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Impact of preexisting nucleos(t)ide reverse transcriptase inhibitor resistance on the effectiveness of bictegravir/emtricitabine/tenofovir alafenamide in treatment experience patients

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Introduction: Few clinical trials and cohort studies have evaluated the efficacy of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in people with HIV (PWH) with preexisting M184V/I or other nucleos(t)ide reverse transcriptase inhibitor (NRTI) resistance-associated mutations (RAMs). Real-world data are also scarce.

Methods: Retrospective review of treatment-experienced patients who started B/F/TAF in a cohort of PWH. HIV-RNA less than 50 copies/ml was analyzed at 48 weeks in an intention-to-treat (ITT) analysis (missing=failure) and per protocol analysis (patients with missing data or changes for reasons other than virological failure were excluded). Results were compared in patients with and without previous NRTI-RAMs.

Results: Five hundred and six PWH were included (16.2% women). Median age and time with HIV infection were 52.3 and 18.9 years, respectively. At baseline, viral load was less than 50 copies/ml in 440 patients (86.6%). Overall, 69 (13.6%) participants had documented preexisting NRTI-RAMs: 57 (11.2%) M184V/I and 30 (5.9%) tenofovir RAMs. In the ITT analysis, 83% (420/506) had HIV-RNA less than 50 copies/ml [82.2% (359/437) and 88.4% (61/69) in persons without and with NRTI-RAMs, respectively ($P = 0.2$)]. In the per protocol analysis 94.2% (420/445) had HIV-RNA less than 50 copies/ml [94.4% (359/380) vs. 93.8% (61/65); $P = 0.2$]. A total of 61 participants were excluded from the per protocol analysis (23 missing data, 19 discontinued B/F/TAF because of toxicity, 13 for other reasons, and 6 died).

Conclusion: Switching to B/F/TAF is well tolerated and effective in the real-world setting, even in patients with preexisting NRTI RAMs, such as M184V and RAMs conferring resistance to tenofovir. These results confirm the robustness of this combination.

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Keywords: antiretroviral treatment, bictegravir, HIV, real-life, resistance mutation, treatment-experienced

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Introduction

The single-tablet regimen of bictegravir with emtricitabine and tenofovir alafenamide (B/F/TAF) is an effective regimen with a high barrier to resistance and low potential for drug interactions [1]. It is currently recommended as the initial choice in most antiretroviral treatment guidelines [2,3]. International randomized clinical trials have also established that switching to B/F/TAF from other antiretroviral combinations is well tolerated and effective in virologically suppressed patients. Most of these studies were performed in patients with no previously documented resistance-associated mutations (RAMs) to emtricitabine, lamivudine, tenofovir, and integrase strand transfer inhibitors (INSTIs) [4–6]. Recently, some studies have included patients with documented or suspected resistance to nucleoside reverse transcriptase inhibitors (NRTIs) [7–10]. However, data are still scarce. Moreover, most results are from clinical trials. Real-world data may differ from those in trials, where patients are carefully selected and expected to show high levels of therapy adherence and low levels of missed visits. The aims of our study were, first, to evaluate the efficacy of B/F/TAF in treatment-experienced patients in a real-world setting and, second, to compare the efficacy of B/F/TAF between patients with and without preexisting NRTIs RAMs.

Methods

Population

We retrospectively reviewed all persons with HIV (PWH) under regular follow-up at our center (Hospital Universitario La Paz, Madrid) and included those treatment-experienced patients who had started B/F/TAF before February 2020. treatment-experienced patients were defined as those who were receiving another antiretroviral therapy (ART) combination and were switched to B/F/TAF (regardless of having undetectable viral load when the drug was prescribed).

The study was approved by La Paz Ethics Committee. Data were collected retrospectively from patients' medical records, anonymized, and entered into an on-line electronic database. Data collection and inclusion in the electronic database was performed between 1 May and 19 June 2021. All research was carried out in accordance with Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and in accordance with the Declaration of Helsinki. Given that ours was a retrospective study and only de-identified data were extracted from clinical records, the local ethics committee waived the need for consent.

We recorded the main demographic data (age, sex, origin, route of transmission of HIV), HIV-related parameters (duration of infection, former antiretroviral regimens, baseline HIV-RNA nadir, and baseline $CD4^+$ cell count), and hepatitis B and C coinfections. Historical protease, transcriptase, and integrase resistance mutations after a previous virological failure or before first ART initiation were collected. RAMs had been analyzed by Sanger sequencing of RNA. All mutations were included in the HIV drug resistance database (Stanford University) to determine the level of resistance to drugs [11]. In patients with more than one resistance test, the last available was considered.

