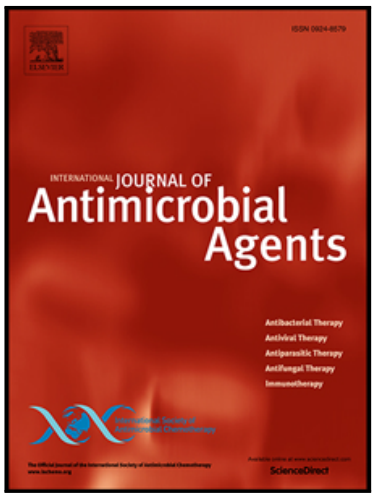

Long term data on the efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multicenter cohort of HIV1-infected, virologically suppressed patients

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Highlights

- 3TC+DTG in simplification showed high efficacy.
- The presence of M184V was significant in patients with shorter time of suppression.
- We registered a rate of discontinuation of 10.7 per 100 PYFU.
- The regimen led to an improvement in lipid profile.

Long term data on the efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multicenter cohort of HIV1-infected, virologically suppressed patients.

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Running title: Lamivudine plus dolutegravir in the long term

Abstract

Background. Results from clinical trials and observational studies suggest that lamivudine plus dolutegravir could be an effective and tolerated option for simplification in HIV-1 positive patients.

Materials and Methods. This was an observational study enrolling HIV-1-infected, virologically suppressed patients switching to lamivudine plus dolutegravir. We performed Kaplan-Meyer 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), Cox-regression to assess predictors and linear mixed model for repeated measures to measure changes in immunological and metabolic parameters.

Results. Five-hundred fifty-six patients were eligible for the analysis: median CD4+ count at baseline was 668 cell/mm3, while median time of virological suppression was 88 months. Estimated probabilities of maintaining virological suppression at weeks 96 and 144 were 97.5% (SD ±0.8) and 96.5% (SD ±1.0). Years from HIV diagnosis were 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 were 79.2% (SD ±1.9) and 75.2% (SD ±2.2). A significant increase in CD4 cell count (+44 cell/mm3, p=0.015), CD4/CD8 ratio (+0.10, p=0.002) and HDL cholesterol (+5.4 mg/dl, p=0.036) was found after 144 weeks; meanwhile total cholesterol (-9.1 mg/dl, p=0.007) and triglycerides (-2.7, p=0.009) significantly decreased.

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

Keywords: HIV; dual therapy; two-drug regimen; ART; simplification; lamivudine; dolutegravir.

Introduction

Combination antiretroviral therapy (cART) has dramatically decreased morbidity and mortality of the HIV-1-infected population,[1] and a prompt initiation of cART has demonstrated to be fundamental in reducing the burden of serious AIDS and non-AIDS related events, independently from CD4 cell counts.[2] However, mathematical models forecast that in next few decades age-related comorbidities will become a substantial issue in HIV-infected individuals,[3] especially 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 the concern of the long-term treatment-related toxicities (especially those related to nucleoside reverse transcriptase inhibitors, NRTIs)[5] and patients' adherence.[4,6] Finally, the increasing prevalence of HIV infection, of life expectancy of the infected population, and of projected lifetime healthcare costs also prompt the need for new treatment paradigms.[7]

In selected patients, treatment simplification with two-drug regimens after achieving a stable virological suppression represents one of the recommended switch strategies in treatment guidelines.[4,8] Among these strategies, in the recent past, lamivudine with boosted protease inhibitors (bPIs),[9-12] and particularly with 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 could be a safe and effective option as well as a very well tolerated one but long-term data are still lacking in literature.

We previously reported a single-center, long term analysis on 221 virologically suppressed switching to dolutegravir plus lamivudine patients with a median time of follow-up of 96 months.[20] Goal of the present study was to confirm our preliminary findings in a multicenter cohort of adult HIV-1-infected patients, unselected for any criteria except for virological suppression at the time of switch.

