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Highlights

- In real-life settings, virological rebound after B/F/TAF switch is rare.
- Previous resistance alone does not affect B/F/TAF virological response.
- Previous INI-failures are associated with virological rebound under B/F/TAF.
- Previous resistance and INI-failures further increase the risk of B/F/TAF failure.

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

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Running head (50 caratteri spazi inclusi):

B/F/TAF optimization regimen response in real-life

Keywords: treatment optimization strategies, integrase inhibitors, bictegravir, HIV drug resistance, virological response

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ABSTRACT

Introduction: We evaluated virological response and resistance profile in virologically suppressed individuals switching 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) before switch were evaluated.

Results: Overall, 283 individuals virologically suppressed for a median (interquartile, IQR) time of 7 (3-9) years were analyzed. Of these, 20.8% were in first-line treatment, 13.1% was highly-treatment experienced and 8.5% experienced previous INI-failures. Before switch, NRTI MRM prevalence was 29% (M184V:13.8%; any thymidine analogue mutation: 14.1%; K65R: 0.7%; K70E 0.4%); only 3 (2.1%) individuals showed INI major resistance mutations (Y143C/H/R [n=1]; Y143C [n=1]; N155H [n=1]); 82.0% of individuals received fully active B/F/TAF. By 96 weeks 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 was observed. People who experienced previous INI failures showed a significantly higher adjusted hazard (AHR [95% C.I.]) 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 weeks, B/F/TAF treatment switch in virologically suppressed individuals ensures a very high rate of virological control in a clinical setting. Previous

resistance alone does not affect B/F/TAF response. However, people who had previous INI failures resulted in being more prone to losing virological control under B/F/TAF.

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INTRODUCTION

Due to 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 a 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 of switch in virologically suppressed HIV-1 infected individuals in clinical settings[3]. Given that it is fundamental to maintain virological suppression without jeopardizing future treatment options, treatment switch should be considered only after a revision of full patient's ART history including cumulative resistance, previous failures, time of virological suppression before switch and tolerability issues [4,5]. Single tablet regimens (STRs) have played an important role in treatment optimization strategies; by considering the fact that the current STRs available contain potent and high genetic barrier drugs, these strategies are taking over multi-pills 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 STR (B/F/TAF)[6]. B/F/TAF showed excellent results in terms of efficacy, tolerability and genetic barrier in both clinical trials and observational studies as a treatment optimization strategy in virologically suppressed individuals [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 switched to B/F/TAF with previous resistance affecting the NRTIs 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 data from real-life confirm that previous resistance did not affect B/F/TAF response at 48 weeks of observation[7,13]. Despite these reassuring results, it should be taken into account that among the individuals in stable suppression, there are also a number of highly-treatment-experienced people, with complex previous history of failures and/or resistance, present in clinical settings[14–16]. These individuals might cause uncertainty in clinicians' decisions; potent and high genetic barrier STR based on 3 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 due to the fact that 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.

MATERIALS AND METHODS

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 years; (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 testing (GRT); (iv) availability of a virological follow-up after switching to B/F/TAF. Individuals were considered HTE if they had accumulated resistance to at least 2 drug classes and had previously experienced at least four therapy changes before B/F/TAF switch as previously described[14].

Ethics

This study was approved by the ethics committee of Tor Vergata Hospital (Ethics Approval No. 216/16, 26 January 2022). The research was conducted on data routinely collected for clinical purposes, 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.

Sanger sequencing and drug resistance evaluation

Sanger sequencing for protease, reverse transcriptase and integrase were 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), nucleos(t)ide reverse transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs) and integrase inhibitors (INIs) was evaluated by considering the resistance detected in all available GRTs before B/F/TAF switch. Cumulative genotypic susceptibility score (cGSS) for BIC, FTC and

TAF was 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.

Objectives

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

Secondary objectives were: (i) to determine the impact of previous INI failures before B/F/TAF switch on VR; (ii) to determine the impact of combination of previous INI failures and cGSS before 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; (v) to evaluate the role of previous resistance on

experiencing a blip after B/F/TAF switch. Viral blip was defined as a single HIV-RNA in the range 51-199 copies/mL preceded and followed by ≤50 copies/mL measurements.

Statistical analysis

All analyses were executed using the SPSS v.26.0 software package for Windows (IBM, Armonk, New York, Illinois). For all the analyses, P values of less than 0.05 were considered significant.

Kaplan-Meier curves were used to evaluate the probability of experiencing VR after B/F/TAF switch on the overall population and according to cGSS and INI failure experience. Cox regression analysis was performed to investigate the role of factors associated to virological response by considering demographic, viro-immunological and treatment parameters (variables included in the models are mentioned in footnote of Table 2 and reported in Supplementary table 1). Only variables significantly associated to 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-up was 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.

