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Impact of pre-existent drug resistance on virological efficacy of single-tablet regimens in people living with HIV

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ABSTRACT

Despite the wide use of single-tablet regimens (STRs), few real-life data are available regarding the impact of pre-existent drug resistance on virological failure (VF). We aimed to fill this gap by analysing a large cohort of individuals selected from the ARCA database. The impact on VF of pre-existent resistance-associated mutations (RAMs) and cumulative genotypic susceptibility score (cGSS) before STR start was evaluated through survival analysis. Potential emergence of resistance at VF was also evaluated. Overall, 3916 individuals were included, comprising 678 treatment-naïve (G1), 2309 treatment-experienced aviraemic (G2) and 929 viraemic (G3), of whom 65.2% were treated with a STR based on efavirenz (35.2%) or rilpivirine (30.0%). At 2 years after starting a STR, the overall probability of VF was 5.9% in G1, 8.7% in G2 and 20.8% in G3. No impact of pre-existent resistance on VF was found in G1. The probability of VF was higher in patients with cGSS < 3 (reduced susceptibility to at least one drug) than in those with cGSS = 3 (full susceptibility to STR drugs) both in G2 and G3. A higher probability of VF was also found in the presence of pre-existent M184V (alone or in combination with pre-existent thymidine analogue mutations). Among patients who failed STR, a significant emergence of RAMs was found only in those exposed to EFV/FTC/TDF in G3 (specifically K103N and M184V). Our results confirm a high efficacy of STRs in clinical settings. Pre-existent resistance appears to influence virological efficacy of STRs in treatment-experienced individuals (both aviraemic and viraemic).

1. Introduction

Combined multiple-tablet antiretroviral therapy (ART) has been the milestone for the treatment of human immunodeficiency virus (HIV) infection for over 20 years, while the advent of once-daily single-tablet regimens (STRs) represented a landscape revolution for people living with HIV (PLWH) [1]. The era of STRs began in 2006 with the marketing authorisation of efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) combination. Since then, ten more STRs have been developed and marketed [2]. The recognised advantages of a single pill administered daily include simplification, reduced pill burden, improved quality of life and increased adherence to therapy, resulting in a higher number of patients with undetectable vi-

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ral load, decreased hospitalisation rates and increased retention in care compared with multiple-tablet regimens [1,3,4]. Furthermore, three of the available STRs have been included among preferred initial regimens in the recently updated European AIDS Clinical Society (EACS) guidelines [5] and the US Department of Health and Human Services (DHHS) guidelines [6].

Regarding the role of pre-existent resistance on virological response under STRs, in the 96-week resistance analysis of the STaR trial, the authors reported that pre-existent nucleos(t)ide reverse transcriptase inhibitor (NRTI) and non-NRTI (NNRTI) resistance-associated mutations (RAMs) did not impact treatment response to either rilpivirine/emtricitabine/tenofovir disoproxil fumarate (RPV/FTC/TDF) or EFV/FTC/TDF [7]. Similarly, in the SPIRIT study, a high rate of virological success was reported in virologically suppressed individuals with pre-existent RAMs to NRTIs and NNRTIs who switched to RPV/FTC/TDF [8]. Margot et al. observed that pre-existent RAMs did not affect response at Week 144 in an integrated resistance analysis of two phase 3 randomised, double-blind trials comparing STRs of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) and elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (EVG/COBI/FTC/TAF) in 1733 HIV-1-infected treatment-naïve adults [9]. Andreatta et al. detected high levels of pre-existent resistance among suppressed HIV subjects switching to bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) from boosted protease inhibitor (PI)-based three-drug regimens or dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) in two randomised non-inferiority trials. Nevertheless, the virological suppression rate maintained high for up to 48 weeks in individuals with archived drug resistance mutations, including those with M184V/I [10].

Despite the broad use of STRs, few data from real-life are available regarding the potential impact on virological efficacy of pre-existent drug resistance to each compound of STRs.

The present study aimed to evaluate the impact of pre-existent resistance on virological failure (VF) in PLWH who started a STR. In addition, other factors potentially associated with VF were investigated and, finally, the emergence of RAMs at VF was also evaluated.

2. Materials and methods

2.1. Study population

This was a retrospective observational study performed using the Antiviral Response Cohort Analysis (ARCA) database, which contains data on HIV resistance and ART for more than 40 000 patients in Italy. Data collection was approved by the local ethics committees, and written informed consent was obtained from all patients before participation. The study was performed in accordance with the ethical principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization.

HIV-1-infected individuals who started a STR were selected on the basis of the following criteria: (i) STR start period between July 2006 and April 2019; (ii) availability of at least one plasma HIV-RNA quantification after STR start; and (iii) availability of at least one plasma-derived genotypic resistance test (GRT) for protease/reverse transcriptase before STR start. GRT for integrase was also collected when available. Individuals included in the study were divided into three groups, as follows: treatment-naïve (G1); treatment-experienced virologically suppressed (G2); and treatment-experienced viraemic (G3).

The following STRs were considered in the analysis: EFV/FTC/TDF; RPV/FTC/TDF; rilpivirine/emtricitabine/tenofovir alafenamide (RPV/FTC/TAF); EVG/COBI/FTC/TDF; EVG/COBI/FTC/TAF; and DTG/ABC/3TC. The regimens that differed only because of the presence of TDF or TAF were considered as a whole in the analysis.

For each group, when more than one STR resulted in the patient treatment history, the last STR within each group was considered.

2.2. Evaluation of resistance and genotypic susceptibility score to single-tablet regimen (STR)

For each individual in a specific group, RAMs before STR start and cumulative genotypic susceptibility score (cGSS) were calculated by cumulating all the mutations observed in all available GRTs before starting STR. Major RAMs panelled by the Stanford HIV Drug Resistance Database (HIVdb v.8.9-1) were considered for the analysis. cGSS was calculated using the HIV_DB algorithm (https://hivdb.stanford.edu/hivalg/by-sequences/), adding the score of each single drug composing the regimen taken into account at a specific time point. Specifically, the GSS for individual drugs was derived with a score of 0 (resistant virus), 0.5 (virus with intermediate resistance) and 1 (susceptible virus). cGSS was stratified in two levels: cGSS = 3, indicating full susceptibility; and cGSS < 3, indicating reduced susceptibility to at least one drug.