Materials and methods

1 Study design. This was a retrospective, observational study in which we enrolled HIV-1-infected patients from nine Italian clinical centers. Criteria for eligibility were: patient's informed consent to data collection,

being at least 18 years-old, being on stable (i.e. at least 6 months) cART with viral suppression (HIV-RNA<50 copies/mL) at the moment of switch to lamivudine plus dolutegravir (baseline) and HBsAg negative. All patients switched for clinical reason to lamivudine plus dolutegravir, following the principles expressed by Italian Guidelines on the management of HIV infection.[21]

2 Ethic statement. 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). All patients signed informed consent.

3 Statistical analysis. The primary study objective was to evaluate the 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 TD and VF and the respective predictors were analyzed 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/HDL cholesterol ratio, triglycerides) at weeks 48, 96 and 144 were evaluated via linear mixed models for repeated measures. Linear regression was performed to explore variables associated to significant changes in laboratory parameters.

Results

1 Study population

Five-hundred fifty-six patients were eligible for the analysis: 391 (70.3%) were males, 125 (22.5%) were HCV-coinfected while 81 (14.6%) had a previous AIDS-defining event. Median age at baseline was 51.7 years (IQR 45.3-57.4), median time from HIV diagnosis was 15.4 years (IQR 8.5-22.1), with a median time of cART exposure of 11.5 years (IQR 6.1-18.3).

Two hundred twenty-six patients (40.6%) had experienced at least one virological failure; among them, 158 (69.9%) had more than 1 virological failure and median number of previous VF was 2 (IQR 1-4). Almost all of

them (223/226, 98.7%) experienced at least one VF while in therapy with NRTIs and, in particular, 93 (41.1%) with TDF and 172 (76.1%) with 3TC. One hundred seventy-two patients (76.1%) had a VF while on a NNRTI, while 163 (72.1%) while in therapy with a PI (21 of which while on DRV). Finally, 9 (4.0%) experienced a VF while on a INI-based regimen (7 with RGV and 2 with EVG).

Median CD4+ count at baseline was 668 cell/mm3 (IQR 495-890), while 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%) among the 270 patients with a time of virological suppression over 88 months and 17 (6.1%) among the 277 patients with a time of virological suppression below 88 months. Full patients' characteristics are shown in Table 1.

At the moment of switch, 224 (40.3%) patients were already on a dual ART (171 of whom with lamivudine plus bPI), while 307 (55.7%) were on a standard triple regimen with 2NRTIs and a third drug (141 with a NNRTI, 89 with an InSTI and 77 with a boosted PI). Fifty-two patients (9.4%) were on a regimen containing DTG before switching to the study regimen. Reasons for switching were mainly represented by simplification (27.9%), dyslipidemia (16.5%), gastro-intestinal toxicity (7.9%) or other toxicities (13.9%). Of note, the M184V resistance mutation to lamivudine was present in 45 (8.1%) patients in at least one previous genotypic resistance test.

2 Virological efficacy

The median follow-up time was 22.1 months (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: 4 were switched to a dolutegravir-based triple-regimen (2 with ABC/3TC and 2 with FTC/TDF), 2 were switched to FTC/TDF plus boosted DRV and 1 patient started ATV+DTG. The remaining five patients maintained study regimen. All of the patients experiencing VF re-achieved virologic control subsequently, while none of them developed resistance mutation after failure. The Kaplan-Meier curve for time to VF is shown in figure 1. The estimated probability of maintaining virological suppression at weeks 48, 96 and 144 were 98.7% (SD ±0.5), 97.5% (SD ±0.8) and 96.5% (SD ±1.0), respectively. We found that

years from HIV diagnosis were the only predictor of VF (aHR 1.1, 95% CI 1.1 – 1.2, p=0.030) after adjusting for the presence of the M184V resistance mutation, time of virological suppression, nadir and baseline CD4+ cells count, HIV risk factor and switching from a PI-based regimen.

The presence of the M184V resistance mutation alone was not a predictor of VF; however, stratifying by time of virological suppression, we observed that, in patients with time of virological suppression < 88 months, the rate of VF was higher in the presence of the M184V mutation (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 longer than 96 months, independently from M184V mutation (Log Rank p=0.308) (Table 2 and Figure 1).

