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Effectiveness of switching to B/F/TAF in virologically suppressed people with HIV and with preexisting resistance-associated mutations in Italy: the **BIC-BARRIER Study**

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Background

Bictegravir/emtricitabine/tenofovir alafenamide fumarate (B/F/TAF) is a potent antiretroviral regimen with high efficacy and a strong barrier to resistance[1], currently one of the recommended regimens for people living with HIV (PWH) starting therapy[2]. Registrational randomized clinical trials conducted in patients with no documented resistance associated mutations (RAMs) affecting emtricitabine (FTC), lamivudine (3TC), tenofovir (TFV), and integrase strand transfer inhibitors (INSTIs) have also shown that switching to B/F/TAF from other antiretroviral combinations is effective and well tolerated in virologically suppressed patients[3,4]. Similar results have been observed in patients with known or suspected NRTI resistance, both in clinical trials[5,6] and in real-world studies[7,8].

In PWH who have been exposed to partially suppressive regimens containing 3TC or FTC, the M184V and M184I reverse transcriptase (RT) RAMs frequently emerge[9]. Additionally, the K65R RT RAM can be selected by non-suppressive regimens containing TFV [10]. Resistance to INSTIs is estimated to be around 1% in treatment-naïve individuals[11]. However, viral failure (VF) during combined ART based on raltegravir (RAL) and elvitegravir (EVG) has frequently been associated with the emergence of mutations at positions 66, 92, 143, 148, and 155[12,13].

The aim of our analysis is to estimate the prevalence of RAMs among virologically suppressed bictegravir-naïve PWH switching to B/F/TAF and to evaluate factors associated with viral rebound (VR) during B/F/TAF treatment.

Methods

We investigated the prevalence of preexisting RAMs and Stanford Genotypic Susceptibility Scores (GSS) (with 95% confidence interval, CI) in adult PWH enrolled in the Antiviral Response Cohort Analysis (ARCA - https://www.dbarca.net/) with HIV-RNA<=50 copies/mL at time of their first switching to B/F/TAF (baseline, BL) using cumulative RNA/DNA genotypic resistance test (GRT) results. Mutations with a score of 15 or higher for at least one drug according to Stanford HIV database were classified as major.

In a subset of PWH with virological follow up, we conducted a survival analysis of the time to VR (defined as 2 viral load (VL)>50 copies/mL) using Kaplan-Meier curves and evaluated the association between a number of exposure factors linked to resistance or history of previous virological failure and risk of VR by standard Cox regression analysis after controlling for confounding factors. A sensitivity analysis was conducted using the 200 copies/mL threshold for VR.

Results

We included 739 PWH in the primary analysis, 617 with virological follow-up were included in the survival analysis. Overall, 25.2% were female, median age was 53 years (IQR 43,59). Median nadir of CD4+ T-cells was 165 cells/mL (IQR 39-314), and the median zenith of HIV-1 RNA was 5.06 log copies/mL (IQR 4.37, 5.58). The median CD4+ T-cell count at baseline was 659 cells/mL (IQR 451,881). At time of switching to B/F/TAF, the median time since HIV-1 diagnosis was 16 years (IQR 8,27), and the median duration of virological suppression was 40 months (IQR 14,86). 35.2% of participants had received seven or more ART lines and 9.6% had a history of four or more viral failures. Overall study population and subjects included in the time to failure analysis are detailed in table 1.

Major RAMs to NRTI in use were present in 25.8% (95% CI 22.7-29.2%) and minor RAMs in 19.6% (95% CI 16.8-22.7%) of subjects, TAMs in 19.9% (95% CI 17.1-23.0%). Mutations M184V, M41L and K70R had the highest prevalence. When considering only those who had an available INSTI GRT (N=350), 29.7% (CI 95% 25.0-34.8%) had a cGSS for B/F/TAF <3. Minor INSTI RAMs were present in 10.3% (CI 95% 7.3-14.0%) of subjects, major RAMs in 3.4% (CI 95% 1.8-5.9). Most prevalent mutations were E157Q, T97A, G163R and N155H. RAMs detected, including those against non-nucleoside reverse transcriptase Inhibitors (NNRTIs) and protease inhibitors (Pis), are described in figures 1, 2 and 3.

A previous history of major INSTI RAMs was associated with a risk of VR at >50 copies/mL cut-off, with an unadjusted hazard ratio (HR) of 6.97 (95% CI 1.97-24.60; p=0.003). Despite not statistically significant, a clear trend remained after adjusting for confounding factors (table 2). Conversely, we found no significant association between VR and NRTI RAMs.

