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Long-term data on the efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multi-centre cohort of HIV-1-infected, virologically suppressed patients

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ABSTRACT

Background: Results from clinical trials and observational studies suggest that lamivudine plus dolutegravir (3TC+DTG) could be an effective and tolerated option for simplification in human immunodeficiency virus (HIV)-1-positive patients.

Materials and methods: This observational study enrolled HIV-1-infected, virologically suppressed patients switching to 3TC+DTG. Kaplan–Meyer survival analysis was performed to evaluate time to virological failure (VF; defined by a single HIV-RNA determination ≥1000 copies/mL or by two consecutive HIV-RNA determinations ≥50 copies/mL) and time to treatment discontinuation (TD; defined as interruption of either 3TC or DTG), Cox regression was performed to assess predictors, and linear mixed model was performed for repeated measures to measure changes in immunological and metabolic parameters.

Results: Five hundred and fifty-six patients were eligible for analysis. Their median CD4+ count at baseline was 668 cells/mm^3 and median time of virological suppression was 88 months. Estimated probabilities of maintaining virological suppression at 96 and 144 weeks of follow-up were 97.5% [standard deviation (SD) 0.8] and 96.5% (SD 1.0), respectively. Years since HIV diagnosis was the only predictor of VF. In patients with time of virological suppression <88 months, the rate of VF was higher in the presence of the M184V mutation. Estimated probabilities of remaining on 3TC+DTG at 96 and 144 weeks of follow-up were 79.2% (SD 1.9) and 75.2% (SD 2.2), respectively. A significant increase in CD4 cell count (+44 cells/mm^3, *P*=0.015), CD4/CD8 ratio (+0.10, *P*=0.002) and high-density lipoprotein cholesterol (+5.4 mg/dL, *P*=0.036) was found at 144 weeks of follow-up; meanwhile, total cholesterol (-9.1 mg/dL, *P*=0.007) and triglycerides (-2.7, *P*=0.009) decreased significantly.

Conclusions: These findings confirm the efficacy and tolerability of 3TC+DTG in virologically suppressed patients.

1. Introduction

Combination antiretroviral therapy (cART) has dramatically decreased morbidity and mortality of patients infected with human immunodeficiency virus (HIV)-1 [1], and prompt initiation of cART

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has been shown to be fundamental in reducing the burden of serious acquired immunodeficiency syndrome (AIDS) and non-AIDS related events, independent of CD4 cell counts [2]. However, mathematical models forecast that in the next few decades, age-related comorbidities will become a substantial issue in HIV-infected individuals [3], particularly due to an increased burden of cardiovascular diseases, diabetes and chronic kidney disease. Moreover, the indication to treat all HIV-1-infected patients regardless of CD4 count [4] raises concerns regarding long-term-treatment-related toxicities [especially those related to nucleoside reverse transcriptase inhibitors (NRTIs)] [5] and patient adherence [4,6]. Finally, the increasing prevalence of HIV infection, life expectancy of the infected population, and projected lifetime healthcare costs also prompt the need for new treatment paradigms [7].

In selected patients, treatment simplification with two-drug regimens after achieving stable virological suppression represents one of the recommended switch strategies in treatment guidelines [4,8]. Among these strategies, in the recent past, lamivudine (3TC) with boosted protease inhibitors (bPIs) [9–12], particularly atazanavir [10,11], has shown the most robust data in terms of efficacy and safety. However, given the toxicity of bPIs, their impact on the individual's metabolic profile [9–12] and the potential for drug–drug interactions determined by the boosting agents [13], new switch strategies have emerged. Results from clinical trials and observational studies [14–19] suggest that lamivudine plus dolutegravir (3TC+DTG) could be a safe, effective and very-well-tolerated option, but long-term data are lacking in the literature.

The authors previously reported a single-centre, long-term analysis on 221 virologically suppressed patients switching to 3TC+DTG with a median follow-up of 96 months [20]. The aim of the present study was to confirm these preliminary findings in a multi-centre cohort of adult HIV-1-infected patients, unselected for any criteria except for virological suppression at the time of switching.

2. Materials and methods

2.1. Study design

This was a retrospective, observational study. HIV-1-infected patients were enrolled from nine Italian clinical centres. Criteria for eligibility were: patient's informed consent to data collection, age ≥18 years, on stable (i.e. ≥6 months) cART with viral suppression (HIV-RNA<50 copies/mL) at the time of switching to 3TC+DTG (baseline) and HBsAg negative. All patients switched to 3TC+DTG for clinical reasons following the principles expressed by the Italian guidelines on the management of HIV infection [21].

