Journal of Microbiology, Immunology and Infection (2019) 52, 865–871

Available online at www.sciencedirect.com

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Original Article

Dual therapy with ritonavir-boosted protease inhibitor (PI) plus lamivudine versus triple therapy with ritonavir-boosted PI plus two nucleos(t)ide reverse-transcriptase inhibitor in HIV-infected patients with viral suppression

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Received 22 January 2019; received in revised form 8 July 2019; accepted 16 July 2019
Available online 6 August 2019

KEYWORDS
Combination antiretroviral therapy;
Stable switch;

Abstract *Background:* Dual antiretroviral regimens are attractive options to optimize the combination antiretroviral therapy in light of potential toxicities with long-term cumulative exposure to nucleos(t)ide reverse-transcriptase inhibitors (NRTIs).
Methods: In this retrospective observational study, we included HIV-infected patients on suppressive antiretroviral therapy with plasma viral load (PVL) < 200 copies/mL for at least 6

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https://doi.org/10.1016/j.jmii.2019.07.002

Simplification;
Adverse effect;
Mitochondrial toxicity

months who were switched to dual regimens containing lamivudine (3TC) (150 mg twice daily or 300 mg once daily) plus lopinavir/ritonavir (LPV/r) 250/50 mg twice daily or darunavir/ritonavir (DRV/r) 800/100 mg once daily. Patients maintaining on suppressive triple therapy with DRV/r or LPV/r plus two NRTIs were included for comparisons. The primary endpoint was the proportion of patients with PVL <50 copies/mL after 48 weeks of follow-up.

Results: In total, 364 patients were included with 93 (25.5%) switched to dual therapy After 48 weeks of observation, PVL <50 copies/mL was observed in 96.8% and 94.1% of dual-therapy and triple-therapy group, respectively, in per-protocol analysis (difference 2.7%; 95% CI -2.5%—7.9%). Nineteen patients (3 [3.2%] in dual-therapy and 16 [7.6%] in triple-therapy group) developed virologic failure, with none having emergent M184V resistance-associated mutation. A statistically significant increase of cholesterol level (13 mg/dL versus 2 mg/dL, $p = 0.003$) and high-density lipoprotein (3 mg/dL versus −2 mg/dL, $p = 0.019$) were observed in dual-therapy than in triple-therapy group. Changes of triglyceride, low-density lipoprotein and glycated hemoglobin levels were similar between the two groups.

Conclusion: Dual therapy with DRV/r or LPV/r plus lamivudine demonstrated similar effectiveness in maintaining viral suppression to triple therapy.

Introduction

Combination antiretroviral therapy (cART) containing two nucleos(t)ide reverse-transcriptase inhibitors (NRTIs) combined with one third agent, including non-nucleoside reverse-transcriptase inhibitor (nNRTI), protease inhibitor (PI) or integrase inhibitor (INSTI) is the mainstay of treatment of HIV infection in most guidelines.[1—3] However, long-term exposure to NRTIs may increase the cumulative risk of adverse effects, such as bone marrow suppression, mitochondrial toxicity, and lipodystrophy with zidovuine (AZT),[4,5] didanosine and stavudine,[6,7] myocardial infarction with abacavir (ABC),[8] and kidney tubular dysfunction and reduced bone mineral density or osteomalacia with tenofovir disoproxil fumarate (TDF).[9,10] Compared to those five NRTIs, lamivudine and emtricitabine are two of current NRTI backbones with least adverse effects. Reported trials also showed that efficacy, safety and tolerability of lamivudine as a component of two-drug regimen.[11—15]

In order to avoid long-term drug exposure and toxicities while maintaining viral suppression, 2-drug regimens containing one or no NRTIs have been explored. The AIDS Clinical Trials Group A5142 team reported of similar efficacy in dual therapy with efavirenz (EFV) plus ritonavir-boosted lopinavir (LPV/r) compared with either EFV plus two NRTIs or LPV/r plus two NRTIs.[16] Also, in three prospective trials (KITE study, PROBE study and NEAT001 study), NRTI-sparing regimen with PI/r plus raltegravir also showed good efficacy of viral suppression in NRTI-sparing arm with non-inferiority compared with triple therapy.[17—19]

Clinical trials in investigating the efficacy and safety of dual therapy with lamivudine and ritonavir-boosted lopinavir, atazanavir or darunavir showed non-inferior results in treating either naïve or virally suppressed patients to the standard, triple cART, and only few resistance-associated mutations (RAMs) emerged in participants with virologic failure.[11—15,20,21] Moreover, 2-drug regimen containing dolutegravir plus rilpivirine also showed non-inferiority to triple cART in maintaining viral suppression among patients without previous virological failure.[18,22,23] Improvements in the lipid profiles, renal and bone turnover biomarkers were observed after switch of TDF- or protease inhibitors (PIs)-containing regimens to 2-drug regimens dolutegravir plus rilpivirine or lamivudine.[15,22,24,25]

