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Five years with dolutegravir plus lamivudine as a switch strategy: much more than a positive finding.

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Abstract

Background. Results from clinical trials and observational studies suggest that dolutegravir plus lamivudine could be an effective and well-tolerated option for simplification in HIV-1 positive patients. We aimed to assess long-time efficacy and safety in our multicenter cohort.

Methods. This was a retrospective study enrolling HIV-1-infected, virologically suppressed patients switching to dolutegravir+lamivudine. We performed survival analysis to evaluate time to virological failure (VF, defined by a single HIV-RNA ≥1,000 copies/mL or by two consecutive HIV-RNA ≥ 50 copies/mL) and treatment discontinuation (TD, defined as the interruption of either 3TC or DTG), assessing predictors via Cox regression analyses.

Results. Seven-hundred eighty-five patients were considered for the analysis: 554 were males (70.6%), with a median age of 52 years (IQR 45-58). Estimated probabilities of maintaining virological suppression at weeks 96, 144 and 240 were 97.7% (SD ±0.6), 96.9% (SD ±0.8) and 96.4% (SD ±0.9). A non-B HIV subtype (p=0.014) and a previous VF (p=0.037), resulted

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predictors of VF. We did not observe differences in probability of VF in PLWHIV with a M184V resistance mutation (p=0.689); however, in a deeper analysis, M184V mutation was a predictor of VF (p=0.038) in patients with time of virological suppression < 88 months. Estimated probabilities of remaining on study regimen at 96, 144 and 240 weeks were 82.9% (SD±1.4), 79.7% (SD±1.6) and 74.3% (SD±2.2), respectively.

Conclusions. Our findings show the long-term efficacy and tolerability of dolutegravir plus lamivudine in virologically suppressed patients.

Keywords: HIV, HAART, dolutegravir, lamivudine

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Transparency Declarations

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Introduction

In the last decade, less-drug regimens, mainly 2-drug regimens (2DR), have been widely regarded as a plausible alternative to "standard" 3-drug regimens in virologically suppressed people living with HIV (PLWHIV), in particular in situations where data on pre-switch resistance mutations are available [1]. The rationale of 2DR strategies lies in the expected better tolerability and safety profile without sacrificing the virological efficacy [2, 3]. Lamivudine (3TC)-based 2DR have been among the most studied switch strategies in latest years; clinical trials and observational studies analyzed the efficacy, safety and tolerability of several 2DR with 3TC and a boosted protease inhibitor [3-6]. Since the introduction of second-generation integrase inhibitor (INI) dolutegravir (DTG), real-life reports emerged, describing the high efficacy and good tolerability profile of a 2DR with DTG+3TC [7-9]. Recently, the TANGO study [10], a randomized clinical trial, has been published, highlighting that a 2DR of DTG+3TC was non-inferior in maintaining virological suppression compared with a TAF-based 3-drug regimen. In a previous work [11], a reply to the authors of the TANGO study, we observed that there were non-significant differences between patients who met the TANGO inclusion criteria and those who did not, in our multicenter cohort, showing that the analyzed regimen could be effective and safe on an even larger scale. Goal of the present study, five years after switching our first treatment-experienced patients to DTG+3TC, was to investigate the long-term efficacy and safety of DTG+3TC in a multicenter real-life observational cohort of adult PLWHIV.

Methods

We performed a retrospective, observational study in which we enrolled treatment-experienced, virologically suppressed PLWHIV from 9 Italian clinical centers [12]. Criteria for eligibility were: patient's informed consent to data collection, being at least 18 years-old, being on stable (i.e. at

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least 6 months) antiretroviral therapy (ARV) with viral suppression (HIV-RNA<50 copies/mL) at the moment of switch to lamivudine plus dolutegravir (baseline) and being HBsAg negative.

The primary study objective was to evaluate time to virological failure (VF, defined by a single HIV-1 RNA ≥1,000 copies/mL or by two consecutive HIV-1 RNA ≥ 50 copies/mL) and the time to treatment discontinuation (TD, defined as the interruption of either 3TC or DTG) for any cause. Survival analysis was employed to determine the time to VF and TD and the respective predictors were analyzed by Cox regression. The study was performed according to the principles of the Declaration of Helsinki and received the approval by each independent local Ethics Committee (study coordination site protocol number 5284/15). Data was analyzed by using SPSS Statistics for Windows, Version 23.0 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp).