2.2. Ethics statement

This study was performed in accordance with the principles of the Declaration of Helsinki, and received approval from each independent local ethics committee (Study Coordination Site Protocol No. 5284/15). All patients signed informed consent forms.

2.3. Statistical analysis

The primary objective of this study was to evaluate the time to virological failure (VF; defined as a single HIV-1 RNA determination ≥1000 copies/mL or by two consecutive HIV-1 RNA determinations ≥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 TD and VF, and the respective predictors were analysed by Cox regression. Changes from baseline in immunological parameters (absolute and percentage CD4+ T-cell counts, CD4/CD8 ratio), estimated glomerular filtration rate (eGFR) (by the MDRD study equation) and blood lipids [total/high-density lipoprotein (HDL) cholesterol ratio, triglycerides] at 48, 96 and 144 weeks of follow-up were evaluated via linear mixed models for repeated measures. Linear regression was performed to explore variables associated with significant changes in laboratory parameters.

3. Results

3.1. Study population

Five hundred and fifty-six patients were eligible for analysis: 391 (70.3%) were males, 125 (22.5%) were co-infected with hepatitis C virus (HCV), and 81 (14.6%) had a previous AIDS-defining event. Median age at baseline was 51.7 years [interquartile range (IQR) 45.3–57.4], median time since HIV diagnosis was 15.4 years (IQR 8.5–22.1), and median time of cART exposure was 11.5 years (IQR 6.1–18.3).

Two hundred and twenty-six (40.6%) patients had experienced at least one VF; among them, 158 (69.9%) had experienced more than one VF and the median number of previous VFs was 2 (IQR 1–4). Almost all patients (223/226, 98.7%) experienced at least one VF while receiving NRTI therapy; in particular, 93 (41.1%) with tenofovir (TDF) and 172 (76.1%) with 3TC. One hundred and seventy-two (76.1%) patients experienced VF while on a non-NRTI (NNRTI), and 163 (72.1%) patients experienced VF while receiving a protease inhibitor (PI; 21 while on darunavir). Finally, nine (4.0%) patients experienced VF while on an integrase-inhibitor-based regimen (seven with raltegravir and two with elvitegravir).

Median CD4+ count at baseline was 668 cells/mm^3 (IQR 495–890), while the median time of virological suppression was 88.0 months (IQR 44.1–122.7). The M184V resistance mutation was present in 45 (8.1%) patients, of which 28 (10.4%) were among the 270 patients with a time of virological suppression ≥88 months and 17 (6.1%) were among the 277 patients with a time of virological suppression <88 months. Full patient characteristics are shown in Table 1.

At the time of switching, 224 (40.3%) patients were already on dual ART (171 on 3TC+bPI), while 307 (55.7%) patients were on a standard triple regimen with two NRTIs and a third drug (141 with an NNRTI, 89 with an integrase strand transfer inhibitor and 77 with a bPI). Fifty-two (9.4%) patients were on a regimen containing DTG before switching to the study regimen. Reasons for switching were mainly represented by simplification (27.9%), dyslipidaemia (16.5%), gastrointestinal toxicity (7.9%) or other toxicities (13.9%). Of note, the M184V resistance mutation to 3TC was present in 45 (8.1%) patients in at least one previous genotypic resistance test.

3.2. Virological efficacy

Median follow-up was 22.1 months (IQR 11.4–33.5). Twelve VF were detected over 1020.1 person-years of follow-up (PYFU) with an overall incidence of 1.2 VF per 100 PYFU. Seven of these patients discontinued 3TC+DTG: four were switched to a DTG-based triple regimen [two to abacavir/3TC and two to emtricitabine (FTC)/TDF], two were switched to FTC/TDF plus boosted darunavir, and one patient was switched to atazanavir+DTG. The remaining five patients maintained the study regimen. All of the patients experiencing VF subsequently re-achieved virologic control, and none of them developed resistance mutation after failure. The Kaplan–Meier curve for time to VF is shown in Fig. 1. The estimated probability of maintaining virological suppression at 48, 96 and 144 weeks of follow-up were 98.7% [standard deviation (SD) 0.5], 97.5% (SD 0.8) and 96.5% (SD 1.0), respectively. Years since HIV diagnosis was found to be the only predictor of VF [adjusted hazard ratio (aHR) 1.1, 95% confidence interval (CI) 1.1–1.2; P=0.030] after adjusting

Table 1
Patients' characteristics at baseline (n=556).

