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Impact of resistance mutations on efficacy of dolutegravir plus rilpivirine or plus lamivudine as maintenance regimens: a cohort study

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ABSTRACT

Objectives: The aim of this study was to evaluate the impact of resistance mutations on efficacy of dolutegravir-based two-drug regimens (2DR).

Methods: Virologically suppressed patients with HIV-1 switching to dolutegravir + lamivudine or rilpivirine or to a dolutegravir-based three-drug regimen (3DR) with pre-baseline genotype were selected. Virological failure (VF) was defined as one HIV-RNA viral load (VL) >200 cps/mL or two consecutive VL >50 cps/mL; treatment failure (TF) was defined as VF or treatment discontinuation (TD). Resistance was defined as at least low-level resistance to at least one drug of the current regimen. Propensity score matching was used to conduct adjusted analyses within a competing risks framework.

Results: A total of 971 dolutegravir-based regimens were selected: 339 (34.9%) 2DR and 632 (65.1%) 3DR. The adjusted cumulative 48-week incidence of VF was 4.2% (90% CI 3.1%–5.3%) with 2DR and 4.7% (90% CI 3.5%–5.8%) with 3DR. The cumulative 48-week incidence of TF was 15.8% (90% CI 13.9%–17.9%) with 2DR and 24.5% (90% CI 22.2%–27.0%) with 3DR. For VF, the estimated hazard ratio (HR) for 2DR vs. 3DR was 1.02 (90% CI: 0.78–1.34), with evidence of effect modification by low-level resistance (HR 3.96, 90% CI: 2.10–7.46). The estimated HR of TF for 2DR vs. 3DR was 0.54 (90% CI: 0.48–0.60). The 48-week cumulative incidence of TD was 11.7% (8.7%, 14.6%) in 2DR and 19.6% (16.9%, 22.4%) in 3DR.

Conclusions: Dolutegravir-based 2DR showed high virological efficacy and durability; however, past resistance increased the risk of VF, but not of TD or TF.

1. Background

HIV infection has become a chronic disease requiring life-long treatment and posing issues of tolerability, toxicity and adherence. In this context, the availability of newer, highly potent drugs paved

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the way to the introduction of two-drug regimens (2DR), as opposed to standard three-drug regimens (3DR), potentially improving tolerability and reducing toxicity and cost. Current guidelines recommend 2DR based on dolutegravir (DTG), a second-generation high-genetic barrier integrase inhibitor (INSTI), as maintenance therapy in people with HIV (PWHIV) [1–3].

Previous accumulation of drug resistance is a critical factor in antiretroviral therapy (ART) switching strategies [4,5]; thus, simplifying ART in the setting of drug resistance remains a potential issue that needs to be further explored. Due to the chronicisation of HIV infection, with more and more PWHIV with a long history of antiretroviral exposure, it is crucial to explore ART simplification options even for experienced PWHIV, including patients with previously documented drug resistance. Although some data have been reported about the impact of pre-existing resistance mutations on 2DR with boosted protease inhibitors (PI) plus lamivudine (3TC) [6,7], limited information on DTG-based 2DR is available, mainly from retrospective studies [7–11]. In fact, randomised controlled studies [12–14] reported high rates of virological success with DTG-based 2DR but enrolled almost exclusively patients with either no previous treatment failure or no documented previous resistance, with the exception of just four patients with the M184V/I 3TC resistance mutation in proviral DNA detected in a post hoc analysis of the Tango study. Similarly, most uncontrolled prospective and retrospective studies on DTG + 3TC or emtricitabine (FTC) [15–17] and DTG + rilpivirine (RPV) [18] excluded patients with pre-existing resistance mutations. A few pertinent data came from the Dolulam study, a very small prospective study of DTG + 3TC as a switch strategy, where nucleoside reverse transcriptase inhibitors (NRTI) mutations were detected at least once in HIV-RNA and/or DNA by standard Sanger sequencing or next-generation sequencing in more than half of the patients, without a detrimental effect in terms of maintenance of virological suppression [19]. Similarly, a small pilot study assessed the switch to DTG + 3TC in patients without previous exposure to INSTI with and without previously acquired 3TC resistance, showing that this regimen maintained virological suppression despite the presence of 3TC resistance [20]. More recently, the LAMRES study also found no difference in the probability of VF in patients switching to DTG + 3TC when stratifying for the presence vs. absence of historical M184V/I, although a more recent detection of the mutation increased the rate of failure [21]. Likewise, there was no difference in results when stratifying patients switched to DTG + 3TC based on the presence of historical M184V/I or a history of VF in another observational multicentre study [22].

