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Switching to bictegravir/emtricitabine/tenofovir alafenamide in people with HIV and prior resistance mutations. Data from the Italian ARCA cohort: the BIC-BARRIER study. B/F/TAF switch: mutations and outcomes

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Objectives: To estimate the prevalence of NRTI and integrase strand transfer inhibitor (INSTI), drug resistance mutations (DRMs) in antiretroviral therapy (ART)-experienced people with HIV-1 (PWH) switched to bictegravir/emtricitabine/tenofovir alafenamide fumarate (B/F/TAF) and among those with HIV-RNA ≤50 copies/mL to assess the association with risk of viral rebound (VR).

Methods: Data from the ARCA cohort were used to estimate resistance prevalence assuming a binomial distribution; 95% confidence intervals (CIs) were reported. Standard survival analysis with time-fixed covariate measured at B/F/TAF initiation was used to evaluate the association between detected resistance and risk of confirmed VR >50 copies/mL (2 consecutive values).

Findings: We included 1414 PWH (973—69%—in the VR analysis). Overall, 27% were female, median age was 53 years (IQR 44–59). Major NRTI-DRMs were detected in 25% (95% CI: 22.5, 27.1). Major INSTI-DRMs affecting bictegravir were rare (0.6%, 95% CI: 0.2, 1.4). The overall rate of VR by 36 months was 5.3% (95% CI: 3.7–6.9%), confirming that viral rebound on B/F/TAF is a rare event. After controlling for confounding, NRTI resistance was not associated with VR, whereas a history of INSTI virological failure (VF) and major INSTI-DRMs were associated with VR (aRH 2.68, 95% CI: 1.40, 5.12; and aRH 4.21, 95% CI: 1.18, 15.02, respectively).

Conclusions: In our cohort of PWH who were switched to B/F/TAF, NRTI-DRMs were common, but B/F/TAF remained effective in maintaining viral suppression despite their presence. However, previous failure to INSTI-based regimens and major INSTI-DRMs were risk factors for VR.

Introduction

Treatment optimization is the most common reason for switching antiretroviral treatment (ART) in virologically suppressed people with HIV (PWH).[1] Since maintaining virological suppression (VS) without compromising future treatment options is essential, treatment switch should be considered only after a thorough review of ART history, cumulative resistance, duration of VS and tolerability issues.[2] Bictegravir/emtricitabine/tenofovir alafenamide fumarate (B/F/TAF) is a potent integrase strand transfer inhibitor (INSTI)-based regimen with high efficacy and high barrier to resistance, currently recommended both in the ART-naive and ART-experienced setting by international guidelines.[2–4]

Registrational randomized clinical trials (RCTs) conducted in VS subjects with no documented DRMs affecting lamivudine, emtricitabine, tenofovir and INSTIs have also shown that switching to B/F/TAF from other ART combinations with high genetic barriers [based on dolutegravir or boosted protease inhibitors (PIs)] is effective and well tolerated.[5–7] Similar results have been observed in PWH with NRTI resistance, both in RCTs and in real-world studies.[8–12] The M184V and M184I mutations confer high-level resistance to lamivudine and emtricitabine, although they appear to increase susceptibility to tenofovir.[13] The K65R substitution in RT results in a 3- to 4-fold decrease in the phenotypic susceptibility to tenofovir and intermediate-level resistance to emtricitabine and lamivudine.[14]

Resistance to INSTIs is estimated to be around 1% in treatment-naive individuals in a small study; [15] studies in VS pretreated PWH show a prevalence ranging between 1% in RCTs and 6.7% in real-world data.[11, 16] Moreover, virological failure (VF) of ART based on raltegravir and elvitegravir has been associated with the emergence of mutations,[17, 18] while bictegravir shows a higher barrier to resistance.

Most of the evidence regarding the efficacy of B/F/TAF comes from RCTs, which often include selected populations. The FDA considers B/F/TAF a safe and effective option for patients with pre-existing NRTI resistance, particularly the M184V/I mutation, provided they are virologically suppressed and do not have resistance to bictegravir.[4] Despite this, most previous observational studies were unable to evaluate the impact of resistance on the risk of failure of B/F/TAF because either did not have data on genotypic resistance or had a small sample size; few studies evaluated the association between NRTI- and INSTI-DRMs and risk of viral rebound (VR) with B/F/TAF or were able to adequately control for confounding (Table S0, available as Supplementary data at *JAC* Online).

The primary objective of our study was to estimate the prevalence of NRTI- and INSTI-DRMs in ART-experienced PWH switching to B/F/TAF for the first time; the secondary objective was to evaluate the potential association between these DRMs and the risk of VR in those switching with HIV-RNA ≤ 50 copies/mL.

Methods

Study participants

BIC-BARRIER is a real-world, observational, retrospective study to estimate the prevalence and impact of pre-existing DRMs in adult PWH switching to B/F/TAF by using medical records from the Antiviral Response Cohort Analysis (ARCA) database (www.dbarca.net). Local Ethics Committees approved data collection, and all participants in the ARCA database provided written informed consent for using their pseudo-anonymized data for research purposes.