RESULTS

Patients' characteristics

Overall, 283 virologically suppressed individuals composed mainly of males (82.7%) with a median (interquartile range, IQR) age of 50 (42-56) were analysed (Table 1). They had a long treatment history with a median (IQR) of 8 (4-13) years under ART,

with a median (IQR) duration of virological suppression of 7 (3-9) years. Almost half of them had previously received raltegravir or elvitegravir (51.9%) and 18.0% had previously received dolutegravir; 8.5% of individuals failed a previous regimen containing INI (mainly elvitegravir and/or raltegravir). The majority of individuals switched to B/F/TAF to increase genetic barrier of the regimen; in fact, most of them (72.8%) were under a low genetic barrier regimen, containing NNRTIs or first-generation INIs, before B/F/TAF switch. A considerable proportion of 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 them, 28 (75.7%) and 9 (24.3%) had accumulated resistance to 2 and 3 drug-classes, respectively.

Cumulative resistance at B/F/TAF switch

An overview of cumulative resistance and genotypic susceptibility is reported in Figure 1. All individuals had an available GRT before B/F/TAF switch, 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 related to RTIs (NRTI: 19.1%; NNRTI: 19.4%). cGSS revealed that 91.9% of individuals had at least two active drugs among B/F/TAF (cGSS≥2); 82.0% of individuals showed a completely active regimen (cGSS=3).

Regarding NRTI resistance, 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, among the 145 patients

for whom an integrase GRT was available before B/F/TAF switch, only 3 (2.1%) showed INI major resistance mutations (Y143C/H/R [n=1]; Y143C [n=1]; N155H [n=1]), while 6.7% showed INI accessory resistance mutations (L74I/M, T97A, V151I, E157Q).

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. By 96 weeks after B/F/TAF switch the probability of losing virological control was 5.0% (Figure 2, panel A). By stratifying VR probability according to cGSS at B/F/TAF switch, no significant difference among individuals who received a fully active regimen compared to those who received a partially active regimen was observed (7.6% vs. 4.5%; P=0.463; Figure 2, Panel B). Regarding the stratifications according to past INI failures, individuals who had experienced virological failures to INI before B/F/TAF switch showed a significantly higher probability of experiencing VR under B/F/TAF compared to those who never failed INI regimens (25.6% vs. 3.4%, P=0.003; Figure 2, Panel C). By combining information on previous INI failures and cGSS, individuals who had experienced previous INI virological failures and received B/F/TAF as partially active regimen showed the highest probability (26.5%) of experiencing VR (P=0.003; Figure 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 those who had experienced an INI virological failure before B/F/TAF switch showed a higher adjusted hazard ratio (AHR) [95% Confidence interval, C.I.] of experiencing virological rebound compared to those had never failed regimen containing this drug class (3.5 [1.0-12.7], P=0.047). Considering previous failures

combined with partial susceptibility (cGSS<3), those individuals who had experienced an INI virological failure before B/F/TAF switch and received the regimen as partially active, showed a significantly higher AHR of experiencing VR, compared to those never failed to INI and did not show any resistance related to B/F/TAF at switch (5.4 [1.4-20.7], P=0.014). Among other predictors, only a virological suppression of more than 5 years was associated with a significantly lower AHR to experience VR compared to a time of virological suppression under one year (0.1 [0.0-0.8], P=0.029).

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

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

In Table 3 an overview of the 12 individuals who experienced VR is reported. Among them, 4 had experienced a previous failure to first-generation INIs; 3 of these 4 individuals (25.0%) were HTE and had accumulated resistance to at least one drug included in B/F/TAF (2 to FTC, 1 to FTC and TAF). With regards to resistance, a GRT was performed for 3 individuals. No new resistance was observed neither in reverse transcriptase nor in integrase.

Ten of these individuals with VR (83.3%) re-suppressed without changing treatment, 1 (8.3%) changed treatment and 1 (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.

DISCUSSION

In the present manuscript, the impact 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, by 96 weeks after B/F/TAF start, the probability of VR was low (5%), with only 12 events of VR recorded mainly at low-level viremia. These few events were mostly transitory due to the fact that 10 out 12 of these individual re-suppressed without therapy change; moreover, among the three patients for whom resistance was tested, none of them developed resistance after virological rebound. These reassuring results are of great importance because they were retrieved from a heterogenous population of PLWH followed for clinical routine in real-life. In fact, in this study a consistent proportion of individuals switching from their first-line treatment was included; but, on the other hand, people with long treatment history, previous experience to INIs, past resistance to NRTIs and (even though few) people who experienced previous INI virological failures and INI resistance were also present. Despite this, even though a consistent part of individuals received B/F/TAF as a not fully active regimen (around 20%), mainly due to 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 impact of pre-existent INI resistance on B/F/TAF showed that patients with primary INI resistance maintained virological suppression

through 48 weeks of B/F/TAF treatment [21]. These results were similar in our population, where among the 3 cases of individuals that switched to B/F/TAF having pre-existent INI resistance, one of them with N155H mutation (theoretically not associated with BIC resistance) experienced a virological rebound after 88 weeks of B/F/TAF treatment, followed by re-suppression without therapy change.

