



## No impact of previous NRTIs resistance in HIV positive patients switched to DTG + 2NRTIs under virological control: Time of viral suppression makes the difference.

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### ABSTRACT

The accumulation of drug-resistance mutations on combined antiretroviral regimens (ART) backbone could affect the virological efficacy of the regimen. Our aim was to assess the impact of previous drug resistance to nucleoside reverse transcriptase inhibitors (NRTIs) on the probability of virological failure (VF) in patients, under virological control, who switched to dolutegravir (DTG) + 2NRTIs regimens. All HIV-1 positive drug-experienced patients who started a regimen composed by DTG + 2NRTIs [abacavir/lamivudine or tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF)/emtricitabine (FTC)] in the ARCA collaborative group with HIV-RNA < 50 cp/mL were included in the analysis. Patients with a previous VF to integrase inhibitors were excluded. The impact of single and combined NRTIs mutations on the probability of VF (defined as 2 consecutive HIV-RNA > 50 copies/mL or one HIV-RNA > 1000 copies/mL) was assessed by Kaplan Meier curves. A multivariable Cox regression analysis was constructed to assess factors potentially related to VF. Five hundred and eighty-eight patients were included in the analysis with a median time of viral suppression before the switch of 37 months (IQR 12–78), of whom 148 (25.2%) had at least one previous NRTIs resistance mutation. In the multivariable model no association was observed between NRTIs mutations and VF. Conversely, the duration of viral suppression before switch resulted associated with a lower risk of VF (for 1 month increase, adjusted Hazard Ratio 0.98, 95%CI 0.96–0.99;  $p = 0.024$ ). Previous NRTIs mutations appeared to have no impact on the risk of VF in patients switched to DTG + 2NRTIs, whereas a longer interval on a controlled viremia decreased significantly the risk of VF.

In the past decades antiretroviral therapy (ART) has dramatically changed the natural history of HIV-1 infection by transforming an invariably fatal disease into a chronic one (Palella et al., 2006). The

advent of a new class of antiretroviral, integrase inhibitors (INIs), has provided new effective and well tolerated ART options both in naïve (Raffi et al., 2013; Molina et al., 2015; Wohl et al., 2019; Stellbrink

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et al., 2019) and experienced patients (Gatell et al., 2019; Trottier et al., 2017). Simplification strategies based on INIs are increasingly used in clinical practice with the aim to improve the tolerability and to avoid potential long-term metabolic untoward effects of other antiretrovirals, i.e. boosted protease inhibitors (PIs) (Raffi et al., 2016; Andreoni et al., 2015; Giacomelli et al., 2019). In the first simplification studies assessing the efficacy of INIs (SWITCHMRK and SPIRAL) the switch to raltegravir (RAL) was compared with maintaining PIs-based regimens. The inclusion criteria of both studies allowed the enrolment of patients with previous virological failure (VF) (Eron et al., 2010; Martinez et al., 2010). In the SWITCHMRK, RAL based regimens failed to meet non inferiority when compared to boosted lopinavir containing regimens, with a not negligible percentage of patients developing resistance to RAL documented by the genotypic resistance test (GRT) (Eron et al., 2010). Conversely, the SPIRAL study established the non-inferiority of RAL to PIs-containing regimens (Martinez et al., 2010). When compared to first generation INIs (i.e. RAL and elvitegravir), dolutegravir (DTG) presents a higher genetic barrier (Kobayashi et al., 2011). Nevertheless, due to the high rate of VF observed in the SWITCHMRK, patients with previous VF, with documented resistance to one of the investigated ART components, were subsequently excluded from the DTG switch studies (Gatell et al., 2019; Trottier et al., 2017; Eron et al., 2010). Therefore, only data derived from observational studies are available regarding the potential impact of previous reverse transcriptase (RT) mutations on the virological efficacy of DTG triple therapy (Sörstedt et al., 2018; Olearo et al., 2019; Chen et al., 2019).

The aim of the present study was to assess the impact of previous drug resistance to nucleoside reverse transcriptase inhibitors (NRTIs) on the probability of VF in HIV-1 positive drug-experienced patients, with an undetectable HIV-RNA (< 50cp/mL) and at least one previous GRT, who switched to a dolutegravir (DTG) + 2NRTIs regimen.