Regarding DTG+RPV, one Italian retrospective study analysed 145 patients who switched to DTG + RPV, 57.2% of whom harboured drug-resistant strains, finding high efficacy in terms of virological suppression [10]. In the French Dat'AIDS cohort, 152 virologically suppressed patients were switched to DTG + RPV, half of them with a history of previous failures (not on DTG- or RPV-based regimens; no genotypic resistance data available), and at week 24, 90.5% of patients remained free of therapeutic failure [23].

The present study aimed at evaluating virological response and treatment durability of DTG-based 2DR maintenance ART in clinical practice. In particular, we focused on the occurrence of treatment failure in an observational cohort of patients, distinguishing between virological and treatment discontinuation (TD). We used 1:1 nearest neighbour matching based on propensity score (PS) to conduct causal analyses within this competing risk framework. We compared hazards and cumulative incidence functions under 2DR and 3DR, with the aim to compare the two treatment strategies in both relative and absolute terms. We finally investigated the effect modification by resistance.

2. Materials and methods

2.1. Study design and population

This is a retrospective observational study performed on the Antiviral Response Cohort Analysis (ARCA) database, which contains data on HIV resistance and ART from more than 40 000 patients in Italy. We selected treatment-experienced patients with HIV-1 switching to a 2DR containing DTG with 3TC or RPV or to a 3DR containing DTG with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) or tenofovir alafenamide/emtricitabine (TAF/FTC) or abacavir/lamivudine (ABC/3TC) from 2013 to 2019. The inclusion criteria were age ≥18 years, HIV-1 RNA ≤50 copies/mL at the time of the switch to 2DR or 3DR (baseline), with at least one protease (PR)/reverse transcriptase (RT) genotypic resistance testing (GRT) available before switching (and if available one integrase GRT) and at least one HIV-1 RNA available during follow-up. HIV-1 sequences were determined using the Viroseq HIV-1 Genotyping System or by homebrew technology. Viral subtype was determined by the Rega HIV-1 subtyping tool (version 3.0).

Major NRTI, nucleoside reverse transcriptase inhibitors (NNRTI), PI or INSTI resistance mutations were reported according to the 2019 IAS drug resistance mutation list [24], and HIV-1 genotype was considered based on last available test and on all tests available (cumulative genotype, CGRT). The Genotypic Susceptibility Score (GSS) and the Cumulative Genotypic Susceptibility Score (CGSS) of the current regimen were calculated for the last and cumulative genotype, respectively, by using the Stanford algorithm interpretation version 8.8 (https://hivdb.stanford.edu/hivdb/by-mutations/) and summing the scores of the individual drugs contained in the regimen. Resistance to the switch regimen was defined as the occurrence of at least low-level resistance (LLR) to at least one drug included in the current regimen (2DR or 3DR), based on cumulative genotype.

The study endpoints included (i) the proportion and estimated risk of VF, defined as a single VL ≥200 copies/mL or two consecutive VL >50 copies/mL; (ii) the proportion and estimated risk of TD for any reason; and (iii) the proportion and estimated risk of the composite outcome of treatment failure (TF), defined as TD for any reason or VF. The impact of baseline drug resistance and switching to 2DR vs. 3DR was assessed for all endpoints.

Switching from TDF/FTC to TAF/FTC or vice versa was not considered as a treatment change.

2.2. Statistical analysis

Baseline patient characteristics were described as proportions for qualitative variables, medians and interquartile ranges (IQR) for continuous variables. For the composite outcome of TF (VF or TD, whichever was first), the cumulative incidence functions were obtained as the complement of the corresponding Kaplan-Meier survival curves. For VF and TD, the cumulative incidence functions were obtained by using the Aalen-Johansen estimator.

The average causal effect of the treatment (ATE) was estimated on all outcomes by a PS matching approach [25]. The approach consisted of the following steps:

1 Through a logistic regression, the PS was estimated for each patient in the study as the predicted probability of receiving 2DR treatment conditional to the patient's main baseline characteristics, as defined later in Results.
2 According to the estimated PS, each patient in the 2DR group was matched with the patient in 3DR group having the closest PS, and vice versa (1:1 nearest neighbour matching). The distributions of the baseline characteristics of the patients in the two

treatment groups were compared before and after matching to check the balancing property of the PS.

3 A univariate Cox regression model was fitted on the matched sample to estimate ATE in the form of the marginal hazard ratio of 3DR vs. 2DR; a robust estimate of the standard errors was obtained to account for the clustering of subjects in matched pairs.

