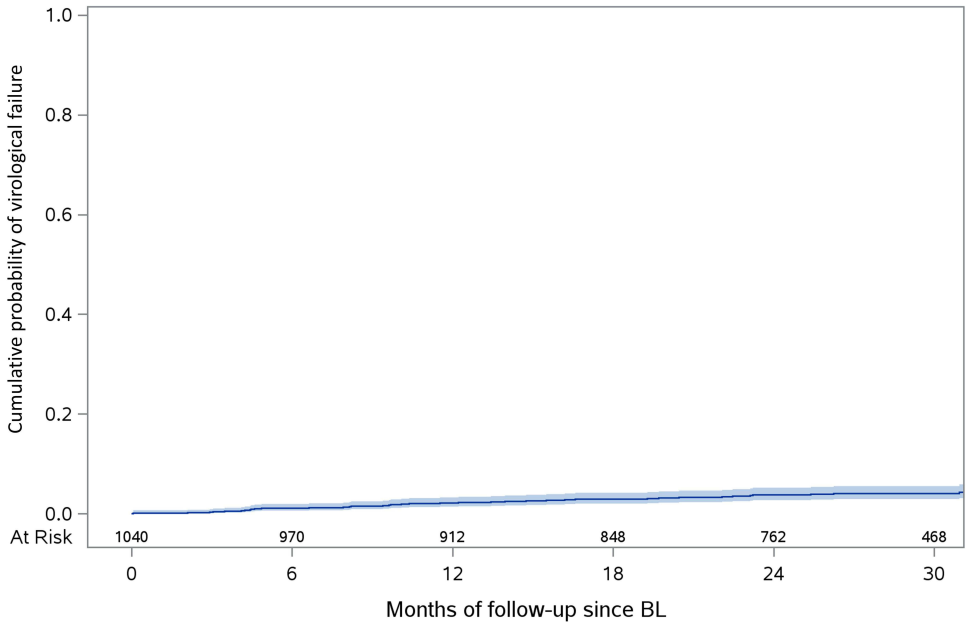

Figure 2 Probability of virological failure, Kaplan–Meier curve.

Table 2 Results of Genotypic Resistance Tests (GRTs) Available on Partially or Completely Amplifiable Samples

ID and Type of Sample	VL at VF (cp/mL)	Months to VF	InSTI RAMs	NRTI RAMs	Other RAMs	Follow-Up	Potential Reason of VF
1. RNA	319	31.5	Na	None	K20R	Spontaneous stable VS in BFTAF	Recent vaccination
2. RNA	81	10.4	None	None	PI na	LLV in BFTAF	Not identified
3. RNA	1570	2.9	None	Na	None	Spontaneous stable VS in BFTAF	Not identified
4. RNA + DNA	201	11.5	None	None	None	Spontaneous stable VS in BFTAF	DDIs (mineral supplements containing Mg)
5. RNA + DNA	168	15.5	None	None	K103N*	Switch to DTG +DcFTAF	Suspected HIV-1/2 co-infection

Note: *Present since pre-ART GRT.

Abbreviations: VL, viral load; VF, virological failure; cp, copies; InSTI, Integrase Strand Transfer Inhibitor; NRTI, Nucleoside Reverse Transcriptase Inhibitor; RAMs, resistance associated mutations; na, not amplifiable; VS virological suppression; PI, Protease Inhibitor; LLV, low-level viremia defined as a confirmed detectable HIV-RNA level <200 cp/mL according to DHHS 2021 Guidelines; DTG, dolutegravir; DcFTAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide.

then, as already mentioned, the reason for discontinuation was VF in 5 cases (3.2%), death in 8 cases (5.1%) and a miscellanea of other reasons including patient's wish in 14 cases (9%).

TF occurred in 193 (18.6%) patients, with an incidence rate of 7.01 (95% CI 6.02–8) per 1000 PMFU, after a median of 13.6 (7.1–23.4) months of observation.

The probability of TF at 12, 24 and 30 months was 8.2% (95% CI 6.7–10.1%), 14.8% (95% CI 12.7–17.2%), and 18.4% (95% CI 16.0–21.0%), respectively. The estimate of the probability of outage up to 30 months is illustrated in Figure 4.

There were not statistically significant differences in the probability of TF between patients whose prior regimen was ECFTAF and those who were on a regimen other than ECFTAF at the time of initiating BFTAF. During the follow-up, statistically significant changes were found in CD4+ lymphocytes, CD4+/CD8+ ratio, haemoglobin, neutrophil

