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Bictegravir/emtricitabine/tenofovir alafenamide ensures high rates of virological suppression maintenance despite previous resistance in PLWH who optimize treatment in clinical practice ☆

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ABSTRACT

Objectives: We evaluated virological response and resistance profiles in individuals who were virologically suppressed who switched to bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) in real life.
Methods: Survival analysis was used to assess probability of virological rebound (VR). Cumulative major resistance mutations (MRM) and cumulative genotypic susceptibility score (cGSS) were evaluated before the switch.
Results: Overall, 283 individuals virologically suppressed for a median (interquartile [IQR]) time of 7 (3–9) y were analyzed. Of these, 20.8% were in first-line treatment, 13.1% were highly treatment-experienced (HTE), and 8.5% had experienced previous integrase inhibitor (INI)-failures. Before the switch, nucleotide reverse transcriptase inhibitor NRTI MRM prevalence was 29% (M184V:13.8%; any thymidine analogue mutation: 14.1%; K65R: 0.7%; K70E 0.4%); only three (2.1%) individuals showed INI major resistance mutations (Y143C/H/R [n = 1]; Y143C [n = 1]; N155H [n = 1]), and 82.0% of individuals received fully active B/F/TAF. Ninety-six wk after switch, the probability of VR was 5%, with only 12 events of VR at a median (IQR) viremia level of 284 (187–980) copies/mL, mainly transient. No significant associations between virological outcomes and genotypic susceptibility to B/F/TAF were observed. People who experienced previous INI failures showed a significantly higher adjusted hazard ratio (AHR [95% CI]) to experience VR under B/F/TAF (3.9 [1.1–13.4], $P = 0.031$). This AHR increased in people who experienced INI failures and received partially active B/F/TAF (5.5 [1.4–21.1], $P = 0.013$).
Conclusion: Within 96 wk, a switch to B/F/TAF in individuals who were virologically suppressed ensured a very high rate of virological control in a clinical setting. Previous resistance alone did not affect B/F/TAF response. However, people who had previous INI failures were more prone to losing virological control under B/F/TAF.

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1. Introduction

Because of the overwhelming success of combined antiretroviral therapy (cART), people living with HIV (PLWH) have improved their quality of life so much that HIV infection has become a manageable chronic disease in the majority of cases [1]. However, considering that cART is lifelong, PLWH, despite commonly attaining stable virological suppression, may need to change their treatment to improve convenience and tolerability, increase genetic barrier, and avoid long term toxicity [2]. In this context, treatment optimization is currently the most frequent reason for switching in individuals who are virologically suppressed and HIV-1–positive [3]. Given that it is fundamental to maintain virological suppression without jeopardizing future treatment options, a treatment switch should be considered only after full revision of a patient's antiretroviral therapy (ART) history, including cumulative resistance, previous failures, time of virological suppression before the switch, and tolerability issues [4,5]. Single tablet regimens (STRs) have played an important role in treatment optimization strategies; the current STRs available contain potent and high genetic barrier drugs, and these strategies are taking over multipill regimens [3]. This is the case of bictegravir, the latest approved second-generation integrase inhibitor (INI), which is administered in combination with emtricitabine and tenofovir alafenamide as an STR (B/F/TAF) [6]. In both clinical trials and observational studies, B/F/TAF showed excellent results in terms of efficacy, tolerability, and genetic barrier as a treatment optimization strategy in individuals who were virologically suppressed [7–9]. In clinical trials, the role of previous resistance on B/F/TAF efficacy was not relevant; several studies demonstrated that, despite a considerable number of patients switching to B/F/TAF with previous resistance affecting the nucleotide reverse transcriptase inhibitors (NRTI) backbone of the regimen (including M184V mutations or thymidine analogue associated mutations), no effect on virological response was observed [9–12]. The usage of B/F/TAF is increasing in clinical settings and the first real-life data confirm that previous resistance did not affect B/F/TAF response at 48 wk of observation [7,13]. Despite these reassuring results, it should be taken into account that amongst the individuals in stable suppression, there are a number of highly treatment-experienced (HTE) people with complex histories of previous failures and/or resistance in clinical settings [14–16]. These individuals might generate uncertainty in clinicians' decision-making; potent and high genetic barrier STRs based on three drugs, such as B/F/TAF, might be a good option for their treatment optimization. However, this category of individuals is poorly represented in clinical trials because individuals with previous failures and/or resistance are often excluded. Thus, in this context, additional evaluation of data from real-life settings might provide important information. Based on these considerations, the aim of this study was to evaluate virological response according to previous NRTI-resistance and/or previous INI virological failures in virologically suppressed PLWH who switched to B/F/TAF in real-life settings.

