Journal of Global Antimicrobial Resistance xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Short Communication

Real world efficacy of dolutegravir plus lamivudine in people living with HIV with undetectable viral load after previous failures

Roberta Gagliardini[a,*], Patrizia Lorenzini[a], Alessandro Cozzi-Lepri[b], Alessandro Tavelli[c], Vanni Borghi[d], Laura Galli[e], Gianmarco Tagliaferri[f], Franco Maggiolo[g], Cristina Mussini[d], Antonella Castagna[e,h], Antonella d'Arminio Monforte[f], Andrea Antinori[a]

[a] IRCCS Lazzaro Spallanzani, Rome, Italy
[b] University College London, London, United Kingdom
[c] Icona Foundation, Milan, Italy
[d] Azienda Ospedaliera Universitaria Policlinico di Modena, Modena, Italy
[e] Infectious Diseases Clinic, IRCCS San Raffaele, Milan, Italy
[f] ASST Santi Paolo e Carlo, Department of Health Sciences, University of Milan, Milan, Italy
[g] Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy
[h] San Raffaele Vita-Salute University, Milan, Italy

ARTICLE INFO

Article history:
Received 15 September 2022
Revised 28 October 2022
Accepted 9 November 2022
Available online xxx

Editor: Dr Michele Bartoletti

Keywords:
HIV-1
Antiretroviral therapy
Switch therapy
Two-drug regimens
Integrase inhibitors

ABSTRACT

Background: Dolutegravir (DTG) +lamivudine (3TC) combination has been found to be as effective as triple therapies, and has been extensively prescribed in clinical practice as a maintenance therapy. We aimed to investigate the effect of previous virological failures (VFs) on virological efficacy.

Methods: The analysis included data of people living with HIV (PLWH) with HIV-RNA ≤50 copies/mL enrolled in an Italian retrospective multicohort study who were switching to DTG+3TC. Primary endpoint was viral rebound (VR; confirmed HIV-RNA ≥50 copies/mL or single HIV-RNA ≥50 copies/mL followed by change of antiretroviral therapies [ART]). Kaplan-Meier curves were used to estimate probabilities of VR based upon histories of previous VFs (single HIV-RNA ≥1000 copies/mL or confirmed HIV-RNA ≥50 copies/mL). A weighted Cox regression model was fitted to estimate the causal hazard ratio (HR) of history of failure on the risk of VR.

Results: A total of 966 PLWH were included; 20.1% had a history of previous VF.

VR was detected in 23 PLWH. The one-year probability was 1.2% (95% confidence interval [CI], 0.2%–2.2%) in PLWH without previous VF and 3.3% (95% CI, 0.4%–6.2%) in those with ≥1 VF (log-rank $P=0.042$). By multivariate analysis adjusted for CD4+ cell count at nadir, duration of virological suppression, and mode of HIV transmission, PLWH with ≥1 previous VF had a higher risk of virological rebound than those without previous VF (adjusted hazard ratio 3.06 [95% CI, 1.00–9.44], $P=0.051$).

Conclusion: Despite the low absolute one-year risk in both groups, real-world data confirmed that PLWH with a previous failure have an increased risk of viral rebound.

1. Introduction

As HIV has become a chronic condition, there is a growing interest in simpler antiretroviral therapies (ART) that are better tolerated. In this context, two-drug regimens (2DRs) for maintenance therapy in people living with HIV (PLWH) have been developed and are increasingly used in clinical practice.

A 2DR with dolutegravir (DTG) plus lamivudine (3TC) was found to be effective as a maintenance therapy in randomized trials [1,2] in a selected population of PLWH who were virologically suppressed, with no prior virological failures and no documented nucleos(t)ide reverse-transcriptase inhibitor (NRTI) or integrase inhibitor (INSTI) resistance mutations at pre-treatment genotype.

* Corresponding author. Mailing addres: UOC Immunodeficienze Virali INMI Lazzaro Spallanzani, IRCCS via Portuense 292–00149, Rome, Italy.
E-mail address: roberta.gagliardini@inmi.it (R. Gagliardini).

https://doi.org/10.1016/j.jgar.2022.11.010

Many cohort studies, conducted mainly in Europe, have confirmed the high virological efficacy of dolutegravir plus lamivudine combination in different real-life settings [3–9].

Different co-factors, such as quantitative HIV-DNA, CD4+ T cell count at nadir, duration of virological suppression, specific previous resistance mutations, and previous failures may contribute to different risks associated with virological failure during treatment with 2DRs [10].

Interestingly, real-life data revealed that a relevant proportion of all 2DR prescriptions are in PLWH with a history of virological failures (VFs) (up to 14%, considering dolutegravir plus lamivudine combination) [11].

However, limited data about the prevalence of use and virological potency of DTG+3TC in target populations with histories of previous VF and/or previous detection of resistance mutations are available to date.