We stratified participants according to resistance to NRTIs into four categories: no resistance, any NRTI resistance, M184V/I (conferring high-level resistance to lamivudine and emtricitabine), and resistance to tenofovir.

Outcomes

The primary efficacy endpoint was the percentage of patients with HIV-RNA less than 50 copies/ml in the first visit performed at week 48 of initiation of B/F/TAF in both the intention-to-treat (ITT) and the per protocol analysis. For week 48, a window of 3 months after or before was allowed. The ITT analysis included all patients who had received at least one dose of B/F/TAF. The per protocol analysis excluded patients who did not have a plasma HIV-RNA value at week 48 owing to lack of data or drug discontinuation for reasons other than lack of efficacy. Patients with and without resistance to NRTIs were compared.

Statistical analysis

Descriptive features of the patient population are reported as absolute number and percentage or as median and interquartile range (IQR). Baseline characteristics were compared between patients with and without NRTI RAMs using the χ^2 test and Fisher exact test for categorical variables and the Wilcoxon test for continuous variables. Comparisons between the groups based on the ITT and per protocol analyses were also performed using the χ^2 test.

Results

Baseline characteristics

Of 4397 PWH in regular follow-up at our clinic, 506 switched from other antiretroviral combinations to B/F/TAF between April 2019 and February 2020. Table 1 shows the baseline characteristics. Women accounted for 16.2%; the median (IQR) age and time of HIV infection were 52.3 (43.5–57.8) and 18.9 (9.4–26.4) years, respectively. Most of the patients (73.9%) switched from a previous combination that included two NRTIs with an INSTI (41.5% elvitegravir/cobicistat/TAF; 23.5% dolutegravir +

Table 1. Baseline characteristics of people with HIV switching to bictegravir/emtricitabine/tenofovir alafenamide.

	No resistance to NRTIs ($N = 437$)	Resistance to NRTIs ($N = 69$)	ALL ($N = 506$)	*P*
Female sex	63 (14.4%)	19 (27.7%)	82 (16.2%)	<0.01
Age	51.3 (42–57.3)	55.3 (49.6–58.9)	52.3 (43.5–57.8)	<0.01
Origin				0.05
Spanish	312 (71.9%)	61 (88.4%)	373 (74.2%)	
Latin-American	97 (22.4%)	8 (11.6%)	105 (20.9%)	
Other	25 (5.7%)	0	25 (5%)	
Risk group				<0.01
IDU	87 (21.5%)	22 (37.9%)	109 (23.6%)	
MSM	237 (58.7%)	21 (36.2%)	258 (55.8%)	
Heterosexual	77 (19.1%)	14 (24.1%)	91 (19.7%)	
Transgender	3 (0.7%)	1 (1.7%)	4 (0.9%)	
Chronic hepatitis B	20 (4.8%)	4 (6.1%)	24 (5%)	0.2
Duration of HIV infection (years)	16.8 (8.8–24.3)	25.7 (19.4–29.7)	18.9 (9.4–26.4)	<0.01
Viral load >50 copies/ml	58 (13.6%)	8 (11.6%)	66 (13.4%)	0.6
$CD4^+$ cell count	676 (413–861)	567 (375–690)	645 (411–854)	0.08
Last previous treatment				<0.01
INSTI + 2NRTI	326 (75.3%)	45 (65.2%)	371 (73.9%)	
PI + 2NRTI	23 (5.3%)	8 (11.6%)	31 (6.2%)	
NNRTI + 2NRTI	59 (13.6%)	4 (5.8%)	63 (12.5%)	
Other	25 (5.8%)	12 (17.3%)	37 (6.4%)	
Time on ARV treatment (years)	12.6 (7.2–20.1)	21.6 (16.9–24)	13.8 (7.6–21–3)	<0.01
Number of previous ARV combinations	5 (3–7)	11 (7.2–14)	5 (3–8)	<0.01
Preexisting resistance mutations				<0.01
NNRTI	23 (5.3%)	36 (52.2%)	59 (11.7%)	
Major PI	7 (1.6%)	19 (27.5%)	26 (5.1%)	
Number of drug families affected by mutations				<0.01
0	408 (93.4%)	0	408 (80.6%)	
1	28 (6.4%)	25 (36.2%)	53 (10.5%)	
2	1 (0.2%)	33 (47.8%)	34 (6.7%)	
3	0	11 (15.9%)	11 (2.2%)	

ARV, antiretroviral; IDU, intravenous drug addict; INSTI, integrase strand transcriptase inhibitor; *N*, number of patients; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor.