3 Treatment discontinuations

One hundred and ten treatment discontinuations occurred over 1025.6 PYFU (10.7 per 100 PYFU), with an estimated probability of remaining on lamivudine plus dolutegravir of 86.1% (SD ±1.5), 79.2% (SD ±1.9) and 75.2% (SD ±2.2) at weeks 48, 96 and 144, respectively. Median time to TD was 29.6 weeks (IQR 12.4-59.6). Reasons for TD were represented by: virological failure (7 of 556, 1.3%), toxicity (43, 7.7%, of which 18 for neuropsychological events, 9 for gastrointestinal and hepatic toxicity, 6 for renal toxicity, 1 following a hypersensitivity reaction and 9 for other toxicities), further simplification to a single tablet regimen (7 cases, 1.3%), drug-drug interactions (2 cases, 0.4%), death (6, 1.1%) and other/unknown causes (41, 7.4%). Among the 18 discontinuations caused by neuropsychological events, 8 were due to insomnia, 5 to headache, 3 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 study regimen for drug-drug interaction (vs switching for simplification, aHR 2.4, 95% CI 1.4-4.4, p=0.003) was a predictor of discontinuation, after adjusting for clinical center, years of HIV and HIV risk factor.

Evaluating discontinuations due to overall toxicity, the estimated probabilities of maintaining study regimen were 93.8% (SD ±1.1) at week 48, 91.4% (SD ±1.3) at week 96 and 90.4% (SD ±1.5). Switching to study regimen for toxicity (vs switching for simplification, aHR 3.1, 95% CI 1.4-6.9, p=0.006) was the only

predictor of TD at a multivariate analysis, after adjusting for clinical center, HIV risk factor and a history of a previous dual regimen.

A specific survival analysis evaluating TD due only to neuropsychological events show that the estimated probabilities of remaining free from TD were 97.2% (SD ±0.7) at week 48 and 96.1% (SD ±0.9) at weeks 96 and 144 (Figure 2). At a multivariate regression analysis, we found that HCV-coinfection (aHR 6.2, 95% CI 2.3-16.4, p<0.001) was a predictor of discontinuations due to CNS toxicity after adjusting for age, sex and previous cART.

4 Immunological assessment

Absolute CD4+ T-cell count significantly increased in patients with available data at 96 weeks of follow-up (median change +60 cell/mm3, p<0.001) as well as in patients with available data at 144 weeks (median change +44 cell/mm3, p=0.015). At a multivariate analysis both age (per 10 years more, -31.7, 95% CI -54.7 ; -8.5, p=0.007) and baseline CD4+ T-cell count (per 10 cell/mm3 more, -2.4, 95% CI -3.3 ; -1.5, p<0.001) negatively predicted an improvement in CD4+ T-cell count at 96 weeks after adjusting for peak HIV-RNA viral load. Baseline CD4+ T-cell count was the only negative predictor (per 10 cell/mm3 more, -2.7, 95% CI -4.0 ; -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 at 144 weeks of follow-up, with a median change in CD4/CD8 ratio of +0.10 (p=0.002) (Figure 2a). Evaluating the proportion of patients achieving a CD4/CD8 ratio ≥1, this was significantly higher both at 96 and 144 weeks of follow-up compared with baseline values; in particular, CD4/CD8 ratio was ≥1 in 39/125 patients (31.2%) at baseline and in 51/125 (40.8%) at 96 weeks (p<0.001). Among patients with 144 weeks of follow-up, 13/53 (24.5%) had a CD4/CD8 ratio ≥1 at baseline while the proportion was significantly higher at 144 weeks (20/53, 37.7%, p<0.001). At a multivariate analysis, time of virological suppression was the only predictor of change in CD4/CD8 ratio both at 96 and 144 weeks.

5 Metabolic profile

A significant reduction in total cholesterol was found in patients with 144 weeks of follow-up (median change -9.1 mg/dl, p=0.007) (Figure 2b) while it was not observed among patients with only 96 weeks of follow-up (p=0.075). An increase in total cholesterol at 144 weeks was observed in patients switching from a 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 (-0.4 mg/dl, 95% CI -0.5 ; -0.2, p<0.001), after adjusting for triglycerides' baseline value. In our cohort we also registered a significant improvement in HDL cholesterol both in patients with 144 weeks (+5.4 mg/dl, p=0.036) (Figure 2c). A greater improvement was predicted at both 96 (per 1 mg/dL more, -0.2, 95% CI -0.3 ; -0.1, p<0.001) and 144 weeks (per 1 mg/dL more, -0.3, 95% CI -0.4 ; -0.1, p<0.001) by baseline HDL values, after adjusting for LDL cholesterol values at baseline and time of virological suppression.