Results

We analyzed 785 patients: 554 were males (70.6%), with a median age of 52 years (Interquartile Range [IQR] 45 – 58), a median time from HIV diagnosis of 14.8 years (IQR 8.0 – 22.0) and a median time of ARV exposure of 11.5 years (IQR 5.8 – 18.6). One hundred thirty-two patients (16.8%) had at least one previous AIDS-defining event, 175 (22.3%) experienced at least one virological failure while 282 (35.9%) were previously prescribed a 2DR. Thirty-three (4.2%) had a previously detected M184V resistance mutation. Complete patients' characteristics are shown in Table 1.

During 1992.6 Patient-Years of Follow-Up (PYFU), we observed 18 VF, with a rate of 0.9 VF per 100 PYFU. Median time to VF was 25.8 months (IQR 14.1-47.4); ten VF (55.5%) occurred in the first 48 weeks of follow-up. Nine of the18 patients experiencing a VF discontinued study regimen, while the others maintained DTG+3TC: all of the patients experiencing VF re-achieved virologic

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control subsequently. Moreover, none of the patients experiencing VF developed resistance mutation to either NRTIs or INIs after failure, including patients with a previously detected M184V mutation. Estimated probability of maintaining virological suppression was 98.5% (SD±0.5) at 48 weeks, 97.7% (SD±0.6) at 96 weeks, 96,9% (SD±0.8) at 144 weeks and 96.4% (SD±0.9) at 240 weeks. In a multivariate regression analysis, a non-B HIV subtype (vs subtype B, aHR 31.5, 95%CI 2.0-488.9, p=0.014) and a previous VF (aHR 24.0, 95%CI 1.2-475.7, p=0.037), resulted predictors of VF, after adjusting for nadir CD4+ cell count and peak HIV-RNA.

In appropriate survival analyses, we observed a higher probability of VF in PLWHIV with a peak HIV-RNA >500.000 copies/mL compared to others (log-rank p=0.002), in PLWHIV with a previous VF compared to those who had never experienced a VF (log-rank p=0.031) and in PLWHIV with a HIV subtype non-B compared to those with a subtype B (log-rank p=0.014) [Figure 1]. We did not observe differences in probability of VF in PLWHIV with a M184V resistance mutation (log-rank p=0.689); however, in a dedicated analysis, in patients with time of virological suppression < 88 months, the M184V mutation was a predictor of VF (aHR 11.62, 95%CI 1.15-117.57, p=0.038).

During 2014.7 PYFU, we censored 150 TD, with a rate of 7.5 TD per 100 PYFU. Median time to TD was 28.6 months (IQR 14.3-47.6). Estimated probability of maintaining study regimen was 89.0% (SD±1.1) at 48 weeks, 82.9% (SD±1.4) at 96 weeks, 79.7% (SD±1.6) at 144 weeks and 74.3% (SD±2.2) at 240 weeks. In our cohort, main reasons for TD were: toxicity in 54 (6.9% of total population) cases (21 for neuropsychiatric events, 11 for GI toxicity, 9 for renal toxicity and 13 for other/unspecified toxicity), simplification to STR in 13 (1.7%) cases, weight gain in 8 cases (1.0%), death (unrelated to HIV/AIDS) in 6 cases (0.8%), virological failure in 9 cases (1.1%), other/unknown in 60 cases (7.6%).

In a specific sub-analysis, probability of TD following neuropsychiatric events was 9.6% at week 48 and 13.3% at weeks 96 and 144; HCV-coinfection resulted the sole predictor (aHR 3.90, 95%CI

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1.05-14.52, p=0.043). Among the 21 discontinuations caused by neuropsychological events, 9 were due to insomnia, 6 to headache, 5 to mood disorders and one was due to the sudden onset of nightmares.

As far as immunological parameters, we observed a significant increase in CD4+ cell count at 48 weeks (median +27 cell/mm3, p<0.001), 96 weeks (median +30 cell/mm3, p=0.001) and 144 weeks (median +11 cell/mm3, p=0.038). A median increase of +49 cell/mm3 was observed after 240 weeks, although it resulted non-significant (p=0.073).