Variables	
Age (years), median (IQR)	51.7 (45.3–57.4)
Female, *n* (%)	165 (29.7)
Risk factor for HIV infection, *n* (%):	
- Heterosexual	225 (40.5)
- MSM	145 (26.1)
- IDU	100 (18.0)
- Others	86 (15.5)
Anti-HCV antibodies positive, *n* (%)	125 (23.0)
Time since HIV diagnosis (years), median (IQR)	15.4 (8.5–22.1)
CDC stage C, *n* (%)	81/325 (24.9)
Time on antiretroviral therapy (years), median (IQR)	11.5 (6.1–18.3)
Nadir of CD4+ (cells/μL), median (IQR)	230 (98–328)
Zenith HIV-RNA (log10 copies/mL), median (IQR)	4.93 (4.39–5.42)
Patients with a zenith HIV-RNA >500,000 copies/mL, *n* (%)	73 (14.1)
Previous virological failure, *n* (%)	226 (40.7)
CD4+ count (cells/μL), median (IQR)	668 (495–890)
CD4/CD8 ratio, median (IQR)	0.85 (0.61–1.13)
Time of virological suppression (months), median (IQR)	88.0 (44.1–122.7)
M184V resistance mutation, *n* (%)	
- Present	45 (8.1)
- Absent	406 (73.0)
- Unknown	105 (18.9)
Previous HAART regimen, *n* (%)	
- Two NRTIs+NNRTI	141 (25.6)
- Two NRTIs+PI or b/PI	77 (14.0)
- Two NRTIs+INI	89 (16.2)
- Dual therapy	224 (40.7)
- Other	20 (3.6)
FTC/TDF in previous regimen, *n* (%)	231 (41.9)
DTG in previous regimen, *n* (%)	52 (9.4)
3TC+PI in previous regime, *n* (%)	171 (31.0)
Reasons for switch, *n* (%)	
- Simplification	155 (27.9)
- Dyslipidaemia	92 (16.5)
- Gastrointestinal or liver toxicity	44 (7.9)
- Renal toxicity	30 (5.4)
- Osteoporosis	27 (4.9)
- Neurological toxicity	7 (1.3)
- Other toxicities	13 (2.3)
- Drug–drug interactions	36 (6.5)
- Cardiovascular risk	16 (2.9)
- Other/unknown reasons	136 (24.5)

IQR, interquartile range; HIV, human immunodeficiency virus; MSM, men who have sex with men, IDU, injection drug users; HCV, hepatitis C virus; CDC, Centers for Disease Control and Prevention; HAART, highly active antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitor; bPI, boosted protease inhibitor; INI, integrase inhibitor; FTC, emtricitabine; TDF, tenofovir; DTG, dolutegravir; 3TC, lamivudine.

for the presence of the M184V resistance mutation, time of virological suppression, nadir and baseline CD4+ cell count, HIV risk factor and switching from a PI-based regimen.

The presence of the M184V resistance mutation alone was not predictive of VF; however, stratifying by time of virological suppression, it was observed that the rate of VF was higher in patients with the M184V mutation with time of virological suppression <88 months (6.7 per 100 PYFU vs 1.0 per 100 PYFU; log-rank P=0.014). Conversely, VF rates were not different in patients with time of virological suppression >96 months, independent of M184V mutation (log rank P=0.308) (Table 2 and Fig. 1).

3.3. Treatment discontinuation

One hundred and ten TDs occurred over 1025.6 PYFU (10.7 per 100 PYFU), with an estimated probability of remaining on 3TC+DTG of 86.1% (SD 1.5), 79.2% (SD 1.9) and 75.2% (SD 2.2) at 48, 96 and 144 weeks of follow-up, respectively. Median time to TD was 29.6 weeks (IQR 12.4–59.6).

Reasons for TD were represented by: virological failure [7/556 (1.3%)], toxicity [43/556 (7.7%), of which 18 were for neuropsychological events, nine were for gastrointestinal and hepatic toxicity, six were for renal toxicity, one was following a hypersensitivity reaction and nine were for other toxicities], further simplification to a single tablet regimen [7/556 (1.3%)], drug–drug interactions [2/556 (0.4%)], death [6/556 (1.1%)] and other/unknown causes [41/556 (7.4%)]. Among the 18 TDs caused by neuropsychological events, eight were due to insomnia, five were due to headache, three were due to mood disorders, and one was due to the sudden onset of nightmares. Of note, all of the adverse events leading to TD were of mild or moderate severity. Switching to the study regimen due to drug–drug interactions (vs switching for simplification; aHR 2.4, 95% CI 1.4–4.4, P=0.003) was predictive of TD, after adjusting for clinical centre, years since HIV diagnosis and HIV risk factor.