We observed a significant decrease in triglycerides' levels in patients with data at 96 (median change -10.8, p<0.001) and 144 weeks (-2.7, p=0.009) (Figure 2d). Baseline values were predictive of a more pronounced improvement at both 96 (per 1 mg/dl more, -0.5, 95% CI -0.6 ; -0.3, p<0.001) and 144 weeks (per 1 mg/dl more, -0.8, 95% CI -0.9 ; -0.6, p<0.001), after adjusting for HIV risk factors and total cholesterol baseline levels.

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

As to the renal function, we observed a significant decrease in eGFR in patients with data at 96 weeks (median change -9.6 ml/min, p<0.001) and in those with data at 144 weeks (-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 ; -0.1, p<0.001) and 144 weeks (per 1 ml/min more, -0.3, 95% CI -0.5 ; -0.1, p<0.001); also, female sex (vs male sex, -7.4, 95% CI -13.1; -1.6, p=0.013) and coming from PI-based dual regimen (-5.4, 95% CI -10.7 ; -0.1, p=0.046) resulted protective at 96 weeks.

Discussion

Results from this multicenter study, conducted in a real-life setting, strengthen our 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 lamivudine and dolutegravir in virologically suppressed HIV1-infected patients.[14,16,17,22]

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

In our population we observed 110 discontinuations (19.8% of the total population), the majority of which (91) during the first 60 weeks of follow-up. Overall toxicity was the main reason for discontinuing study

regimen (43 cases, 7.7% of our cohort) and, among those, the majority (18) were due to neuropsychological events. The rate of overall discontinuations appears in line with other studies on dolutegravir,[29] while it appears sensibly higher when compared to other cohorts.[22] This difference might be related to the longer follow-up time of our study, a unique finding not present in other works form the literature, that further reinforces our results. Focusing on CNS toxicity, a feature already described in other studies on DTG[29,30] we reported that eighteen patients, the majority of which reported sleep disorders or a newly onset headache as the main problems, discontinued study regimen following these adverse events. The rate of discontinuations due to neuropsychological events appears higher compared to the cohort of Maggiolo *et al,*[22] in which just 2/218 patients discontinued 3TC+DTG, one for headache and one for vertigo. Interesting is the correlation between treatment discontinuations due to neuropsychiatric disorders and co-infection with hepatitis C virus, which has previously been associated with multiple neuropsychiatric disorders, in particular asthenia, depression and cognitive dysfunction.[31] Factors predisposing to the onset of neuropsychiatric disorders in patients on therapy in DTG have already been investigated[31,32] and could be a starting point for further research and analysis within our cohort. The limitation of our study is that of not having collected any adverse events occurred during therapy not causing discontinuation of the regimen. Regarding the improvement in immunological parameters, particularly interesting is the increase of the CD4/CD8 ratio, providing further evidence of the efficacy of this regimen also on the immunological level, with the limitation of the lack of a control group. As to the apparent worsening of renal function, the decrease in the glomerular filtration rate found in our population, predominantly in the first 48 weeks of follow-up, could probably be attributed to an intrinsic characteristic of dolutegravir. In fact, it inhibits the organic cation transporter 2 (OCT2), reducing the excretion at the tubular level of creatinine.[33] In agreement with previous results and other studies in the literature,[22,34] the lipid profile of the patients in the study finds benefit from the simplification to the dual regimen with lamivudine and dolutegravir. In fact, both total cholesterol and triglyceride levels decrease during follow-up, especially in those patients who have a higher starting value at the time of the switch. It is to be noted that almost a third of the patients switched from another dual regimen with 3TC + bPI; in those patients the improvement in lipid profile was more pronounced.

In our experience, the two-drug regimen with lamivudine and dolutegravir in the context of therapeutic optimization with suppressed viremia has shown excellent virological efficacy and good tolerability. Alongside these, the low presence of drug interactions and independence from food intake make this regime 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 our study are the sample size of our cohort, the real life setting and the duration of the follow-up; the limits are dictated, instead, by the retrospective nature of the study, the lack of a control arm and the lack of recording of some data, in particular adverse events that did not lead to suspension of the regime and further virological investigations (i.e. HIV-DNA).