Participants were >18-year-old bictegravir-naive PWH switching for the first time from any ART regimen to an exclusive B/F/TAF regimen over 2018–23 regardless of the reason. The date of first switching to B/F/TAF was defined as baseline (BL) for the analyses.

Study endpoints and statistical analysis

The main characteristics of the participants included in the primary analysis were described overall and after stratification for HIV-1-RNA at BL (≤50 versus >50 copies/mL).

For the primary objective, the study required the availability of at least one genotypic resistance test (GRT) result after first-line ART initiation and before BL. Genotypic testing in ARCA covers the whole treatment history of PWH with multiple genotypes per participant performed on HIV-1-RNA (when detectable) or on HIV-1-DNA (when HIV-1-RNA was undetectable). Data reflect clinical practice and for some participants testing was only performed on HIV-1-DNA.

All the sequences were generated by Sanger sequencing, with an estimated capacity of detecting species above 25% of the total quasispecies. Both sequences from plasma RNA and whole blood or peripheral blood mononuclear cells (PBMC) DNA were included. To control for the Apolipoprotein B mRNA Editing Catalytic Polypeptide-like proteins (APOBEC) editing, the reference Stanford APOBEC mutation list was used, as available at https://hivdb.stanford.edu/page/apobecs/. DNA sequences were defined as APOBEC edited and excluded based on the classification made with Hypermut3 as available at https://github.com/MolEvolEpid/hypermut3.

We estimated the prevalence of DRMs to NRTIs, and INSTIs detected at BL, by compiling all their GRTs results on HIV-1-RNA and HIV-1-DNA recorded up to BL. Results of the testing were cumulated, so if the DRM was detected at time T, we assumed it was still present in the virus population even if it was never detected again. The prevalence of resistance was calculated as the number of participants with at least one major mutation to each drug class divided by the total number of participants with at least one GRT for the corresponding drug class.

We used the most recent version of the Stanford HIVdb algorithm [v9.8 as of November 24, 2025 (https://hivdb.stanford.edu/)]. We distinguished between major and minor mutations using the Stanford scores: major if they scored 15 or higher for at least one drug and minor if they scored 5 or higher for at least one drug but <15 for all the drugs in the class (Supplementary Materials). The prevalence of specific mutations was calculated by dividing the number of participants with that specific mutation by the total number of participants with at least one GRT for the corresponding HIV-1 genome region. All participants had ≥1 GRT for the NRTI region, while the INSTI region had been sequenced only in a subset. Exact binomial 95% confidence intervals (CIs) were also calculated for all prevalence estimates. HIVdb v9.8 was used to calculate the cumulative genotypic susceptibility scores (cGSS) for B/F/TAF and for each of the drugs. The activity of each drug was quantified using the 5-level HIVdb interpretation: 0 (high level resistance), 0.25 (intermediate resistance), 0.5 (low-level resistance), 0.75 (potential low-level resistance) and 1 (fully susceptible/no resistance).[19–21] The cGSS for the entire regimen (cGSS-reg) was calculated as the sum of the cGSS of the three individual drugs included in B/F/TAF. A sensitivity analysis was conducted after restricting the prevalence estimates to GRT tests performed only on HIV-1-RNA.

The main characteristics of the subset of participants, who had HIV-1-RNA ≤ 50 copies/mL at BL and virological follow-up post BL, were described overall and after stratification for evidence of previous VF and INSTI-GRT availability.

In the population of VS PWH, we performed a secondary survival analysis evaluating the time to viral rebound (VR)>50 copies/mL (defined at

the time of the first of two consecutive HIV-1-RNA levels >50 copies/mL post BL while the participant was still receiving B/F/TAF).

The reasons for stopping B/F/TAF as reported by the treating physicians, although recorded in the database, were not used to define this endpoint.

Sensitivity analyses were conducted after restricting to GRT performed on HIV-1-RNA; after stratifying the population according to the time between the last GRT and BL (≤36 or >36 months before BL); and using a threshold of 200 copies/mL to define VR. We hypothesized that the timing of the last GRT could be an effect measure modifier for the association between risk of VR and previous VF to INSTI and/or detection of INSTI-DRMs. We formally tested these interactions in the Cox regression model. We used Kaplan–Meier (KM) curves to estimate the incidence of VR by 36 months from BL and both unweighted and weighted KM estimators and standard Cox proportional hazard models to evaluate the association between several *a priori* key exposure factors and the risk of VR in separate models. We also performed a sensitivity analysis controlling for potential informative censoring using inverse probability of censoring weights. Details regarding the choice of the exposures of interest (revolving around cumulated resistance and history of VF) and the corresponding set of covariates can be found in Supplementary Materials.

Results

Study population

The characteristics of the population included in the primary prevalence of resistance analysis are shown in Table 1. Our sample included 1414 subjects, 27% of whom were female, with a median age of 53 years (IQR 44–59). Median time since HIV-1 diagnosis was 16 years (IQR 10–28), and the median length of VS preceding the switch was 42 months (IQR 14–85). Overall, 469 (33%) PWH received ≥7 ART lines and 144 (10%) had a history of four or more previous virological failures. A total of 161 (11%) PWH switched to B/F/TAF from an NNRTI-containing regimen, 224 (16%) from a boosted PI and 902 (64%) from an INSTI. The overall prevalence of PWH coinfected with HBV virus was high (21%), but consistent with data from the literature in similar populations selected by using TAF-based regimens.