Relevant data came from the Dolulam study, a small prospective study of dolutegravir plus lamivudine as a switch strategy, where the detection of NRTI mutations at least once in RNA/DNA genotypes in more than half of the patients did not alter the probability of maintaining virological suppression [12]. More recently, a prospective pilot study assessed the switch strategy to DTG+3TC in patients with and without previously acquired lamivudine resistance. This regimen was effective in maintaining virological suppression despite the presence of lamivudine resistance mutations in the cumulative genotype and archived mutations assessed by next-generation sequencing [13]. In two retrospective studies, the M184V/I lamivudine resistance mutation was found in the historical genotype of 9 to 17% of virologically suppressed PLWH who switched to DTG+3TC; no clear effect on risk of VF was found, even though some concerns for viral blips and viral efficacy in the context of a short time of viral suppression were raised [6,14,15].

The purpose of this study was to explore the virological potency of DTG+3TC in patients with and without prior VF, estimate the risk of viral rebound (VR), and evaluate whether there was an association between this risk and a history of previous failure.

2. Materials and methods

We conducted a retrospective cohort study that included patients enrolled in the Icona Foundation Study or in five Italian monocentric clinical databases (National Institute for Infectious Diseases L. Spallanzani of Rome, Azienda Ospedaliera San Paolo of Milan, Azienda Ospedaliera Universitaria Policlinico of Modena, San Raffaele Hospital in Milan, Azienda Ospedaliera Papa Giovanni XXIII of Bergamo) that met common sets of inclusion criteria. The Icona Foundation Study is a multicentre prospective observational study of patients with HIV-1. The Icona Foundation study has been approved by the institutional review boards of all participating centres; sensitive data from patients are seen only in aggregate form. Demographics, clinical and laboratory data, and information on therapies are collected for all participants and recorded using electronic data collection [www.icona.org].

All patients signed a consent form to participate in the cohorts in accordance with the ethical standards of the committee on human experimentation and the Helsinki Declaration (last amended in October 2013). All information, including virological and therapeutic data, was recorded and merged in an anonymized database.

Patients were included in this analysis if the following inclusion criteria were satisfied: ≥18 y of age, currently receiving ART (regardless of the type of regimen), starting for the first time DTG 50 mg plus 3TC 300 mg as two-pills or a single-pill regimen, with current HIV-1 RNA <50 copies/mL, with known history of ART use, and with at least one virological follow-up visit within six months thereafter.

Primary study endpoint was defined as the composite outcome of confirmed HIV-RNA ≥50 copies/mL on DTG+3TC (with or without ART change) or a single HIV-RNA ≥50 copies/mL on DTG+3TC followed by change of ART.

Secondary endpoint was the cumulative probability of viral blips (VBs, a single HIV-RNA ≥50 copies/mL followed by a value ≤50 without a change of ART).

We also considered an alternative endpoint in which VR was defined as the first confirmed count of HIV-RNA ≥50 copies/mL.

The follow-up accrued from baseline (BL, time of switch to DTG+3TC) to the occurrence of the outcome or last observation or DTG+3TC discontinuation, whichever came first.

Two different definitions of past VF were applied: (i) having experienced a single HIV-RNA ≥1000 copies/mL or confirmed HIV-RNA ≥50 copies/mL on any ART before BL or (ii) on an NRTI or INSTI-containing regimen.

A sensitivity analysis excluding PLWH with incomplete histories of viral load data, defined as one-year or more gaps in HIV-RNA measurements, was also performed. For statistical analysis, differences between groups of characteristics at baseline were assessed by means of Chi-square or Wilcoxon rank sum (Mann-Whitney) test, as appropriate. Kaplan-Meier survival method was used to estimate the cumulative proportion of patients experiencing the study endpoints, with corresponding 95% confidence intervals (CIs); differences between groups were evaluated by the log-rank test.

We used Cox proportional hazard models with censoring weights and with exposure (past VF) weights to estimate the hazard ratios (HRs) for each outcome. To reduce the potentially confounding effect of the different distributions of characteristics in exposed and unexposed (to past VF) patients with distributions of censoring on the outcome, we calculated the inverse probability of weights and of censoring weights using two separate logistic regression models. We fitted a pooled logistic regression model weighted for inverse probability of both stabilized weights. Confounding variables analysed were CD4+ cell count at nadir (equal/higher or lower than 350 cells/mmc), duration of virological suppression, and mode of HIV transmission.

All statistical analyses were performed with STATA, version 15.1 (College Station, Texas).

3. Results

A total of 966 PLWH were included in the analysis and their baseline characteristics are shown in Table 1. Of 966, 248 (25.7%) were female with a median age of 51 y (interquartile range [IQR], 44–57), and 150 (15%) were at the CDC-C stage with a median CD4+ cell count at nadir of 247 cells/mmc (IQR, 98–372) and a median time of HIV-RNA suppression before switching to DTG+3TC of 7 y (IQR, 3–12).