Conclusions.

Lamivudine plus dolutegravir was effective in maintaining viral suppression in a large proportion of patients from a multicenter cohort of long term treated, HIV-1-positive patients with undetectable HIV-RNA at the time of switch. Even though further studies will be needed to assess the efficacy and safety of the regimen, in our opinion the patients' clinical history, including any co-infections with hepatitis viruses, and the patient's viro-immunological status at the time of therapeutic optimization should be carefully analyzed by the clinician when considering the switch to a dual therapy.

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Declarations

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Competing Interests: SR received research grants to his Institution from ViiV Heathcare, Gilead Sciences and Janssen, outside the submitted work; he was also a paid consultant for ViiV Heathcare, Gilead Sciences, Merck Sharp and Dohme, Bristol-Myers Squibb and Janssen. ACa has received a personal grant from AB, Gilead and ViiV. GS has received funds for speaking by Gilead, Merk, Janssen, Abbvie, ViiV. AG reports grants and/or personal fees from BMS, Gliead, Janssen, MSD and ViiV Healthcare. AB has received non-financial support from Bristol-Myers Squibb and ViiV Healthcare, and personal fees from Gilead Sciences. CM has participated in advisory boards, received study grants and/or speaker honoraria from: Abbvie, Gilead, Viiv, Janssen, Angelini, BMS, MSD. SDG was a paid consultant or member of advisory boards for Gilead, ViiV Healthcare, Janssen-Cilag, Merck Sharp & Dohme and Bristol-Myers Squibb. All other authors: none to declare.

Ethical Approval: 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). All patients signed informed consent.

Contributions.

GB, ACi, AB and SDG contributed to the conception and design of the study. ACi and GB contributed to the draft of the paper. SR, Aca, GS, MC, GdE, AG, MVC, WG and VB contributed to tha acquisition of the data, GB, ACi, AB, VB and CM contributed to the analysis and interpretation of data. SR, Aca, GS, AB, CM and VB contributed to the critical revision of the paper for important intellectual content. All Authors approved the final version of the paper.

References

1) Broder S. The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic. *Antiviral Res*. 2010 Jan; **85**(1): 1.

2) Lundgren JD, Babiker AG, Gordin FI, *et al.* Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. The INSIGHT START Study Group. *N Engl J Med* 2015; **373:**795-807

3) Mikaela S, Cassidy R, Cozzi-Lepri A, *et al.* Quantifying the future clinical burden of an ageing HIVpositive population in Italy: a mathematical modelling study. In: *Abstracts of the International Congress of Drug Therapy in HIV Infection 23-26 October 2016, Glasgow, UK.* Abstract P156.

4) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Accessed on 5/09/2016. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

5) Margolis AM, Heverling H, Pham PA, *et al.* A review of the toxicity of HIV medications. *J Med Toxicol* 2014; **10(1)**: 26-39.

6) Nakagawa F, Miners A, Colette JS, *et al.* Projected Lifetime Healthcare Costs Associated with HIV Infection. *PLoS One*. 2015; **10(4)**: e0125018.

7) Langebeek N, Gisolf EH, Reiss P, *et al.* Predictors and correlates of adherence to combination antiretroviral therapy (ART) for chronic HIV infection: a meta-analysis. *BMC Med*. 2014; **12**: 142.

8) EACS Guidelines version 9.1, October 2018.

9) Arribas JR, Girard PM, Landman R, *et al.* Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open-label, non-inferiority trial. *Lancet Infect Dis*. 2015 Jul;**15(7)**:785-92.

10) Perez-Molina JA, Rubio R, Rivero A, *et al.* Simplification to dual therapy (atazanavir/ritonavir + lamivudine) versus standard triple therapy [atazanavir/ritonavir + two nucleos(t)ides]

in virologically stable patients on antiretroviral therapy: 96 week results from an open-label, non-inferiority, randomized clinical trial (SALT study). *J Antimicrob Chemother*. 2017 Jan;**72(1)**:246-253.

11) Di Giambenedetto S, Fabbiani M, Quiros Roldan E, *et al.* Treatment simplification to atazanavir/ritonavir + lamivudine versus maintenance of atazanavir/ritonavir + two NRTIs in virologically suppressed HIV-1-infected patients: 48 week results from a randomized trial (ATLAS-M). *J Antimicrob Chemother*. 2017 Apr 1;**72(4)**:1163-1171.

