

This is the peer reviewed version of the following article:

Five years with dolutegravir plus lamivudine as a switch strategy: much more than a positive finding / Ciccullo, A; Borghi, V; Giacomelli, A; Cossu, M V; Sterrantino, G; Latini, A; Giacometti, A; De Vito, A; Gennari, W; Madeddu, G; Capetti, A; D'Ettorre, G; Mussini, C; Rusconi, S; Di Giambenedetto, S; Baldin, G. - In: JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES. - ISSN 1525-4135. - 88:3(2021), pp. 234-237. [10.1097/QAI.0000000000002787]

Terms of use:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

08/08/2024 20:30

(Article begins on next page)

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

A. Ciccullo,^{1,2} V. Borghi,³ A. Giacomelli,⁴ MV Cossu,⁵ G. Sterrantino,⁶ A. Latini,⁷ A. Giacometti,⁸
A. De Vito,⁹ W. Gennari,¹⁰ G. Madeddu,⁹ A. Capetti,⁵ G. d'Ettorre,¹¹ C. Mussini,³ S. Rusconi,⁴ S.
Di Giambenedetto^{2,12} and G. Baldin^{12,13}

¹UOC Malattie Infettive, P.O. San Salvatore, L'Aquila, Italy

²Catholic University of the Sacred Heart, Rome, Italy

³Azienda Ospedaliero Universitaria di Modena, Clinica Malattie Infettive e Tropicali, Modena, Italy.

⁴Infectious Diseases Unit, DIBIC Luigi Sacco, University of Milan, Milan, Italy.

⁵Division of Infectious Diseases, Department of Infectious Diseases, Luigi Sacco University Hospital, Milan, Italy.

⁶Infectious Diseases Unit, Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy

⁷Infectious Dermatology and Allergology Unit, IFO S. Gallicano Institute (IRCCS), Rome, Italy.

⁸Clinic of Infectious Diseases, Dept. of Biomedical Sciences and Public Health, Polytechnic University of Marche, Ancona. Italy.

⁹Unit of Infectious Diseases, Department of Medical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy

¹⁰Azienda Ospedaliero Universitaria di Modena Laboratorio di Microbiologia e Virologia, Modena, Italy

¹¹Department of Public Health and Infectious Diseases, Azienda Policlinico Umberto I, Rome, Italy.

¹²UOC Malattie Infettive, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

¹³Mater Olbia Hospital, Olbia, Italy

Funding: This study was funded by ViiV Healthcare. Study sponsor did not contribute to design of the study and collection, analysis and interpretation of data and in writing the manuscript.

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 $\geq 1,000$ 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

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% ($SD\pm 1.4$), 79.7% ($SD\pm 1.6$) and 74.3% ($SD\pm 2.2$), respectively.

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

Keywords: HIV, HAART, dolutegravir, lamivudine

Transparency Declarations

AC received travel grants from ViiV Healthcare. AG reports grants and/or personal fees from BMS, Gliead, Janssen, MSD and ViiV Healthcare. ACa has received a personal grant from AB, Gilead and ViiV. GS has received funds for speaking by Gilead, Merk, Janssen, Abbvie, ViiV. CM has participated in advisory boards, received study grants and/or speaker honoraria from: Abbvie, Gilead, ViiV, Janssen, Angelini, BMS, MSD. SR received research grants to his Institution from ViiV Healthcare, Gilead Sciences and Janssen, outside the submitted work; he was also a paid consultant for ViiV Healthcare, Gilead Sciences, Merck Sharp and Dohme, Bristol-Myers Squibb and Janssen. 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.

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

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 $\geq 1,000$ 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 the 18 patients experiencing a VF discontinued study regimen, while the others maintained DTG+3TC: all of the patients experiencing VF re-achieved virologic

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

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

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. However, 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.

References

1. European AIDS Clinical Society. EACS Guidelines for the management of people living with HIV (PLWH) in Europe. Version 10.1. Accessed on November 21st 2020. https://www.eacsociety.org/files/guidelines-10.1_5.pdf
2. 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.
3. Fabbiani M, Gagliardini R, Ciccarelli N, Quiros Roldan E, Latini A, d'Ettorre G, Antinori A, Castagna A, Orofino G, Francisci D, Chinello P, Madeddu G, Grima P, Rusconi S, Del Pin B, Lombardi F, D'Avino A, Focà E, Colafigli M, Cauda R, Di Giambenedetto S, De Luca A; ATLAS-M Study Group. Atazanavir/ritonavir with lamivudine as maintenance therapy in