Evaluating TD due to overall toxicity, the estimated probabilities of maintaining the study regimen were 93.8% (SD 1.1) at 48 weeks, 91.4% (SD 1.3) at 96 weeks and 90.4% (SD 1.5) at 144 weeks of follow-up. Switching to the study regimen due to toxicity (vs switching for simplification; aHR 3.1, 95% CI 1.4–6.9; P=0.006) was the only predictor of TD on multi-variate analysis, after adjusting for clinical centre, HIV risk factor and history of a previous dual regimen.

A specific survival analysis evaluating TD due to neuropsychological events alone showed that the estimated probabilities of remaining free of TD were 97.2% (SD 0.7) at 48 weeks and 96.1% (SD 0.9) at 96 and 144 weeks of follow-up (Fig. 2). On multi-variate regression, HCV co-infection (aHR 6.2, 95% CI 2.3–16.4; P<0.001) was found to be predictive of TD due to central nervous system (CNS) toxicity after adjusting for age, sex and previous cART.

3.4. Immunological assessment

Absolute CD4+ T-cell count increased significantly in patients with available data at 96 weeks of follow-up (median change +60 cells/mm^3; P<0.001) and in patients with available data at 144 weeks of follow-up (median change +44 cells/mm^3, P=0.015). On multi-variate analysis, both age (per 10 years more, -31.7, 95% CI -54.7 to -8.5; P=0.007) and baseline CD4+ T-cell count (per 10 cells/mm^3 more, -2.4, 95% CI -3.3 to -1.5; P<0.001) negatively predicted an improvement in CD4+ T-cell count at 96 weeks of follow-up after adjusting for peak HIV-RNA viral load. Baseline CD4+ T-cell count was the only negative predictor (per 10 cells/mm^3 more, -2.7, 95% CI -4.0 to -1.3; P<0.001) of CD4+ improvement at 144 weeks.

An increase in CD4/CD8 ratio was evidenced overall considering patients with available data at 96 weeks of follow-up, with a significant difference in median change (+0.06; P=0.001). The trend was confirmed in the group of 46 patients with data available at 144 weeks of follow-up, with a median change in CD4/CD8 ratio of +0.10 (P=0.002) (Fig. 2a). Evaluating the proportion of patients achieving CD4/CD8 ratio ≥1, this was significantly higher at both 96 and 144 weeks of follow-up compared with baseline values; in particular, CD4/CD8 ratio was ≥1 in 39/125 (31.2%) patients at baseline and in 51/125 (40.8%) patients at 96 weeks of follow-up (P<0.001). Among patients with data available at 144 weeks of follow-up, 13/53 (24.5%) had CD4/CD8 ratio ≥1 at baseline while the proportion was significantly higher at 144 weeks of follow-up [20/53 (37.7%); P<0.001). On multi-variate analysis, time of virological suppression was the only predictor of change in CD4/CD8 ratio at both 96 and 144 weeks of follow-up.

3.5. Metabolic profile

A significant reduction in total cholesterol was found in patients at 144 weeks of follow-up (median change -9.1 mg/dL; P=0.007) (Fig. 2b), while it was not observed among patients at