Discussion

In our multicenter cohort of virologically suppressed PLWHIV switched to DTG+3TC, we were able to assess the efficacy, safety and overall tolerability of this 2DR in the long period. It's been over five years that DTG+3TC has been introduced in clinical practice as a feasible switch strategy and results from this study appear in line with the results from clinical trials [10] and other observational studies, including previous results from our cohort [8,9]. Compared with patients enrolled in the TANGO study, our cohort is composed of older patients, with a longer history of HIV and antiretroviral therapy and over one fifth of the analyzed patients have experienced at least one virological failure; these differences further reinforces the strenght of this combination in the real-life setting.

In this work we observed a low VF rate (0.9 VF per 100 PYFU), with no patient experiencing the emergence of resistance mutation at failure, reflecting the safety and high genetic barrier of dolutegravir. Moreover, confirming previous findings [13], we did not observe an overall increase in VF rate in patients with the M184V resistance mutation but those with a reduced time of virological suppression at baseline, showed an increased risk of VF in the presence of M184V.

In patients discontinuing study regimen, toxicity remained the leading cause of treatment interruption [8], with the majority of events being of neuropsychological nature. The previously

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observed correlation between neuropsychiatric disorders and HCV-coinfections was confirmed [8, 14].

Our study has some limitations, such as its retrospective nature, the lack of a control group and the lack of recording of data on patients' compliance or minor adverse events not leading to TD. Other limitations are the low number of patients with available information regarding previous M184V mutation and the wide confidence intervals for some of the findings. H owever, the study also presents several strengths, including its long follow-up time, its sample size and the real-life setting.

In conclusion, DTG+3TC confirmed its efficacy in maintaining virological suppression in a large proportion of PLWHIV in a real-life setting; clinicians should always consider patients' clinical and viro-immunological history when considering the switch to a dual regimen.

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Figure 1. Kaplan Meier survival analyses. A. stratified for Zenith HIV-RNA; B Stratified for previous virological failures; C Stratified for the presence of the M184V mutation; D Stratified for HIV subtype.

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Table 1. Patients' characteristics at baseline (N 785)

Variables	
Age (years), Median (IQR)	52.3 (44.9 – 58.2)
Female, n (%)	231 (29.4)
Risk factor for HIV infection, n (%): - Heterosexual - MSM - IDU - Others	 319 (40.6) 305 (38.9) 119 (15.2) 42 (5.3)
Anti-HCV antibodies positive, n (%)	64 (8.2)
Time from HIV diagnosis (years), Median (IQR)	14.9 (8.0 – 22.0)
CDC stage C, n (%)	132 (16.8)
Time on antiretroviral therapy (years), Median (IQR)	11.5 (5.9 – 18.6)
Nadir of CD4+ (cell/µL), Median (IQR)	225 (96 - 331)
Zenith HIV-RNA (log copies/mL), Median (IQR)	4.94 (4.39 – 5.45)
Zenith HIV-RNA > 500.000 copies/mL, n (%)	110 (14.0)
Previous virological failure, n (%)	175 (22.3)
CD4+ count (cell/µL), Median (IQR)	680 (500 - 889)
Time of virological suppression (months), Median (IQR)	29.1 (14.6 – 49.5)
M184V resistance mutation, n (%) - Present - Absent - Unknown	 33 (4.2) 214 (27.3) 538 (68.5)
Previous HAART regimen, n (%): - 2NRTIs+NNRTI - 2NRTIs+PI or b/PI - 2NRTIs+INI - Dual therapy - Other	 180 (22.9) 92 (11.7) 216 (27.5) 268 (34.1) 29 (3.7)
HIV subtype B, n (%)	91 (11.6)
FTC/TDF in previous regimen, n (%)	253 (32.3)
DTG in previous regimen, n (%)	147 (18.7)
3TC + PI in previous regime, n (%)	216 (27.5)
Reasons for switch, n (%): - Simplification - Dyslipidemia	 302 (38.5) 96 (12.2)

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- Gastrointestinal or liver toxicity	49 (6.2)
- Renal toxicity	32 (4.1)
- Osteoporosis	27 (3.4)
- Neurological toxicity	6 (0.8)
- Other toxicities	28 (3.6)
- Drug-drug interactions	50 (6.4)
- Cardiovascular risk	21 (2.7)
- Other/Unknown reasons	174 (22.2)