The PS matching was performed accounting for the following variables: age, sex, duration of virological suppression, HIV risk factor, years from HIV diagnosis, HIV-RNA at zenith, nadir CD4+ cell counts, baseline CD4+ cell counts, B viral subtype, presence of at least LLR, number of antiretroviral regimens and number of previous ART failures. These variables were selected on the basis of prior knowledge from the literature, excluding those that, even if associated with the treatment group, are not usually considered as predictors of the outcome (e.g., last regimen prior to switch).

The effect modification by resistance was investigated by including in the model an interaction term between resistance and treatment; the value of the χ^2 statistics with 1 degree of freedom (df) for the null hypothesis of no effect modification and the related *P*-value were calculated. The proportional hazard assumption in the Cox regression was always checked. Cumulative incidence functions and Nelson-Aalen cumulative hazard functions were estimated on the matched sample separately for the two treatment groups [26]. In this case, the curves estimated for 3DR should be interpreted as those we would observe if all patients in the study were treated with a 3DR regimen; likewise, the curves for 2DR should be interpreted as those we would observe if all patients in the study were treated with a 2DR regimen. Two sensitivity analyses were conducted: one after trimming the patients for whom matching appeared to be unsatisfactory and another after removing DTG/RPV patients (n = 63) from the data set to specifically focus on the DTG 2DR more commonly prescribed (DTG plus 3TC).

Analyses were performed by using IBM SPSS Statistics, version 24 (IBM Corp. Armonk, NY, USA), R software [27] and STATA 15 [28].

2.3. Ethics

The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and later amendments. All patients signed an informed consent for use of their clinical and laboratory data in aggregated and anonymous form. Access to the database and data analyses were regulated by local institutional ethics committees and by Italian and European privacy legislation.

3. Results

3.1. Descriptive analysis

We selected 971 antiretroviral regimens containing DTG: 339 (34.9%) in the 2DR group and 632 (65.1%) in the 3DR group. A total of 917 patients contributed to these regimens. In the 2DR group, 276 (81.4%) regimens included 3TC and 63 (18.6%) RPV as second drug. The most frequent backbone used in the 3DR group was ABC/3TC (423; 66.9%), followed by TDF/FTC (161; 25.5%) and TAF/FTC (48; 7.6%).

Table 1 shows baseline characteristics of the patient population. The 2DR group differed from the 3DR group in having a longer history of HIV infection and ART exposure and a longer duration of viral suppression at the time of treatment switch. A previous failure to PI was reported for around 40% of patients, with a higher frequency for the 2DR compared to the 3DR group, whereas a previous failure to NNRTI was recorded in a lower proportion of cases. Within the 2DR group, patients switching to DTG + RPV had a higher number of previous antiretroviral regimens and a higher rate of PI failures with respect to those switching to DTG + 3TC.

Importantly, the cumulative incidence of at least LLR was 21.1%, with a higher prevalence in the 3DR (24.2%) vs. the 2DR (15.3%) group Table 2. shows the baseline characteristics of patients with and without at least LLR. Patients with resistance were more often infected with subtype B virus, had a much longer history of HIV infection and duration of ART and a lower nadir CD4+ cell count, compared with patients without resistance. Overall, 247 (25.4%) cases had at least one resistance mutation to NRTIs, 198 (20.4%) to NNRTIs, 86 (8.9%) to PIs and only 2 (0.2%) to INSTIs. The M184V/I mutation occurred in 168 (17.3%) CGRT (Fig. 1). Integrase genotype (INSTI GRT) was available in 179 patients. Among patients in the 3DR group, there were only two with a major INSTI resistance mutation (Y143R and E138K), but none experienced VF, whereas in the 2DR group there were no INSTI resistance mutations.

The GSS calculated on the last GRT available, and the CGSS were stratified according to susceptibility to the drugs included in the current regimen as “susceptible” (GSS/CGSS = 2 for 2DR and ≥2 for 3DR group), “intermediate” (GSS/CGSS between 1 and <2) or “resistant” (GSS/CGSS <1). In more than 85% (n = 829) of cases, GSS was fully susceptible, whereas only 14% (n = 136) and 0.6% (n = 6) of patients showed an intermediate and resistant GSS, respectively, with no difference between 2DR and 3DR. Concerning CGSS, the proportion of patients fully susceptible to their current regimen was slightly lower (82%, n = 802), with intermediate and resistant CGSS reported for 16.7% (n = 162) and 0.4% (n = 7) of patients, respectively, again without differences between 2DR and 3DR.