2. Materials and methods

2.1. Study population

This is an Italian retrospective, observational study including several clinical and virological centers involved in HIV care in Central-Northern Italy. Individuals who switched to B/F/TAF for any reason were included in the analysis according to the following criteria: (i) age ≥18 y, (ii) virologically suppressed (plasma HIV-RNA ≤50 copies/mL) on any ART regimen at the moment of B/F/TAF switch, (iii) availability of at least one previous plasma HIV-1 RNA or HIV-DNA genotype resistance test (GRT), and (iv) availability of a virological follow-up after switching to B/F/TAF. As previously described, individuals were considered HTE if they had accumulated resistance to at least two drug classes and had previously experienced at least four therapy changes before the B/F/TAF switch [14].

2.2. Ethics

This study was approved by the ethics committee of Tor Vergata Hospital (Ethics Approval No. 216/16, 26 January2022). The research was conducted on data routinely collected for clinical purposes and in accordance with the principles of the Declaration of Helsinki and the Italian Ministry of Health. All data used in the study were previously anonymized according to the requirements set by the EU Regulation 2016/679 and by Italian Data Protection Code. All information, including virological and clinical data, was recorded in an anonymized database.

2.3. Sanger sequencing and drug resistance evaluation

Sanger sequencing for protease, reverse transcriptase, and integrase was carried out as previously described [17,18]. Resistance interpretation was made according to the Stanford algorithm HIVdb version 9.0 (https://hivdb.stanford.edu/). For each individual, the cumulative resistance to protease inhibitors (PIs), NRTIs, non-NRTIs (NNRTIs), and INIs was evaluated by considering the resistance detected in all available GRTs before the B/F/TAF switch. Cumulative genotypic susceptibility scores (cGSS) for bictegravir (BIC), emtricitabine (FTC), and TAF were carried out using the Stanford algorithm by imputing all cumulative mutations detected in previous GRTs (https://hivdb.stanford.edu/hivalg/by-mutations/). Each drug was considered fully susceptible (no resistance or potential low-level resistance) or not susceptible (low-level resistance or intermediate resistance or high-level resistance) according to algorithm results.

Regarding BIC, patients for whom an integrase GRT was not available were considered infected with viruses susceptible to BIC if they never failed or were never previously exposed to INIs. In the case of individuals with previous virological failure to first-generation INIs, they were considered infected with viruses harboring intermediate resistance to BIC. In individuals who experienced virological rebound for whom a GRT was requested under B/F/TAF, potential selection of new resistance mutations was evaluated.

2.4. Objectives

The primary objective of the study was to evaluate the probability of virological rebound (VR) after starting B/F/TAF according to the presence of cumulative previous resistance before the switch. Virological rebound was defined as two consecutive viremia >50 copies/mL or one viremia >200 copies/mL. The effect of previous resistance was evaluated according to cGSS calculation.

Secondary objectives were: (i) to determine the effect of previous INI failures before the B/F/TAF switch on VR, (ii) to determine the effect of a combination of previous INI failures and cGSS before the B/F/TAF switch on VR, (iii) to evaluate other potential predictors of VR, (iv) to evaluate the emergence of resistance in individuals who experienced VR under B/F/TAF, and (v) to evaluate the role of previous resistance on experiencing a blip after the B/F/TAF switch. Viral blip was defined as a single HIV-RNA in the range of 51–199 copies/mL preceded and followed by ≤50 copies/mL measurements.

2.5. Statistical analysis

All analyses were executed using the SPSS version 26.0 software package for Windows (SPSS Inc., Chicago, IL; IBM, Armonk,

Table 1
Patients' characteristics at the moment of B/F/TAF switch.