Moreover, a history of INSTI VF was associated with VR, showing HR of 3.08 (95% CI 1.37-6.93; p=0.006) which remained significant after adjusting for one set of confounders, with an adjusted HR (aHR) of 3.05 (95% CI 1.32-7.03; p=0.009). Similarly, a history of any VF was associated with VF, showing HR of 2.14 (95% CI 1.03-4.44; p=0.042) which remained significant after adjusting for one set of confounders, with an adjusted HR (aHR) of 2.40 (95% CI 1.12-5.16; p=0.024). Figure 4A and 4B shows Kaplan-Meier (KM) curve for risk of VR according to history of previous VF and major INSTI RAMs.

Similar results were observed when considering 200 cp/ml cut-off for VR. However, while a robust association with previous INSTI VF remained, no significant association with previous VF to any drug was observed (data not shown).

Figure 1. Major and minor RAMs per drug class

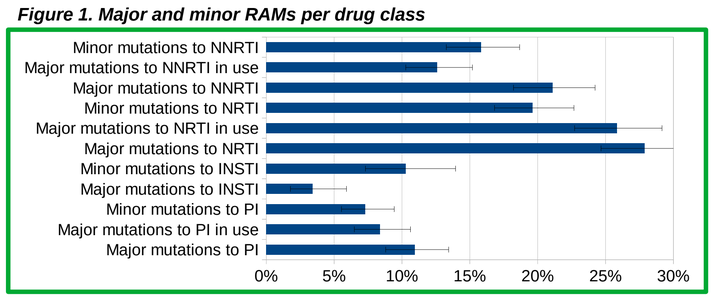


Table 1. Study population

	Overall (N = 739)	Survival analysis (N = 617)
Age, years		
Median (IQR)	53 (43, 59)	53 (43, 58)
Gender, n(%)		
Female	186 (25.2%)	158 (25.6%)
Male	547 (74.0%)	453 (73.4%)
Trans	6 (0.8%)	6 (1.0%)
Mode of HIV Transmission, n(%)		
PWID	148 (20.0%)	119 (19.3%)
Sexual contacts	523 (70.8%)	447 (72.4%)
Other	21 (2.8%)	16 (2.6%)
Unknown	47 (6.4%)	35 (5.7%)
Ethnicity, n(%)		
Caucasian	381 (51.6%)	327 (53.0%)
Black	48 (6.5%)	43 (7.0%)
Asian	2 (0.3%)	1 (0.2%)
Hispanic	19 (2.6%)	16 (2.6%)
Other/Unknown	289 (39.1%)	230 (37.3%)
HBsAg, n(%)		
Negative	506 (82.1%)	418 (82.1%)
Positive	110 (17.9%)	91 (17.9%)
Not tested	0 (0.0%)	0 (0.0%)
HCVAb, n(%)		
Negative	266 (60.5%)	196 (57.1%)
Positive	174 (39.5%)	147 (42.9%)
Not tested	0 (0.0%)	0 (0.0%)
Calendar year of switch		
Median (IQR)	2020 (2020, 2021)	2020 (2020, 2021)
CD4 count, cells/mmc		
Median (IQR)	659 (451, 881)	673 (456, 898)
Viral load, log10 copies/mL		
Median (IQR)	1.30 (1.30, 1.30)	1.30 (1.30, 1.30)
Time from last GRT, months		
Median (IQR)	79 (30, 140)	74 (28, 134)
Duration of VL below 50 copies/mL, months		
Median (IQR)	40 (14, 86)	41 (16, 88)
HIV subtype, n(%)		
B	544 (73.6%)	441 (71.5%)
Number of previous ART lines		
Median (IQR)	4 (2, 8)	4 (2, 8)
1-3	302 (40.9%)	254 (41.2%)
4-6	177 (24.0%)	146 (23.7%)
7+	260 (35.2%)	217 (35.2%)
Number of previous ART failures		
Median (IQR)	0 (0, 2)	0 (0, 2)
None	429 (58.1%)	357 (57.9%)
1-3	239 (32.3%)	202 (32.7%)
4+	71 (9.6%)	58 (9.4%)
HIV drug resistance, n(%)		
Minor NRTI	145 (19.6%)	123 (19.9%)
Major NRTI	206 (27.9%)	170 (27.6%)
Minor NNRTI	117 (15.8%)	100 (16.2%)
Major NNRTI	156 (21.1%)	127 (20.6%)
Minor PI	54 (7.3%)	42 (6.8%)
Major PI	81 (11.0%)	68 (11.0%)
Minor INSTI	36 (4.9%)	30 (4.9%)
Major BIC	12 (1.6%)	12 (1.9%)
Nadir CD4 count, cells/mm³		
Median (IQR)	165 (39, 314)	161 (31, 309)
Zenith HIV-RNA, log copies/mL		
Median (IQR)	5.06 (4.37, 5.58)	5.04 (4.35, 5.58)
Time for HIV diagnosis, years		
Median (IQR)	16 (8, 27)	15 (7, 27)
Class of anchor of previous regimen, n(%)		
INSTI	521 (70.5%)	441 (71.5%)
NNRTI	63 (8.5%)	49 (7.9%)
PI	102 (13.8%)	87 (14.1%)