We performed a retrospective observational study using the Antiviral Response Cohort Analysis (ARCA) database (<https://www.dbarca.net/>), which prospectively collects data on HIV resistance and ART; at present, data from > 41,000 patients in Italy are available ([www.dbarca.net](http://www.dbarca.net)). The ARCA database was queried to retrieve the data of HIV-1-positive patients with (i) age  $\geq 18$  years, (ii) HIV-RNA < 50 copies/mL at the time of the switch, (iii) subsequently switching to DTG + tenofovir/emtricitabine (TDF/FTC) or tenofovir alafenamide (TAF)/FTC or abacavir/lamivudine (ABC/3 TC) for any reason, (iv) with at least 1 previous GRT, (v) with at least 1 virological and clinical follow-up after switching to DTG + 2NRTIs. Patients with a previous VF to INIs-containing regimens were excluded from the analysis.

The occurrence of any NRTIs mutation was determined using historical GRT; mutations were assessed by the Stanford list Version 8.7 update 2018-10-19 (<https://hivdb.stanford.edu/hivdb/by-mutations/>). The mutations considered in the analysis were M184V/I, K65R, Q151M, the T69 insertion, the thymidine analogues mutations (TAM)-1 (M41L, L210W, and T215Y), TAM-2 (D67N, K70R, T215F, and K219Q/E) and cumulative TAM; moreover, any of these mutations in whatever previous GRT was considered as positive.

The primary end-point was to assess the impact of single and combined RT mutations in the historical GRT on the probability of VF (defined as 2 consecutive HIV-RNA > 50 copies/mL or one HIV-RNA > 1000 copies/mL) after the switch to an antiretroviral regimen composed by DTG + TDF/FTC or TAF/FTC or ABC/3TC in patients with an HIV-RNA < 50 copies/mL at the time of switching.

Standard survival analyses with Kaplan-Meier curves were used to analyse the probability of time to VF. Patients were followed from the switch to DTG + 2NRTIs to the study outcomes, last available follow-up, or December 5, 2018, whichever occurred first.

Patients switching for any reason to an ART other than DTG + 2NRTIs or loss to follow up were censored in the survival analysis.

To assess the predictors of VF a univariate and multivariable Cox proportional hazard model was built. The following variables were

**Table 1**

Characteristic of the study population at time of the switch.

Patients characteristics	Total n = 588
Gender, n (%)	
Male	423 (71.9)
Female	165 (28.1)
Median Age (yrs), (IQR)	51 (44–56)
Epidemiology, n (%)	
Sexual Risk	327 (55.6)
IDUs	109 (18.5)
Other	9 (1.6)
Unknown	143 (24.3)
Years on ART, median (IQR)	8 (4–17)
Number of previous ART regimens, median (IQR)	3 (1–6)
Months of viral suppression before switch, median (IQR)	31 (12–78)
CD4 cells nadir < 200 cell/ $\mu$ L, n (%)	302 (51.4)
HIV-RNA zenit cp/mL Log, median (IQR)	5.0 (4.4–5.6)
Previous AIDS events, n (%)	56 (9.5%)
Backbone, n (%)	
ABC	423 (71.9)
TDF/TAF	165 (28.1)
Switch from a PIs containing regimen, n (%)	323 (54.9)
HCV, n (%)	
Positive	145 (24.7)
Negative	234 (39.8)
Unknown	209 (35.5)
HBV, n (%)	
Positive	82 (14)
Negative	307 (52.2)
Unknown	199 (33.8)
Previous NRTIs resistance, n (%)	
M184V/I	102 (17.3)
K65R	6 (1.0)
3 or more TAMs	77 (13.1)
Any NRTIs mutation	148 (25.2)

List of abbreviations: n = number, yrs = years, IDUs = intravenous drug users, ABC = abacavir, TDF = tenofovir disoproxil fumarate, TAF = tenofovir alafenamide, PIs = protease inhibitors, NRTIs = nucleoside reverse transcriptase inhibitors, TAMs = thymidine analogues mutations.

considered in the final model: age, gender, transmission route, concomitant use of ABC or TDF/TAF backbone, HIV-RNA zenit, CD4 cell counts nadir, number of previous antiretroviral lines, years on combined antiretroviral treatment, time of pre-switch viral suppression, the presence of K65R, M184V/I or 3 or more TAMs.

All analyses were performed using the SPSS v.22.0 software package. *P* values of less than 0.05 were considered significant.

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.