Variables	Overall (N=283)
Male sex, n (%)	234 (82.7)
Age, median (IQR), y	50 (42-56)
Risk Factor, n (%)	
Homosexual	139 (49.1)
Heterosexual	93 (32.9)
Drug abuser	27 (9.5)
Sexual[a]	6 (2.1)
Other/Unknown	18 (6.4)
HBV coinfection[b]**, n (%)**	60 (21.1)
HCV coinfection, n (%)	21 (7.4)
Subtype B, n (%)	224 (79.2)
Nationality, n (%)	
Italian	238 (84.1)
Foreigner	34 (12.0)
Unknown	11 (3.9)
Time under cART, median (IQR), y	8 (4-13)
Time under cART, y, n (%)	
<1	32 (11.3)
1-5	50 (17.7)
5-10	107 (37.8)
>10	94 (33.2)
Time under virological suppression, median (IQR), y	7 (3-9)
Time under virological suppression, y, n (%)	
<1	19 (6.7)
1-5	82 (29.0)
>5	182 (64.3)
Viremia Zenit, copies/mL, n (%)	
<100,000	119 (42.0)
100,000-500,000	100 (35.3)
>500,000	51 (18.0)
Unknown	13 (4.6)
Nadir CD4 count, cells/mm^3, n (%)	
≤200	122 (43.1)
>200	148 (52.3)
Unknown	13 (4.6)
HIV-RNA Target not detected at baseline, n (%)	149 (52.7)
Baseline CD4 cell count, median (IQR) cells/mm^3	662 (505-867)
Number of previous regimens received	
1	59 (20.8)
2	75 (26.5)
3	88 (31.1)
≥4	61 (21.6)
Previous exposure to RAL/EVG	147 (51.9)
Previous exposure to DTG	51 (18.0)
Previous virological failures, n (%)	
None	161 (56.9)
1	56 (19.9)
2	27 (9.5)
≥3	29 (10.2)
Unknown	10 (3.5)
Previous INI virological failures, n (%)	
None	258 (91.2)
≥1[c]	24 (8.5)
Highly-treatment experienced individuals, n (%)	37 (13.1)
Last regimen before switch, n (%)	
EVGb + 2 NRTIs	106 (37.5)
NNRTI + 2 NRTIs	90 (31.8)
DTG + 2 NRTIs	29 (10.2)
DRVb or ATVb + 2 NRTIs	20 (7.1)
RAL + 2 NRTIs	10 (3.5)
Other[d]	15 (5.3)
Unknown	13 (4.6)
Year of B/F/TAF start, median (IQR)	2019 (2019-2020)
Reasons of switch	
Increasing genetic barrier	206 (72.8)
Decreasing number of pills and/or drugs	36 (12.7)
Increasing number of drugs	13 (4.6)
Clinician's decision	3 (1.0)
Toxicity	5 (1.8)
Unknown	20 (7.1)

(*continued on next page*)

Table 1 (*continued*)

Variables	Overall (N=283)
GRT available at B/F/TAF start, n (%)	
≥1 only from plasma samples	235 (83.0)
≥1 from plasma & PBMC samples	38 (13.4)
≥1 only from PBMC samples	10 (3.5)
Time of last viremia follow up available, median (IQR), wk	83 (68-96)

ATVb, boosted-atazanavir; B/F/TAF, bictegravir/emtricitabine/tenofovir; cART, combined antiretroviral therapy; CD4; DRVb, boosted-darunavir; DTG, dolutegravir; EVG, elvitegravir; HBV, hepatitis B virus; HCV, hepatitis C virus; INI, integrase inhibitor; IQR, interquartile range; NNRTI, non–nucleotide reverse transcriptase inhibitors; NRTI, nucleotide reverse transcriptase inhibitor; RAL, raltegravir.

[a] Unknown sexual behaviours.

[b] Individuals positive for HBsAg or reported as HBV$^+$ by clinicians.

[c] INI failures experienced with corresponding drugs: RAL n = 11; RAL and EVG n = 6; RAL and DTG n = 1; DTG n = 2; and EVG n = 4.

[d] DTG + 3TC (n = 3); DTG + RPV (n = 1), RAL + PI (n = 6); RAL + NNRTI (n = 2), DRVb monotherapy (N=1), RAL + 2NRTIs + DRVb (n = 2).

NY). For all analyses, *P* values of less than 0.05 were considered significant.

Kaplan-Meier curves were used to evaluate the probability of experiencing VR after the switch to B/F/TAF on the overall population and according to cGSS and INI failure experience. Cox regression analysis was performed to investigate the role of factors associated with virological response by considering demographic, viro-immunological, and treatment parameters (variables included in the models are mentioned in the footnotes of Table 2 and reported in Supplementary Table 1). Only variables significantly associated with virological response at univariable analysis ($P < 0.05$) were retained in multivariable models. Analyses were performed on patients that did not discontinue B/F/TAF (on treatment approach). Patients' follow-ups were censored at B/F/TAF discontinuation. In individuals who experienced VR and for whom a subsequent GRT was available, resistance after VR was evaluated with a descriptive analysis.

3. Results and discussion

3.1. Patients' characteristics

Overall, 283 individuals who were virologically suppressed, mainly males (82.7%) with a median (interquartile range [IQR]) age of 50 (42–56) y, were analyzed (Table 1). They had a long treatment history with a median IQR of 8 (4–13) y under ART, with a median IQR duration of virological suppression of 7 (3–9) y. Almost half of the participants had previously received raltegravir or elvitegravir (51.9%), and 18.0% had previously received dolutegravir; 8.5% of the individuals failed a previous regimen containing an INI drug (mainly elvitegravir and/or raltegravir). The majority of the individuals switched to B/F/TAF to increase genetic barrier of the regimen; in fact, most (72.8%) were under a low genetic barrier regimen containing NNRTIs or first-generation INIs before switching to B/F/TAF. A considerable proportion of the individuals switched to B/F/TAF after first-line treatment (20.8%) and around half of the individuals (52.7%) started B/F/TAF with viremia target not detected. Of note, 37 (13.1%) HTE individuals started B/F/TAF; of these, 28 (75.7%) and 9 (24.3%) had accumulated resistance to two and three drug classes, respectively.