3.2. Crude comparisons

During a median follow-up of 63 weeks (IQR 31–100), 416 treatment failures occurred, 102 in the 2DR group (83 with DTG + 3TC and 19 with DTG + RPV) and 314 in the 3DR group. The probability of experiencing a treatment failure in the first 48 weeks from the beginning of therapy was 14.3% (90% CI: 11.3%–17.8%) in the 2DR group and 24.6% (90% CI: 21.8%–27.7%) in the 3DR group. Sixty-one patients experienced VF, 22 in the 2DR group (19 with DTG + 3TC and 3 with DTG + RPV) and 39 in the 3DR group. The estimated cumulative incidence of VF at 48 weeks was 4.1% (3.0%–5.2%) in the whole data set, 2.6% (1.1%–4.0%) in the 2DR group and 5.0% (3.5%–6.5%) in the 3DR group. Among the 355 patients who experienced TD, 80 were in the 2DR group and 275 in the 3DR group. The estimated cumulative incidence of TD at 48 weeks was 16.8% (14.8%–18.9%): 11.7% (8.7%–14.6%) in the 2DR group and 19.6% (16.9%–22.4%) in the 3DR group.

3.3. Adjusted analyses

In Supplementary Table S1, a comparison of the baseline characteristics between treatment groups before and after matching is provided. After matching, the two treatment groups were balanced with respect to the baseline characteristics that were most unbalanced before matching. Balancing was not completely satisfactory with respect to resistance. After matching, the distributions were very similar, although for a few patients with high PS in the 2DR group matching was not completely satisfactory.

The cumulative incidence functions of VF and TD by treatment group, estimated on the matched data set, are shown in Fig. 2. The estimated cumulative incidence function for TD under 2DR was lower than under 3DR. The estimated cumulative incidences at 48 and 72 weeks for treatment failure were 24.5% (90% CI 22.2%–27.0%) for 3DR and 15.8% (90% CI 13.9%–17.9%) for 2DR, 37.1% (90% CI 34.3%–40.0%) for 3DR and 23.1% (90% CI 20.8%–25.7%) for 2DR, respectively (Table 3). The estimated cumulative incidences at 48

Table 1
Baseline characteristics of the overall population and of the 2DR (grouped, DTG + 3TC and DTG + RPV) and 3DR group.

	Overall(n = 971)	2DR(n = 339)	3DR(n = 632)	2DR(n = 339)	
				DTG + 3TC(n = 276)	DTG + RPV(n = 63)
Males, n (%)	675 (69.5)	231 (68.1)	444 (70.3)	198 (71.7)	33 (52.4)
Age, years, median (IQR)	50 (43–56)	51 (45–56)	50 (43–56)	50 (44–56)	54 (47–58)
Risk factor, n (%)					
MSM intercourse	166 (17.1)	64 (18.9)	102 (16.1)	56 (20.3)	18 (28.6)
Heterosexual intercourse	238 (24.5)	63 (18.6)	175 (27.7)	45 (16.3)	8 (12.7)
IDU	163 (16.8)	69 (20.4)	94 (14.9)	48 (17.4)	21 (33.3)
Other	404 (41.6)	143 (42.2)	261 (41.3)	127 (46)	16 (25.4)
B subtype carriers, n (%)	801 (82.4)	286 (84.4)	515 (81.4)	232 (84.1)	54 (85.7)
Years from HIV diagnosis, median (IQR)	12 (6–23)	13 (7–24)	11 (5–22)	11 (6–21)	23 (17–29)
Years of ART, median (IQR)	9 (4–18)	10 (5–19)	7 (3–17)	8 (5–18)	16 (9–21)
Time of undetectable VL before baseline, years, median (IQR)	4.04 (1.32–7.52)	5.18 (2.65–8.52)	3.01 (0.86– 6.80)	4.82 (2.61–8.21)	7.10 (2.95–10.46)
Nadir CD4$^+$, cells/mm^3, median (IQR)	205 (81–320)	227 (101– 321)	189 (74–319)	240 (122–324)	180 (69–296)
Baseline CD4$^+$, cells/mm^3, median (IQR)	630 (450–846)	646 (500–864)	617 (429–829)	634 (483–860)	694 (554–883)
Zenith VL, Log_{10} cps/mL, median (IQR)	4.95 (4.27– 5.48)	4.90 (4.25– 5.39)	5.00 (4.29–5.55)	4.86 (4.19 - 5.36)	5.06 (4.46 - 5.53)
Previous ART use, n (%)					
NRTI	946 (97.4)	337 (99.4)	609 (96.4)	274 (99.3)	63 (100)
NNRTI	519 (53.5)	208 (61.4)	311 (49.2)	161 (58.3)	47 (74.6)
PI	773 (79.6)	291 (85.8)	482 (76.3)	236 (85.5)	55 (87.3)
bPI	717 (73.8)	274 (80.8)	443 (70.1)	221 (80.1)	53 (84.1)
INSTI	378 (38.9)	140 (41.3)	238 (37.7)	104 (37.7)	36 (57.1)
Previous number of ART regimens, median (IQR)	4 (3–8)	5 (3–9)	4 (3–7)	5 (3–8)	7 (5–13)
Previous failure to					
NNRTI	246 (25.3)	93 (27.4)	153 (24.2)	70 (25.4)	23 (36.5)
PI	390 (40.3)	157 (46.4)	233 (37.0)	115 (41.8)	42 (66.7)
At least LLR	205 (21.1)	52 (15.3)	153 (24.2)	38 (13.8)	14 (22.0)
Resistance level according to Stanford					
0–1	766 (78.9)	287 (84.7)	479 (75.8)	238 (86.2)	49 (78.0)
2–3	50 (5.1)	18 (5.3)	32 (5.1)	7 (2.5)	11 (18.0)
4	155 (16.0)	34 (10)	121 (19.1)	31 (11.2)	3 (5.0)