There was no evidence for a difference in the prevalence of NRTI and INSTI-DRMs according to VL at time of initiation of B/F/TAF. Only 727 (51%) subjects had an available integrase GRT. The breakdown of prior regimens is shown in Figure S0. The breakdown of the study population is shown in Table S1.

Controlling for APOBEC editing

Extensive APOBEC signatures (>3 APOBEC mutations) were detected in only 13 (1.25%) DNA sequences and 7 (0.25%) RNA sequences. Hypermut3 detected hypermutation in 32 sequences, including 16 from DNA (8 PR+RT and 8 IN) and 16 from RNA (14 PR+RT and 2 IN), which coincided with sequences having >2 APOBEC mutations as defined by the Stanford HIVdb list. Of these, 19 sequences involved mutation M184IV. All these 32 sequences were removed from the final analysis.

DRMs prevalence

Most participants (1289/1414, 91%) had ≥1 GRT performed on RNA while failing one of the regimens received prior to BL. Of these, 335 (26%) had ≥1 GRT performed also on DNA while HIV-1-RNA was ≤50 copies/mL. The remaining 9% of participants only had tests performed on DNA. The median number of RNA GRT tests was 2.5 (IQR 1–3) and the median number of DNA tests was 2 (IQR 2–3).

Major NRTI-DRMs were detected in 24.8% (95% CI: 22.5,27.1; $n=350$) while minor NRTI-DRMs only were detected in 17.7% (95% CI: 15.7,19.8; $n=250$) of subjects and TAMs in 17.7% (95% CI: 15.7,19.8; $n=250$). Mutations M184 V, M41L and K70R had the highest prevalence: 18.1% (95% CI: 16.2,20.2; $n=256$), 8.2% (95% CI: 6.8, 9.8; $n=116$) and 7.5% (95% CI: 6.2, 9.0; $n=106$), respectively.

Of the 727 subjects with an available INSTI-GRT, 26.5% (95% CI: 23.4,29.9; $n=193$) had a cGSS for B/F/TAF <3 (i.e. at least one of the drugs included in the regimen was not fully active). GSS for single drugs are shown in Figure 1a and Table S2A. Major INSTI-DRMs were detected in 3.3% (95% CI: 2.1,4.9; $n=24$) of subjects; major INSTI-DRMs affecting bictegravir were detected in 0.6% (95% CI: 0.2,1.4; $n=4$), while minor INSTI-DRMs in 8% (95% CI: 6.1,10.2; $n=58$) of subjects. The most prevalent mutations were T97A (2.8%, 95% CI: 1.7,4.2; $n=20$), G163R (1.8%, 95% CI: 1.0,3.0; $n=13$) and E157Q (1.7%, 95% CI: 0.9,2.9; $n=12$). A detailed description of the prevalence of NRTI- and INSTI-DRMs is shown in Supplementary Materials (Figure 1b-c, Table S2B-C and S3A-C).

Time to viral rebound >50 copies/mL analysis

A subset of 973 (68.8%) subjects was included in the time-to-failure analysis. The main characteristics of this population are described in Table S4. On average, there were 2.3 measures of HIV-1-RNA per year after initiation of B/F/TAF. Monitoring appeared to be slightly more frequent in participants with major INSTI-DRMs (3.2 measures/year) versus those without (2.4 measures/year, Mann–Whitney P value=0.04).

We investigated whether the lack of virological follow-up or a missing INSTI-GRT could have introduced selection bias. Compared to all participants with HIV-1-RNA ≤50 copies/mL at baseline, PWH included in the survival analysis differed for HIV transmission route, ethnicity and previous anchor drug; they were more likely to harbour hepatitis B virus, had a lower CD4+ T-cell nadir, but higher CD4+ T-cell counts at baseline, they also exhibited a shorter time since their last GRT (Table S5). Participants for whom an INSTI GRT was missing were people selected to be at lower risk of subsequent viral rebound; our analysis, excluding these individuals, is unlikely to show biased results for this association (Figure S1).

There were 13 PWH included in the survival analysis who carried major INSTI-DRMs: only three of them carried major bictegravir mutations and none of them experienced VR.

Overall, 55 participants experienced VR >50 copies/mL by the end of follow-up. The cumulative risk of VR >50 copies/mL by 12, 24 and 36 months from BL was 3.1% (2.0,4.3%), 4.4% (3.0,5.8%) and 5.3% (3.7,6.9%), respectively (Figure S2). This was the incidence of VR obtained using only the HIV-1-RNA values, ignoring reasons for discontinuation. These estimates were higher at 12 months for people with evidence of prior VF to an INSTI-based ART (Figure 2a) or ≥1 major INSTI-DRMs at BL (Figure 2b).