3.2. Cumulative resistance at B/F/TAF switch

An overview of cumulative resistance and genotypic susceptibility is reported in Fig. 1. All individuals had an available GRT before switching to B/F/TAF, mainly performed from plasma samples (96.4%, Table 1). Overall, 29.0% of individuals showed at least one cumulative major resistance mutation before switch, mainly

Table 2
Factors associated with virological rebound in virologically suppressed patients switching to B/F/TAF treatment.

Variables	HR to experience virological rebound					
	Crude[a]		Adjusted[b]		Adjusted[c]	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age, per 5 y older	**0.7 (0.5-0.9)**	**0.011**	0.8 (0.6-1.1)	0.144	0.8 (0.6-1.1)	0.119
Time of previous virological suppression, y						
<1 y[d]	1		1		1	
1-5 ys	0.9 (0.2-3.9)	0.821	1.0 (0.2-4.7)	0.970	0.7 (0.1-3.4)	0.681
>5 ys	**0.1 (0.0-0.6)**	**0.015**	0.2 (0.0-1.2)	0.080	**0.1 (0.0-0.8)**	**0.031**
Any INI failure before B/F/TAF switch	**6.4 (1.9-21.2)**	**0.003**	**3.9 (1.1-13.4)**	**0.031**		
cGSS & INI failure before B/F/TAF						
Fully active regimen & no INI failure[d]	1		-	-	1	
Partially active regimen or INI failure	0.6 (0.1-4.9)	0.646	-	-	0.7 (0.1-5.6)	0.677
Partially active regimen & INI failure	**6.7 (1.8-25.3)**	**0.005**	-	-	**5.5 (1.4-21.1)**	**0.013**

NOTE: Only the variables significantly associated with virological rebound ($P < 0.05$) at univariable analysis are reported.
CI, confidence ratio; B/F/TAF, bictegravir/emtricitabine/tenofovir; HR, hazard ratio; INI, integrase inhibitor.

[a] The following variables were tested for their potential role as predictors of virological rebound after B/F/TAF: sex, age, risk factors, HCV/HBV coinfection, subtype, CD4 count at switch, nadir CD4 count, viremia Zenith, viremia target not detected at switch, time of previous virological suppression, time under antiretroviral therapy, number of previous virological failures, previous INI failure experience, number of regimens experienced, being HTE, reasons of switch, cumulative drug resistance, cumulative genotypic susceptibility score, combined cumulative genotypic susceptibility score, and previous INI failure experience.

[b] Adjusted for variables significantly associated ($P < 0.05$) with virological rebound at univariable analyses considering only previous virological INI failures.

[c] Adjusted for variables significantly associated ($P < 0.05$) with virological rebound at univariable analyses considering the presence of resistance and previous virological INI failures in combination.

[d] Reference (dummy). 95% CI.