2DR, two-drug regimen; 3DR, three-drug regimen; IQR, interquartile range; MSM, men who have sex with men; IDU, injective drug users; HBV, hepatitis B virus; HCV, hepatitis C virus; ART, antiretroviral therapy; VL, viral load; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non- nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; b, boosted; INSTI, integrase inhibitors; T20, enfuvirtide; MVC, maraviroc; LLR, low-level resistance.

Table 2
Baseline characteristics of the overall population according to resistance.

	At least LLR(n = 205)	No resistance(n = 766)
Males, n (%)	126 (61.5)	549 (71.7)
Age, years, median (IQR)	53 (49–56)	49 (42–56)
Risk factor, n (%)MSM/bisexual intercourseHeterosexual intercourseIDUOther	24 (11.7)63 (30.7)70 (34.1)48 (23.4)	142 (18.5)175 (22.8)93 (12.1)356 (46.5)
B subtype carriers, n (%)	193 (94.1)	608 (79.4)
Years from HIV diagnosis, median (IQR)	24 (20–28)	9 (4–16)
Years of ART, median (IQR)	19 (14–21)	6 (3–12)
Time of VL undetectability before baseline, years, median (IQR)	5.86 (2.21–8.99)	3.59 (1.06–6.86)
Nadir CD4$^+$, cells/mm^3, median (IQR)	166 (58–253)	221 (88–342)
Baseline CD4$^+$, cells/mm^3, median (IQR)	652 (475–867)	630 (440–840)
Zenith HIV- 1 RNA, Log_{10} cps/mL, median (IQR)	4.82 (3.84–5.41)	4.98 (4.37–5.51)
Previous number of ART regimens, median (IQR)	9 (5–13)	4 (3–6)
Previous failure to		
NNRTI	94 (45.9)	152 (19.8)
PI	119 (58.0)	271 (35.4)

IQR, interquartile range; MSM, men who have sex with men; IDU, injective drug users; HBV, hepatitis B virus; HCV, hepatitis C virus; ART, antiretroviral therapy; VL, viral load; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; b, boosted; INSTI, integrase inhibitors; T20, enfuvirtide; MVC, maraviroc; LLR, low-level resistance.

and 72 weeks for VF were 4.7% (90% CI 3.5%–5.8%) for 3DR and 4.2% (90% CI 3.1%–5.3%) for 2DR, 6.5% (90% CI 5.1%–8.0%) for 3DR and 7.4% (90% CI 5.8%–9.0%) for 2DR, respectively (Table 3). The estimated cumulative incidences at 48 and 72 weeks for TD were 19.9% (90% CI 17.7%–22.1%) for 3DR and 11.6% (90% CI 9.9%–13.3%) for 2DR, 30.5% (90% CI 27.8%–33.2%) for 3DR and 15.7% (90% CI 13.6%–17.8%) for 2DR, respectively (Table 3).

3.3.1. Treatment failure

Through a Cox regression model comparing the two matched groups, the hazard ratio (HR) of treatment failure for 2DR vs. 3DR was 0.54 (90% CI: 0.48–0.60), after adjusting for background characteristics (Table 4). When an interaction term between treatment and resistance was included in the Cox regression model, a clear effect modification arose ($\chi^2 = 9.49$, $df = 1$, $P = 0.002$): in patients