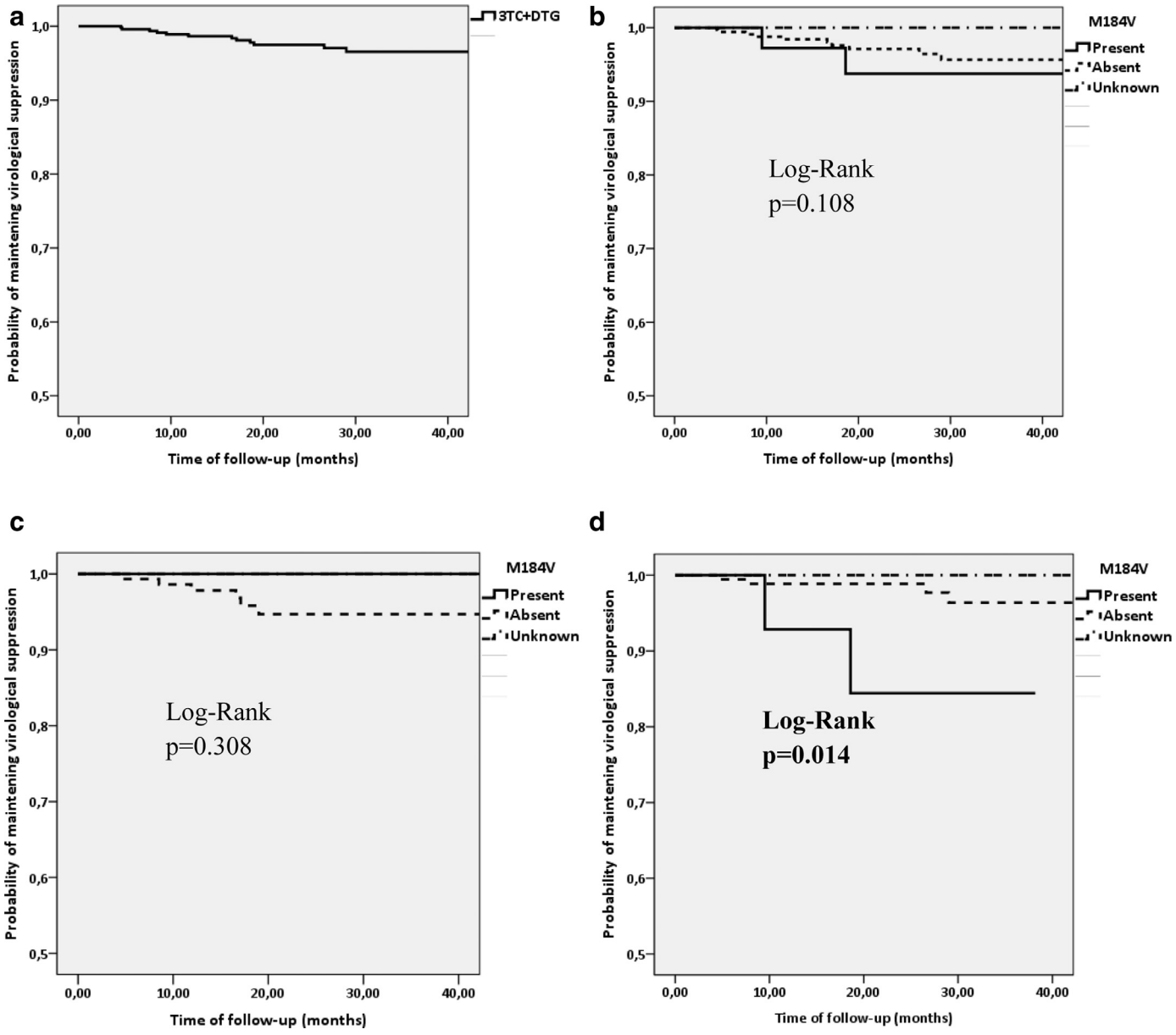

Fig. 1. Kaplan–Meyer survival curves for the probability of maintaining virological suppression: (a) overall; (b) stratified for the presence of M184V resistance mutation; (c) stratified for the presence of M184V mutation in patients with virological suppression ≥88 months; and (d) stratified for the presence of M184V mutation in patients with virological suppression <88 months.

96 weeks of follow-up (P=0.075). An increase in total cholesterol at 144 weeks of follow-up was observed in patients switching from an FTC/tenofovir-based regimen (+21.7 mg/dL, 95% CI 2.0–41.3; P=0.031), while a higher value of total cholesterol at baseline was associated with a more pronounced improvement at 144 weeks of follow-up (-0.4 mg/dL, 95% CI -0.5 to -0.2; P<0.001), after adjusting for the baseline value for triglycerides. A significant improvement in HDL cholesterol was observed in patients at 144 weeks of follow-up (+5.4 mg/dL, P=0.036) (Fig. 2c). A greater improvement was predicted at both 96 (per 1 mg/dL more, -0.2, 95% CI -0.3 to -0.1; P<0.001) and 144 weeks (per 1 mg/dL more, -0.3, 95% CI -0.4 to -0.1; P<0.001) by baseline HDL values, after adjusting for low-density lipoprotein cholesterol values at baseline and time of virological suppression.

A significant decrease in triglyceride level was observed in patients at 96 (median change -10.8; P<0.001) and 144 weeks (-2.7, P=0.009) of follow-up (Fig. 2d). Baseline values were predictive of a more pronounced improvement at both 96 (per 1 mg/dL more, -0.5, 95% CI -0.6 to -0.3; P<0.001) and 144 weeks (per 1 mg/dL more, -0.8, 95% CI -0.9 to -0.6; P<0.001) of follow-up, after adjusting for HIV risk factors and total cholesterol baseline level.