As shown in Table 2A, results were confirmed after controlling for confounding in the multivariable Cox regression models

Table 1. Characteristics of the study populations according to HIV-RNA at BL (primary analysis)

	HIV-RNA at time of switch, copies/mL			
Characteristics at time of switching to bictegravir	Below 50	Above 50	*P* value[a]	Total
	n = 1119	*n* = 295		*n* = 1414
Age, years			0.363	
Median (IQR)	53 (44, 60)	54 (44, 59)		53 (44, 59)
Gender, n(%)			0.077	
Female	288 (25.7%)	93 (31.5%)		381 (26.9%)
Male	826 (73.8%)	202 (68.5%)		1028 (72.7%)
TGW	5 (0.4%)	0 (0.0%)		5 (0.4%)
Mode of HIV Transmission, n(%)			0.327	
PWID	191 (17.1%)	57 (19.3%)		248 (17.5%)
Sexual contacts	686 (61.3%)	162 (54.9%)		848 (60.0%)
Other	21 (1.9%)	8 (2.7%)		29 (2.1%)
Unknown	221 (19.7%)	68 (23.1%)		289 (20.4%)
Ethnicity, n(%)			0.016	
Caucasian	747 (66.8%)	177 (60.0%)		924 (65.3%)
Black	65 (5.8%)	31 (10.5%)		96 (6.8%)
Asian	2 (0.2%)	0 (0.0%)		2 (0.1%)
Hispanic	17 (1.5%)	4 (1.4%)		21 (1.5%)
Other/Unknown	288 (25.7%)	82 (27.8%)		370 (26.2%)
HBsAg, n(%)			0.346	
Negative	613 (78.8%)	161 (79.7%)		774 (79.0%)
Positive	165 (21.2%)	41 (20.3%)		206 (21.0%)
Not tested	0 (0.0%)	0 (0.0%)		0 (0.0%)
CD4 count, cells/mcL			<0.001	
Median (IQR)	638 (426, 869)	479 (215, 757)		602 (392, 847)
Viral load, log10 copies/mL			<0.001	
Median (IQR)	1.30 (1.30, 1.30)	2.40 (1.95, 4.31)		1.30 (1.30, 1.61)
Time from last GRT, months			<0.001	
Median (IQR)	75 (32, 137)	29 (4, 89)		65 (24, 131)
Duration of VL below 50 copies/mL, months				
Median (IQR)	48 (19, 91)			42 (14, 85)
HIV subtype, n(%)			0.085	
B	772 (69.0%)	188 (63.7%)		960 (67.9%)
Cumulative GSS, n(%)			<0.001	
≥3 active drugs	729 (65.1%)	151 (51.2%)		880 (62.2%)
Number of previous ART lines			0.694	
Median (IQR)	4 (2, 8)	4 (2, 8)		4 (2, 8)
1–3	473 (42.3%)	126 (42.7%)		599 (42.4%)
4–6	274 (24.5%)	72 (24.4%)		346 (24.5%)
7+	372 (33.2%)	97 (32.9%)		469 (33.2%)
Number of previous ART failures			<0.001	
Median (IQR)	0 (0, 1)	1 (0, 3)		0 (0, 2)
None	667 (59.6%)	106 (35.9%)		773 (54.7%)
1–3	359 (32.1%)	138 (46.8%)		497 (35.1%)
4+	93 (8.3%)	51 (17.3%)		144 (10.2%)
HIV drug resistance, n(%)				
Minor NRTI	198 (17.7%)	52 (17.6%)	0.979	250 (17.7%)
Major NRTI	279 (24.9%)	71 (24.1%)	0.759	350 (24.8%)
Minor INSTI	43 (8.2%)	15 (7.5%)	0.770	58 (8.0%)
Major BIC	3 (0.6%)	1 (0.5%)	0.910	4 (0.6%)
Nadir CD4 count, cells/mcL				
Median (IQR)	163 (44, 318)	160 (42, 292)	0.584	162 (43, 313)

Continued

Table 1. *Continued*

Characteristics at time of switching to bictegravir	HIV-RNA at time of switch, copies/mL			
	Below 50	Above 50	*P* value[a]	Total
Zenith HIV-RNA, log copies/mL				
Median (IQR)	5.07 (4.37, 5.60)	5.27 (4.74, 5.70)	<0.001	5.10 (4.43, 5.62)
Time for HIV diagnosis, years				
Median (IQR)	16 (10, 28)	16 (10, 27)	0.687	16 (10, 28)
Reason for discontinuing B/F/TAF, n(%)			<0.001	
Failure	9 (4.0%)	18 (26.1%)		27 (9.2%)
Toxicity	73 (32.4%)	24 (34.8%)		97 (33.0%)
Simplification	61 (27.1%)	7 (10.1%)		68 (23.1%)
Other/unknown	82 (36.4%)	20 (29.0%)		102 (34.7%)
Class of anchor of previous regimen, n(%)			<0.001	
INSTI	753 (67.3%)	149 (50.5%)		902 (63.8%)
NNRTI	106 (9.5%)	55 (18.6%)		161 (11.4%)
PI	162 (14.5%)	62 (21.0%)		224 (15.8%)
Other	98 (8.8%)	29 (9.8%)		127 (9.0%)

[a]Chi-square or Mann–Whitney test as appropriate.
TGW, transgender women; PWID, people who inject drugs; mcL, microlitre; mL, millilitre; ART, antiretroviral treatment; BIC, another abbreviation for bictegravir.