2 NRTIs; 7.5% raltegravir +2 NRTIs). However, others switched from two NRTIs with a nonnucleoside reverse transcriptase inhibitor (12.5%) or 2 NRTIs with a protease inhibitor (6.2%). At baseline, 86.6% of the patients had viral load less than 50 copies/ml and a mean $CD4^+$ cell count of 645 cells/μl (411–854).

Resistance test was available in 190 patients after virological breakthrough. In the rest of patients, baseline resistance test before ART introduction was considered. The most recent resistance test had been performed a median (IQR) of 8.8 (4.2–12.4) years before switching to B/F/TAF. Preexisting NRTI-RAMs were recorded in 69 patients (13.6%), to NNRTIs in 59 patients (11.7%), and to protease inhibitors in 26 patients (5.1%). No patients had INSTI resistance mutations. The number of antiretroviral families affected by resistance mutations was one in 53 patients (10.5%), two in 34 patients (6.7%), and three in 11 patients (2.2%).

Regarding patients with preexisting NRTI resistance mutations, 57 had M184V/I; 15 had mutations conferring high-level resistance to TDF (K65R in 3 cases, accompanied by M184V in 9) and 15 had mutations conferring low or intermedial level resistance to TDF (5 accompanied by M184V) (Table 2). Patients harboring previous NRTI resistance mutations were older, more often women, had been HIV-infected for longer, had been on antiretroviral treatment for longer, and had received more antiretroviral combinations. They also had more resistance mutations to other antiretroviral families (Table 1).

Efficacy

Week 48 was performed at a median time of 11.9 months (IQR 11.2–13 months; range 9–15 months, without

Table 2. Preexisting nucleoside reverse transcriptase inhibitor resistance mutations.

Pre-existing NRTI resistances	Number of patients
Only M184V/I	27
K65R + M184V/I	2
≥3 TAMS + M184V	7
2 TAMS + M184V	12
Other + M184V	9
K65R	1
≥3 TAMS	5
2 TAMS	3
Other	3

NRTI, nucleoside reverse transcriptase inhibitors; TAMS, timidine analogue-associated mutations (M41L, D67N, K70R, L210W, T251Y/F, K219Q/E).

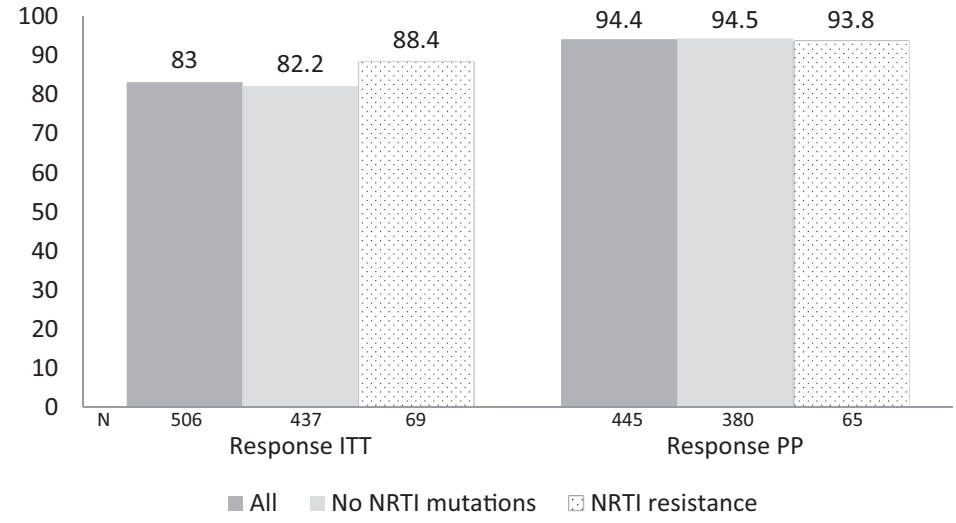

Fig. 1. Percentage of patients with HIV-RNA less than 50 copies at week 48. ITT, intention-to-treat analysis (missing=failure); NRTI, nucleoside reverse transcriptase inhibitor; PP, per protocol analysis (data missing for reasons other than lack of efficacy are excluded). No differences between groups (all comparisons $P < 0.05$).

differences between groups). At 48 weeks, the proportion of patients with HIV-RNA less than 50 copies/ml in the ITT analysis was 83% (420/506) (Fig. 1). No statistically significant differences were seen between persons without and with NRTI-RAMs: 82.2% (359/437) vs. 88.4% (61/69); $P = 0.2$. Efficacy was 86% (49/57) in the subgroup of patients with M184V/I and 96.7% (29/30) in patients with resistance to TDF ($P = 0.5$ and $P = 0.04$ vs. patients without NRTI resistance, respectively). Of note, all nine patients who had preexisting high-level resistance to TDF and M184V, had HIV-RNA less than 50 copies/ml at week 48.