Focusing on patients switching from 3TC+PI, a more pronounced improvement was observed in both total cholesterol and triglycerides at 144 weeks of follow-up: in particular, a median decrease in total cholesterol of -19.0 mg/dL (P=0.036) and a median decrease in triglycerides of -52.1 mg/dL (P=0.006) were noted.

Regarding renal function, a significant decrease in eGFR was observed in patients with data available at 96 weeks of follow-up (median change -9.6 mL/min; P<0.001) and in those with data available at 144 weeks of follow-up (-5.2 mL/min; P<0.001). Baseline eGFR was related to a less marked decrease at both 96 (per 1 mL/min more, -0.3, 95% CI -0.4 to -0.1; P<0.001) and 144 weeks (per 1 mL/min more, -0.3, 95% CI -0.5 to -0.1; P<0.001) of follow-up; in addition, female sex (vs male sex, -7.4, 95% CI -13.1 to -1.6;

Table 2
Patients (Pt) that incurred virological failure (VF) during follow-up.

Pt	Sex, age	Time to VF (months)	Type of VF[a]	HIV-RNA at VF (cp/mL)	Subsequent therapy	Presence of M184V/I mutation	Comments
Pt 1	Female, 50 years	8.5	1	74.570	FTC/TDF+DRV/rit	No	She reported lack of adherence
Pt 2	Male, 40 years	29.0	1	4.057	3TC+DTG	No	He reported lack of adherence. The study regimen was not interrupted and following HIV-RNA determination was <50 cp/mL
Pt 3	Female, 43 years	11.9	1	775.000	FTC/TAF/EVG/cob	No	She reported lack of adherence. Following HIV-RNA determination was >50 cp/mL
Pt 4	Male, 45 years	4.7	1	1.808	3TC+DTG	No	The study regimen was not interrupted. Following HIV-RNA determination was <50 cp/mL
Pt 5	Male, 55 years	19.0	2	112; 64	3TC/ABC/DTG	No	He achieved virological suppression after 4 months
Pt 6	Male, 49 years	18.6	2	69; 108	ATV+DTG	Yes	He achieved virological suppression at the following determination of HIV-RNA
Pt 7	Male, 31 years	4.6	2	58.830	FTC/TDF+ATV/rit	No	He reported lack of adherence. Following HIV-RNA determination was <50 cp/mL
Pt 8	Female, 51 years	17.1	2	79; 59	3TC/ABC/DTG	No	She achieved virological suppression at the following HIV-RNA determination
Pt 9	Female, 48 years	16.6	2	58; 53	3TC+DRV/cob	No	Confirmed blips in two consecutive viraemia; lack of adherence not known
Pt 10	Female, 50 years	26.6	1	15.893	Unknown	No	Lack of adherence. She restarted the same treatment with undetectability after 2 months
Pt 11	Male, 28 years	9.5	1	1.232	TDF/FTC+DTG	Yes	He reported lack of adherence with treatment interruption, switched to triple treatment considering the presence of 184V in a previous GRT in paediatrics; vertically infected
Pt 12	Male, 64 years	7.7	2	75; 65	TDF/FTC+DTG	No	Confirmed blips in two consecutive viraemia but during flu vaccination; good adherence but GRT not performed at failure

ABC, abacavir; ATV, atazanavir; EVG, elvitegravir; GRT, genotypic resistance test; FTC, emtricitabine; TDF, tenofovir; DTG, dolutegravir; 3TC, lamivudine; DRV, **darunavir**; TAF, tenofovir alafenamide; cob, cobicistat; rit, ritonavir.
[a] 1, one single HIV-RNA determination ≥ 1000 cp/mL; 2, two consecutive HIV-RNA determinations ≥ 50 cp/mL.