- virologically suppressed HIV-infected patients: 96 week outcomes of a randomized trial. *J Antimicrob Chemother.* 2018 Jul 1;73(7):1955-1964. doi: 10.1093/jac/dky123.
4. Pulido F, Ribera E, Lagarde M, Pérez-Valero I, Palacios R, Iribarren JA, Payeras A, Domingo P, Sanz J, Cervero M, Curran A, Rodríguez-Gómez FJ, Téllez MJ, Ryan P, Barrufet P, Knobel H, Rivero A, Alejos B, Yllescas M, Arribas JR; DUAL-GESIDA-8014-RIS-EST45 Study Group. Dual Therapy With Darunavir and Ritonavir Plus Lamivudine vs Triple Therapy With Darunavir and Ritonavir Plus Tenofovir Disoproxil Fumarate and Emtricitabine or Abacavir and Lamivudine for Maintenance of Human Immunodeficiency Virus Type 1 Viral Suppression: Randomized, Open-Label, Noninferiority DUAL-GESIDA 8014-RIS-EST45 Trial. *Clin Infect Dis.* 2017 Nov 29;65(12):2112-2118. doi: 10.1093/cid/cix734.
 5. Arribas JR, Girard PM, Landman R, Pich J, Mallolas J, Martínez-Rebollar M, Zamora FX, Estrada V, Crespo M, Podzamczek D, Portilla J, Dronda F, Iribarren JA, Domingo P, Pulido F, Montero M, Knobel H, Cabié A, Weiss L, Gatell JM; OLE/RIS-EST13 Study Group. 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. doi: 10.1016/S1473-3099(15)00096-1. Epub 2015 Jun 7. Erratum in: *Lancet Infect Dis.* 2015 Aug;15(8):875.
 6. Casado JL, Bañón S, Moreno A, de Santiago AD, Gomez C, Perez-Elías MJ, Moreno S. Lamivudine plus darunavir boosted with ritonavir as simplification dual regimen in HIV-infected patients. *J Int AIDS Soc.* 2014 Nov 2;17(4 Suppl 3):19801. doi: 10.7448/IAS.17.4.19801.
 7. Borghetti A, Lombardi F, Gagliardini R, Baldin G, Ciccullo A, Moschese D, Emiliozzi A, Belmonti S, Lamonica S, Montagnani F, Visconti E, De Luca A, Di Giambenedetto S.

- Efficacy and tolerability of lamivudine plus dolutegravir compared with lamivudine plus boosted PIs in HIV-1 positive individuals with virologic suppression: a retrospective study from the clinical practice. *BMC Infect Dis.* 2019 Jan 17;19(1):59. doi: 10.1186/s12879-018-3666-8.
8. Baldin G, Ciccullo A, Rusconi S, Capetti A, Sterrantino G, Colafigli M, d'Ettorre G, Giacometti A, Cossu MV, Borghetti A, Gennari W, Mussini C, Borghi V, Di Giambenedetto S. 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. *Int J Antimicrob Agents.* 2019 Dec;54(6):728-734. doi: 10.1016/j.ijantimicag.2019.09.002. Epub 2019 Sep 12.
 9. Hidalgo-Tenorio C, Cortés LL, Gutiérrez A, Santos J, Omar M, Gálvez C, Sequera S, Jesús SE, Téllez F, Fernández E, García C, Pasquau J. DOLAMA study: Effectiveness, safety and pharmacoeconomic analysis of dual therapy with dolutegravir and lamivudine in virologically suppressed HIV-1 patients. *Medicine (Baltimore).* 2019 Aug;98(32):e16813. doi: 10.1097/MD.00000000000016813.
 10. van Wyk J, Ajana F, Bisshop F et al. Switching to DTG / 3TC fixed-dose combination (FDC) is non-inferior to continuing a TAF-based regimen (TBR) in maintaining virologic suppression through 96 weeks (TANGO study). Exhib. HIV Drug Therapy Glasgow Congress, 5-8 October, 2020. Abstract O441
 11. Borghetti A, Ciccullo A, Baldin G, Rusconi S, Capetti A, Sterrantino G, Gennari W, Mussini C, Borghi V, Di Giambenedetto S. Shall We Dance? Extending TANGO's Results to Clinical Practice. *Clin Infect Dis.* 2020 Oct 23;71(7):e200-e201. doi: 10.1093/cid/ciaa313.
 12. Ciccullo A, Baldin G, Capetti A, Borghi V, Sterrantino G, Latini A, Madeddu G, Celani L, Vignale F, Rossetti B, Dusina A, Cossu MV, Restelli S, Gennari W, Lagi F, Giacomelli A, Colafigli M, Brescini L, Borghetti A, Mussini C, Rusconi S, Di Giambenedetto S. Cohort

- profile: The Observational cohort for the study of Dolutegravir in Antiretroviral Combination Regimens (ODOACRE). *BMJ Open*. 2019 Dec 2;9(12):e029960. doi: 10.1136/bmjopen-2019-029960.
13. Gagliardini R, Ciccullo A, Borghetti A, Maggiolo F, Bartolozzi D, Borghi V, Pecorari M, Di Biagio A, Callegaro AP, Bruzzzone B, Saladini F, Paolucci S, Maserati R, Zazzi M, Di Giambenedetto S, De Luca A; ARCA Study Group. 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. doi: 10.1093/ofid/ofy113
14. Hilsabeck RC, Castellon SA, Hinkin CH. Neuropsychological aspects of coinfection with HIV and hepatitis C virus. *Clin Infect Dis*. 2005 Jul 1;41 Suppl 1(Suppl 1):S38-44. doi: 10.1086/429494. PMID: 16265612; PMCID: PMC2879257.