12) Fabbiani M, Di Giambenedetto S, Poli A, *et al.* Simplification to a dual regimen with darunavir/ritonavir plus lamivudine or emtricitabine in virologically-suppressed HIV-infected patients. *J Infect. 2016* Dec;**73(6)**:619-623.

13) Marzolini C, Gibbons S, Khoo S, *et al.* Cobicistat versus ritonavir boosting and differences in the drug–drug interaction profiles with co-medications. *J Antimicrob Chemother* (2016) **71 (7)**: 1755-1758.

14) Taiwo BO, Marconi VC, Berzins B et al. Dolutegravir Plus Lamivudine Maintains Human Immunodeficiency Virus-1 Suppression Through Week 48 in a Pilot Randomized Trial. Clin Infect Dis. 2018 May 17;**66(11):**1794-1797. doi: 10.1093/cid/cix1131.

15) Li JZ, Sax PE, Marconi VC et al. No Significant Changes to Residual Viremia After Switch to Dolutegravir and Lamivudine in a Randomized Trial. Open Forum Infect Dis. 2019 Feb 11;**6(3)**: ofz056. doi:10.1093/ofid/ofz056

16) Joly V, Burdet C, Landman R et al. Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL). J Antimicrob Chemother. 2019 Mar 1;**74(3):**739-745. doi:10.1093/jac/dky467.

17) Reynes J, Meftah N, Tuaillon E, *et al.* Dual regimen with Dolutegravir and Lamivudine maintains virologic suppression even in heavily treatment experienced HIV-infected patients: 96 weeks results from maintenance DOLULAM study. In: *Abstract of the Conference on HIV Pathogenesis Treatment and Prevention Paris, France July 23-26 2017.* Abstract MOPEB0322.

18) Boswell R, Foisy MM, Hughes CA. Dolutegravir Dual Therapy as Maintenance Treatment in HIV-Infected Patients: A Review. Ann Pharmacother. 2018 Jul;**52(7)**:681-689. doi: 10.1177/1060028018758432.

19) Rossetti B, Montagnani F, De Luca A. Current and emerging two-drug approaches for HIV-1 therapy in ART-naïve and ART-experienced, virologically suppressed patients. Expert Opin Pharmacother. 2018 May;**19(7)**:713-738. doi:10.1080/14656566.2018.1457648

20) Baldin G, Ciccullo A, Borghetti A et al. 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 Feb 5. doi: 10.1093/jac/dkz009. [Epub ahead of print]

21) Linee Guida Italiane sull'utilizzo della Terapia Antiretrovirale e la gestione diagnostico-clinica delle persone con infezione da HIV-1 – Edizione 2017

22) Maggiolo F, Gulminetti R, Pagnucco L, et al. Lamivudine/dolutegravir dual therapy in HIV-infected, virologically suppressed patients. BMC Infect Dis. 2017 Mar 16;**17(1)**:215.

23) Llibre JM, Pulido F, García F, et al. Genetic barrier to resistance for dolutegravir. AIDS Rev. 2015 Jan-Mar;**17(1)**:56-64.

24) Lombardi F, Belmonti S, Quiros-Roldan E, et al. Evolution of blood-associated HIV-1 DNA levels after 48 weeks of switching to atazanavir/ritonavir+lamivudine dual therapy versus continuing triple therapy in the randomized AtLaS-M trial. J Antimicrob Chemother. 2017 Jul 1;**72(7)**:2055-2059.

25) Miller V1, Stark T, Loeliger AE, Lange JM. The impact of the M184V substitution in HIV-1 reverse transcriptase on treatment response. HIV Med. 2002 Apr;**3(2)**:135-45.

26) Paredes R1, Sagar M, Marconi VC, et al. In vivo fitness cost of the M184V mutation in multidrug-resistant human immunodeficiency virus type 1 in the absence of lamivudine. J Virol. 2009 Feb;**83(4)**:2038-43.

27) Campbell TB, Shulman NS, Johnson SC, et al. Antiviral activity of lamivudine in salvage therapy for multidrug-resistant HIV-1 infection. Clin Infect Dis. 2005 Jul 15;**41(2)**:236-42.