For regimens including an integrase strand transfer inhibitor (INSTI) for which an integrase GRT was not available before STR switch, the INSTI failure prior to switch was considered as follows: a greater weight in terms of reduced susceptibility was given to a previous failure to DTG, which has the highest INSTI genetic barrier to resistance, thus a score of 0 was assigned; following the same logic, if individuals had failed raltegravir or elvitegravir the score was 0.5; if individuals had not failed to any INSTI, the score was 1 [11].

For individuals undergoing VF during a STR, the emergence of resistance was calculated if a GRT performed after failure was available.

2.3. Statistical analysis

All statistical analyses were performed using the statistical software R version 4.0.3 and IBM SPSS Statistics v.25 (IBM Corp., Armonk, NY, USA). A *P*-value of <0.05 was considered statistically significant.

2.3.1. Evaluation of patient characteristics among different single-tablet regimens (STRs)

Potential differences among patients treated with different STRs were evaluated by Kruskal–Wallis or analysis of variance (ANOVA) test for quantitative variables as appropriate, and by χ^2 or Fisher's exact test for qualitative variables as appropriate.

2.3.2. Evaluation of probability and factors associated with virological failure (VF)

Evaluation of probability and factors associated with VF were assessed using the survival analysis approach. In viraemic individuals [both naïve (G1) and treatment-experienced (G3)], VF was defined as incomplete virological suppression 6 months after the start of a STR, or as virological rebound after achievement of virological suppression (defined as one viraemia value <50 copies/mL). In treatment-experienced virologically suppressed individuals (G2), VF was defined as the first of two consecutive plasma viral loads >50 copies/mL, or as one plasma viral load >1000 copies/mL after the treatment change, or one plasma viral load >50 copies/mL followed by a treatment change.

Within each group, Kaplan–Meier curves were used to assess the probability of VF overall and by stratifying for the STRs presence/absence of specific major pre-existent RAMs or for cGSS (<3 vs. =3). The following major RAMs were specifically considered:

(i) the 3TC/FTC-associated mutations M184V/I; (ii) thymidine analogue mutations (TAMs); and (iii) the major NNRTI RAMs for STRs including a drug within this class.

Cox regression models were built by evaluating the proportional hazards (PHs) assumption to evaluate potential factors associated with VF among the following variables: sex; age; calendar year of diagnosis; HIV subtype; hepatitis C virus (HCV) infection (based on serological data); hepatitis B virus HBV infection (based on serological data); nadir CD4+ cell count; zenith viral load; pre-existent RAMs; cGSS; treatment history (for G2 and G3; previous drug classes administered, previous number of regimens and years on ART); and length of virological suppression (for G2). In case of non-PH assumption, weighted Cox regression was performed [12].

2.3.3. Evaluation of emergence of resistance at virological failure (VF)

In individuals who failed a STR and for whom a GRT at VF was available, the emergence of RAMs was also evaluated. In particular, for each specific RAM, McNemar's test was used to compare its frequency detected before and after STR failure. All *P*-values for multiple pairwise comparisons were adjusted by using the Benjamini–Hochberg correction [13].

3. Results

3.1. Baseline characteristics of patients

Baseline characteristics of the study population, according to treatment status and STR received, are reported in Table 1 and Supplementary Tables S1–S3. Overall, 3916 individuals were included: 73.1% of them were male, their median [interquartile range (IQR)] age was 44 (36–52) years, their median (IQR) nadir CD4+ cell count was 248 (119–350) cells/mm^3 and their median (IQR) zenith viral load was 5.0 (4.3–5.5) $\log_{10}$ copies/mL (Table 1). Considering the treatment status at baseline (before STR start), 678 (17.3%) were naïve (G1), 2309 (59.0%) were treatment-experienced virologically suppressed (G2) and 929 (23.7%) were treatment-experienced viraemic (G3). The median (IQR) duration of ART exposure in the drug-experienced population was 5 (2–10) years: 5 (2–10) years in G2 and 5 (1–11) years in G3.

EFV/FTC/TDF was the most prescribed STR in the whole cohort (35.2%) as well as in G1 and G3 (63.9% and 48.4%, respectively), had the earliest calendar year of prescription ($P < 0.001$) and had the highest prevalence of anti-HCV+ or anti-HBc+ in all treatment subgroups (Supplementary Tables S1–S3), while RPV/FTC/(TDF or TAF) was the most prescribed in G2 (37.1%).

3.2. Evaluation of pre-existent resistance and cumulative genotypic susceptibility score (cGSS) before single-tablet regimen (STR) start

The prevalence of pre-existent RAMs and cGSS, overall and according to treatment status, is reported in Table 1 and Supplementary Tables S1–S3. Before STR start, any pre-existent RAM was present in 941 individuals (24.0%) of the overall population, comprising 82 (12.1%) in G1, 580 (25.1%) in G2 and 279 (30.0%) in G3 (Table 1). Pre-existent M184V was present in 307 individuals (7.8%), comprising 3 (0.4%) in G1, 187 (8.1%) in G2 and 117 (12.6%) in G3. Any pre-existent TAM was present in 358 (9.1%) individuals, comprising 15 (2.2%) in G1, 232 (10.0%) in G2 and 111 (11.9%) in G3. The co-presence of at least one pre-existent TAM and pre-existent M184V was found in 171 individuals (4.4%). At least one pre-existent NNRTI RAM was found in 567 individuals (14.5%) of the overall population, comprising 56 (8.3%) in G1, 344 (14.9%) in G2 and 167 (18.0%) in G3. The median (IQR) cGSS was 3 (2.5–3) overall, 3 (IQR 3–3) in G1 and 3 (IQR 2.5–3) in G2 and G3.

3.3. Evaluation of probability of virological failure (VF)

The 2-year probability of VF in G1 was 5.9%, with no difference according to cGSS (Fig. 1A) or STR type (data not shown). In G2, the 2-year probability of VF was 8.7% (Fig. 1B). By considering the type of STR, a higher probability of VF (16.0%) was found among individuals treated with EVG/COBI/FTC/(TDF or TAF) compared with others [EFV/FTC/TDF, 9.3%; RPV/FTC/(TDF or TAF), 7.3%; and DTG/ABC/3TC, 7.0%; $P = 0.031$]. A higher probability was also found in individuals with cGSS < 3 compared with those with cGSS = 3 (12.6% vs. 7.3%; $P = 0.003$) (Fig. 1E).