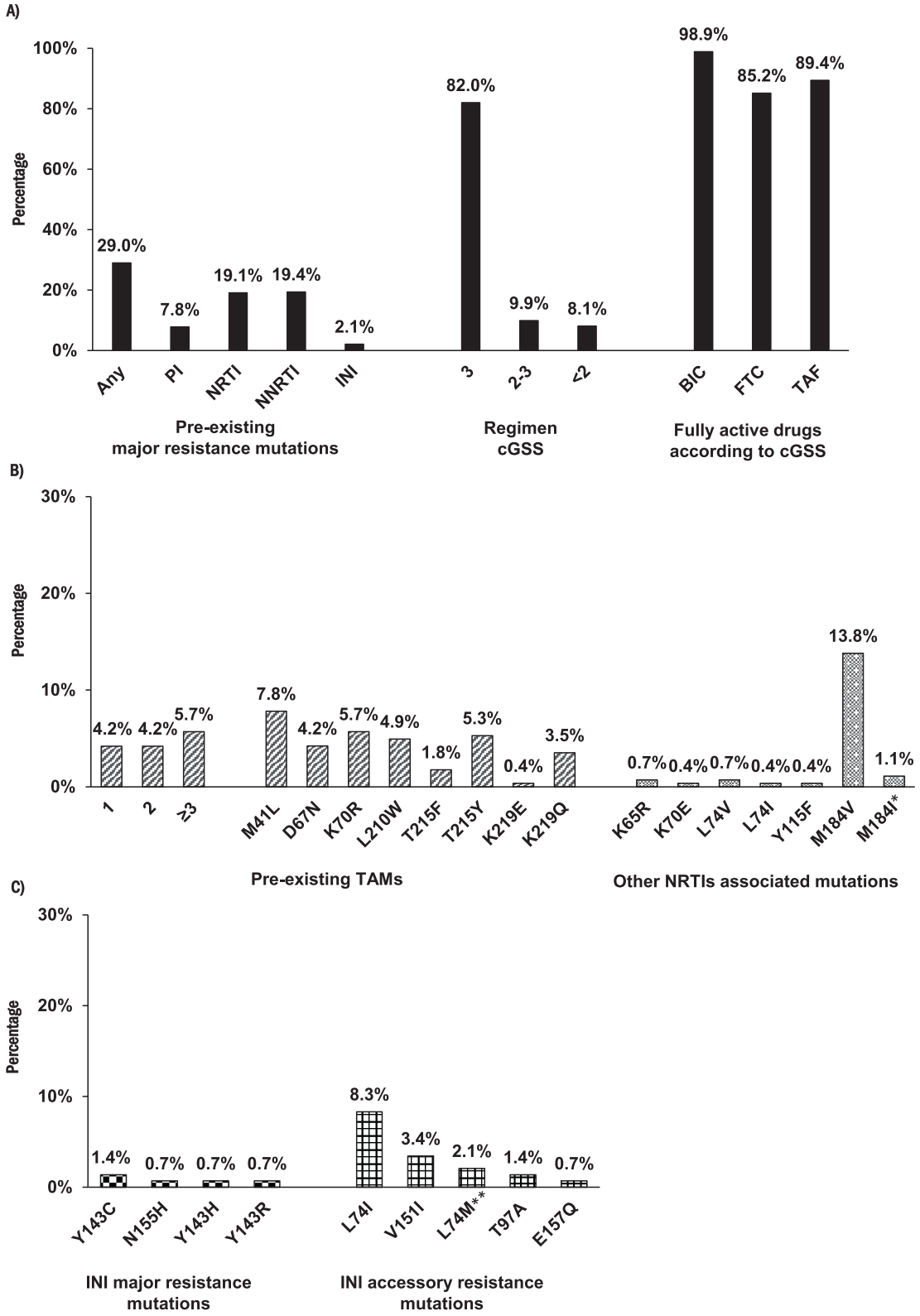

Fig. 1. Overview of cumulative resistance and genotypic susceptibility score (cGSS) at Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) switch. A) Prevalence of individuals harbouring resistance to protease inhibitors (PIs), nucleot(s)ide reverse transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs), and integrase inhibitors (INIs) and cGSS at B/F/TAF switch. B) Detailed overview of NRTI resistance at B/F/TAF switch. *Two of three individuals harboured M184I/V as mixture. C) Detailed overview of INI resistance at B/F/TAF switch. Analyses performed on 145 individuals for whom an integrase GRT was available before switch. **Two of three individuals harboured L74I/M as mixture.