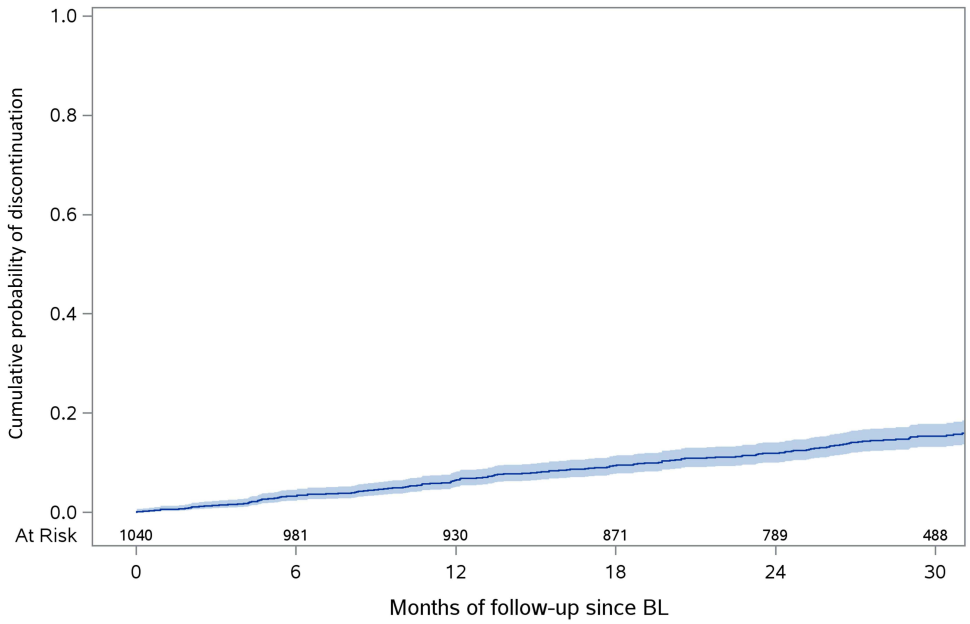

Figure 3 Probability of discontinuing BFTAF, Kaplan–Meier curve.

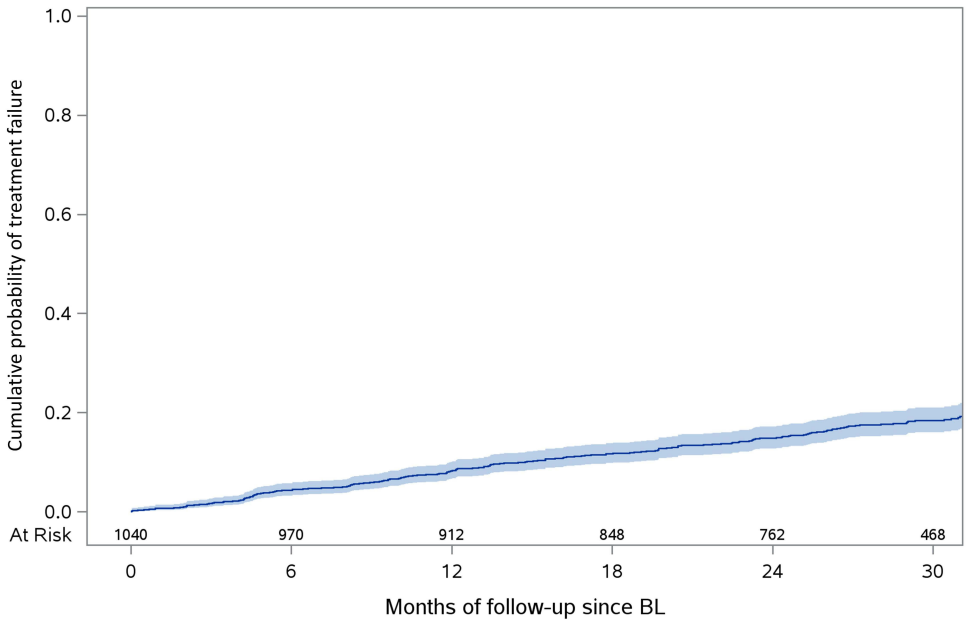

Figure 4 Probability of treatment failure, Kaplan–Meier curve.

granulocytes, creatinine and estimated glomerular filtration rate, glucose, total cholesterol, HDL, LDL, FIB-4. No significant changes were observed in CD8+ lymphocytes, nor in the total cholesterol/HDL ratio. Laboratory parameters with a significant monthly increase or decrease over the study period are shown in Table 3. During the observation period 11 (1.1%) patients developed diabetes.

Table 3 Monthly Changes of Some Parameters of Interest After Starting BFTAF

Variable	Mean Change per Month of Change FROM BL (95% Confidence Interval)	P value
CD4+ lymphocytes (cells/μL)	0.51 (0.058; 0.97)	0.027
CD4+ lymphocytes (%)	0.035 (0.025; 0.045)	<0.0001
CD4+ and CD8+ ratio	0.001 (0.0004; 0.0015)	0.0008
Haemoglobin (g/dL)	0.006 (0.004; 0.009)	<0.0001
Total neutrophils (10^9/L)	0.006 (0.002; 0.009)	0.001
Creatinine (mg/dL)	0.001 (0.0007; 0.0015)	<0.0001
eGFR (mL/min/1.73m2)	−0.135 (−0.161; −0.110)	<0.0001
Glucose (mg/dL)	0.108 (0.063; 0.152)	<0.0001
Triglycerides (mg/dL)	−0.344 (−0.507; −0.181)	<0.0001
Total cholesterol (mg/dL)	−0.106 (−0.185; −0.028)	0.008
HDL cholesterol (mg/dL)	−0.043 (−0.067; −0.019)	0.0005
LDL cholesterol (mg/dL)	−0.407 (−0.485; −0.328)	<0.0001
Fib-4 Index	0.006 (0.004; 0.008)	<0.0001

Abbreviations: BFTAF, bictegravir/emtricitabine/tenofovir alafenamide; BL, baseline; eGFR, estimated Glomerular Filtration Rate; HDL, High-density lipoproteins; LDL, Low-density lipoproteins; Fib-4, Fibrosis-4 index for liver fibrosis.