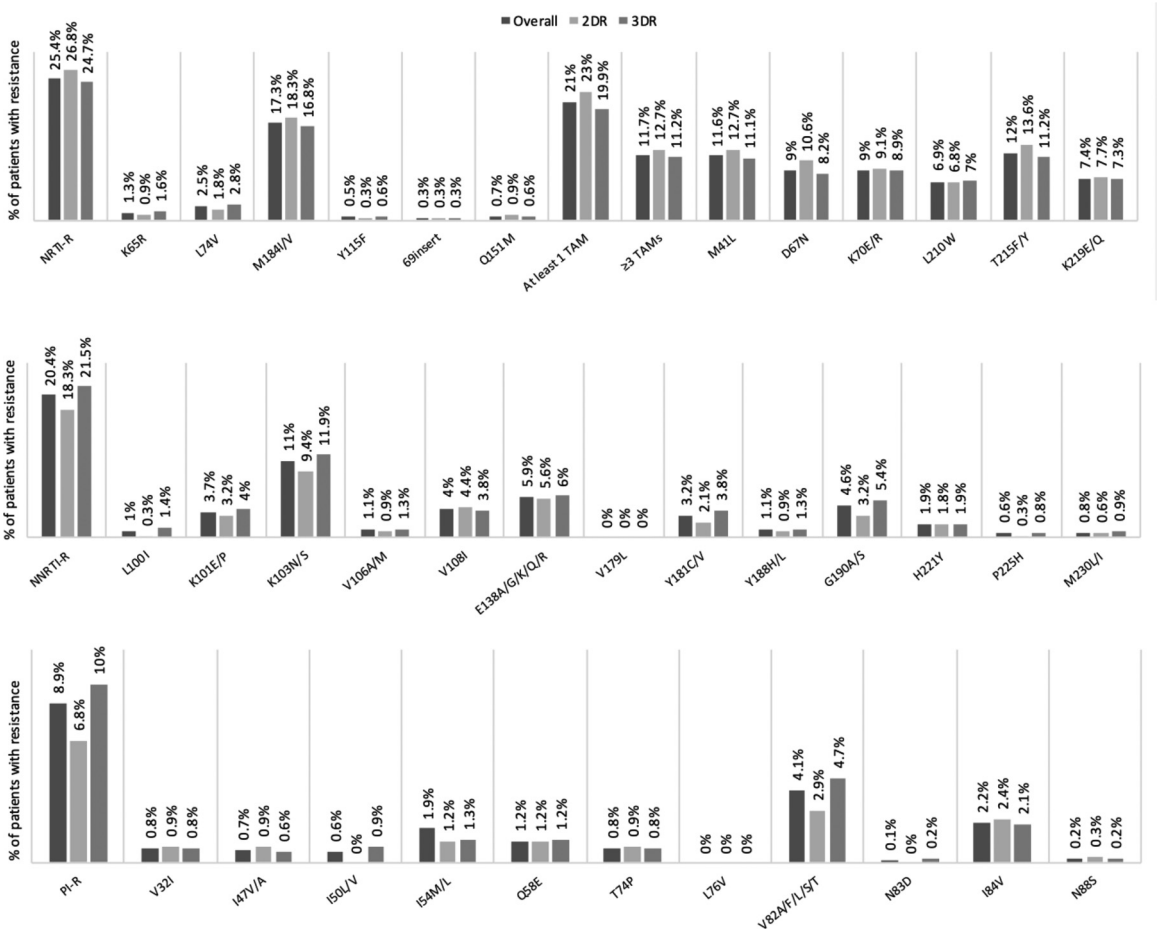

Fig. 1. Frequency of NRTI/NNRTI/PI resistance mutations.

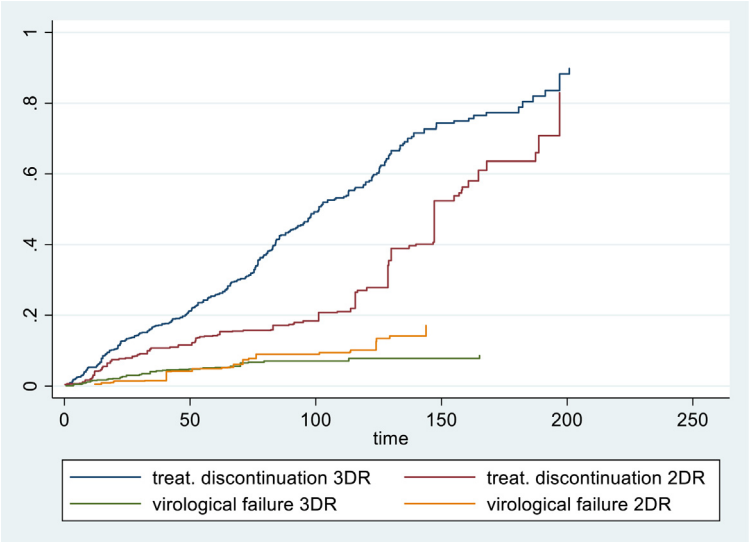

Fig. 2. Cumulative incidence functions for virological failure and treatment discontinuation, by treatment group, calculated on the matched sample.

without resistance, the estimated HR of treatment failure was 0.48 (90% CI: 0.42–0.55); in patients with at least LLR, the effect was smaller, with an HR of 0.78 (90% CI: 0.62–0.99).