PIs have high genetic barrier to development of drug resistance, and are widely suggested as antiretroviral regimens for treatment-experienced patients with documented resistance to nNRTIs.[26] In clinical trials or observational studies, dual therapy with ritonavir-boosted lopinavir (LPV/r) or darunavir (DRV/r) plus lamivudine have shown non-inferiority to triple therapy with boosted PI plus 2 NRTIs in virally suppressed HIV-positive patients after 48 weeks of treatment.[11,27] In the multicenter open-label DUAL-GESIDA trial, the efficacy of 2-drug therapy with lamivudine plus DRV/r with viral suppression was non-inferior to 3-drug therapy with two NRTIs and DRV/r (88.9% in 2-drug group and 92.7% in 3-drug group).[14] Week 48 results of the ANDES study also revealed less adverse effect with similar viral efficacy using ritonavir-boosted darunavir plus lamivudine.[21] However, elevation of total cholesterol (T-CHOL), low-density lipoprotein cholesterol (LDL-C), and total triglyceride (TG) were noted in the patients receiving two-drug regimens in these clinical trials.[11—13,21,28] Clinical studies with boosted protease inhibitors plus lamivudine are limited in this Asia—Pacific region. In this retrospective observational cohort study, we aimed to compare the effectiveness and changes of metabolic parameters between dual therapy containing lamivudine and boosted PI and triple therapy containing two NRTIs and boosted PI in HIV-positive patients who had achieved viral suppression.

Methods

Study population

Between January 2014 and May 2016, HIV-positive adults aged 18 years or greater who received cART at two major

designated hospitals for HIV care in northern Taiwan (National Taiwan University Hospital, Taipei and Taoyuan General Hospital, Taoyuan) were screening for eligibility for inclusion in this study. Patients who had taken LPV/r or DRV/r-containing triple therapy with 2 NRTIs were switched to dual therapy with one NRTI (lamivudine 150 mg twice per day or 300 mg once per day) plus LPV/r or DRV/r due to intolerance or toxicity of other NRTIs than lamivudine or simplification consideration at the discretion of the treating physicians. Eligible patients for switch to 2-drug regimens were those on a stable antiretroviral regimen consisting of lopinavir/ritonavir (200/50 mg) twice daily or darunavir/ritonavir (800/100 mg) once daily plus lamivudine or emtricitabine plus AZT, ABC or TDF for at least 6 months, with a plasma HIV RNA load (PVL) $<$ 200 copies/ml in at least the previous 6 months. Those patients who continued to take triple therapy for 6 months or longer with viral suppression ($<$200 copies/ml) during the same study period were included as a comparator group.

Patients were excluded from our study who had previous virological failure to regimens containing lamivudine or PI/r; available genotypic testing showing reduced sensitivity to lamivudine or PIs; or active opportunistic diseases or severe infectious diseases, acute or chronic inflammatory diseases, Cushing's syndrome, acute or chronic kidney diseases, acute and chronic hepatitis B virus (HBV) infection, or acute hepatitis with undefined causes.

Laboratory investigations

Per the national HIV treatment guidelines in Taiwan, determinations of hemogram, creatinine, lipid profiles, HbA1C, PVL, and CD4 in HIV-positive individuals having achieved viral suppression with cART were performed at least every 24 weeks. In each clinic follow-up, adherence was evaluated with the assistance of case managers who also provided support and counseling. PVL was measured using Cobas Amplicor HIV-1 Monitor™ Test, version 1.5, (Roche Diagnostics Corporation, Indianapolis, USA) with a detection limit of 20 copies/mL. Among the individuals with virologic failure (PVL $>$1000 copies/mL), genotypic resistance testing was performed with the use of in-house methods at the National Taiwan University Hospital.[29]

Assessment of effectiveness and safety

Virologic success was defined as PVL $<$50 copies/mL while taking dual therapy or triple therapy at the end of the 48-weeks follow-up. Treatment failure was defined by virologic failure ($\geq$50 copies/ml) or permanent discontinuation of antiretroviral therapy. Primary endpoint of this study was the proportion of PVL $<$50 copies/mL after 48 weeks of switch to dual therapy, compared with triple therapy in per-protocol (PP) analysis. The intention-to-treat (ITT) analysis included all patients who switched to dual therapy and those who maintained on triple therapy, while PP analysis included all patients except those who discontinued the treatment for reasons other than virological failure.