Beside resistance, another important fact to point out is that in our study 13% of individuals were HTE and around 9% had experienced a virological failure to an INI-based regimen before switch to B/F/TAF. Virologically suppressed HTE individuals remain a category of individuals that leads to concerns in clinical practice [14–16]; despite this, we did not observe any significant difference in B/F/TAF response in the HTE population compared to other people. Despite this, it should be taken into account that only around a quarter of HTE individuals in our population showed a high level of resistance (specifically to 3 drug classes) and very few individuals showed resistance to INIs. Therefore, our results could be not applicable on fragile HTE individuals with multidrug-resistance (including resistance to INIs).

Noteworthy, we found that the subgroup of HTE individuals who 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. Even though supported by few numbers, previous failures to first-generation INI (combined or not with poor susceptibility to NRTI backbone) might be the driving factor leading to virological rebound under B/F/TAF, thus this factor should be carefully considered before the switch to this regimen.

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

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

This study has some limitations mainly related to the low number of VR events recorded due to 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 due to the transient rebounds observed. Moreover, even though Sanger sequencing remains the most used and standardized technique to test resistance, our resistance evaluation is partial due to 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, with the exception of people with previous history of failures to INIs, it can be used without particular concerns in virologically suppressed individuals, regardless of previous NRTI resistance. Further studies collecting a larger number of VR are needed to confirm these results and better evaluate the impact of previous INI resistance.

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HIV-drug resistance group

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Author contributions

DA, MMS and FCS carried out study conception and design. DA and MMS carried out analysis and interpretation of data and drafting of manuscript. FF, AB, GB and WG contributed in sequencing and retrieving resistance data. VM, RG, VB, SC, AB, ET, SL contributed to data collection. AL, LS, CM, MA, AA, CFP and FCS carried out a critical

revision of the manuscript. All authors approved the final version of the manuscript for submission.

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Conflict of interest

The authors have no conflicts of interest related to this manuscript.

FIGURE LEGENDS

Figure 1. **Overview of cumulative resistance and genotypic susceptibility score (cGSS) at B/F/TAF switch.** A) Prevalence of individuals harboring resistance to PIs, NRTIs, NNRTIs and INIs and cGSS at B/F/TAF switch. B) Detailed overview of NRTI resistance at B/F//TAF switch. * 2 out of 3 individuals harbored 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. **2 out of 3 individuals harbored L74I/M as mixture.