Considering the effect on VF of pre-existent M184V and TAMs (alone or in combination) in G2, the presence of pre-existent M184V conferred the highest probability of VF (Fig. 2A). According to STR types, pre-existent M184V had a relevant effect among subjects receiving EFV/FTC/TDF (2-year probability of VF: with pre-existent M184V, 32.5%; with pre-existent M184V+TAMs, 13.5%; with pre-existent TAMs, 9.1%; without pre-existent M184V and without pre-existent TAMs, 8%; $P = 0.041$) or EVG/COBI/FTC/(TDF or TAF) (2-year probability of VF: with pre-existent M184V, 54.7%; with pre-existent M184V+TAMs, 18.7%; with pre-existent TAMs, 11.1%; without pre-existent M184V and without pre-existent TAMs, 13.5%; $P = 0.004$), while the association pre-existent M184V+TAMs had more impact in individuals treated with RPV/FTC/(TDF or TAF) (2-year probability of VF: with pre-existent M184V+TAMs, 39.5%; with pre-existent M184V, 19.8%; with pre-existent TAMs, 5.0%; without pre-existent M184V and without pre-existent TAMs, 6.0%; $P = 0.004$) (Supplementary Fig. S1).

In G3, the 2-year probability of VF was 20.8% (Fig. 1C) and was significantly higher among those taking DTG/ABC/3TC (32.2%) or EVG/COBI/FTC/(TDF or TAF) (27.5%) compared with others (EFV/FTC/TDF, 18.4%; RPV/FTC/(TDF or TAF), 17.5%; $P = 0.002$).

By stratifying for cGSS, a significantly higher probability of VF was found in individuals in G3 with cGSS < 3 compared with those with cGSS = 3 (34.9% vs. 16.8%; $P < 0.001$) (Fig. 1F). By considering the treatment subgroups, the impact of lower cGSS was still present among the subpopulations taking EFV/FTC/TDF (39.3% vs. 15.2%; $P < 0.001$) and RPV/FTC/(TDF or TAF) (49.0% vs. 12.2%; $P < 0.001$), while no effect of the cGSS was found in individuals treated with DTG/ABC/3TC or EVG/COBI/FTC/(TDF or TAF) (data not shown).

By considering the impact of M184V and TAMs, individuals in G3 harbouring the M184V or the M184V+TAMs had the highest probability of VF at 2 years after STR switch compared with others (Fig. 2B).

Regarding treatment subgroups, the effect of pre-existent M184V+TAMs on VF was relevant in subjects treated with EFV/FTC/TDF (2-year probability of VF: with pre-existent M184V+TAMs, 44.6%; with pre-existent M184V, 31.2%; with pre-existent TAMs, 15.1%; without pre-existent M184V and without pre-existent TAMs, 16.6%; $P = 0.005$). The effect of M184V mutation alone was recognisable among individuals taking RPV/FTC/(TDF or TAF), despite the low number of individuals (2-year probability of VF: with pre-existent M814V+TAMs, 37.5%; with pre-existent M184V, 80.0%; with pre-existent TAMs, 0%; without pre-existent M184V and without pre-existent TAMs, 12.7%; $P < 0.001$) (data not shown).

As reported in Table 1, the baseline prevalence of pre-existent M184I mutation before STR start in the study population was very low (0.5%), so we did not evaluate its specific impact on VF in the three subgroups. Additional information about M184I prevalence in individuals treated with EFV- and RPV-based regimens at baseline and at VF is present in Supplementary Table S4. In addition, due to the small sample size and the low event rate, the effect of pre-existent M184V and TAMs was not investigated for G3 subjects receiving DTG/ABC/3TC or EVG/COBI/FTC/(TDF or TAF).

Table 1
Baseline characteristics of patients, overall and according to ART status [a]

Variable	Overall (N = 3916)	G1 (N = 678)	G2 (N = 2309)	G3 (N = 929)
Male [n (%)]	2864 (73.1)	544 (80.2)	1693 (73.3)	627 (67.5)
Age (years) [median (IQR)]	44 (36–52)	38 (32–46)	46 (38–53)	45 (37–51)
Risk factor [b] [n (%)]				
Heterosexual	1257 (40.3)	161 (31.6)	784 (42.1)	312 (41.8)
MSM/bisexual	730 (23.4)	132 (25.9)	451 (24.2)	147 (19.7)
IDU	477 (15.3)	29 (5.7)	279 (15.0)	169 (22.7)
Other	654 (21.0)	187 (36.7)	349 (18.7)	118 (15.8)
Anti-HBc+ [c] [n (%)]	398 (10.2)	57 (8.4)	230 (10.0)	111 (11.9)
Anti-HCV+ [d] [n (%)]	606 (15.5)	52 (7.7)	343 (14.9)	211 (22.7)
HIV-1 subtype B [n (%)]	2926 (74.7)	464 (68.4)	1762 (76.3)	700 (75.3)
Time from HIV diagnosis (years) [e] [median (IQR)]	6 (2–12)	0 (0–3)	7 (7–13)	9 (2–17)
Time on ART (years) [median (IQR)]	5 (2–10) [f]	–	5 (2–10)	5 (1–11)
Year of starting STR [median (IQR)]	2015 (2011–2017)	2012 (2009–2015)	2016 (2014–2017)	2014 (2010–2016)
Nadir CD4+ count (cells/mm^3) [median (IQR)]	248 (119–350)	315 (232–425)	235 (107–336)	217 (76–325)
BL CD4+ count (cells/mm^3) [median (IQR)]	513 (334–742)	340 (251–471.2)	624 (440–832)	400 (252–598.8)
Zenith viral load ($\log_{10}$ copies/mL) [median (IQR)]	5.0 (4.3–5.5)	4.8 (4.3–5.3)	4.9 (4.3–5.4)	5.2 (4.7–5.6)
BL viral load ($\log_{10}$ copies/mL) [median (IQR)]	4.2 (2.8–4.9)	4.6 (4.1–5.1)	–	3.2 (2.1–4.5)
Time on virological suppression before switch (months) [median (IQR)]	28 (10–57) [g]	–	28 (10–57)	–
No. of previous regimens [median (IQR)]	2 (1–4) [f]	–	2 (1–4)	2 (1–5)
STR [n (%)]				
EFV/FTC/TDF	1378 (35.2)	433 (63.9)	495 (21.4)	450 (48.4)
RPV/FTC/(TDF or TAF)	1176 (30.0)	154 (22.7)	856 (37.1)	166 (17.9)
EVG/COBI/FTC/(TDF or TAF)	703 (18.0)	54 (8.0)	468 (20.3)	181 (19.5)
DTG/ABC/3TC	659 (16.8)	37 (5.5)	490 (21.2)	132 (14.2)
Cumulative GSS < 3 [n (%)]	986 (25.2)	31 (4.6)	706 (30.6)	249 (26.8)
Any pre-existent RAM [n (%)]	941 (24.0)	82 (12.1)	580 (25.1)	279 (30.0)
Pre-existent PI RAMs [n (%)]	228 (5.8)	17 (2.5)	143 (6.2)	68 (7.3)
Pre-existent NRTI RAMs [n (%)]	520 (13.3)	17 (2.5)	325 (14.1)	178 (19.1)
Pre-existent NNRTI RAMs [n (%)]	567 (14.5)	56 (8.3)	344 (14.9)	167 (17.9)
Pre-existent INSTI RAMs [h] [n (%)]	14 (3.0)	0 (0.0)	5 (2.2)	9 (7.1)
At least one pre-existent TAM [n (%)]	358 (9.1)	15 (2.2)	232 (10.0)	111 (11.9)
Pre-existent M184V [n (%)]	307 (7.8)	3 (0.4)	187 (8.1)	117 (12.6)
Pre-existent M184I [n (%)]	20 (0.5)	0 (0.0)	11 (0.5)	9 (1.0)
At least one pre-existent TAM + past M184V [n (%)]	171 (4.4)	1 (0.1)	112 (4.9)	58 (6.2)