Seven hundred and seventy-two (79.9%) had no previous VF to any ART and 194 (20.1%) had at least one previous VF (12% had 1 previous VF, 4% had 2 VFs, 3% had 3 VFs, and 1% had 4 or more VFs).

Significant differences among histories of previous failures to any ART group were observed at baseline with respect to age; mode of HIV transmission; CDC-C stage (13.9% in PLWH without previous VF vs. 22.2% in PLWH with at least one previous VF, $P = 0.017$); co-infections; CD4+ cell count at nadir (268 cells/mmc in PLWH without previous VF vs. 165 cells/mmc in PLWH with at least one previous VF, $P < 0.001$); duration of HIV infection, ART exposure, and of HIV-RNA suppression (all longer in PLWH with at least one previous VF); number of therapeutic lines (higher in PLWH with at least one previous VF), and last ART regimen pre-switch (Table 1). Median observation time was 15 months (IQR, 6–32).

Table 1
Characteristics of the overall population and of the two groups at baseline

	Overall population N=966	No previous virological failure to any ART N=772	≥1 previous virological failure to any ART N=194	*P* value
Female sex, n (%)	248 (25.7%)	189 (24.5%)	59 (30.4%)	0.091
Age, median (IQR)	51 (44–57)	50 (42–57)	53 (49–58)	<0.001
Mode of HIV transmission, n(%) heterosexual	340 (35.2%)	274 (35.5%)	66 (34.0%)	<0.001
IVDU	146 (15.1%)	94 (12.2%)	52 (26.8%)	
MSM	356 (36.9%)	307 (39.8%)	49 (25.3%)	
Other/unknown	124 (12.8%)	97 (12.5%)	27 (13.9%)	
CDC stage C, n(%)	150 (15.5%)	107 (13.9%)	43 (22.2%)	0.017
HCV Ab, n(%)				
negative	753 (78.0%)	623 (80.7%)	130 (67.0%)	<0.001
positive	172 (17.8%)	111 (14.4%)	61 (31.4%)	
unknown	41 (4.2%)	38 (4.9%)	3 (1.6%)	
HBsAg, n(%)				
negative	834 (87.7%)	653 (86.3%)	181 (93.3%)	0.008
positive	15 (1.6%)	11 (1.4%)	4 (2.1%)	
unknown	102 (10.7%)	93 (12.3%)	9 (4.6%)	
Nadir CD4, cell/mmc, median (IQR)	247 (98–372)	268 (126–400)	165 (44–270)	<0.001
CD4 at switch, cell/mmc, median (IQR)	699 (541–888)	695 (545–898)	714 (525–864)	0.870
Years of HIV infection, median (IQR)	12 (6–21)	9 (5–17)	22 (19–27)	<0.001
Years of ART, median (IQR)	8.4 (4.0–17.5)	6.6 (3.3–12.1)	18.9 (16.5–20.7)	<0.001
Years of viral suppression, median (IQR)	7.0 (3.4–12.0)	5.9 (2.9–10.6)	12.0 (8.4–14.3)	<0.001
Therapeutic lines, median (IQR)	5 (3–9)	4 (3–6)	11 (7–15)	<0.001
Calendar year of switch, median (IQR)	2017 (2016–2018)	2017 (2016–2018)	2017 (2016–2018)	0.545
ART pre-BL, n(%)				
2 NRTI + PI	102 (10.6%)	73 (9.5%)	29 (15.0%)	<0.001
2 NRTI + INSTI	214 (22.2%)	177 (22.9%)	37 (19.1%)	
2NRTI + NNRTI	178 (18.4%)	158 (20.5%)	2.0 (10.3%)	
2DR	205 (21.2%)	144 (18.6%)	61 (31.4%)	
Others	267 (27.6%)	220 (28.5%)	47 (24.2%)	

ART, antiretroviral therapy; BL, baseline; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; INSTIs, integrase inhibitors; IQR, interquartile range; IVDU, intravenous drug use; MSM, men who have sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; 2DR, two-drug regimens.

Seven-hundred-and-eighty (80.1%) participants had no previous VF to NRTI or INSTI and 186 (19.2%) had at least one previous VF to these classes of antiretrovirals.

The study population included in the sensitivity analysis (excluding PLWH with incomplete histories of viral load data) consisted of 667 PLWH, with baseline characteristics like those described above (Supplementary Table S1).

3.1. Virological rebound

Virological rebounds defined as confirmed HIV-RNA ≥50 copies/mL or a single HIV-RNA ≥50 copies/mL followed by change of ART occurred in 23 patients (14 in PLWH without previous VF and 9 in PLWH with at least one previous VF) over 1504 person-year follow-up (PYFU) for an overall incidence rate (IR) of 1.5 per 100 PYFU (95% CI, 1.0–2.3). This rate was 1.2 × 100 PYFU (95% CI, 0.7–2.0) in PLWH without previous VF and 2.4 × 100 PYFU (95% CI, 1.2–4.9) in PLWH with at least one previous VF.