Table 2. Unadjusted and adjusted relative hazards of VR>50 copies/mL from fitting a Cox regression model.

	Unadjusted RH (95% CI)	p-value	Adjusted[1] RH (95% CI)	p-value	Adjusted[2] RH (95% CI)	p-value
Any NRTI DRM						
No	1.00		1.00		1.00	
Yes	1.22 (0.57, 2.61)	0.609	0.88 (0.34, 2.31)	0.802	1.44 (0.65, 3.21)	0.367
M184I or M184V						
No	1.00		1.00		1.00	
Yes	1.20 (0.51, 2.79)	0.680	0.74 (0.26, 2.06)	0.561	1.31 (0.55, 3.13)	0.542
Any major NRTI DRM						
No	1.00		1.00		1.00	
Yes	1.12 (0.51, 2.46)	0.768	0.76 (0.28, 2.08)	0.588	1.35 (0.59, 3.05)	0.477
Any INSTI DRM						
No	1.00		1.00		1.00	
Yes	2.94 (0.95, 9.14)	0.063	1.67 (0.46, 6.08)	0.438	1.69 (0.51, 5.57)	0.392
Any major INSTI DRM						
No	1.00		1.00		1.00	
Yes	6.97 (1.97, 24.60)	0.003	4.73 (1.00, 22.44)	0.050	4.00 (0.99, 16.24)	0.052
Any major BIC DRM						
No	1.00		1.00		1.00	
Yes	6.97 (1.97, 24.60)	0.003	4.73 (1.00, 22.44)	0.050	4.00 (0.99, 16.24)	0.052
GSS of BIC regimen						
>=3	1.00		1.00		1.00	
0-2.75	2.06 (0.77, 5.54)	0.152	2.64 (0.76, 9.13)	0.126	2.41 (0.83, 7.00)	0.106
GSS of BIC drug						
Sensitive	1.00		1.00		1.00	
Resistant	5.85 (1.65, 20.65)	0.006	4.11 (0.88, 19.23)	0.073	3.59 (0.90, 14.23)	0.069
Previous history of VF						
No	1.00		1.00		1.00	
Yes	2.14 (1.03, 4.44)	0.042	1.94 (0.68, 5.60)	0.218	2.40 (1.12, 5.16)	0.024
Previous history of INSTI VF						
No	1.00		1.00		1.00	
Yes	3.08 (1.37, 6.93)	0.006	2.47 (0.93, 6.51)	0.069	3.05 (1.32, 7.03)	0.009
Previous number of VF						
per 1 additional	1.15 (0.96, 1.38)	0.131	1.16 (0.95, 1.42)	0.146	1.21 (1.00, 1.46)	0.055

[1]for age, gender, ethnicity, HIV subtpye , year of BIC initiation,number of previous regimens failure, HIV-RNA at switch and time from last available GRT

[2]for ethnicity, HIV subtpye , year of BIC initiation,HIV-RNA at switch and time from last available GRT

Figure 4A. KM of the time to viral rebound > 50 copies/mL by history of previous VF

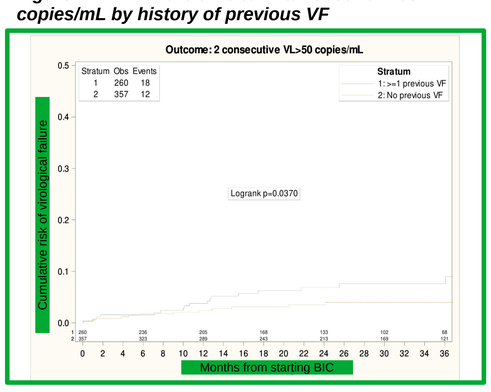


Figure 4B. KM of the time to VR > 50 copies/ml by detection of major INSTI resistance