Overall, 61 patients were excluded from the per protocol analysis: data were missing for 23 patients (13 patients moved to other hospital and 10 were lost to follow-up), 19 discontinued B/F/TAF because of toxicity, 13 discontinued for other reasons, and 6 died during follow-up (Table 3). Meanwhile, the per protocol analysis showed HIV-RNA to be less than 50 copies/ml in 94.4% (420/445): 94.5% (359/380) for patients without an NRTI resistance mutation vs. 93.8% (61/65) for patients with NRTI resistance mutations ($P = 0.2$) (Fig. 1). Patients with M184V or TDF resistance mutations had HIV-RNA less than 50 copies/ml in the per protocol analysis in 92.5% (49/53) and 96.7% (29/30) of cases, respectively ($P = 0.3$ in both groups when compared with no NRTI-RAMs).

The only factor that was associated with having HIV-RNA less than 50 copies/ml at week 48 in both ITT and per protocol was having viral load less than 50 copies/ml at baseline. In the ITT analysis, HIV-RNA less than 50 copies/ml was seen in 86.6% (369/426) of patients with baseline viral load less than 50 copies/ml and in 65% (43/66) of patients with baseline viral load greater than 50 copies/ml ($P < 0.01$). This figure was 96.6% (43/54) and 79.6% (369/382) in the per protocol analysis ($P < 0.01$).

Regarding the 25 patients with viral load greater than 50 copies/ml at week 48, only eight had viral load greater than 200 copies/ml. Resistance test was performed in six patients: no mutations were detected in four, one patient acquired M184V and the other one showed the same complex pattern that had in the past (M41L, D67N,

Table 3. Virological outcomes at week 48.

	No NRTI resistance ($N = 437$)	NRTI resistance ($N = 69$)	All ($N = 506$)
HIV viral load <50 copies/ml	359 (82.2%)	61 (88.4%)	420 (83%)
HIV viral load >50 copies/ml	21 (4.8%)	4 (5.7%)	25 (5.1%)
No data	57 (13%)	4 (5.7%)	61 (11.8%)
Missing data	22	1	23
Switch because of toxicity	17	2	19
Deaths	6	0	6
Switch for simplification	5	0	5
Switch for other reasons	7	1	8

N, number of patients; NRTI, nucleoside reverse transcriptase inhibitor.

K70R, M184V, T215F, K219Q). All but three patients continued with B/F/TAF after week 48 as viral load was attributed to poor adherence and not to lack of B/F/TAF efficacy.

At 48 weeks, there was a median (IQR) increase in the $CD4^+$ cell count of 23.8 cells/μl (−58 to 143); $P = 0.05$. No differences were seen between patients with and without resistance to NRTIs: 16 (−79 to 130) vs. 35 (−56 to 147); $P = 0.68$.

Safety

B/F/TAF was well tolerated. Only 19 (3.7%) patients discontinued owing to adverse events as follows: neurocognitive toxicity, five; gastrointestinal toxicity, four; weight gain, three; renal toxicity, two; muscle pain, two; metabolic toxicity, one; pruritus, one; and rash, one. Six patients died during follow-up, although reasons of death were probably not related with B/F/TAF [sudden death, 3 (probably cardiovascular disease); prostate cancer, 1; lung disease, 1; and SARS-CoV-2 pneumonia, 1].

In 12 cases, patients or doctors decided to change medication for reasons not related to toxicity (simplification or other), and 23 (4.5%) patients were missing at week 48 [probably owing to access problems during the coronavirus disease 2019 (COVID-19) pandemic in most cases].

Discussion

Our results are in line with those reported in clinical trials and demonstrate that switching to B/F/TAF is well tolerated and effective in the real world, even in patients with preexisting NRTI resistance mutations. Virological suppression was 94.4% in patients who continued with B/F/TAF after 48 weeks. Moreover, treatment was switched by the physician in only three of the 25 patients with viral load greater than 50 copies/ml at week 48. The remaining 22 patients continued to take the drug as their physicians considered viral replication to be a blip or a consequence of low adherence. Genotypic resistance analysis was performed in six patients and only in one patient emerged a new RAM (M184V). In the other 19 patients, viral load was very low and RNA amplification for performing resistance test was not possible.