3.3.2. Virological failure

The adjusted HR of VF for 2DR vs. 3DR was very close to the null hypothesis of no effect: 1.02 (90% CI: 0.78–1.34) (Table 4). However, this result should be read considering that clear evidence of violation of the proportional hazard assumption arose in this specific analysis ($\chi^2 = 14.69$, $df = 1$, $P < 0.001$). Such a violation implies that the HR may vary over time and, in the case of an effect that has a different sign depending on the phase of follow-up (e.g., HR <1 in the early phase and HR ≥1 in the late phase), may lead to a balancing toward the null, as in our analysis. Similar be-

Table 3
Estimated cumulative incidence at 48 and 72 weeks and 90% confidence intervals for the composite outcome, virological failure and treatment discontinuation, by treatment group, calculated on the matched sample.

Outcome	Treatment	48 weeks			72 weeks		
		Cumulative incidence	90% Confidence interval		Cumulative incidence	90% Confidence interval	
Treatment failure	3DR	24.5%	22.2%	27.0%	37.1%	34.3%	40.0%
	2DR	15.8%	13.9%	17.9%	23.1%	20.8%	25.7%
Virological failure	3DR	4.7%	3.5%	5.8%	6.5%	5.1%	8.0%
	2DR	4.2%	3.1%	5.3%	7.4%	5.8%	9.0%
Treatment discontinuation	3DR	19.9%	17.7%	22.1%	30.5%	27.8%	33.2%
	2DR	11.6%	9.9%	13.3%	15.7%	13.6%	17.8%

2DR, two-drug regimen; 3DR, three-drug regimen.

Table 4
Estimated hazard ratios of 2DR vs. 3DR and 90% confidence intervals from the Cox regression models on the matching sample.

Outcome	Patients group	HR	90% Confidence interval	
Treatment failure	All patients	0.54	0.48	0.60
	Not resistant	0.48	0.42	0.55
	At least LLR	0.78	0.62	0.99
Virological failure	All patients	1.02	0.78	1.34
	Not resistant	0.64	0.45	0.89
	At least LLR	3.96	2.10	7.46
Treatment discontinuation	All patients	0.45	0.40	0.51
	Not resistant	0.45	0.39	0.53
	At least LLR	0.46	0.35	0.60

HR, hazard ratio; LLR, low-level resistance.

haviour is visible if we compare the Nelson-Aalen cumulative hazard estimates calculated under 2DR and 3DR on the matched data set.

As for the composite outcome, a clear effect modification by resistance arose ($\chi^2 = 17.3$, $df = 1$, $P < 0.001$): for patients without resistance, the estimated HR of VF for 2DR vs. 3DR was 0.64 (90% CI: 0.45–0.89), whereas for patients with at least LLR, the HR was 3.96 (90% CI: 2.10–7.46) (Table 3). Certain evidence of a violation of the proportional hazard assumption remained also when the effect modification by resistance was considered (results not shown).

3.3.3. Treatment discontinuation

The HR of TD for 2DR vs. 3DR, adjusted for background characteristics, was 0.45 (90% CI: 0.40–0.51) (Table 4). There was no evidence of effect modification by resistance ($P = 0.99$): the estimated HR of 2DR vs. 3DR was 0.45 (90% CI: 0.39–0.53) and 0.46 (90% CI: 0.35–0.60) in patients without resistance and in patients with at least LLR, respectively.

3.3.4. Sensitivity analyses

We repeated the adjusted analysis after trimming the patients for whom matching was not completely satisfactory: four patients in the 2DR group with estimated PS larger than the maximum PS estimated in the 3DR group (two of them discontinued treatment) and seven patients in the 3DR group with estimated PS lower than the minimum PS estimated in the 2DR group (two of them experienced VF, and three discontinued treatment). The results, reported in Supplementary Table S2, were very close to those obtained without trimming.

In the other sensitivity analysis, after removing the DTG + RPV patients from the dual treatment group, we obtained very similar adjusted cumulative incidences (Supplementary Fig. S1). The hazard ratios of treatment failure and TD remained substantially unchanged (Supplementary Table S3), whereas the hazard ratio of VF became 1.35 (90% CI: 0.99–1.82). In more detail, after removing DTG/RPV patients from the 2DR group, the risk of VF became the same under the two treatment regimens among not-resistant patients (HR 1.08; in the analysis on the entire data set, the risk was lower under 2DR). On the other hand, among patients with at least LLR, the estimated hazard ratio slightly decreased, becoming 3.06 (90% CI: 1.43–6.54).