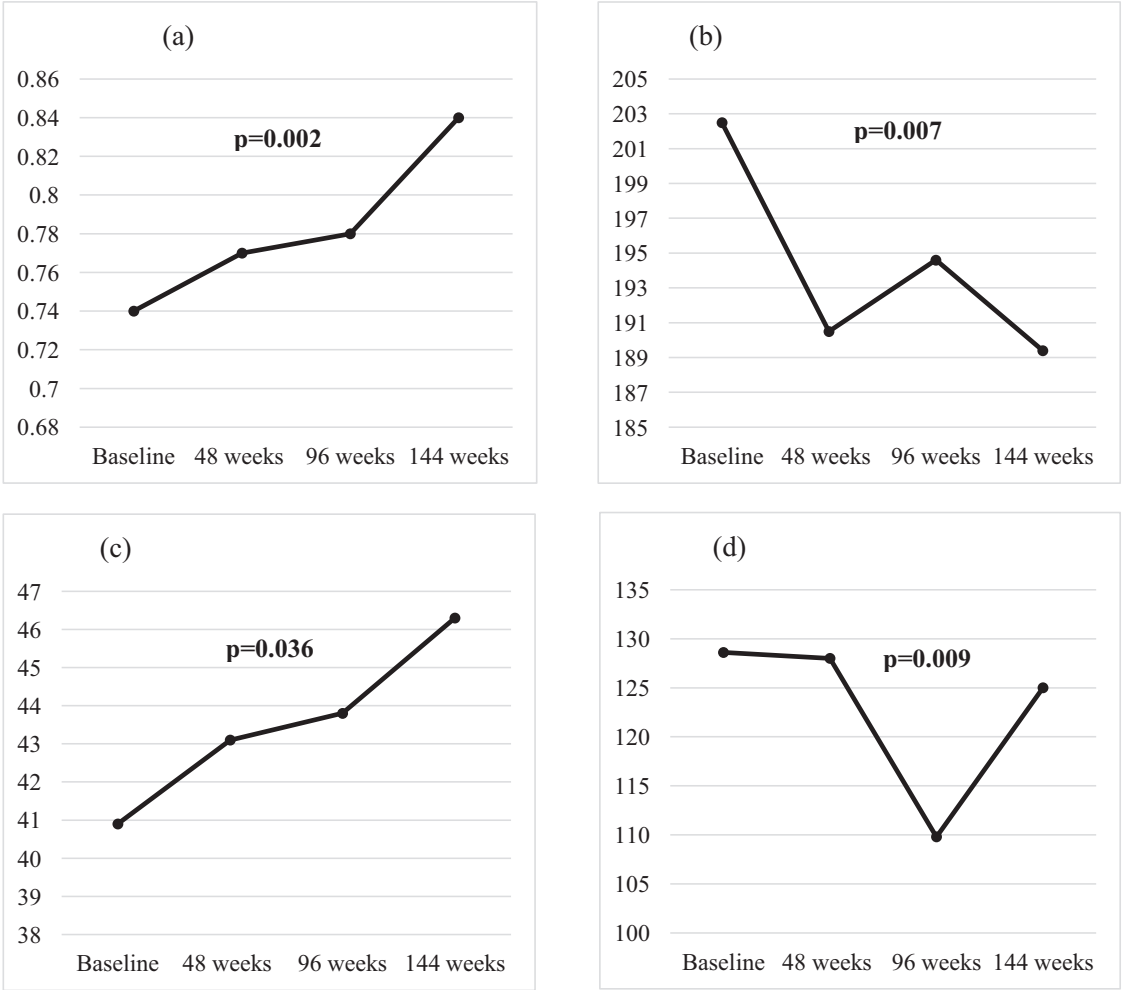

Fig. 2. Variation in (a) median CD4/CD8 ratio, (b) median total cholesterol (mg/dL), (c) median high-density lipoprotein cholesterol (mg/dL) and (d) median triglycerides (mg/dL) during follow-up.

P=0.013) and coming from a PI-based dual regimen (-5.4, 95% CI -10.7 to -0.1; *P*=0.046) were found to be protective at 96 weeks of follow-up.

4. Discussion

Results from this multi-centre study, conducted in a real-life setting, strengthen the results from the authors' previous monocentric work [20] with a large sample size (556 vs 221) and a longer follow-up time (1020.1 vs 419.7 PYFU), and confirm findings on the efficacy of a dual regimen of 3TC+DTG in virologically suppressed HIV-1-infected patients [14,16,17,22].