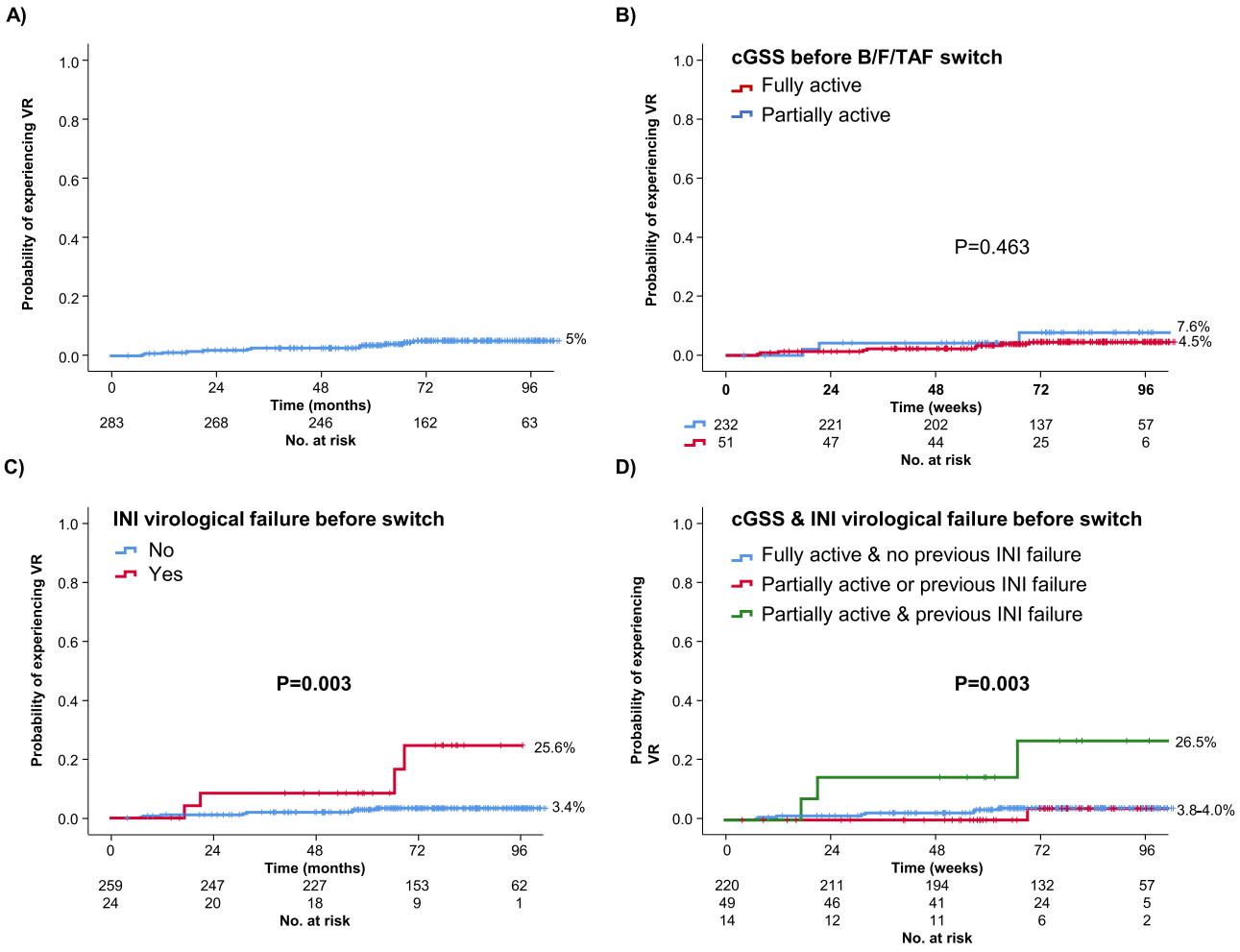

Fig. 2. Kaplan-Meir estimates of the probability of experiencing virological rebound at 24 mo under B/F/TAF treatment stratified according to genotypic susceptibility and previous INI failure experience. A) Virological rebound stratified in overall population. B) Virological rebound stratified according to B/F/TAF genotypic susceptibility. C) Virological rebound stratified according to previous INI failure experience D) Virological rebound stratified according to B/F/TAF genotypic susceptibility and previous INI failure experience. *P* values were calculated using the Peto and Peto modification of the Gehan–Wilcoxon test and Log-rank test, when appropriate. A *P* value < 0.05 was considered statistically significant. VR, virological rebound.

related to RTIs (NRTI: 19.1%; NNRTI: 19.4%). cGSS revealed that 91.9% of individuals had at least two active drugs amongst B/F/TAF (cGSS $\geq$2); 82.0% of individuals showed a completely active regimen (cGSS = 3).

Regarding NRTI resistance, the M184V mutation showed the highest prevalence in the population (13.8%); thymidine analogue associated mutations (TAMs) were detected in 14.1% of individuals, while other NRTI mutations such as K65R, K70E, L74I/V, and Y115Y showed a prevalence <1%. Regarding INI resistance, of the 145 patients for whom an integrase GRT was available before the switch to B/F/TAF, only three (2.1%) showed INI major resistance mutations (Y143C/H/R [n = 1]; Y143C [n = 1]; and N155H [n = 1]), while 6.7% showed INI accessory resistance mutations (L74I/M, T97A, V151I, and E157Q).

3.3. Virological response to B/F/TAF switch

Overall, 12 events of VR at a median IQR viremia level of 284 (187–980) copies/mL were recorded. Ninety-six wk after the switch to B/F/TAF, the probability of losing virological control was 5.0% (Fig. 2, Panel A). By stratifying VR probability according to cGSS at the B/F/TAF switch, no significant difference amongst individuals who received a fully active regimen in comparison with those who received a partially active regimen was observed (7.6% vs. 4.5%; *P* = 0.463; Fig. 2, Panel B). Regarding the stratifications according to past INI failures, individuals who had experienced virological failures with INI before switching to B/F/TAF showed a significantly higher probability of experiencing VR under B/F/TAF compared with those who never failed INI regimens (25.6% vs. 3.4%, *P* = 0.003; Fig. 2, Panel C). By combining information on previous INI failures with cGSS, individuals who had experienced previous INI virological failures and received B/F/TAF as a partially active regimen showed the highest probability (26.5%) of experiencing VR (*P* = 0.003; Fig. 2, Panel D).

Uni-multivariable Cox regression analyses are summarized in Table 2, while a complete overview of all univariable models built is reported in Supplementary Table 1. Individuals who had experienced an INI virological failure before the B/F/TAF switch showed a higher AHR (95% CI) of experiencing VR compared with those had never failed regimens containing this drug class (3.5 [1.0–12.7], *P* = 0.047). Considering previous failures combined with partial susceptibility (cGSS <3), those who had experienced an INI virological failure before switching to B/F/TAF and received the regimen as partially active showed a significantly higher AHR of experiencing VR compared with those who had never failed with INI and did not show any resistance related to B/F/TAF at the time of the switch (5.4 [1.4–20.7], *P* = 0.014). Amongst other predictors, only a virological suppression of more than 5 y was associated

with a significantly lower AHR to experience VR compared with a time of virological suppression under 1 y (0.1 [0.0–0.8], $P = 0.029$).