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.

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	319 (40.6)
- MSM	305 (38.9)
- IDU	119 (15.2)
- Others	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/ μ L), 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/ μ L), Median (IQR)	680 (500 - 889)
Time of virological suppression (months), Median (IQR)	29.1 (14.6 – 49.5)
M184V resistance mutation, n (%)	
- Present	33 (4.2)
- Absent	214 (27.3)
- Unknown	538 (68.5)
Previous HAART regimen, n (%):	
- 2NRTIs+NNRTI	180 (22.9)
- 2NRTIs+PI or b/PI	92 (11.7)
- 2NRTIs+INI	216 (27.5)
- Dual therapy	268 (34.1)
- Other	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	302 (38.5)
- Dyslipidemia	96 (12.2)

- 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)

ACCEPTED

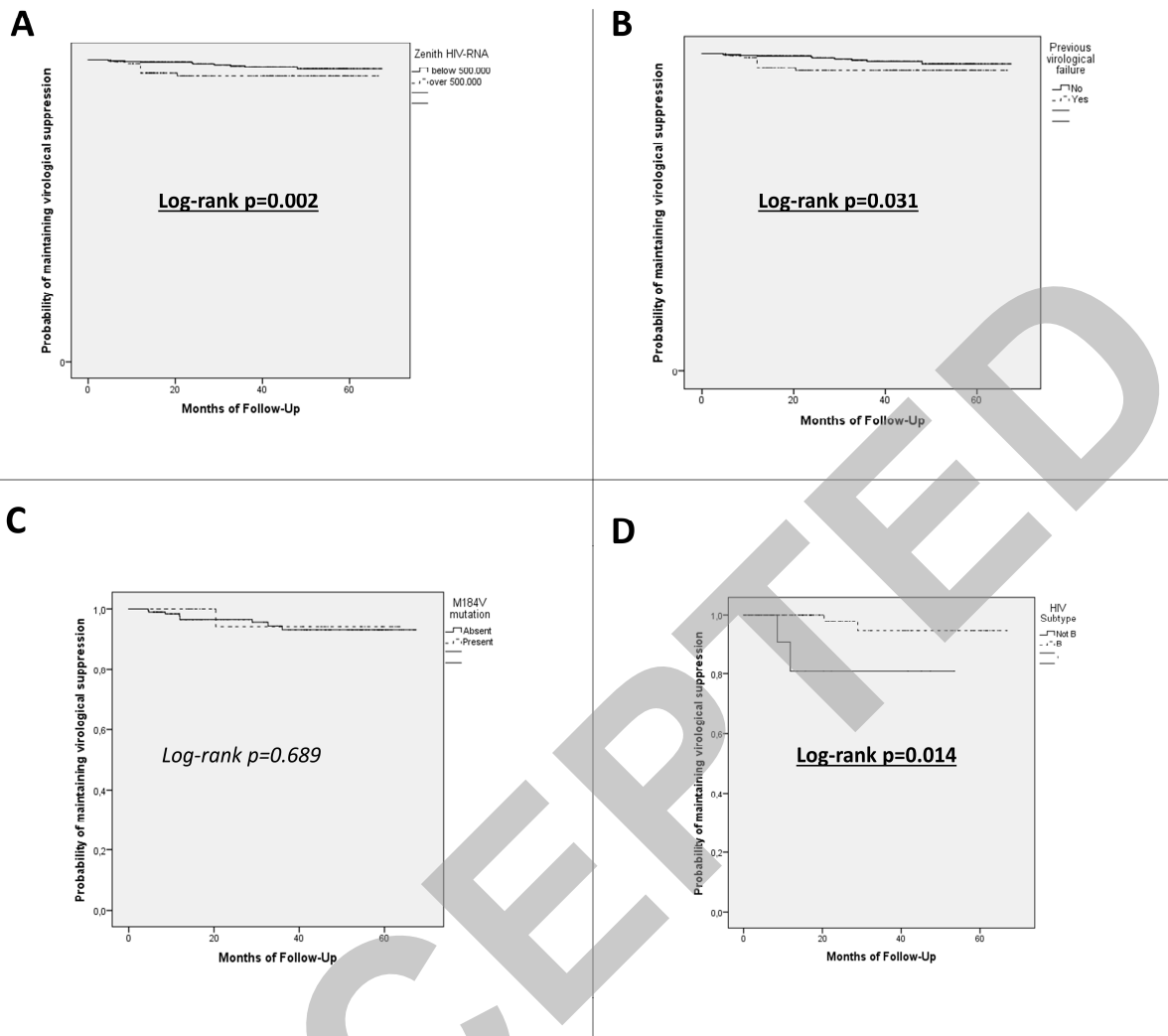


Figure 1. Kaplan Meier survival analyses. A. stratified for Zenith HIV-RNA; B Stratified for previous virological failures; C Stratified for the presence of the M184V mutation; D Stratified for HIV subtype.