As median, VF occurred after 245 d (IQR, 203–404) from the switch to DTG+3TC and with 74 copies/mL (IQR, 58–92). All but one VF occurred with HIV-RNA <1000 copies/mL.

The cumulative estimated probability of virological rebound according to the presence (or not) of ≥1 previous VF to any ART was 1.2% (95% CI, 0.2%–2.2%) in PLWH without previous VF vs. 3.3% (95% CI, 0.4%–6.2%) in PLWH with at least one previous VF at one year and 3.3% (95% CI, 1.5%–5.1%) vs. 5.2% (95% CI, 1.2%–9.1%) at two years ($P = 0.042$).

For the alternative endpoint in which viral rebound was defined as confirmed HIV-RNA ≥50 copies/mL, 15 events over 1504 PYFU were detected, with an IR of 1.0 × 100 PYFU (95% CI, 0.6–1.6).

In this context, the cumulative estimated probability of virological rebound was 0.6% (95% CI, 0.1%–1.2%) in PLWH without previous VF vs. 2.1% (95% CI, 0.0%–4.5%) in PLWH with at least one previous VF to any ART at one year ($P = 0.094$).

Risks of viral rebound from fitting a separate Cox regression model according to previous VF are also shown in Table 2. After controlling for potential confounding factors, participants with at least one previous VF showed a tendency for a higher risk of virological rebound than those without previous VF to any ART, even if not statistically significant (adjusted HR, aHR of 3.06 [95% CI, 1.00–9.44], $P = 0.051$) (Table 2). Participants with exactly one previous VF had an aHR of 4.20 (95% CI, 1.36–12.94). Similar risks were observed throughout the other analyses, including a sensitivity analysis with a different definition of VF that only included VF to NRTIs or INSTIs and an aHR of 3.52 (95% CI, 0.75–16.53) for the alternative endpoint in which viral rebound was defined as confirmed HIV-RNA ≥50 copies/mL (Table 2).

3.2. Viral blips

Viral blips occurred in 59 PLWH, with an IR of 4.0 × 100 PYFU (95% CI, 3.1–5.2). One-year cumulative estimated probability of viral blips was 3.9% (95% CI, 2.3%–5.5%) in PLWH without previous VF vs. 3.5% (95% CI, 0.6%–6.4%) in PLWH with at least one previous VF to any ART ($P = 0.486$). Again, results were similar in the sensitivity analysis restricted to people with more complete virological monitoring before the date of the switch.

By multivariable analysis, after controlling for the same set of potentially confounding factors, PLWH with at least one previous VF to any ART had a higher risk of having viral blips than those without previous VF (aHR of 1.81 [95% CI, 0.95–3.42], $P = 0.069$) (Table 2). Similarly, restricting the analysis to those with complete histories of viral load data (sensitivity analysis), PLWH with at least one previous VF to any ART were confirmed to have a higher risk of viral blips, with an aHR of 2.64 (95% CI, 1.18–5.90) ($P = 0.018$).

Table 2
Crude and aHR (95% CIs) of the risk of viral rebound (A) and viral blips (B) from fitting a weighted Cox regression model by standard definition (confirmed HIV-RNA ≥50 copies/mL or a single HIV-RNA ≥50 copies/mL followed by change of ART) and modified definition (confirmed HIV-RNA ≥50 copies/mL)

Viral Rebound [standard definition]	HR 95% CI	*P* value	AHR 95% CI	*P* value	AHR 95% CI (sensitivity analysis)	*P* value
Previous VF to any ART ≥1 vs 0	2.20 (0.95–5.09)	0.065	3.06 (1.00–9.44)	0.051	6.62 (1.25–35.11)	0.026
Previous VF to any ART 1 vs. 0	3.31 (1.38–7.92)	0.007	4.20 (1.36–12.94)	0.013	7.71 (1.46–40.62)	0.016
Previous VF to NRTI or INSTI ≥ 1 vs. 0	1.90 (0.81–4.48)	0.140	2.15 (0.78–5.92)	0.137	3.25 (0.75–14.04)	0.114
Previous VF to NRTI or INSTI 1 vs. 0	2.75 (1.12–6.75)	0.027	2.86 (1.03–7.92)	0.044	3.46 (0.78–15.27)	0.102
Viral Rebound [modified definition]						
Previous VF to any ART ≥1 vs. 0	2.23 (0.79–6.29)	0.129	3.52 (0.75–16.50)	0.110	4.87 (0.53–44.91)	0.163
Previous VF to any ART 1 vs. 0	3.15 (1.05–9.48)	0.041	4.37 (0.84–22.85)	0.080	5.59 (0.40–78.59)	0.202
Previous VF to NRTI or INSTI ≥1 vs. 0	1.74 (0.60–5.08)	0.311	1.72 (0.55–5.41)	0.355	1.40 (0.27–7.27)	0.687
Previous VF to NRTI or INSTI 1 vs. 0	2.29 (0.71–7.32)	0.164	1.75 (0.55–5.49)	0.347	1.07 (0.12–9.13)	0.952