ART, antiretroviral therapy; BL, baseline; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; EVG/COBI/FTC/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; EVG/COBI/FTC/TDF, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; IDU, intravenous drug use; GSS, genotypic susceptibility score; HBc, hepatitis B core antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; MSM, men who have sex with men; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, non-nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance-associated mutation; RPV/FTC/TAF, rilpivirine/emtricitabine/tenofovir alafenamide; RPV/FTC/TDF, rilpivirine/emtricitabine/tenofovir disoproxil fumarate; STR, single-tablet regimen; TAM, thymidine analogue mutation.

[a] G1, treatment-naïve individuals; G2, treatment-experienced virologically suppressed individuals; G3, treatment-experienced viraemic individuals.
[b] Data available for 3118 individuals.
[c] Data available for 2569 individuals
[d] Data available for 2551 individuals.
[e] Data available for 2971 cases.
[f] Calculated considering G2 and G3.
[g] Calculated only considering G2.
[h] Data available for 446 individuals with at least one integrase genotypic resistance test.

By focusing the attention on NNRTI-based STRs, individuals in G2 and G3 harbouring viral strains with at least one pre-existent NNRTI mutation had a higher probability of VF at 2 years of treatment with EFV/FTC/TDF compared with those without any pre-existent resistance (Fig. 3A,C). The presence of pre-existent NNRTI mutations increased the probability of VF also in individuals treated with RPV/FTC/(TDF or TAF) in G2, but not in G3 (Fig. 3B,D).

3.4. Factors associated with virological failure (VF)

By evaluating factors potentially associated with VF, in G1 the zenith viral load was the only independent predictor of VF. In particular, a higher zenith viral load was associated with a higher hazard ratio (HR) of VF, not only in the univariable but also in the multivariable Cox model (per 1 log increase of zenith viral load, HR = 1.47, 95% confidence interval 1.01–2.15; P = 0.047). No effect on VF of cGSS was found in G1.

In G2, by Cox multivariable analysis, factors positively associated with VF were female sex, previous PI use, higher zenith viral load and higher number of years on ART (Table 2). Previous PI use was a factor positively associated with VF also in G3, while a higher nadir CD4+ cell count and previous NNRTI use were negatively associated with VF (Table 3). cGSS was positively associated with VF both in G2 and G3 at univariable analysis, but its effect was not confirmed at multivariable analysis (Tables 2 and 3).

Cox models were also built to evaluate the effect of pre-existent M184V (alone or with pre-existent TAMs) on VF (Table 2). Univariable analysis confirmed the results obtained by Kaplan–Meier estimates both for G2 and G3. In particular, in G2 the presence of pre-existent M184V was associated with a higher HR of VF compared with its absence; a trend of significance was found in the multivariable model. In G3, at univariable analysis pre-existent M184V (both alone and with pre-existent TAMs) had a higher HR of VF compared with its absence, although this finding was not confirmed at multivariable analysis.

HBV/HCV co-infection was not included in the analysis of factors associated with VF because in the ARCA database this information was reported only on a serological basis and also we found a high number of missing data.