Five hundred and eighty-eight patients were included in the analysis, 423 (71.9%) of whom were males, with a median age of 51 years [Inter quartile range (IQR) 44–56] and 165 (28.1%) were receiving TDF or TAF/FTC. Patient's baseline characteristics at the time of the switch are reported in Table 1. Overall, the median number of previous regimens was 3 (IQR 1–6) and the median time of viral suppression before the switch was 31 months (IQR 12–78). One hundred and forty-eight patients (25.2%) presented at least one NRTIs mutations in their historical GRT, 102 (17.3) had the M184V/I mutation and 77 (13.1%) 3 or more TAMs.

The median time of observation was 12 months (IQR 6–19). During this time, 259 (44%) patients discontinued DTG + 2NRTIs for any reason (20.8% were for toxicity, 13.1% for simplification, 15.9% for other reasons, 2.3% for VF and not reported for 47.9% of patients). Cumulative VF occurred in 19 (3.2%) subjects. At 12 months the overall probability of experiencing a VF was 4% [95% Confidence Interval (95% CI 1.6–5.5)].

**Table 2**  
Uni and multivariable analysis of factors associated with VF after switching to DTG + 2NRTIs.

	HR	95% CI	p	aHR	95% CI	p
Male vs Female	1.53	0.60–3.90	0.373	2.49	0.90–6.89	0.079
Age (per 1 year more)	0.99	0.95–1.04	0.798	0.99	0.94–1.05	0.767
IDUs vs Sexual Risk	2.75	1.03–7.30	0.043	2.65	0.73–9.57	0.137
Unknown vs Sexual Risk	1.09	0.29–4.11	0.900	1.36	0.32–5.88	0.685
ABC vs TDF/TAF	0.65	0.26–1.64	0.367	1.06	0.35–3.23	0.914
Zenit RNA (per 1 Log increase)	1.63	0.95–2.78	0.077	1.81	0.92–3.58	0.085
CD4 nadir < 200 vs > 200/mm <sup>3</sup>	0.84	0.34–2.06	0.699	0.56	0.20–1.55	0.265
Number of previous lines (per 1 more)	1.05	0.95–1.15	0.333	0.98	0.82–1.17	0.806
Years on cART (per 1 year more)	1.01	0.95–1.08	0.722	1.03	0.93–1.15	0.559
Time of viral suppression (per 1 month increase)	0.98	0.96–0.99	0.019	0.98	0.96–0.99	0.029
Switch from a PIs containing regimen	0.55	0.22–1.41	0.214	0.42	0.15–1.18	0.101
K65R mutation presence	5.14	0.68–38.90	0.112	3.23	0.27–38.40	0.352
3 or more TAMs presence	1.11	0.32–3.82	0.871	2.01	0.30–13.41	0.470
M184V/I mutation presence	1.52	0.55–4.21	0.424	0.99	0.19–5.21	0.986

List of abbreviations: HR = Hazard Ratio, aHR = adjusted Hazard Ratio, CI = Confidence Interval, IDUs = intravenous drug users, ABC = abacavir, TDF = tenofovir disoproxil fumarate, TAF = tenofovir alafenamide, PIs = protease inhibitors, TAMs = thymidine analogues mutations.

According to the historical GRT, the probability of having a VF at 12 months in patients with or without any NRTIs mutation was 5% (95% CI 0.6–10.2) and 3% (95% CI 1–4.9) ( $p = 0.635$ ), respectively. No difference was observed at 12 months in the rate of VF in patients harbouring or not in their historical GRT the M184V/I mutation [7% (95% CI 0.9–13.8) vs 3% (95% CI 0.9–4.5);  $p = 0.420$ ] and 3 or more TAMs [5% (95% CI 0–12) vs 3% (95% CI 1.3–5.4);  $p = 0.871$ ]. Moreover, no difference in the rate of VF failure was observed when combining M184V/I and K65R mutations ( $p = 0.061$ ).

In the multivariable Cox proportional hazard model, after correcting for age, gender, risk factors, immune-virological status and years on ART, no significant association was observed between NRTIs mutations and VF. Conversely, the time of viral suppression before the switch resulted associated with a lower risk of VF [for 1 month increase, adjusted Hazard Ratio 0.98 (95% CI 0.96–0.99);  $p = 0.024$ ] (Table 2).