The probability of experiencing viral blips was 7.2% 96 wk after the B/F/TAF switch. By stratifying the probability according to cGSS, we did not find any statistically significant difference amongst individuals receiving a partially active regimen compared with those who received a fully active regimen (6.3% vs. 7.4%, $P = 0.817$).

3.4. Overview of virological rebound and resistance detected under B/F/TAF treatment

An overview of the 12 individuals who experienced VR is reported (Table 3). Amongst them, four had experienced a previous failure to first-generation INIs; three of these four individuals (25.0%) were HTE and had accumulated resistance to at least one drug included in B/F/TAF (two to FTC, and one to FTC and TAF). With regards to resistance, a GRT was performed for three individuals. No new resistance was observed in reverse transcriptase nor integrase. Ten of these individuals with VR (83.3%) re-suppressed without changing treatment, one (8.3%) changed treatment, and one (8.3%) was lost at follow-up. Of note, a re-suppression without treatment change was observed in one unique individual harbouring N155H in integrase together with M184V and K70R mutations in reverse transcriptase before B/F/TAF.

3.5. Discussion

In the present manuscript, the effect of past resistance together with previous INI virological failures on B/F/TAF treatment in virologically suppressed PLWH was evaluated. B/F/TAF showed excellent efficacy in maintaining virological suppression as previously observed [7,8,19,20]. In fact, 96 wk after starting B/F/TAF, the probability of VR was low (5%), and only 12 events of VR, mainly at low-level viremia, were recorded. These few events were mostly transitory because 10 of these 12 individuals re-suppressed without therapy change; moreover, amongst the three patients for whom resistance was tested, none developed resistance after virological rebound. These reassuring results are of great importance because they were retrieved from a heterogenous population of PLWH who followed a clinical routine in real life. In this study, a consistent proportion of individuals switching from their first-line treatment was included; on the other hand, people with long treatment histories, previous experiences with INIs, past resistance to NRTIs, and even people (although few) who had experienced previous INI virological failures and INI resistance, were present. Despite this, even though a consistent proportion of the individuals received B/F/TAF as a not-fully active regimen (18%), mainly because of the presence of M184V and/or TAMs, the probability of losing virological control was low regardless of past resistance. This result confirms data from clinical trials and from the first preliminary real-life data [9–13]. The prevalence of pre-existent M184V and of other NRTI mutations found in our population was similar to that observed in other studies [10,11,13]. Regarding integrase resistance, a recent pooled analysis evaluating the effect of pre-existent INI resistance on B/F/TAF showed that patients with primary INI resistance maintained virological suppression through 48 wk of B/F/TAF treatment [21]. These results were similar in our population, where amongst the three cases with pre-existent INI resistance that switched to B/F/TAF, one of them with a N155H mutation (theoretically not associated with BIC resistance) experienced a virological rebound after 88 wk of B/F/TAF treatment, followed by re-suppression without therapy change.

Besides resistance, 13% of individuals were HTE and around 9% had experienced a virological failure with an INI-based regimen before the switch to B/F/TAF. Virologically suppressed HTE individuals remain a category of individuals that generates concern in clinical practice [14–16]; despite this, we did not observe any significant difference in B/F/TAF response in the HTE population compared with other people. However, it should be considered that only around a quarter of the HTE individuals in our population showed a high level of resistance (specifically to three drug classes), and very few individuals showed resistance to INIs. Therefore, our results may not be applicable to fragile HTE individuals with multidrug resistance (including resistance to INIs).

Of note, we found that the subgroup of HTE individuals who had previously failed an INI-based regimen had a high risk of experiencing VR under B/F/TAF, and this risk slightly increased when they received a non-fully susceptible regimen. Although supported by few numbers, previous failures to first-generation INIs (combined or not with poor susceptibility to the NRTI backbone) might be the driving factor leading to virological rebound under B/F/TAF. Thus, this factor should be carefully considered before switching to this regimen.

This finding reinforces the fact that the revision of histories on previous INI failures (especially if under first-generation drugs) before switching to B/F/TAF remains crucial, as already recommended by current guidelines [4,5].

Another important piece of information provided by our study is that a long period of virological suppression (>5 y) before switching to B/F/TAF is positively associated with the maintenance of virological control, as previously demonstrated in other studies that evaluated switches in virologically suppressed individuals [22,23].