Viral blips	HR 95%CI	*P* value	AHR 95%CI	*P* value	AHR 95% CI (sensitivity analysis)	*P* value
Previous VF to any ART ≥1 vs. 0	1.39 (0.79–2.42)	0.251	1.81 (0.95–3.42)	0.069	2.64 (1.18–5.90)	0.018
Previous VF to any ART 1 vs. 0	1.38 (0.69–2.74)	0.364	1.74 (0.81–3.73)	0.153	1.98 (0.70–5.60)	0.200
Previous VF to any ART ≥2 vs. 0	1.39 (0.79–2.42)	0.251	1.80 (0.85–3.82)	0.124	2.04 (0.72–5.68)	0.180
Previous VF to NRTI or INSTI ≥1 vs. 0	1.32 (0.77–2.32)	0.341	1.68 (0.87–3.22)	0.121	2.70 (1.22–6.15)	0.014
Previous VF to NRTI or INSTI 1 vs. 0	1.36 (0.69–2.7)	0.376	1.61 (0.74–3.51)	0.230	2.28 (0.856.10)	0.101
Previous VF to NRTI or INSTI ≥2 vs. 0	1.32 (0.75–2.33)	0.341	1.49 (0.76–2.93)	0.247	2.48 (1.10–5.62)	0.029

NOTE: Sensitivity analysis excluded PLWH with uncomplete data about past viral loads.
AHR are adjusted for CD4+ cell counts at nadir (higher or lower than 350 cells/mmc), duration of virological suppression, and mode of HIV transmission.
aHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval; INSTIs, integrase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; VF, virological failure.

Moreover, PLWH with at least one previous VF to NRTIs or INSTIs had a significantly higher risk of having viral blips than those without previous VF in the sensitivity analysis (aHR 2.70 [95% CI, 1.22–6.15], $P=0.014$), which was not confirmed in the analysis of the overall population (aHR 1.68 [95% CI, 0.87–3.22], $P=0.121$).

The risk of viral blips from fitting a separate Cox regression model corresponding to the exact number of previous VFs to any ART (1 VF vs. 0 and ≥2 vs. 0) suggests a greater risk for patients with one or two previous VFs, but the results were not statistically significant.

We report a multicohort study aimed at evaluating the virological potency of 2DR with dolutegravir plus lamivudine in virologically suppressed patients in real-life settings in an ad hoc collaboration constructed for this specific query.

We found that one-year probability of VR was low regardless of the chosen definition of VR and comparable to the estimate provided in two meta-analyses of studies including dolutegravir-based 2DR (0.7%, 95% CI, 0.4–1.3 and 1.3%, 95% CI, 0.6–2.1) [3,16]. It needs to be noted that the first meta-analysis included 2DR regimens based on DTG but also with other companion drugs besides lamivudine, such as rilpivirine, atazanavir, or darunavir.

In our analysis, notwithstanding the optimal virological potency demonstrated, the risk of VR appeared to be increased in PLWH with previous VF, especially in those with one VF in comparison with those without previous VF. To a lesser extent, the risk of viral blips appeared to be increased in PLWH with previous VF.

It is possible that PLWH with a history of previous VF are also those having lower adherence to ART. Indeed, it has been previously found that patients experiencing ART treatment failure remain at higher risk of failing subsequent regimens, and poor adherence is a major determinant of this outcome [17,18].

Previous VF was shown to predict future virological outcome in another large retrospective study including any ART [19] and in one study including dolutegravir plus rilpivirine [20], but not in another study of patients switching to triple therapy with 2NRTI plus DTG [21].

It must be highlighted that, in our dataset, the DTG+3TC regimen has also been prescribed to patients with histories of previous VF (about 20% of this population) in a proportion higher than elsewhere reported [11,22]. Although this is somewhat surprising given the current guidelines, having a larger prevalence facilitated the success of this analysis. In contrast, other retrospective studies with smaller sample sizes reported that DTG+3TC was prescribed in an even greater proportion of patients with previous VF (44%–51%) [5,23], but this was not associated with a higher risk of treatment failure [5]. Of note, these switches are made in clinical practice beyond commercial label therapeutic indications which recommend the switch only for patients with no known or suspected resistance to the INSTI class or lamivudine [24,25].

Our study presents some limitations. First, because it is retrospective and observational, we cannot rule out unmeasured confounding. Particularly, neither a measure of the patients' adherence nor genotype resistance test (GRT) results were available in our dataset. Missing of adherence data is a common issue for many large cohort databases, but the Icona Foundation Cohort is making an effort to fill the gap by implementing an app developed for the evaluation of Patients' Reported Outcomes (PROs) in PLWH (E-qol app). Moreover, our study does not allow for the evaluation of the effect of archived resistance mutations (in particular of M184V) on the risk of VF because cumulative GRTs were not available. We were unable to evaluate if the switch to 2DR was guided by GRT and if patients with previous VF had archived resistance mutations at the time of the switch to control for these likely confounding factors.