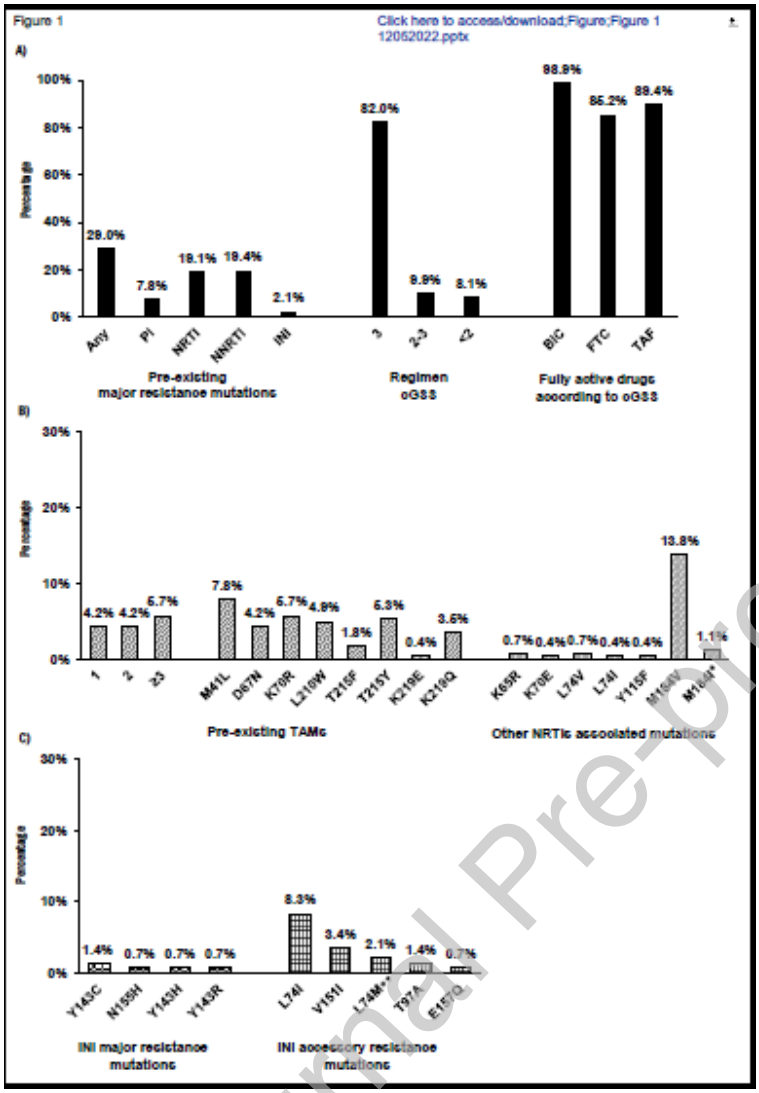

Figure 2. **Kaplan-Meir estimates of the probability of experiencing virological rebound at 24 months under B/F/TAF treatment stratified according to genotypic susceptibility and previous INI failure experience.** A) Virological rebound stratified in overall population. B) Virological rebound stratified 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 & previous INI failure experience. P values were calculated by 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.

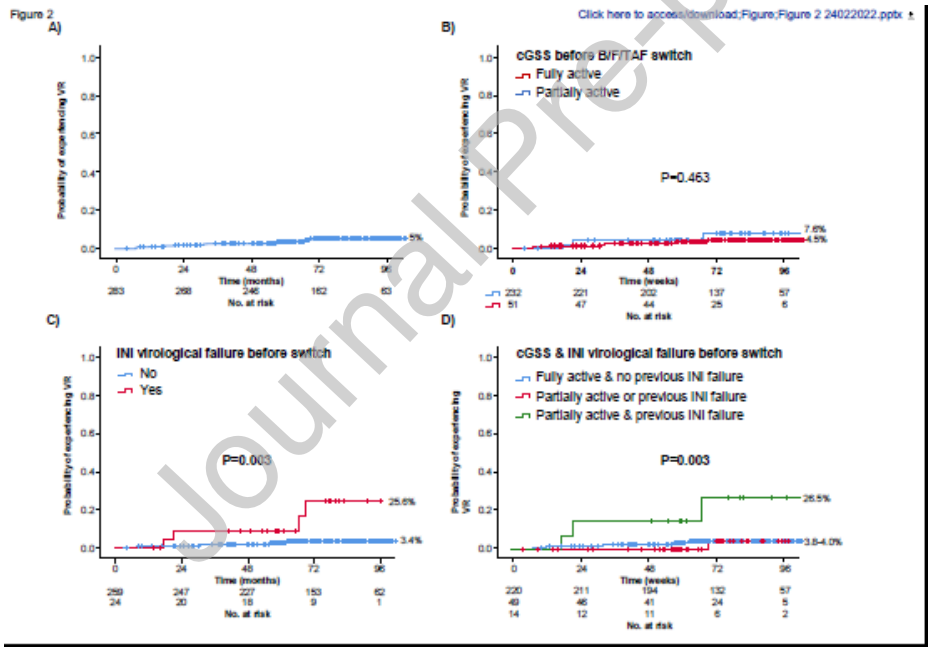

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Table 1. Patients' characteristics at the moment of B/F/TAF switch

Variables	Overall (N=283)
Male gender, n (%)	234 (82.7)
Age, median (IQR), years	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), years	8 (4-13)
Time under cART, years, 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), years	7 (3-9)
Time under virological suppression, years, 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)
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), weeks	83 (68-96)

[a]Unknown sexual behaviours. [b]Individuals with HBsAg positive or reported as HBV^+ by clinicians; [c]INI failures experienced according with drugs: RAL n=11; RAL and EVG n=6; RAL and DTG n=1; DTG n=2; 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).

Variables	Hazard ratio (HR) to experience virological rebound					
	Crude[a]		Adjusted[b]		Adjusted[c]	
	HR (95% C.I.)	P value	HR (95% C.I.)	P value	HR (95% C.I.)	P value
Age, per 5 years higher	**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, years						
<1 year[d]	1		1		1	
1-5 years	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 years	**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**

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

In the table are reported only the variables significantly associated with VR (P <0.05) at univariable analysis. [a]The following variables were tested for their potential role as predictors of virological rebound after B/F/TAF: gender, 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 ART, number of previous virological failures, previous INI failure experience, number of regimens experienced, being HTE, reasons of switch, cumulative drug resistance, cGSS, combined cGSS 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% C.I: 95% confidence interval.

ID	Time under suppression before switch (months)	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 (weeks)	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 Acc.	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	**-**

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

[a]In bold are indicated drugs for whom individual experienced virological failure; [b] Underlined mutations were detected in both plasma and PBMC GRT; [c]VR: virological rebound defined as two consecutive viremia >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 2 values separated by "→" symbol in case of 2 consecutive values >50 copies/mL. [e]GRT performed at resuppression from PBMCs sample. -: not available.