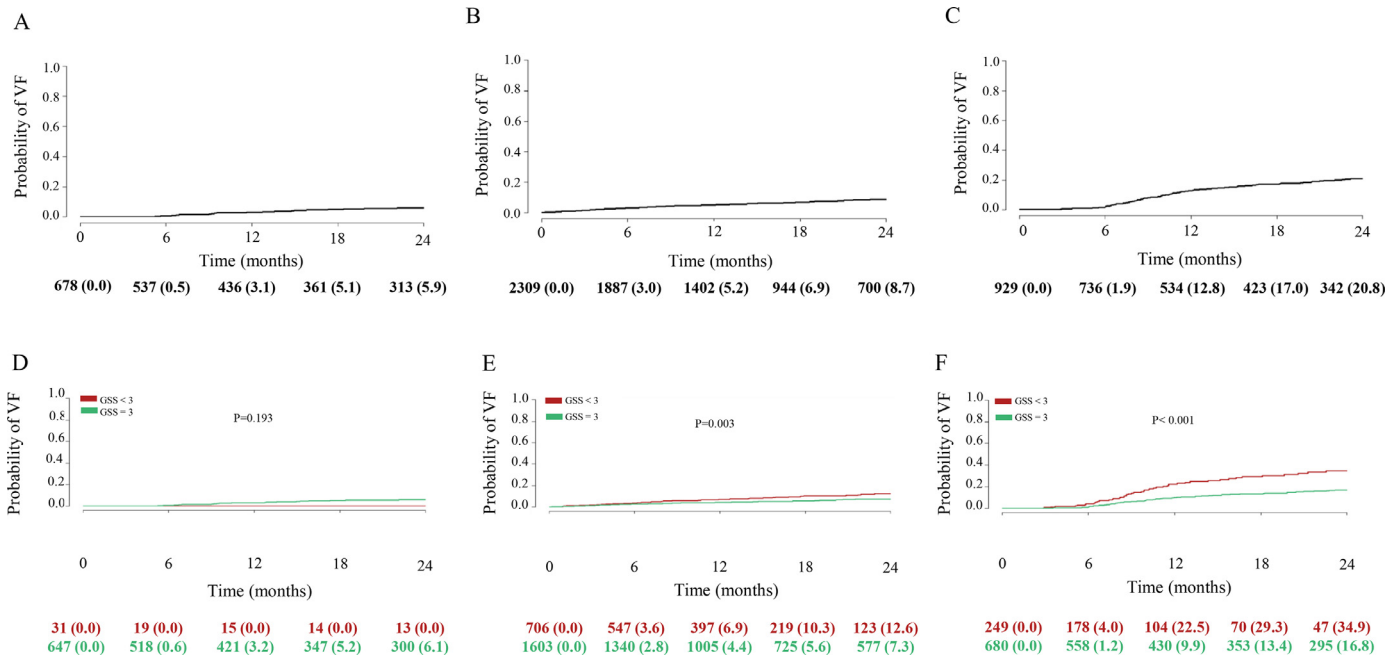

Fig. 1. Kaplan–Meier estimates of the probability of virological failure (VF) in HIV-1-infected individuals who started a single-tablet regimen, overall and according to the cGSS. Kaplan–Meier estimation was performed in: (A,D) naïve individuals; (B,E) virologically suppressed individuals; and (C,F) viraemic individuals. *P*-values were calculated using the log-rank test. For each panel, the number at risk and the probability of VF are reported at each time point (in brackets). cGSS, cumulative genotypic susceptibility score.

Table 2
Factors associated with virological failure in aviraemic HIV-infected individuals (G2) who started a single-tablet regimen

Variable	Unadjusted HR (95% CI)	*P*-value	Adjusted HR [a] (95% CI)	*P*-value	Adjusted HR [b] (95% CI)	*P*-value
Sex (female vs. male)	1.53 (1.14–2.06)	0.004	1.58 (1.14–2.20)	0.007	1.87 (0.98–3.59)	0.059
Risk factor						
Heterosexual [c]	1		1		1	
IDU	1.84 (1.23–2.74)	0.003	1.47 (0.91–2.37)	0.118	0.93 (0.47–1.86)	0.845
Other/unknown	1.29 (0.91–1.83)	0.147	1.61 (1.12–2.32)	0.011	1.14 (0.62–2.10)	0.685
Zenith VL (per 1 $\log_{10}$ copies/mL increase)	1.31 (1.13–1.51)	<0.001	1.30 (1.12–1.50)	<0.001	1.15 (0.91–1.46)	0.247
cGSS (= 3 vs. <3)	0.64 (0.47–0.86)	0.008	0.93 (0.66–1.29)	0.652	–	–
Previous PI use (per 1 PI increase)	2.42 (1.73–3.38)	<0.001	1.70 (1.18–2.45)	0.004	1.16 (0.60–2.24)	0.660
Years of ART (per 1 year increase)	1.07 (1.05–1.09)	<0.001	1.04 (1.01–1.08)	0.014	1.05 (0.99–1.10)	0.090
No. of previous ART regimens (per 1 regimen increase)	1.12 (1.08–1.16)	<0.001	1.02 (0.96–1.08)	0.571	0.97 (0.87–1.09)	0.628
Pre-existent TAMs/past M184V						
No TAMs/no M184V [c]	1		1		1	
TAMs + M184V	0.77 (0.35–1.72)	0.527	–	–	0.59 (0.27–1.31)	0.196
Only M184V	2.74 (1.31–5.75)	0.008	–	–	1.99 (0.94–4.20)	0.071
Only TAMs	1.20 (0.56–2.55)	0.644	–	–	0.91 (0.41–2.01)	0.809

ART, antiretroviral therapy; cGSS, cumulative genotypic susceptibility score; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IDU, intravenous drug use; PI, protease inhibitor; RAM, resistance-associated mutation; TAM, thymidine analogue mutation; VL, viral load.
The following variables were considered in the Cox regression analysis: sex, age, calendar year of diagnosis, HIV subtype, HCV co-infection, HBV co-infection, nadir CD4+ cell count, zenith VL, pre-existing RAMs, cGSS, treatment history (for G2 and G3: previous drug classes administered, previous number of regimens and years on ART) and length of virological suppression (for G2). In the table are reported only variables that were significant in the univariable analysis ($P < 0.05$) and were therefore considered for the multivariable model.
[a] Adjusted for cGSS.
[b] Adjusted for past M184V (alone or together with TAMs).
[c] Reference group.

3.5. Evaluation of emergence of resistance at virological failure (VF)

RAMs were investigated in individuals for whom a GRT was available at VF, including 26 in G1, 62 in G2 and 91 in G3. By comparing the prevalence of RAMs before and after the administration of different STRs, no significant increase was found in G1 and G2 under a STR. Differently, in G3 with the administration of EFV/FTC/TDF (number of GRTs available at failure = 51), but not of other STRs, a significant increase was found for M184V (pre-STR 19.6% vs. post-STR 47.1%; $P < 0.001$), K103N (pre-STR 15.7%, post-STR 56.9%; $P < 0.001$) and K65R [pre-STR 2.0%, post-STR 17.6%; $P = 0.008$, with a trend of significance after the correction with the Benjamini–Hochberg test ($P = 0.062$)].

4. Discussion

In the present study, we analysed the impact of pre-existent HIV drug resistance on STR virological efficacy, investigated factors associated with an increased risk of VF, and evaluated the emergence of new RAMs after VF. To our knowledge, this is the first study evaluating the role of pre-existent resistance in a large cohort of PLWH who started a STR in real life.