Furthermore, despite the large sample size of the cohort including most of the people treated with this combination in Italy who are included in epidemiological studies, the number of rebounds events was extremely small to allow for a comprehensive evaluation of confounding factors. Considering the exact number of previous VFs, having exactly one previous VF is a predictor of VR but not of viral blip, thus a larger sample could be helpful to better categorize the effect of the number of previous VFs and show if a dose-response relationship exists. Moreover, a comparison with dolutegravir-based 3-drug regimens (3DR) was not performed. Consequently, we cannot exclude that PLWH with previous VF may also have an increased risk of VR under a 3DR, but recent Canadian observational data failed to demonstrate this association when switching to dolutegravir plus 2 NRTIs [21].

On the other hand, key strengths of this work are that the past histories of VF were accurately defined and the results of the secondary and sensitivity analyses were largely consistent with those of the main analysis.

To conclude, DTG+3TC demonstrated high virological efficacy but should be cautiously used in PLWH with a history of VF. In fact, a previous history of VF was associated with higher risk of VR and viral blips.

Funding

The Icona Foundation is supported by unrestricted grants from GileadSciences, Janssen-Cilag, MSD, Thera Technologies, and ViiVHealthcare.

Competing interests

RG received grants for speakers's honoraria/advisory board by ViiV Healthcare, MSD, Janssen, Thera Technology, and Gilead; research grants were awarded to her institution from Gilead. AA received grants for speakers's honoraria/advisory board by ViiV Healthcare, MSD, Janssen, Thera Technology, Gilead, GlaxoSmithKline, Pfizer, and Roche. The other authors have nothing to declare.

Ethical approval

All patients signed a consent form to participate in the cohorts in accordance with the ethical standards of the committee on human experimentation and the Helsinki Declaration (last amended in October 2013).

Acknowledgments: Icona Foundation Study Group

BOARD OF DIRECTORS: A d'Arminio Monforte (President), A Antinori (Vice-President), S Antinori, A Castagna, F Castelli, R Cauda, G Di Perri, E Girardi, R Iardino, A Lazzarin, GC Marchetti, C Mussini, L Sarmati, F von Schloesser, P Viale.

SCIENTIFIC SECRETARY: A d'Arminio Monforte, A Antinori, A Castagna, F Ceccherini-Silberstein, A Cingolani, A Cozzi-Lepri, E Girardi, A Gori, S Lo Caputo, G Marchetti, F Maggiolo, C Mussini, M Puoti, CF Perno.

STEERING COMMITTEE: C Agrati, A Antinori, F Bai, A Bandera, S Bonora, A Calcagno, D Cannetti, A Castagna, F Ceccherini-Silberstein, A Cervo, S Cicalini, A Cingolani, P Cinque, A Cozzi-Lepri, A d'Arminio Monforte, A Di Biagio, R Gagliardini, A Giacomelli, E Girardi, N Gianotti, A Gori, G Guaraldi, S Lanini, G Lapadula, M Lichtner, A Lai, S Lo Caputo, G Madeddu, F Maggiolo, V Malagnino, G Marchetti, C Mussini, S Nozza, CF Perno, S Piconi, C Pinnetti, M Puoti, E Quiros Roldan, R Rossotti, S Rusconi, MM Santoro, A Saracino, L Sarmati, V Spagnuolo, N Squillace, V Svicher, L Taramasso, A Vergori.

STATISTICAL AND MONITORING TEAM: A Cozzi-Lepri, I Fanti, A Rodano', A Tavelli, F Vinci.

COMMUNITY ADVISORY BOARD: A Bove, M Cernuschi, L Cosmaro, M Errico, A Perziano, V Calvino.

BIOLOGICAL BANK INMI AND SAN PAOLO: S Carrara, S Graziano, G Prota, S Truffa, D Vincenti, V Yellenki, Y D'Errico.