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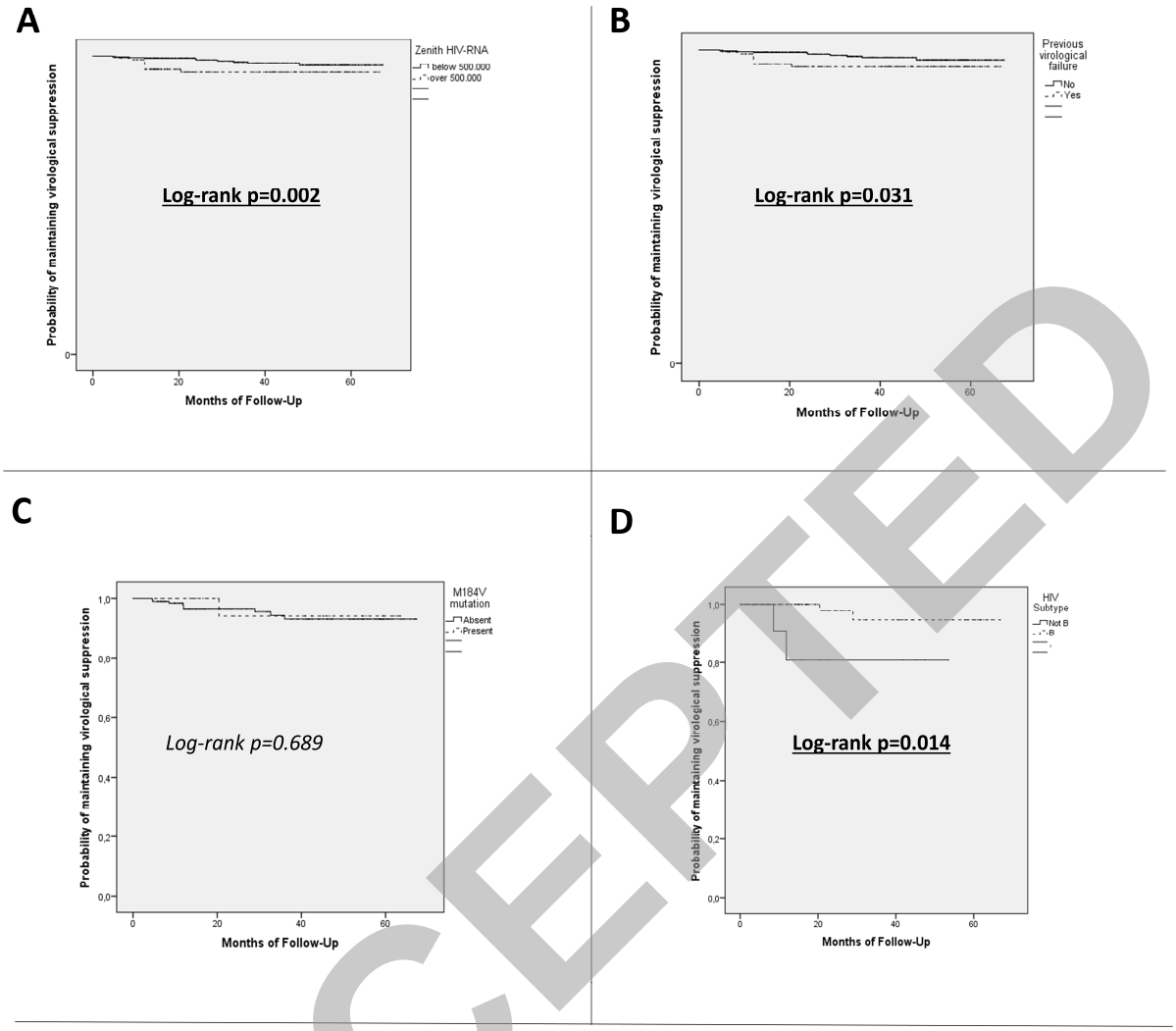


Figure 1. Kaplan Meier survival analyses. A. stratified for Zenith HIV-RNA; B Stratified for previous virological failures; C Stratified for the presence of the M184V mutation; D Stratified for HIV subtype.

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