This study has some limitations, mainly related to the low number of VR events recorded because of the high effectiveness of B/F/TAF. The typical lack of data regarding adherence in observational cohorts might be an additional bias, but it remains anectodical because of the transient rebounds observed. Moreover, even though Sanger sequencing remains the most used and standardized technique to test resistance, our resistance evaluation was partial because of the low sensitivity of this technique [24,25]. In this context, analysis of viral quasispecies in HIV-DNA through next-generation sequencing at B/F/TAF baseline might provide important new information, especially in those patients who experienced previous virological failures to first-generation INIs.

In conclusion, B/F/TAF in a real-life setting showed such high efficacy in maintaining virological control, that, apart from in people who have histories of failure with INIs, it can be used without particular concerns in individuals who are virologically suppressed, regardless of previous NRTI resistance. Further studies collecting a larger number of VR are needed to confirm these results and better evaluate the effect of previous INI resistance.

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Competing interests

None declared.

Ethical approval

This study was approved by the ethics committee of Tor Vergata Hospital (Ethics Approval No. 216/16, 26 January2022). The research was conducted on data routinely collected for clinical purposes and in accordance with the principles of the Declaration of Helsinki and the Italian Ministry of Health. All data used in the study were previously anonymized according to the requirements set by the EU Regulation 2016/679 and by Italian Data Protection

Table 3
Overview of individuals who experienced virological rebound after B/F/TAF switch.

ID	Time under suppression before switch (mo)	Number of previous regimens	Previous INI Exposure[a]	Previous number of INI failures	Cumulative resistance before switch[b]							Cumulative GSS			Time of VR[c] after switch (wk)	Viremia at VR (copies/mL)[d]	Outcome after VR	GRT at VR
					No. plasma GRTs	No. PBMCs GRTs	PI MRM	NRTI MRM	NNRTI MRM	INI MRM	INI Access	BIC	FTC	TAF				
11522	8	4	DTG, **RAL**	1	12	None	90M	184V	103N, 181C	None	None	S	R	S	17.6	225	Resuppression after therapy change	-
1778	56	4	EVG, **RAL**	1	8	None	46I, 54V, 82A, 90M	70E, 184V	103N, 188L	None	None	S	R	I	21.3	274	Lost at follow-up	-
10877	17	18	**RAL,** DTG	1	9	1	None	184V, 70R	None	155H	None	S	R	S	88.7	474	Resuppression without therapy change	**-**
16762	41	5	**RAL, EVG,** DTG	2	3	None	None	None	None	None	None	S	S	S	84.1	1,080	Resuppression without therapy change	No resistance
14654	38	3	EVG	None	2	None	None	None	190A, 106I	None	None	S	S	S	62.5	11,300	Resuppression without therapy change	190A, 106I[e]
17035	54	2	EVG	None	1	None	None	None	None	None	None	S	S	S	7.6	947	Resuppression without therapy change	-
10548	102	2	None	None	1	None	None	None	None	-	-	S	S	S	12.0	63→155	Resuppression without therapy change	-
18735	3	1	EVG	None	1	None	None	None	None	None	74I	S	S	S	7.3	314→410	Resuppression without therapy change	-
18305	34	1	Unknown	None	1	None	None	None	None	None	None	S	S	S	31.3	204	Resuppression without therapy change	-
18327	34	1	EVG	None	1	None	None	None	None	None	None	S	S	S	56.9	137→4,960	Resuppression without therapy change	No resistance
17196	37	1	EVG	None	1	None	None	None	None	None	None	S	S	S	32.1	253,000	Resuppression without therapy change and later lost at follow-up	-
13479	88	3	None	None	1	None	None	None	None	None	None	S	S	S	57.0	54→86	Resuppression without therapy change	**-**

BIC, bictegravir; DTG, dolutegravir; EVG, elvitegravir; FTC, emtricitabine; GRT, genotype resistance test; INI, integrase inhibitor; MRM, major resistance mutations; NNRTI, non–nucleotide reverse transcriptase inhibitor; NRTI, nucleotide reverse transcriptase inhibitor; PBMC, peripheral blood mononuclear cell ; PI, protease inhibitor; R, resistant; RAL, raltegravir; S, susceptible; TAF, tenofovir alafenamide; VR, virological rebound.

[a] Drugs with whom individuals experienced virological failure are indicated in bold.

[b] Underlined mutations were detected in both plasma and PBMC GRT.

[c] VR: virological rebound defined as two consecutive viremias >50 copies/mL or one viremia >200 copies/mL after switch.

[d] Viremia at VR was indicated as one value in case of single viremia >200 copies/mL or as two values separated by "→" symbol in case of two consecutive values >50 copies/mL.

[e] GRT performed at resuppression from PBMCs sample. -: not available.

Code. All information, including virological and clinical data, was recorded in an anonymized database.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2022.06.027.

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