PARTICIPATING PHYSICIANS AND CENTERS: Italy A Giacometti, A Costantini, V Barocci (Ancona); A Saracino, C Santoro, E Milano (Bari); F Maggiolo, C Suardi (Bergamo); P Viale, V Donati, G Verucchi (Bologna); E Quiros Roldan, C Minardi, (Brescia); B Menzaghi, C Abeli (Busto Arsizio); L Chessa, F Pes (Cagliari); P Maggi, L Alessio (Caserta); B Cacopardo, B Celesia (Catania); J Vecchiet, K Falasca (Chieti); A Pan, S Dal Zoppo (Cremona); L Sighinolfi, D Segala (Ferrara); F Vichi, MA Di Pietro (Firenze); T Santantonio, S Ferrara (Foggia); M Bassetti, E Pontali, A Alessandrini, N Bobbio, G Mazzarello (Genova); M Lichtner, L Fondaco (Latina); S Piconi, C Molteni (Lecco); A Chiodera, P Milini (Macerata); G Nunnari, G Pellicanò (Messina); A d'Arminio Monforte, S Antinori, A Lazzarin, G Rizzardini, M Puoti, A Gori, A Castagna, A Bandera, V Bono, MV Cossu, A Giacomelli, R Lolatto, MC Moioli, L Pezzati, C Tincati (Milano); C Mussini, C Puzzolante (Modena); P Bonfanti, G Lapadula (Monza); V Sangiovanni, I Gentile, V Esposito, G Di Flumeri, G Di Filippo, V Rizzo (Napoli); AM Cattelan, S Marinello (Padova); A Cascio, C Colomba (Palermo); D Francisci, E Schiaroli (Perugia); G Parruti, F Sozio (Pescara); P Blanc, A Vivarelli (Pistoia); C Lazzaretti, R Corsini (Reggio Emilia); M Andreoni, A Antinori, R Cauda, C Mastroianni, A Cingolani, V Mazzotta, S Lamonica, M Capozzi, A Mondi, M Rivano Capparuccia, G Iaiani, C Stingone, L Gianserra, J Paulicelli, MM Plazzi, G d'Ettore, M Fusto (Roma); M Cecchetto, F Viviani (Rovigo); G Madeddu, A De Vito (Sassari); M Fabbiani, F Montagnani (Siena); A Franco, R Fontana Del Vecchio (Siracusa); BM Pasticci, C Di Giuli (Terni); GC Orofino, G Calleri, G Di Perri, S Bonora, G Accardo (Torino); C Tascini, A Londero (Udine); V Manfrin, G Battagin (Vicenza); G Starnini, A Ialungo (Viterbo).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jgar.2022.11.010.

References

[1] Van Wyk J, Ajana F, Bisshop F, De Wit S, Osiyemi O, Portilla Sogorb J, et al. Efficacy and safety of switching to dolutegravir/lamivudine fixed-dose 2-drug regimen vs. continuing a tenofovir alafenamide-based 3-or 4-drug regimen for maintenance of virologic suppression in adults living with Human Immunodeficiency Virus type 1: phase. Clin Infect Dis 2020;71:1920–9. doi:10.1093/cid/ciz1243.

[2] Taiwo BO, Marconi VC, Berzins B, Moser CB, Nyaku AN, Fichtenbaum CJ, et al. Dolutegravir plus lamivudine maintains Human Immunodeficiency Virus-1 suppression through week 48 in a pilot randomized trial. Clin Infect Dis 2018;66:1794–7. doi:10.1093/cid/cix1131.

[3] Wandeler G, Buzzi M, Anderegg N, Sculier D, Béguelin C, Egger M, et al. Virologic failure and HIV drug resistance on simplified, dolutegravir-based maintenance therapy: systematic review and meta-analysis. F1000Research 2019;7:1359. doi:10.12688/f1000research.15995.2.

[4] Maggiolo F, Gulminetti R, Pagnucco L, Digaetano M, Benatti S, Valenti D, et al. Lamivudine/dolutegravir dual therapy in HIV-infected, virologically suppressed patients. BMC Infect Dis 2017;17:215. doi:10.1186/s12879-017-2311-2.

[5] Galizzi N, Poli A, Galli L, Muccini C, Mastrangelo A, Dell'Acqua R, et al. Retrospective study on the outcome of two-drug regimens based on dolutegravir plus one reverse transcriptase inhibitor in virologically-suppressed HIV-infected patients. Int J Antimicrob Agents 2020;55:105893. doi:10.1016/j.ijantimicag.2020.105893.

[6] Baldin G, Ciccullo A, Borghetti A, Di Giambenedetto S. Virological efficacy of dual therapy with lamivudine and dolutegravir in HIV-1-infected virologically suppressed patients: Long-term data from clinical practice. J Antimicrob Chemother 2019;74:1461–3. doi:10.1093/jac/dkz009.

[7] Calza L, Colangeli V, Borderi M, Testi D, Granozzi B, Bon I, et al. Simplification to dual therapy containing lamivudine and raltegravir or dolutegravir in HIV-infected patients on virologically suppressive antiretroviral therapy. J Antimicrob Chemother 2020;75:3327–33. doi:10.1093/jac/dkaa319.

[8] Ward D, Ramgopal M, Riedel DJ, Garris C, Dhir S, Waller J, et al. Real-world experience with dolutegravir-based two-drug regimens. AIDS Res Treat 2020;2020:5923256. doi:10.1155/2020/5923256.