Our study highlights the virological efficacy of DTG+2NRTIs combination therapy with only 3.2% of patients who experienced a VF during the time of observation. This finding is in line with the virological efficacy of DTG based regimens reported in observational studies with a mixed population of patients harbouring or not resistance to NRTIs (Oleairo et al., 2019; Chen et al., 2019; Baldin et al., 2019).

In our study we observed no impact of previous NRTIs resistance according to the historical GRT on the risk of VF of ART composed by DTG+2NRTIs. This finding is interesting because no information is available from randomized clinical trial due to the exclusion of patients with previous NRTIs mutations (Gatell et al., 2019; Trottier et al., 2017). Nevertheless, a recent large observational study conducted in several European countries confirmed the absence of the impact of M184V/I on the virological efficacy of ABC/3TC/DTG regimen in switch strategy (Oleairo et al., 2019). Furthermore, the DAWNING study showed that, in patients failing their first antiretroviral regimen, DTG was superior to boosted lopinavir in obtaining virological suppression at 48 weeks (Aboud et al., 2019). Very recently, two Phase 3 TAF/FTC/bictegravir (BIC) switch studies (studies 1878 and 1844) demonstrated a high rate of virological suppression at week 48 in the overall population and in subjects with pre-existing resistance, including M184V/I (Andreatta et al., 2019). Taken together these results support the implementation of DTG or BIC-based ART in resource limited setting also in patients with previous VF to NRTIs containing regimens (Hamers, 2019; Inzaule et al., 2019).

In our study no association was observed between previous PIs exposure and the risk of VF, thereby supporting the findings reported by Chen et al. who evaluated patients switching from boosted PIs to DTG with or without previous NRTIs mutations (Chen et al., 2019). These results highlight the high genetic barrier of DTG (Kobayashi et al., 2011) and they might support the use of DTG-based ART as alternative

regimens in simplification strategies from boosted PIs in patients with previous NRTIs resistance (Gatell et al., 2019; Giacomelli et al., 2019). Nevertheless, in our study we observed a high rate of DTG+2NRTIs treatment interruption due to any causes. Consequently, if on one hand we can infer about the virological efficacy of the DTG-containing regimen, on the other hand the tolerability of such regimen might be questioned, possibly due to central nervous system side effects and weight gain (Hoffmann et al., 2017; Menard et al., 2017).

In our study, we found an association between the time of pre-switch viral suppression and the risk of VF. The importance of the duration of viral suppression before the switch was highlighted by the different results of the first two switch trial of RAL, SWITCHMRK and SPIRAL (Eron et al., 2010; Martinez et al., 2010). In the SWITCHMRK, a pre-switch time of viral suppression of more than 3 months was allowed, with approximately 18% of patients with less than one year of boosted lopinavir exposure before randomization, and the non inferiority of RAL-based regimens was not met (Eron et al., 2010). On the contrary, in the SPIRAL study demonstrating the non inferiority of RAL, patients had a longer median time of viral suppression before the switch [67 months (IQR 59–73)] (Martinez et al., 2010). Moreover, in the study by Oleairo et al., in which patients had a longer viral suppression than in our study before switching to ABC/3TC/DTG (134 months and 83.5 months in those with and without M184V/I vs 31 months, respectively), no impact of the time of viral suppression on VF was observed (Oleairo et al., 2019).

Our study has several limitations. First, the observational nature of the study could have affected the results due to missing or incomplete data. In particular, an intrinsic limitation in the dataset regards the reasons of DTG+2NRTIs discontinuation, thus challenging the inference about tolerability of such ART. Second, the high discontinuation rate and the median time of observation of only 12 months did not allow to assess the long term impact of NRTIs mutations. Third, a very few VFs were observed despite our conservative definition of VF, although in line with the rate reported in previous works (Oleairo et al., 2019; Chen et al., 2019). Finally, when considering the K65R mutation, a type 2 error cannot be excluded due to the low number of cases and consequently our findings should not be generalized to such patients.

According to our findings, the risk of VF after switching to DTG+2NRTIs appears to be low. Previous NRTIs mutations seem to have no impact on the risk of VF in patients under virological control on ART regimens based on DTG+2NRTIs. Moreover, a longer time of virological suppression before the switch resulted associated to a reduced risk of VF. Thus, caution should be warranted when considering the switch to DTG+2NRTIs in patients with a short time of viral suppression.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.antiviral.2019.104635>.

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