28) Gagliardini R, Ciccullo A, Borghetti A, 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 May 15;**5(6)**:ofy113.

29) De Boer MG, van den Berk GE, van Holten N, et al. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. AIDS. 2016 Nov 28;**30(18):**2831-2834.

30) Hoffmann C, Welz T, Sabranski M, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med. 2017 Jan;**18(1)**:56-63.

31) Munjal S, Ferrando S J, Freyberg Z. Neuropsychiatric Aspects of Infectious Diseases An Update. Crit Care Clin. 2017 Jul; **33(3)**: 681–712.

32) Menard A, Montagnac C, Solas C, et al. Neuropsychiatric adverse effects on dolutegravir: an emerging concern in Europe. AIDS 2017;**31**:1201-1203.

33) Reese MJ, Savina PM, Generaux GT, et al. In vitro investigations into the roles of drug transporters and metabolizing enzymes in the disposition and drug interactions of dolutegravir, a HIV integrase inhibitor. Drug Metab Dispos. 2013 Feb;**41(2)**:353-61.

34) Borghetti A, Baldin G, Lombardi F, et al. Efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multicentre cohort of patients with suppressed HIV-1 replication. HIV Med. 2018 Mar 24. doi: 10.1111/hiv.12611.

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 - MSM - IDU - Others	 225 (40.5) 145 (26.1) 100 (18.0) 86 (15.5)
Anti-HCV antibodies positive, n (%)	125 (23.0)
Time from 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+ (cell/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 > 500000 copies/mL, n (%)	73 (14.1)
Previous virological failure, n (%)	226 (40.7)
CD4+ count (cell/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 - Absent - Unknown	 45 (8.1) 406 (73.0) 105 (18.9)
Previous HAART regimen, n (%): - 2NRTIs+NNRTI - 2NRTIs+PI or b/PI - 2NRTIs+INI - Dual therapy - Other	 141 (25.6) 77 (14.0) 89 (16.2) 224 (40.7) 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 - Dyslipidemia	 155 (27.9) 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)

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

Pt	Sex and Age	Time to VF (months)	Type of VF*	HIV-RNA at VF (cp/mL)	Subsequent therapy	Presence of M184V/I mutation	Comments
Pt 1	Female, 50 yrs	8.5	1	74.570	FTC/TDF + DRV/rit	No	She reported lack of adherence
Pt 2	Male, 40 yrs	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 yrs	11.9	1	775.000	FTC/TAF/EVG/cob	No	She reported lack of adherence. Following HIV-RNA determination were > 50 cp/mL
Pt 4	Male, 45 yrs	4.7	1	1.808	3TC + DTG	No	The study regimen was not interrupted and following HIV-RNA determination was < 50 cp/mL.
Pt 5	Male, 55 yrs	19.0	2	112; 64	3TC/ABC/DTG	No	He achieved virological suppression after 4 months.
Pt 6	Male, 49 yrs	18.6	2	69; 108	ATV + DTG	Yes	He achieved virological suppression at the following determination of HIV-RNA.
Pt 7	Male, 31 yrs	4.6	2	58.830	FTC/TDF + ATV/rit	No	He reported lack of adherence. Following HIV-RNA determination < 50 cp/mL.
Pt 8	Female, 51 yrs	17.1	2	79; 59	3TC/ABC/DTG	No	She achieved virological suppression at the following determination of HIV-RNA.
Pt 9	Female, 48 yrs	16.6	2	58; 53	3TC + DRV/cob	No	Confirmed blips in two consecutive viremia; not known lack of adherence.
Pt 10	Female, 50 yrs	26.6	1	15.893	Unknown	No	Lack of adherence. She re-started the same treatment with undetectability after 2 months.

Pt 11	Male, 28 yrs	9.5	1	1.232	TDF/FTC + DTG	Yes	He reported lack of adherence with treatment interruption, switched in triple treatment considering the presence of 184V in a previous GRT in Paediatric; vertically infected.
Pt 12	Male, 64 yrs	7.7	2	75; 65	TDF/FTC + DTG	No	Confirmed blips in two consecutive viremia but during flu vaccination; good adherence but GRT not performed at failure.

*1= one single HIV-RNA determination ≥ 1000 cp/mL; 2= two consecutive HIV-RNA determination ≥ 50 cp/mL.