[9] Rolle CP, Nguyen V, Hinestrosa F, DeJesus E. Virologic outcomes of switching to dolutegravir functional mono- or dual therapy with a non-cytosine nucleoside analog: a retrospective study of treatment-experienced, patients living with HIV. AIDS Res Ther 2021;18:1–11. doi:10.1186/s12981-021-00352-0.

[10] Antinori A, Santoro MM, Gagliardini R, Marchetti G, Mondi A, Cento V, et al. Italian expert panel consensus statements on two-drug antiretroviral regimens to treat naïve and virologically suppressed HIV-1 infected patients. New Microbiol 2019;42:69–90.

[11] Allavena C, Deschanvres C, Peytavin G, Rey D, Valantine M, Bani-Sadr F. Factors associated with therapeutic failure of 2 Drug-Regimen (DAT'AIDS cohort). In: Conf Retroviruses Opportunistic IIfections; 2019.

[12] Charpentier C, Montes B, Perrier M, Meftah N, Reynes J. HIV-1 DNA ultra-deep sequencing analysis at initiation of the dual therapy dolutegravir!lamivudine in the maintenance DOLULAM pilot study. J Antimicrob Chemother 2017;72:2831–6. doi:10.1093/jac/dkx233.

[13] Rial-Crestelo D, de Miguel R, Montejano R, Dominguez-Dominguez L, Aranguren-Rivas P, Esteban-Cantos A, et al. Long-term efficacy of dolutegravir plus lamivudine for maintenance of HIV viral suppression in adults with and without historical resistance to lamivudine: week 96 results of ART-PRO pilot study. J Antimicrob Chemother 2020;76:738–42. doi:10.1093/jac/dkaa479.

[14] Gagliardini R, Ciccullo A, Borghetti A, Maggiolo F, Bartolozzi D, Borghi V, et al. Impact of the M184V resistance mutation on virological efficacy and durability of lamivudine-based dual antiretroviral regimens as maintenance therapy in

individuals with suppressed HIV-1 RNA: a cohort study. Open Forum Infect Dis 2018;5:1–8. doi:10.1093/ofid/ofy113.
[15] Santoro MM, Armenia D, Teyssou E, Santos JR, Charpentier C et al. Impact of M184V on the virological efficacy of switch to 3TC/DTG in Real Life. Abstr 429 CROI 2021 Virtual, March 6–10, 2021 n.d.
[16] Punekar YS, Parks D, Joshi M, Kaur S, Evitt L, Chounta V, et al. Effectiveness and safety of dolutegravir two-drug regimens in virologically suppressed people living with HIV: a systematic literature review and meta-analysis of real-world evidence. HIV Med 2021;22:423–33. doi:10.1111/hiv.13050.
[17] Ramadhani H, Bartlett J TN, et al. Association of first-line and second-line antiretroviral therapy adherence. OFID 2014;2:2633851. doi:10.1093/o.
[18] Todd J, Grosskurth H, Changalucha J, Obasi A, Mosha F, Balira R, et al. Risk factors influencing HIV infection incidence in a rural African population: a nested case-control study. J Infect Dis 2006;193:458–66. doi:10.1086/499313.
[19] Rusconi S, Santoro MM, Gianotti N, Antinori A, Bonora S, Cingolani A, et al. Is the rate of virological failure to cART continuing to decline in recent calendar years? J Clin Virol 2019;116:23–8. doi:10.1016/j.jcv.2019.04.009.
[20] Deschanvres C, Reynes J, Lamaury I, Rey D, Palich R, Bani-Sadr F, et al. Dolutegravir-based dual maintenance regimens combined with lamivudine/emtricitabine or rilpivirine: risk of virological failure in a real-life setting. J Antimicrob Chemother 2021;77:196–204. doi:10.1093/jac/dkab367.
[21] dong Sangaré MN, JG Baril, de Pokomandy A, Laprise C, Deshaies C, Klein M, et al. Impact of previous HIV resistance and virologic failures on virologic outcome following a switch to dolutegravir with 2 NRTIs among people living with HIV. Medicine (Baltimore) 2020;99:e23335. doi:10.1097/MD.0000000000023335.
[22] Patel R, Evitt L, Mariolis I, Di Giambenedetto S, d'Arminio Monforte A, Casado J, et al. HIV treatment with the two-drug regimen dolutegravir plus lamivudine in real-world clinical practice: a systematic literature review. Infect Dis Ther 2021;10:2051–70. doi:10.1007/s40121-021-00522-7.
[23] Borghetti A, Lombardi F, Gagliardini R, Baldin G, Ciccullo A, Moschese D, et al. Efficacy and tolerability of lamivudine plus dolutegravir compared with lamivudine plus boosted PIs in HIV-1 positive individuals with virologic suppression: a retrospective study from the clinical practice. BMC Infect Dis 2019;19:59. doi:10.1186/s12879-018-3666-8.
[24] Dovato - SUMMARY OF PRODUCT CHARACTERISTICS. n.d.
[25] Center for Drug Evaluation and Research - Labeling DOVATO. n.d.