(adjusted relative hazard—aRH—for people with major INSTI-DRMs, 4.21, 95% CI: 1.18,15.02; $P=0.027$). Results were similar in a sensitivity analysis, which controlled for potential informative censoring using inverse probability of censoring weights (Table 2B).

A history of previous VF to INSTI was associated with the risk of VR with an RH of 3.18 (95% CI: 1.73,5.84; $P<0.001$), which remained significant after controlling for confounding (2.68, 95% CI: 1.40,5.12; $P=0.003$). Most participants who experienced VR had a single INSTI-associated mutation at baseline (Table S6).

We found no evidence for an association between the detection of NRTI-DRMs at BL or any of the other examined predictors and the risk of VR, including the co-occurrence of tenofovir-associated and emtricitabine-associated mutations (Table 2B). No evidence for a difference in the risk of VR was observed in PWH with detected resistance to emtricitabine and tenofovir (Figure 2c).

We performed three sensitivity analyses. Almost identical results were obtained when restricting the analysis to only GRTs performed on HIV-1-RNA (Table S7a). When using the VR >200 copies/mL outcome, only a history of INSTI VF was associated with VR, possibly due to reduced statistical power (Table S7b). When considering PWH with the most recent available GRT performed over the 36 months preceding the date of BL, an association with similar effect size was observed between VR and both major INSTI-DRMs and with GSS of bictegravir (Table S7c), suggesting that the time elapsed between the most recent GRT and the date of BL is not an effect measure modifier for a history of previous INSTI failure (interaction *P* value =0.26) and for the detection of major INSTI-DRMs ($P=0.99$).

Only for 24 out of 55 PWH with VR (43.6%), there was an available additional GRT in the time window (−3, +12 months of the date of VR): three PWH developed major NRTI-DRMs (i.e. T215A, T215I, M184I), and one PWH (already harbouring G163R) developed the E157Q minor INSTI-DRM. No-one developed major INSTI-DRMs (Table S8).

Discussion

In this cohort of treatment-experienced PWH, mainly with an HIV-1-RNA ≤ 50 copies/mL at the time of switching to B/F/TAF, we observed a high prevalence of DRMs conferring at least low-level resistance to any component of the B/F/TAF regimen. The overall prevalence of major NRTI-DRMs was 24.8%, of major INSTI-DRMs was 3.3% and of major DRMs affecting bictegravir was 0.6%.

Our results confirm and expand those previously reported. In randomized studies conducted in similar settings, the prevalence of NRTI-DRMs at switching to B/F/TAF ranged between 16% and 26%.[22, 23] Real-world studies showed a prevalence of 13.9% in Spain and of 19.1% in Italy in similar settings, although a recent Spanish study found an overall prevalence of NRTI DRMs up to 46% in a cohort of 62 subjects harbouring multidrug-resistant virus.[7, 11, 24] A pooled analysis of randomized trials reported INSTI-DRMs at around 1%, which is lower than what detected in our population, while real-world studies showed a prevalence of 2.1% for major and 6.7% for minor INSTI DRMs.[11, 16] A possible reason for the slightly higher prevalence of INSTI-DRMs in our study is the inclusion of a population with longer exposure and more extensive ART failure. However, our confidence intervals are consistent with the reported estimates (Table S0).

In the time to viral rebound analysis, we observed a 5.3% cumulative risk of VR by 36 months from the date of switching. Our estimate of the low incidence of VR is consistent with those previously shown in the literature in similar settings.[24–27]

As previously reported,[11] our analysis provided evidence that the history of previous failure of INSTI-based regimens and