3.4. Characterization of virological failures

Among patients in 2DR, 22 VFs occurred: 19 in patients in DTG + 3TC (4 of 19 with at least LLR) and 3 in patients in DTG + RPV (2 of 3 with at least LLR). Thirteen of 22 patients in 2DR with VF were male; the median age was 50 (42–55) years, the median nadir CD4+ cell count was 245 (83–358), and they had a median of 18 years (10–25) of ART exposure.

Moreover, among patients with at least LLR, 14 experienced VF: 6 patients in the 2DR group (4 cases on DTG + 3TC and 2 on DTG + RPV treatment) and 8 in the 3DR group (4 cases receiving ABC/3TC, 3 receiving TDF/FTC and 1 receiving TAF/FTC as backbone). These 14 patients did not show a different list of resistance mutations in the PR-RT region through the final GRT and CGRT. In the three patients with INSTI GRT available at baseline, there was no evidence of INSTI resistance mutations. GRT after VF was performed in five patients (one in the 2DR group and four in the 3DR group), but none of them showed the emergence of new resistance mutations in the PR-RT and IN regions compared to pre-baseline GRT.

4. Discussion

We collected HIV routine care data from different Italian clinical centres to compare the efficacy of DTG-based 2DR and 3DR according to baseline drug resistance. This was not previously addressed by clinical trial data because patients with past antiretroviral resistance were excluded in most cases by design.

In the adjusted analyses, the virological efficacy for DTG-based 2DR and 3DR was comparable (4.2%–4.7% of VF at 48 weeks), with lower rates of TD and treatment failure for 2DR. This confirms that treatment with DTG + 3TC or DTG + RPV in clinical practice results in a low rate of VF in virologically suppressed patients with different treatment backgrounds, as recently demonstrated in a meta-analysis of real-world evidence by Punekar et al [29].. However, when comparing the same groups in the presence of at least LLR, a higher risk of VF, but not of TD or treatment failure, was demonstrated with 2DR in comparison to 3DR. These results appear to be in contrast to those found in other studies that explored only DTG + 3TC dual regimens in the context of past resistance [19–22]. Moreover, other previous studies, including one from this same cohort [7,21], explored the efficacy of DTG + 3TC in the presence of the M184V/I 3TC resistance mutation in the cumulative genotype and did not detect any significant impact on the risk of VF, although some concerns for viral blips and virological efficacy in the context of a short time of viral suppression were

raised [7,9,21]. There are important differences between our work and these studies, including the analysis of the 3DR control group with some drug resistance, a more comprehensive scoring of past resistance (i.e., not limited to M184V) and a different statistical approach. Discrepancies between our results and those arising from prior similar studies could be attributable also to differences in the studied populations: Patients in our study had a higher duration of ART exposure and were older than those in previous work [7], and they had higher IDU prevalence than elsewhere [9]. Moreover, the ARCA database includes only cases with at least a genotype resistance test performed. Thus, it is possible that this peculiar characteristic of our cohort selected a more experienced population. Even this aspect should be considered when translating our results in other real-life experiences.

Despite the increased risk of VF in patients with previous LLR, the absolute 1-year rate was very low. Furthermore, for the other two outcomes analysed (TD and treatment failure), 2DR appeared to have better efficacy than 3DR, confirmed even in the presence of LLR. This suggests improved tolerability as a key component of the longer durability of 2DR, even if neither causes of discontinuation nor occurrence of adverse events could be explored in this study. As a matter of fact, this case file reveals an expanded use of DTG-based 2DR in real life, even in patients quite different from those included in clinical trials (e.g., some level of genotypic resistance, previous VF).

Our study presents some limitations. First, because of its observational design we cannot rule out unmeasured confounders. Second, the groups had different characteristics at baseline, and it is possible that patients in the 2DR group might have been a selected population in which better adherence was expected. Moreover, although considering DTG + 3TC and DTG + RPV as one group, as elsewhere reported [30,31], increased the power of the statistical analysis, the individual 2DR groups were not analysed separately. Unfortunately, data on adherence were missing, as measures of medication adherence and exposure were not available in this cohort. Finally, despite the statistical adjustments, we were not able to avoid a certain imbalance relative to resistance. On the other hand, key strengths of this work were the detailed characterisation of the study population, in particular of their cumulative genotype, the large timespan analysed, the national representativeness, the real-life settings and the use of propensity score.

In conclusion, an increased risk of VF can affect DTG-based 2DR, compared with DTG-based 3DR, when at least LLR is present; however, treatment durability is favoured by 2DR. Thus, appropriate patient selection is key to best exploit the potential of this treatment simplification strategy.

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Supplementary materials

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