Discussion

After approximately 30 months of follow-up in a daily clinical practice setting, the probability of virological failure or discontinuation of BFTAF for any reason, although higher than those observed in the pivotal clinical trials,[3–8] was small and consistent with those observed in observational studies in our country.[12,13]

Overall, the results of our analysis confirm that BFTAF is an effective and well-tolerated regimen.

Even in the cases of VF reported here, most patients (75%) developed a spontaneous virological control and, when genotypic resistance testing was feasible, there was no evidence of emerging resistance to integrase inhibitors, emtricitabine (or lamivudine), or tenofovir.

It should be emphasized that over half of interruptions occur due to simplification or enrolment in clinical trials, reasons that cannot be classified as clinical failure of the regimen.

In many cases, the suspension of BFTAF was justified by the will to reduce the drug burden, in the absence of signs or symptoms of toxicity. In this regard, it is necessary to highlight that, unlike the registration studies, the population described has a long history of HIV infection (about 14 years) and antiretroviral therapy exposure behind it, which may explain some treatment switches which should probably appear unjustified in patients on first or second-line therapy.

A similar study was recently conducted in Spain;[14] performing an intention-to-treat analysis, Ambrosioni et al found that 78% of 1371 patients who switched to BFTAF from another regimen had HIV-RNA <50 copies/mL after 12 months of follow-up. Treatment discontinuation occurred in 3% of cases, and the main cause of discontinuation (69% of cases) was toxicity. Less than 1% of patients experienced virological failure during the 12-month follow-up.

Another real-world setting study was realized in Belgium between January 2019 and September 2020.[15] It included 1593 treatment-experienced PLWH, 93.2% of whom maintained virological suppression after 48 weeks; 17 participants (1.1%) experienced viral blips and only a minority (0.7% of overall population including 363 naive-treatment subjects) met the criteria for loss of virological suppression (two consecutive HIV-RNA >200 copies/mL) by week 48. 6.1% (97/1593) discontinued the BFTAF regimen, mainly because of adverse events and then because of switching to dual therapies.

Despite the differences in design, in definition of success parameters and in length of observation period (16 months and 48 weeks, respectively, versus 30 months of our analysis), the three studies run in clinical practice reached similar conclusions with regard to the efficacy and tolerability of BFTAF.

The reported analysis revealed some statistically significant variations in immunological and metabolic parameters, although none of these variations can be considered clinically relevant: a slight increase in the mean change per month from BL of lymphocytes CD4+ percentage, CD4+ and CD8+ ratio, haemoglobin, total neutrophils, creatinine, glucose, and Fib-4 Index, as well as a slight decrease in EGFR, triglycerides, and total cholesterol, LDL, and HDL (Table 3). Pivotal studies in antiretroviral-naive patients have shown a modest worsening of the lipid profile during treatment with BFTAF [3–8]; on the contrary, analyses revealed a trend towards improvement. The difference is probably due to the fact that BFTAF was prescribed in PLWH who were largely already receiving TAF, cobicistat, and sometimes boosted protease inhibitors, differently from what happened in the pivotal studies.[6–8]

The trend towards a monthly increase in glycemia is quantitatively negligible in terms of clinical relevance. In our cohort, during the period of follow-up, 1% of patients developed diabetes, an incidence that seems to agree with data recently reported in similar groups of PLWH.[16] Nevertheless, in an ageing population that is considered at higher risk of metabolic disorders regardless of ART type, it deserves to be kept under observation over time.[17]

The slight increase in creatinine (with a relatively slight decrease in eGFR) is likely related to the known effect of bictegravir on tubular creatine transport, which does not reflect an actual reduction in glomerular filtration rate.[3–9]

Only in rare cases, these changes led to precautional discontinuation of BFTAF, not justified by a current clinical condition but because of a concern of not already known long-term adverse events.

This study presents some limitations, such as retrospectivity, the absence of a standardized evaluation of adherence to treatment, and an amount of missing data for some variables. Nevertheless, the real-world setting and the long duration of follow-up, which largely took place during the problematic period of the coronavirus disease 2019 (COVID-19) pandemic, represent its main strength.

Conclusions

In this context of clinical practice, the treatment of HIV infection with a single daily tablet of BFTAF has proven to be effective and well tolerated, with a low rate of virological failure. The rate of discontinuation and of TF was largely influenced by treatment simplification with 2-drug regimens, rather than toxicity.

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