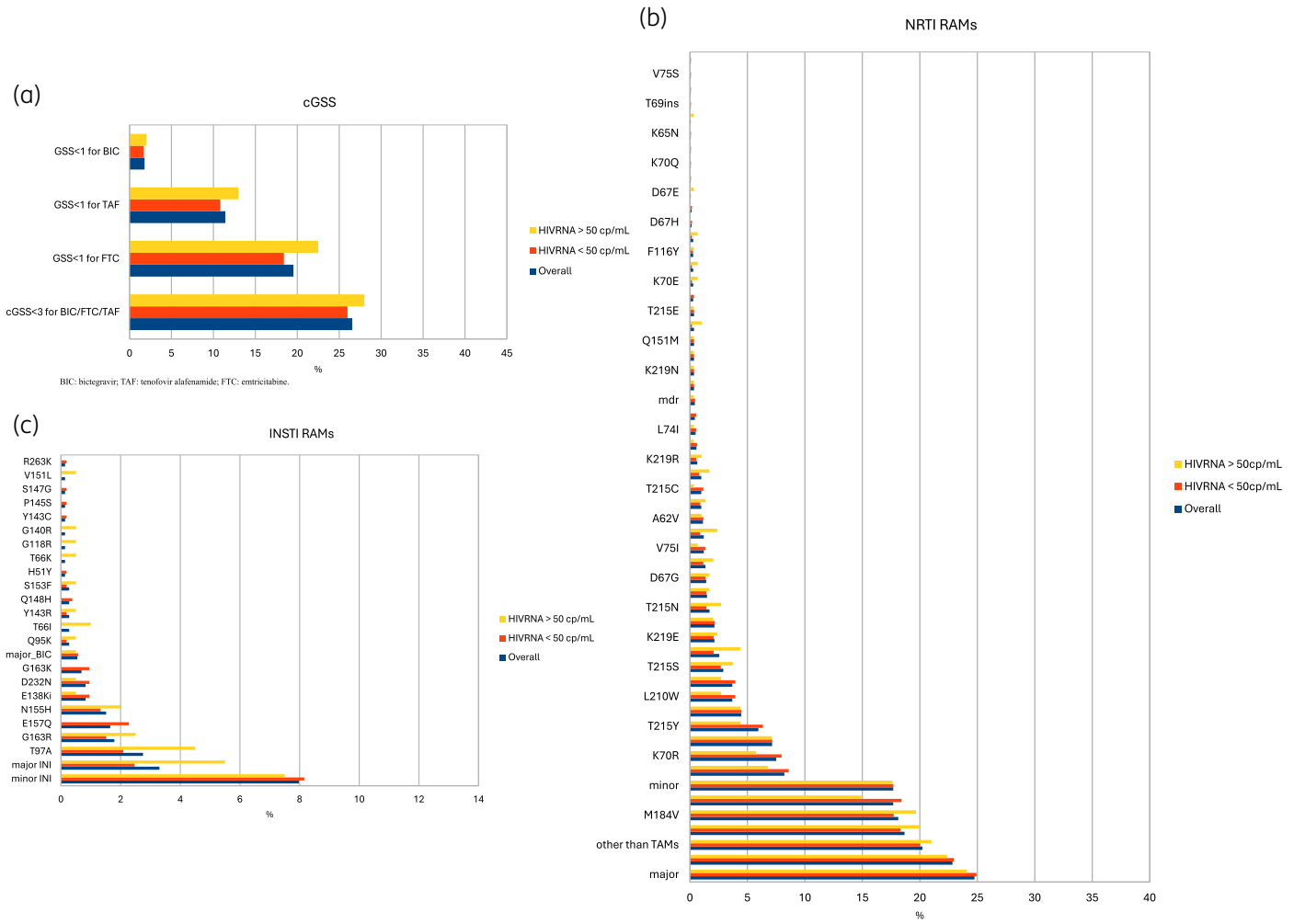

Figure 1. (a) GSS—all class. BIC, bictegravir; TAF, tenofovir alafenamide; FTC, emtricitabine. (b) NRTI-DRMs prevalence ($n = 1414$). (c) INSTI DRMs prevalence ($n = 727$).

cumulative resistance to INSTI are associated with a higher risk of VR.

In contrast, we did not observe a significant association between NRTI-DRMs and risk of VR, not even when specifically restricting to co-detection of tenofovir- and emtricitabine-associated mutations. This is an interesting finding, as monotherapy with dolutegravir (DTG), which has potency and genetic barrier comparable to bictegravir, was consistently shown to have insufficient virological potency.[28] However, several studies, although not investigating B/F/TAF, have demonstrated the limited impact of NRTI-DRMs to failure of regimens containing a high genetic barrier anchor drug (e.g. boosted PIs or DTG) even in the context of switching due to VF.[29, 30]

Out of the 24 PWH with VR who had an available GRT, three developed NRTI major DRMs, one developed an INSTI minor DRM but no one developed major INSTI-DRMs. This is also entirely consistent with what was previously reported (Table S0) and could be explained by the high genetic barrier of B/F/TAF.[18]

Our analysis has several limitations. Firstly, GRT data were incompletely available. For a minority (9%) of our sample, GRTs were conducted only on HIV-1-DNA. While interpretation of DNA resistance test results is still controversial, our estimates were similar when we restricted the analysis to GRT performed only on RNA samples. Only Sanger sequencing has been used and extensive APOBEC signatures (>3 APOBEC mutations) were detected in small proportion of sequences, which were removed at the outset. Only a subset of the study population underwent genotypic testing for the integrase coding region, limiting the precision of these estimates and statistical power in the Cox regression analysis. Missing data could have introduced selection bias. Reasons for missing data are likely to be associated with less recent calendar time, when access to integrase sequencing was limited (and therefore missing at random, controlled by covariate adjustment) but also due to the unobserved test results (people suspected of having resistance may have been tested). However, when using the assumption that participants without a test harboured no INSTI resistance we found similar results (effect size for the association between INSTI-resistance and risk of VR was larger in this alternative analysis). In addition, the analysis with 'detecting a history of failure to INSTI' as a predictor, which included all PWH (therefore not affected by potential