In particular, this study noted a low rate of VF (overall incidence of 1.2 VF per 100 PYFU) and an estimated probability of maintaining virological suppression of 96.5% at 144 weeks of follow-up. None of the 12 patients experiencing VF developed resistance mutations to DTG or 3TC, in line with the results of Joly *et al.* [16], further confirming the high genetic barrier of DTG [23], a characteristic that makes this drug suitable for a two-drug regimen. Regarding the virological efficacy of this regimen, it is worth noting that data on patient compliance to the regimen, a possible factor relating to HIV-RNA increases, were not collected in the present study. Further insights are hence needed to assess the topic. Furthermore, the virological dynamics may be investigated more thoroughly with studies aimed at evaluating the residual viraemia and the viral reservoirs, particularly HIV-DNA dosage, as investigated previously in other two-drug regimens [24]. The present study also allowed framing of the target of patients for whom this switch strategy may be more advantageous; in particular, the data confirm that, even with longer follow-up, the lone presence of the M184V resistance mutation is not predictive of VF for this 3TC-containing dual regimen, probably because of the reduced replicative fitness caused to the virus by this mutation [25–27]. However, as reported by Gagliardini et al. [28], the M184V mutation appears to be associated with VF in patients with a reduced time of virological suppression at baseline. These results must highlight to the clinician the need to collect a precise clinical and virological history of the patient before implementing therapeutic simplification towards a two-drug regimen.

In the study population, 110 TDs (19.8% of the total population) were observed, the majority of which (*n*=91) occurred during the first 60 weeks of follow-up. Overall toxicity was the main reason for discontinuing the study regimen [*n*=43 cases (7.7%)] and, among those, the majority (*n*=18) were due to neuropsychological events. The rate of overall TDs was in line with other studies on DTG [29], while it appears sensibly higher when compared with other cohorts [22]. This difference might be related to the longer follow-up time of the present study compared with other studies, which further reinforces the results. Focusing on CNS toxicity, a feature described in other studies on DTG [29,30], the present study found that 18 patients, the majority of whom reported sleep disorders or new-onset headache as the main problems, discontinued the study regimen following these adverse events. The rate of TD due to neuropsychological events was higher compared with the cohort of Maggiolo et al. [22], in which just two of 218 patients discontinued 3TC+DTG (one for headache, one for vertigo). Of interest is the correlation between TD due to neuropsychiatric disorders and co-infection with HCV, which has previously been associated with multiple neuropsychiatric disorders, particularly asthenia, depression and cognitive dysfunction [31]. Factors predisposing to the onset of neuropsychiatric disorders in patients on DTG therapy have been investigated previously [31,32], and could be a starting point for further research and analysis within the present study cohort. A limitation of the present study is that details of any adverse events that occurred during therapy but which did not lead to TD were not collected. Regarding the improvement in immunological parameters, the increase in CD4/CD8 ratio is of particular interest, providing further evidence of the efficacy of this regimen at the immunological level, with the limitation of the lack of a control group. Regarding the apparent worsening of renal function, the decrease in eGFR found in the study population, predominantly in the first 48 weeks of follow-up, could probably be attributed to an intrinsic characteristic of DTG. In fact, it inhibits the organic cation transporter 2, reducing excretion of creatinine at the tubular level [33]. In agreement with previous results and other studies [22,34], the lipid profile of the patients in the present study found that simplification to the dual regimen of 3TC+DTG was beneficial. In fact, both total cholesterol and triglyceride levels decreased during follow-up, especially in those patients with a higher starting value at the time of switching. It should be noted that almost one-third of the patients switched from another dual regimen (3TC+bPI), and the improvement in lipid profile was more pronounced in those patients.

In the authors' experience, the two-drug regimen with 3TC+DTG in the context of therapeutic optimization with suppressed viraemia has shown excellent virological efficacy and good tolerability. Given the low presence of drug interactions and independence from food intake, this regime is suitable for a very large population of HIV-infected patients, given the current trend of an aging population and the increase in incidence of comorbidity and polypharmacy. The strengths of this study include the sample size, the real-life setting and the duration of follow-up; limitations include the retrospective nature of the study, the lack of a control arm and the lack of recording of some data, particularly adverse events that did not lead to suspension of the regime and further virological investigations (i.e. HIV-DNA).

5. Conclusions

3TC+DTG was effective in maintaining viral suppression in a large proportion of patients from a multi-centre cohort of long-term-treated, HIV-1-positive patients with undetectable HIV-RNA at the time of switching. Although further studies will be needed to assess the efficacy and safety of the regimen, in the authors' opinion, the patients' clinical history (including any co-infections with hepatitis viruses) and viro-immunological status at the time of therapeutic optimization should be analysed by the clinician when considering a switch to dual therapy.

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& Dohme. SDG was a paid consultant or member of advisory boards for Gilead Sciences, ViiV Healthcare, Janssen-Cilag, Merck Sharp & Dohme, and Bristol-Myers Squibb. All other authors report no competing interests.

Ethical approval: This study was performed in accordance with the principles of the Declaration of Helsinki and received approval from each independent local ethics committee (Study Coordination Site Protocol No. 5284/15). All patients signed informed consent forms.

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