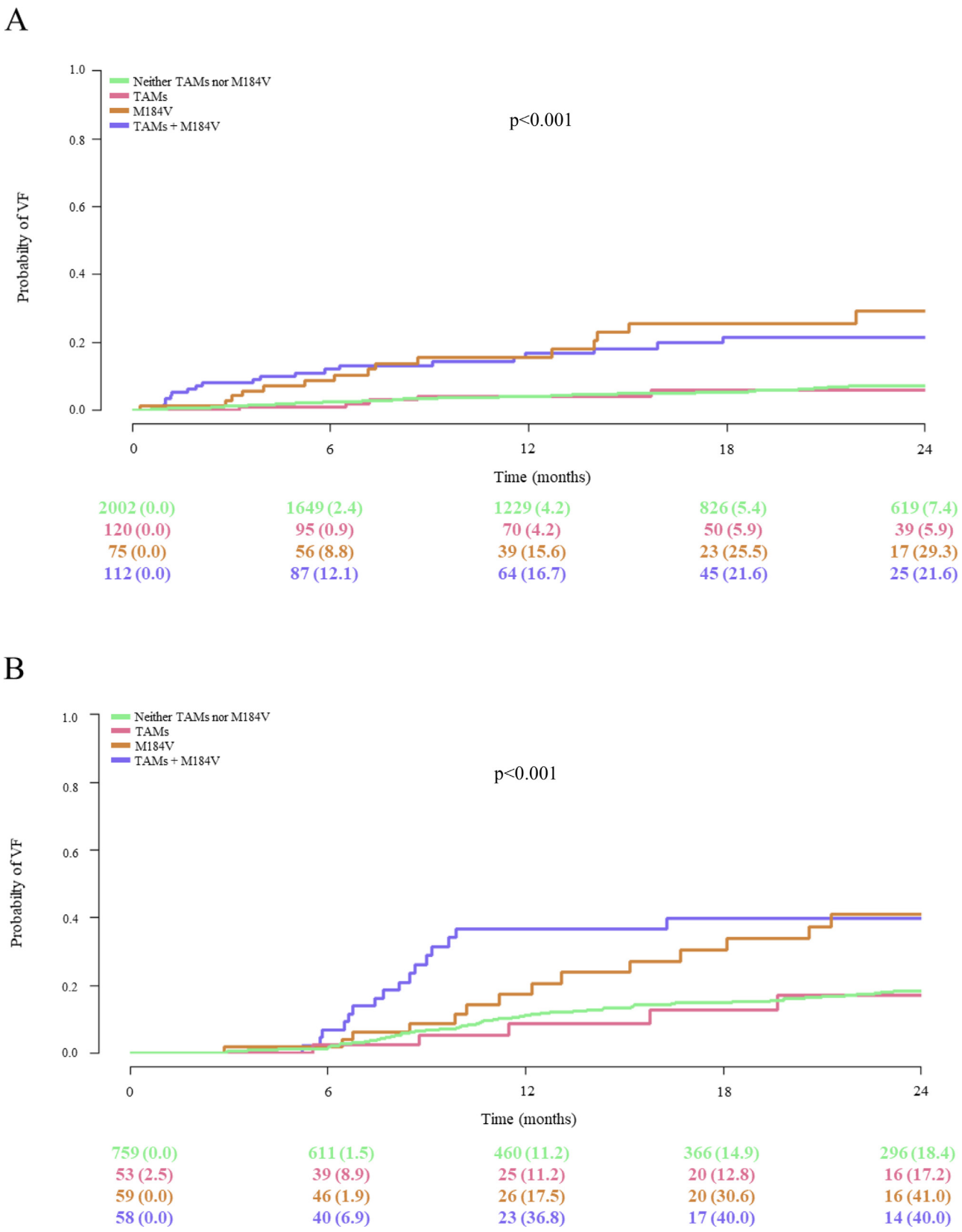

Fig. 2. Kaplan–Meier estimates of the probability of virological failure (VF) in HIV-1-infected individuals who started a single-tablet regimen, according to presence/absence of pre-existent TAMs and/or pre-existent M184V. Kaplan–Meier estimation was performed in: (A) virologically suppressed individuals; and (B) viraemic individuals. *P*-values were calculated using the log-rank test. For each panel, the number at risk and the probability of VF are reported at each time point (in brackets). TAM, thymidine analogue mutation.