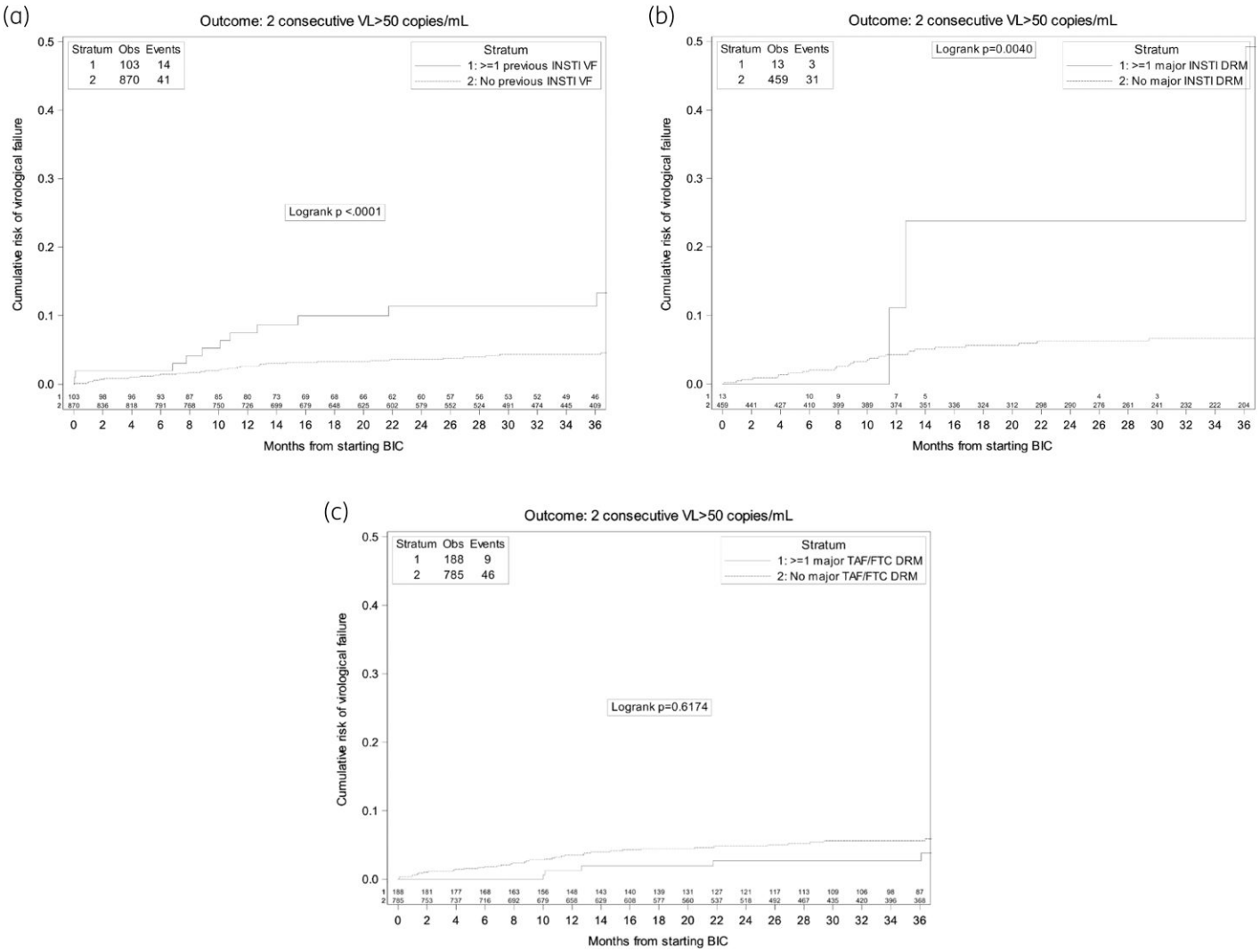

Figure 2. (a) Kaplan–Meier curve of VR >50 copies/mL according to history of previous VF to INSTI-based ART. (b) Kaplan–Meier curve of VR >50 copies/mL according to presence of ≥1 INSTI DRMs at BL. (c) Kaplan–Meier curve of VR >50 copies/mL according to presence of major TAF or FTC DRMs at BL.

Table 2A. Relative hazards of viral rebound >50 copies/mL from fitting a Cox regression model

	Unadjusted and adjusted relative hazards of viral rebound > 50 copies/mL			
	Unadjusted RH (95% CI)	*P* value	Adjusted[a] RH (95% CI)	*P* value
Any NRTI DRM				
No	1.00		1.00	
Yes	0.74 (0.39, 1.40)	0.356	0.88 (0.44, 1.76)	0.723
M184I or M184V				
No	1.00		1.00	
Yes	0.88 (0.43, 1.79)	0.722	1.00 (0.47, 2.13)	0.998
Major FTC/TAF DRM				
No	1.00		1.00	
Yes	0.83 (0.41, 1.70)	0.618	0.95 (0.44, 2.03)	0.891
Any major NRTI DRM				
No	1.00		1.00	
Yes	0.74 (0.38, 1.43)	0.363	0.87 (0.43, 1.78)	0.710
Any INSTI DRM				
No	1.00		1.00	
Yes	1.52 (0.54, 4.33)	0.430	1.17 (0.40, 3.46)	0.777
Any major INSTI DRM[c]				
No	1.00		1.00	
Yes	4.87 (1.48, 16.04)	0.009	4.21 (1.18, 15.02)	0.027
Any major INSTI DRM[d]				
No	1.00		1.00	
Yes	6.49 (2.02, 20.92)	0.002	4.57 (1.31, 15.90)	0.017
GSS of BIC regimen				
≥3	1.00		1.00	
2–2.75	1.04 (0.47, 2.29)	0.916	1.00 (0.44, 2.24)	0.994
0–1.75	1.68 (0.79, 3.58)	0.181	1.09 (0.46, 2.59)	0.843
GSS of BIC regimen				
≥3	1.00		1.00	
0–2.75	0.95 (0.43, 2.09)	0.895	1.01 (0.43, 2.40)	0.976
GSS of BIC drug				
Sensitive	1.00		1.00	
Resistant	2.46 (0.75, 8.06)	0.137	2.22 (0.63, 7.77)	0.213
Previous history of VF				
No	1.00		1.00	
Yes	1.60 (0.94, 2.72)	0.082	1.96 (1.08, 3.55)	0.027
Previous history of VF of INSTI				
No	1.00		1.00	
Yes	3.18 (1.73, 5.84)	<0.001	2.68 (1.40, 5.12)	0.003
Previous number of VF per 1 additional	1.09 (0.94, 1.26)	0.266	1.16 (0.98, 1.37)	0.079