It is important to assess real-world data as patients managed in routine clinical practice are usually more difficult to treat than in clinical trials. Compared with Gilead switch studies 1844 and 1878 [4,5], our population was older, more often female individuals (16.2%), and with a longer duration of HIV infection (13.8 years). Other real-world data on switching to B/F/TAF are consistent with our results and support the use of this combination. Rolle *et al.* [12] reported virological suppression in 94% of 350 PWH older than 50 years. As in our study, patients had long-term antiretroviral experience (median of 20 years and 4 previous combinations; 26 had M184V and 35 NRTI-RAMs). Similarly, in a large cohort of patients treated in Barcelona (Spain), 93% of 695 PWH achieved viral load less than 50 copies/ml at week 48. In this cohort, like ours, M184V was not associated with lower risk of virological failure [10]. Dolutegravir combined with two NRTI has also demonstrated high rates of virological suppression in patients with preexisting or current resistance mutations [13,14].

Data from clinical trials and real-world data show that dolutegravir and bictegravir have a high genetic barrier with no resistance to treatment in patients experiencing virological failure in naive and switching studies of B/F/TAF [5,15,16]. In treatment-experienced individuals, there is growing evidence that even if some NRTI resistance mutations were present, the combination of one INSTI with a high genetic barrier with only one active NRTI may be effective [8,17]. In our study, 93.8% of patients with previous NRTI resistance mutations achieved HIV-RNA less than 50 copies/ml at week 48 (similar to patients with no previously documented resistance). Moreover, although patients with preexisting NRTI RAMs had worse baseline prognostic factors (more time on antiretroviral treatment, a greater number of previous antiretroviral combinations, and a greater number of drug families affected by mutations), the response rate was not penalized. Andreatta *et al.* [7] recently reported similar rates of viral response among virologically suppressed PWH who switched to B/F/TAF. In this study, most of the RAMs detected were performed in pro-viral DNA. Our study goes farther as we evaluate the presence of NRTI resistance mutations in RNA during previous treatment failures. Sequencing with ultrasensitive technique have shown that in virologically suppressed patients, M184V mutation could be progressively cleared over time [18]. This can be the reason why there were no differences between patients with and without previous NRTI resistances. As ultrasensitive techniques are not available in routine practice, we believe our data are of interest for clinicians. New DHHS and European guidelines allow therapy to be switched to a new regimen that includes two fully active drugs (previously three) if at least one has a high genetic barrier [2,3]. Taken together, these data reinforce recent guideline recommendations on the use of bictegravir.

Surprisingly, the greatest efficacy in the ITT analysis was for the group of patients with previous TDF resistance 96.7 vs. 82.2% in no NRTI resistance mutations. This difference was statistically significant. As this data were not confirmed in the per protocol analysis (94.5 vs. 96.7%; $P = 0.3$), this difference was probably because of more missing data in the group without resistance mutations and has no clinical relevance. However, they

reinforce the efficacy of B/F/TAF even with previous mutations associated with loss of TDF sensitivity.

Our study also confirms the good tolerance of the regimen in the real world. Only 19 patients (3.7%) discontinued the drug owing to adverse events. Six deaths were also reported, although none were related to B/F/TAF according to their physicians. Our ITT analysis (83% with viral load <50 copies/ml in week 48) was as we had a high number of missing data at week 48 (11.8%), mainly because of access problems because of the pandemic or patient lost to follow-up. Real-world safety data are important as the HIV population is aging in developed countries, with an increasing number of comorbidities and concomitant medications. Switching to B/F/TAF also provides other benefits in older people, such as low pill burden and fewer drug–drug interactions [19].

The main limitation of our study is its retrospective nature that can lead to some mistakes on data collection. Reasons for B/F/TAF discontinuation may also be missing. In some cases, B/F/TAF was prescribed out of guidelines recommendations. The reasons for a clinician to prescribe a regimen with known resistance may vary, drug interactions, previous drug intolerance, or growing evidence that old genotypes may not have the same impact after years of undetectability [20]. It would have been of great interest to know time of undetectability between resistance test and B/F/TAF switch. Unfortunately, we do not have this data. However, we estimate it was long as median time between resistance test and baseline was 8.8 years, and as routine clinical practice, we perform resistance test when a virological breakthrough is detected. Finally, we have to recognize that more than 50% of the switches were from a regimen with a lower genetic barrier (e.g. NNRTI or RAL with 2 NRTI), this can be a limitation when considering safety of treatment switches from a regimen with potential higher or similar barrier to resistance. In addition to that, we believe that observational retrospective studies based on data from routine clinical practice are necessary to complement data from clinical trials, from patients and situations that are underrepresented in those studies.

In conclusion, switching to B/F/TAF is well tolerated and effective in the real world, even in patients with preexisting M184V or resistance to TDF. These results are in line with those seen in clinical trials and confirm the robustness of this STR combination.

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Conflicts of interest

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