Figure 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 patient with a virological suppression ≥ 88 months; (d) stratified for the presence of M184V mutation in patient with a virological suppression < 88 months.

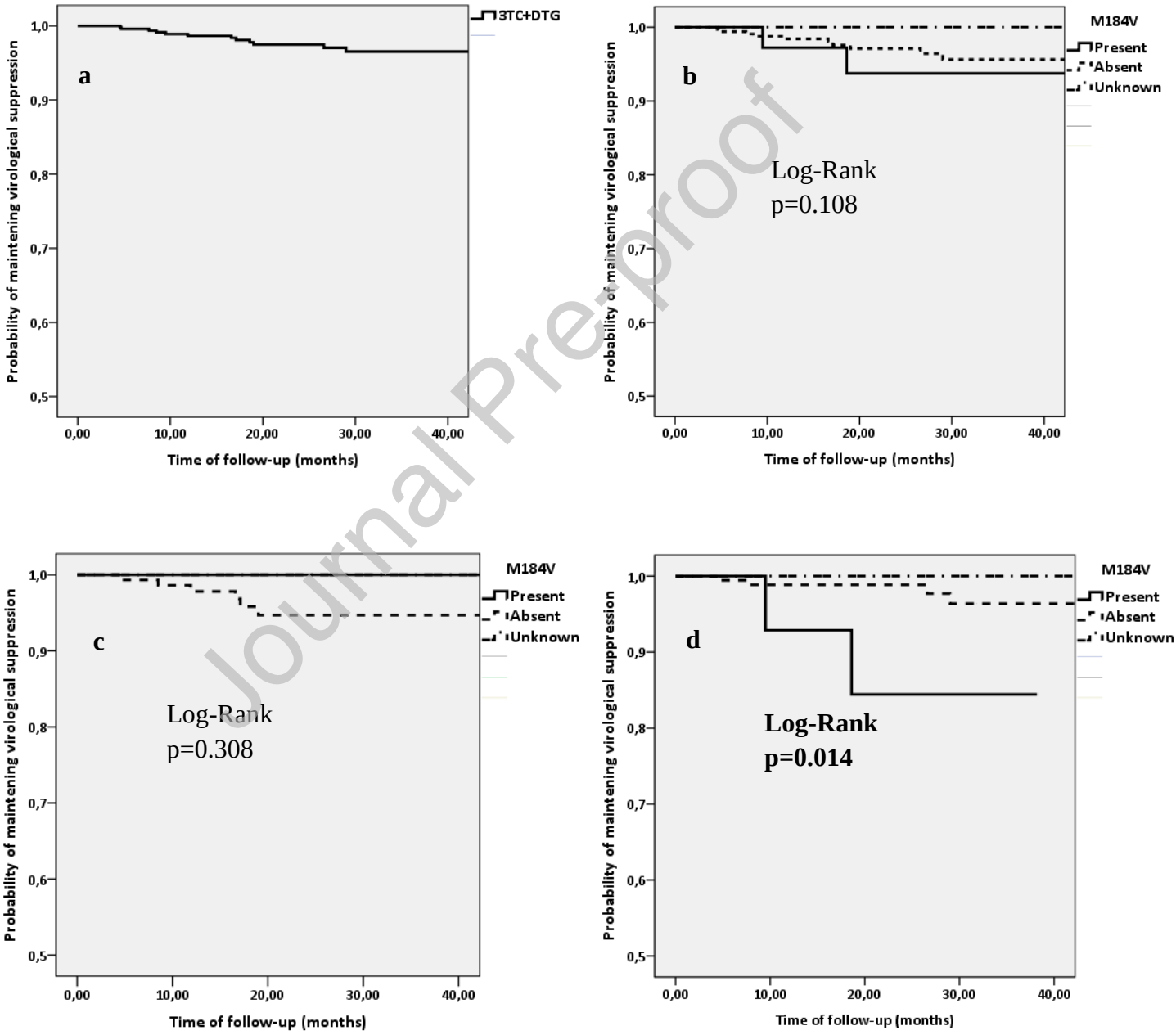

Figure 2. Variation in median CD4/CD8 ratio (a), median total cholesterol (b), median HDL cholesterol (c) and median tryglicerides during the follow-up.