[a]for for age, gender, ethnicity, HIV subtype, year of BIC initiation, time from last available GRT and previous gap in care[b].
[b]at least one episode of >12 months between consecutive visits.
[c]missing INSTI GRT = excluded.
[d]missing INSTI GRT = no resistance.
DRM, drug resistance mutation; BIC, bictegravir; VF, virological failure.

selection bias), also carried consistent results. Effect size was again attenuated, which is also expected as it is conceivable that some of these failures could have occurred due to very poor adherence, not resulting in INSTI-DRMs, hence diluting the effect (this has been documented especially for DTG).[31] Moreover, PWH included in the survival analysis showed higher CD4+ T-cell counts and a longer duration of VS before baseline than the average person included in the sample, likely reflecting greater adherence to therapy, which could have led to an underestimation of the rate of VR.

Secondly, unmeasured confounding cannot be ruled out, and the results are only valid under the assumption that we have adequately controlled for all confounding pathways and that our model is correctly specified. We used gaps in care recorded prior to BL (i.e. having had at least 12 consecutive months with no contact with the clinic) as a proxy measure for adherence, and the results were similar after controlling. A small proportion of participants started B/F/TAF despite harbouring resistance to the INSTI class. Reasons for this are unclear, possibly: (i) the results of the test were not available at BL; (ii) the results were known but were considered minor mutations for BIC and therefore a low risk in the context of the specific participant. The slightly higher frequency in monitoring of HIV-1-RNA in people with major INSTI mutations may indicate that clinicians were alerted to the possible increased risk of rebound although this is unlikely to fully explain our results.

Key strengths of our study are the large sample size including PWH more likely to be representative of the average person seen in clinical practice. Another distinguishing feature is the availability of the results of GRT testing covering the whole history of ART treatment.

Finally, our sample size of participants with detected HIV-1-RNA at BL was too small for this group to be further evaluated. We understand that whether B/F/TAF performs well in PWH switching with HIVRNA >50 cp/mL is a still unanswered question, and we are currently conducting a separate analysis on a larger dataset to address it.

Table 2B. Relative hazards of viral rebound >50 copies/mL from fitting a Cox regression model controlling for potential informative censoring using inverse probability of censoring weights

	Unweighted and weighted relative hazards of VR > 50			
	Unweighted RH (95% CI)	*P* value	Weighted[a] RH (95% CI)	*P* value
Major FTC/TAF DRM				
No	1.00		1.00	
Yes	0.83 (0.41, 1.69)	0.609	0.96 (0.38, 2.41)	0.924
Any major INSTI DRM				
No	1.00		1.00	
Yes	4.87 (1.62, 14.67)	0.005	2.00 (0.53, 7.65)	0.309
Previous history of VF				
No	1.00		1.00	
Yes	1.59 (0.94, 2.70)	0.085	1.99 (1.09, 3.66)	0.026
Previous history of VF of INSTI				
No	1.00		1.00	
Yes	3.15 (1.72, 5.78)	<0.001	3.00 (1.53, 5.85)	0.001

[a]weighted for age, gender, ethnicity, HIV subtype, year of BIC initiation and time from last available GRT.

In conclusion, our analysis provides accurate estimates of the prevalence of NRTI and INSTI-DRMs in a population of PWH switching to B/F/TAF in clinical practice. It confirms that viral rebound on B/F/TAF is a rare event, usually without emergence of resistance. It provides evidence supporting the hypothesis that cumulated major NRTI-DRMs have no or little impact on the virological efficacy of this regimen but that a history of INSTI VF or of major INSTI-DRMs is associated with higher risk of VR during B/F/TAF.

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curation Investigation Methodology Project administration Supervision Validation Writing—original draft Writing—review & editing) and Stefano Rusconi (Conceptualization Data curation Investigation Methodology Project administration Resources Supervision Validation Writing—original draft Writing—review & editing)

Supplementary data

Figures Supplementary 0, Supplementary 2 and S1 and Tables Supplementary 0, Supplementary 1, Supplementary 2, Supplementary 2B to SC and 3A to S, Supplementary 4, Supplementary 5, Supplementary 6, Supplementary 7 and Supplementary 8 are available as Supplementary data at *JAC* Online.

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