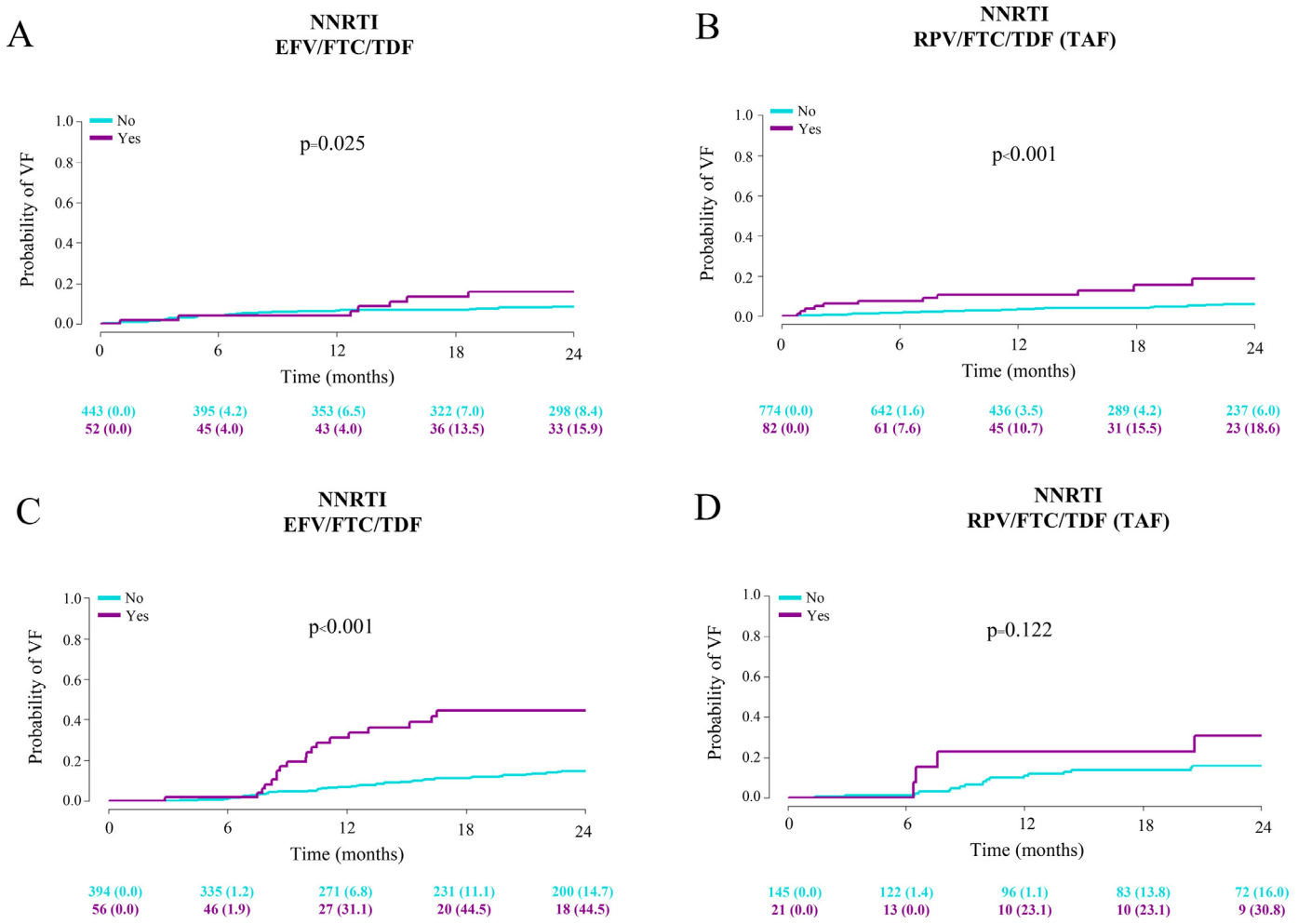

Fig. 3. Kaplan–Meier estimates of the probability of virological failure (VF) in HIV-1-infected individuals who started EFV/FTC/TDF or RPV/FTC/(TDF or TAF), according to presence/absence of pre-existent NNRTI mutations. Kaplan–Meier estimation was performed in: (A,B) virologically suppressed individuals; and (C,D) viraemic individuals. *P*-values were calculated using the log-rank test. For each panel, the number at risk and the probability of VF are reported at each time point (in brackets). EFV, efavirenz; FTC, emtricitabine; NNRTI, non-nucleoside reverse transcriptase inhibitor; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

In general, we found a low probability of VF after 2 years of STR start both in drug-naïve and drug-experienced individuals (either viraemic or virologically suppressed), thus confirming the efficacy of STRs also in real settings. By considering pre-existent resistance, no effect on VF was found in drug-naïve individuals. By contrast, pre-existent drug resistance had an impact on VF in treatment-experienced individuals (both viraemic and virologically suppressed), although not confirmed at multivariable analysis. In particular, the few individuals (n = 31) with cGSS < 3 (therefore with a regimen with at least one non-completely active drug) were associated with a higher probability of VF, especially those viraemic treated with EFV- and RPV-based STRs.

In treatment-experienced individuals, we also found that pre-existent M184V (alone or in combination with TAMs) or the presence of at least one pre-existent NNRTI mutation increased the probability of VF. This is in contrast to some clinical trial findings where pre-existent resistance did not impact on virological response [7,8]. Anyway, it should be specified that, unlike our real-life observational study, these trials excluded subjects with pre-existent mutations related to the study drugs [7,8]. On the other hand, our results are in line with those of other observational studies that reported the association between the presence of previous mutations associated with resistance to reverse transcriptase inhibitors and failure to RPV- or EFV-based STRs. In particular, in virologically suppressed individuals under RPV/FTC/TDF, Armenia et al. found that the probability of virological rebound after 72 weeks from switch was significantly higher among those with pre-existent combination of at least one NRTI RAM (including M184V/I and/or TAMs and/or other NRTI mutations) and at least one NNRTI RAM (including K103N and/or RPV RAMs and /or other NNRTI RAMs), and among those with full/intermediate resistance to both FTC/TDF and RPV; these results were confirmed at multivariable analysis [14]. In an observational study including drug-naïve and experienced individuals starting RPV/FTC/TDF, baseline cumulative genotype showed 4% of RPV resistance mutations (E138A, H221Y, L100I+K103N+H221Y, L100I+K103N and K103N+Y181C) and 16% of NNRTI concerning polymorphisms: after 8 months, a lower proportion of people with these polymorphisms potentially associated with resistance was virologically suppressed compared with those with wild-type genotypes (78% vs. 96%) [15].

We found no impact of pre-existent resistance (and in particular of M184V mutation) on the treatment efficacy of STRs in naive and virologically suppressed individuals switching to DTG/ABC/3TC, and this appears in harmony with the available literature. A recent real-life observational study conducted on a Madrid cohort comprised ART-naïve and -experienced individuals (both previously virologically suppressed and not suppressed) starting a DTG/ABC/3TC STR. Pre-existent RAMs at baseline were found in 52.0% of naïve (9.1% with at least one major NRTI, 27.3% with at least one major NNRTI and 25.0% with at least one major PI mutation) and 24.0%

Table 3
Factors associated with virological failure in viraemic HIV-infected individuals (G3) who started a single-tablet regimen

Variable	Unadjusted HR (95% CI)	*P*-value	Adjusted HR [a] (95% CI)	*P*-value	Adjusted HR [b] (95% CI)	*P*-value
Sex (female vs. male)	1.78 (1.30–2.45)	<0.001	1.27 (0.79–2.02)	0.321	1.27 (0.79–2.05)	0.319
Risk factor						
Heterosexual [c]	1		1		1	
MSM/bisexual	0.55 (0.32–0.96)	0.036	0.57 (0.27–1.16)	0.122	0.57 (0.27–1.17)	0.126
Nadir CD4+ count (per 100 cells increase)	0.71 (0.59–0.84)	<0.001	0.84 (0.72–0.97)	0.015	0.84 (0.73–0.97)	0.016
Zenith VL (per 1 $\log_{10}$ copies/mL increase)	1.35 (1.1–1.64)	0.003	1.22 (0.95–1.56)	0.127	1.23 (0.95–1.60)	0.117
cGSS (=3 vs.<3)	0.42 (0.30–0.58)	<0.001	0.80 (0.53–1.22)	0.305	–	–
Previous NNRTI use	0.66 (0.48–0.91)	0.012	0.61 (0.38–0.96)	0.034	0.63 (0.39–0.99)	0.046
Previous PI use (per 1 PI increase)	3.09 (2.05–4.66)	<0.001	2.31 (1.26–4.22)	0.007	2.33 (1.29–4.22)	0.005
Previous INSTI use (per 1 INSTI increase)	1.86 (1.26–2.74)	0.002	1.22 (0.74–2.01)	0.427	1.36 (0.84–2.19)	0.213
Years of ART (per 1 year increase)	1.06 (1.03–1.08)	<0.001	1.03 (0.99–1.07)	0.105	1.04 (1.00–1.08)	0.078
No. of previous regimens (per 1 regimen increase)	1.11 (1.07–1.15)	<0.001	1.01 (0.93–1.09)	0.856	0.99 (0.91–1.08)	0.894
Pre-existent TAMs/past M184V						
No TAMs/no M184V [c]	1		1		1	
TAMs + M184V	2.84 (1.71–4.74)	<0.001	–	–	1.53 (0.72–3.27)	0.273
Only M184V	2.24 (1.33–3.78)	0.003	–	–	1.14 (0.66–1.95)	0.641
Only TAMs	0.84 (0.37–1.90)	0.668	–	–	0.68 (0.29–1.57)	0.363