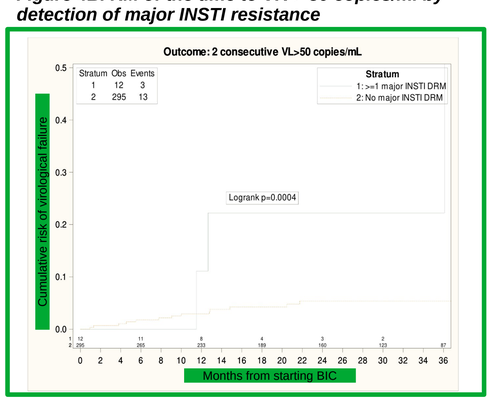


Figure 3. INSTI RAMs

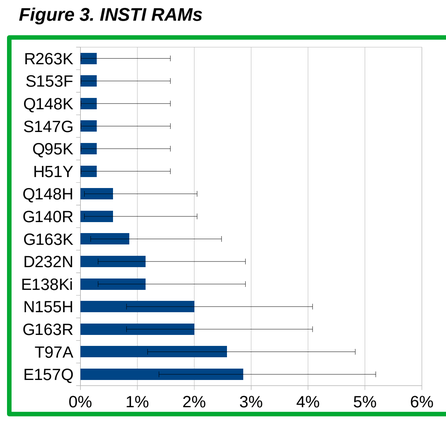


Figure 2. NRTI RAMs

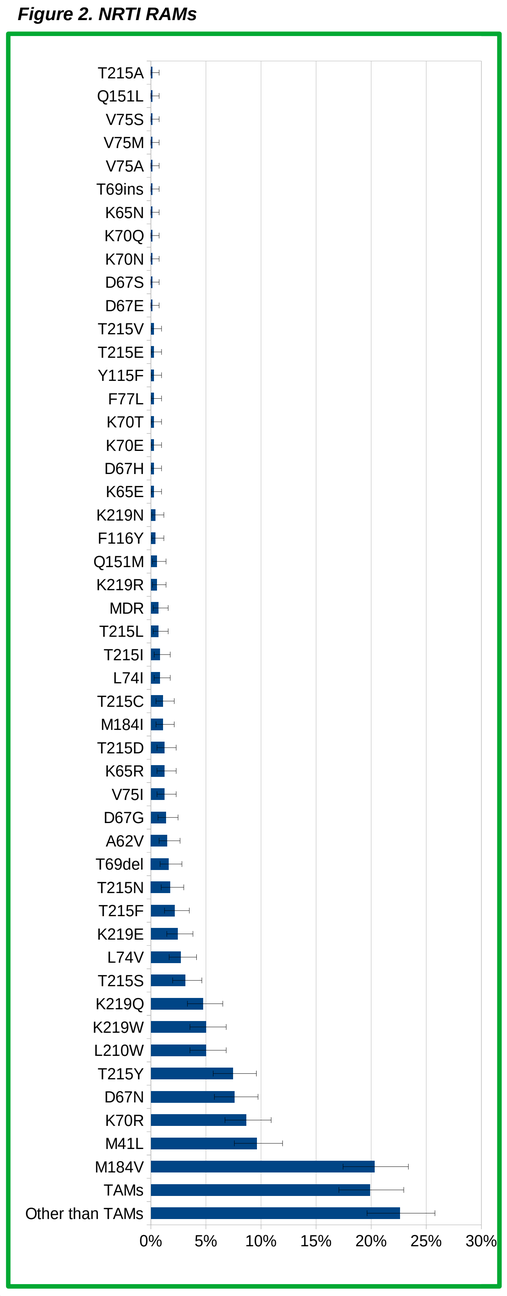
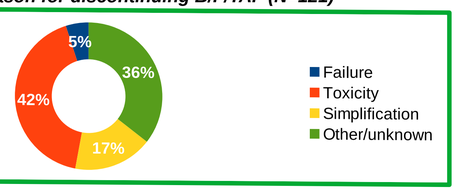


Figure 5. Reason for discontinuing B/F/TAF (N=121)



Conclusions

We found a prevalence of major NRTI RAMs among virologically suppressed subjects switching to B/F/TAF of 25.8%, which is comparable with that seen in a clinical trial (26% in trial 4030[6]), but higher than that reported by an Italian retrospective study (19.1%[8]) and a Spanish study (13.9%[14]). Prevalence of major INSTI RAMs was infrequent (3.4%) and comparable with that found in a previous Italian retrospective study (2.1%[8]).

B/F/TAF appears to remain effective in the presence of NRTI RAMs; however, evidence of past INSTI failures and of major INSTI RAMs pose a risk for VR. These findings are in line with those shown by other previous observational studies[8,14].

Analysis sponsored by Gilead Sciences

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