ART, antiretroviral therapy; cGSS, cumulative genotypic susceptibility score; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; IDU, intravenous drug use; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NNRTI, non-nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitor; RAM, resistance-associated mutation; TAM, thymidine analogue mutation; VL, viral load.
The following variables were considered in the Cox regression analysis: sex, age, calendar year of diagnosis, HIV subtype, HCV co-infection, HBV co-infection, nadir CD4+ cell count, zenith VL, pre-existing RAMs, cGSS, treatment history (for G2 and G3: previous drug classes administered, previous number of regimens and years on ART) and length of virological suppression (for G2). In the table are reported only variables that were significant in the univariable analysis ($P < 0.05$) and were therefore considered for the multivariable model.
[a] Adjusted for cGSS.
[b] Adjusted for past M184V (alone or together with TAMs).
[c] Reference group.

of treatment-experienced (4.8% with at least one major NRTI, 7.6% with at least one major NNRTI and 10% with at least one major PI mutation) subjects, but no major INSTI, ABC or 3TC mutations were recognisable. Furthermore, no major INSTI, ABC or 3TC RAM was detectable in those undergoing VF within 48 weeks [16].

A longitudinal analysis of five HIV European cohorts (including ARCA) analysed the outcomes of ART-experienced virologically suppressed individuals switching to DTG/ABC/3TC. The VF rate was very low (1.3%) and its incidence was not significantly different among individuals with and without baseline M184V/I mutation [17]. Similar results were also reported in the work by Jary et al. [18].

In our study, the 2-year probability of VF in treatment-experienced viraemic individuals starting a STR was higher among the subgroups taking DTG/ABC/3TC (32.2%) or EVG/COBI/FTC/(TDF or TAF) (27.5%). The high rate of VF that we have reported among individuals treated with INSTI-based regimens could be explained considering the longer history of infection and the higher number of years passed on a potentially suboptimal ART (Supplementary Table S3). Beyond pre-existent resistance, we found other viro-immnuological factors to be associated with VF. In particular, in naïve individuals and in those virologically suppressed, a higher zenith viral load was associated with VF. We found no previous report in the literature on the effect of zenith viral load in PLWH treated with STRs, but the detrimental effect of an elevated pre-ART viraemia has already been described both in drug-naïve and treatment-experienced individuals under virological control [14,19,20]. Recently, it was reported that a higher baseline viral load and a lower nadir CD4+ count independently predicted VF in naïve patients starting an INSTI-based regimen [21,22].

In viraemic subjects, nadir CD4+ count was a predictive factor of VF. The negative effect of a low baseline CD4 cell count is not surprising considering the known correlations to a larger viral reservoir and a more advanced disease stage [23], to relevant co-morbidities [24] and to higher risk of VF in virologically suppressed individuals [25]. Moreover, in a multicentre, retrospective, observational study, a lower nadir CD4+ cell count was associated with loss of virological suppression in subjects starting a raltegravir-based salvage regimen [26]. In a retrospective study conducted in Shenyang (northeastern China), a low nadir CD4+ cell count was independently associated with a high-risk of low-level viraemia and subsequent VF [27].

Although our population was not made up of heavily drug-experienced individuals (median ART exposure 5 years), treatment history was also associated with VF both in virologically suppressed individuals (as previous use of PIs and longer time passed on ART) and viraemic individuals (as previous use of NNRTIs and PIs).

Overall, our findings confirm the need for an accurate evaluation of historical resistance (together with the treatment history, previous virological trends and immunological impairment) to prevent a negative response due to archived resistance when switches are planned [5,6].

By considering the emergence of RAMs at VF to STRs, in our cohort we found a significant increase of resistance only in drug-experienced viraemic individuals who failed EFV/FTC/TDF. In particular, we found an increased prevalence of K103N, M184V and K65R.

These data may be explained by the EFV low genetic barrier to resistance, especially in a setting of incomplete viral suppression [28]. Noteworthy, Charpentier et al. reported a significant reduction of K65R, K103N and M184V/I prevalence after the introduction of the EFV/FTC/TDF STR, which prevented selective adherence [29]. Similarly, in our work, inadequate compliance to treatment prescriptions could speculatively explain the increased prevalence of the aforementioned mutations only in the viraemic group of less-adherent individuals. Regarding this point, in our cohort the subjects on EFV/FTC/TDF had a higher rate of anti-HBc+ and/or anti-HCV+, which is considered a proxy of reduced adherence [30]. Another explanation of the significant emergence of resistance mutations in drug-experienced viraemic individuals who failed EFV/FTC/TDF may be related to the pharmacokinetic properties of EFV. In fact, due to the long half-lives of this NNRTI, individuals with lengthy periods of non-adherence or with treatment interruptions who stop all their antiretrovirals simultaneously may have had a lengthy exposure to EFV and were thus prone to selec-

tively acquire NNRTI resistance mutations with little or no cost in terms of viral fitness [31–33].

This study does, however, present some limitations. First, the retrospective nature may have made some data, such as treatment compliance and pharmacological dosages, difficult to retrieve and analyse. Second, the STRs recently introduced into clinical practice (darunavir/cobicistat/emtricitabine/tenofovir alafenamide, bictegravir/emtricitabine/tenofovir alafenamide, dolutegravir/lamivudine and dolutegravir/rilpivirine) were not considered in the analysis because they were poorly represented in the cohort and with a too short follow-up period available. At any rate, this limitation probably reflects the real-life situation, where newer STRs are still much less represented than the older ones such as EFV/FTC/TDF regimen. Third, despite the high number of individuals analysed in the overall cohort, we could not always correctly estimate the events of VF within some subgroups of STRs because of the low number of individuals within these specific groups. A longer follow-up and additional data from more patients are needed before more definite conclusions can be drawn. Finally, as we considered the STRs differing only in TDF or TAF as a whole, differences related to the pharmaceutical form of tenofovir may have been missed. On the other hand, key strengths of this work are the detailed characterisation of the study population, in particular of their cumulative genotype, the large time span analysed, the national representativeness and the real-life settings.

In conclusion, our study confirmed the high efficacy of the STRs examined, also in real-life settings, and very low emergence of resistance mutations owing to the high genetic barrier of these regimens. Nevertheless, differently from that found in clinical trials, our findings suggest that pre-existent resistance could have an impact on VF in treatment-experienced individuals (both aviraemic and viraemic). For this reason, further cohort studies would be needed to confirm these results.

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Ethical approval

Not required.

Sequence information

Not applicable.

Declaration of Competing Interest

None declared.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2022.106636.

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