Secondary endpoints were interval changes of CD4 cell counts, T-CHOL, TG, LDL-C, high-density lipoprotein cholesterol (HDL-C) and HbA1c after 48 weeks of treatment between the two groups, and incidence of emergence of mutations conferring genotypic resistance to lamivudine plus PI/r or TDF and emtricitabine in patients meeting criteria for confirmed virologic failure with PVL $>$1000 copies/mL. The study was approved by the Research Ethics Committee of the National Taiwan University Hospital and Institutional Review Board at Taoyuan General Hospital, and verbal or written informed consent was waived because of the retrospective study design. The confidentiality of the included patients was protected by adhering to the guidelines of Good Clinical Practice.

Statistical analysis

Categorical data were analyzed using χ^2 or Fisher's exact tests, as appropriate, and continuous variables were compared using the Mann—Whitney U test. The 95% CIs were computed using a binomial distribution. Data were compared between the two groups using logistic regression model. All variables with $p < 0.1$ in univariate analysis were selected for subsequent multivariate analysis. All tests were two-tailed and a p-value $<$0.05 was considered statistically significant. Data were analyzed using STATA version 14.0 (STATA Corp LLC, TX, USA).

Results

During the study period, 409 patients were screening for the eligibility of inclusion in this study (Fig. 1), and 9 patients were switched to single-tablet regimen of abacavir/lamivudine/dolutegravir at the physician's discretion in the 2-drug group; 10 (8.9%) and 26 were recorded as being lost to follow-up in the 2-drug and 3-drug groups within 48-week follow-up, respectively. In total, 364 patients were included, 93 patients in the 2-drug group and 271 patients in the 3-drug group, and met criteria for PP analysis during the 48-weeks follow-up. The clinical characteristics of the patients included in PP analysis are shown in Table 1. The median age (IQR) was 36 (31—42) years and 88 patients (94.6%) were males in the 2-drug group, while the median age (IQR) was 37 (32—44) years and 244 patients (90.0%) were males in the 3-drug group. In the 2-drug group, 73 (78.4%) were previously treated with AZT plus 3TC, 13 (14.0%) with TDF/FTC or TDF and 3TC, and 7 (7.5%) with ABC/3TC. In the 3-drug group, 147 patients were receiving TDF/FTC or TDF plus 3TC (54.2%), 74 (27.3%) ABC/3TC, and 50 (18.5%) AZT/3TC at the time of inclusion in the study. With regard to protease inhibitors, 73 (78.5%) in the 2-drug group were taking LPV/r and 184 (67.9%) in the 3-drug groups were taking LPV/r.

After 48-weeks of follow-up, the proportion of patients in the 2-drug group with virological success was 96.8% (90/93) in the 2-drug group compared with 94.1% (255/271) in the 3-drug group (difference 2.7% [95% CI -2.5%—7.9%]; $p = 0.318$) in the per-protocol population (PP) (Fig. 2). In the ITT analysis, virological success was 80.4% (90/112) in the 2-drug group compared with 85.9% (255/297) in the 3-drug group (difference −5.5% [95% CI -13.4% to 2.4%]; p = 0.173) The median (IQR) increase of CD4 count from baseline to week 48 was 47 (−33 to 145) cells/μL in the 2-drug group and 39 (−27 to 137) cells/μL in the 3-drug group

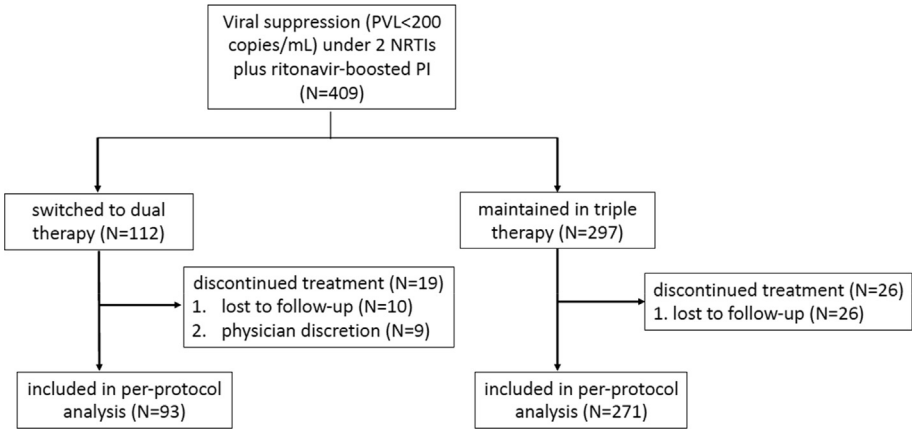

Figure 1. Study flow.

($p = 0.885$). No acute hepatitis B flare up happened in both arms of study groups.

Of the 19 patients with virologic failure (3 [3.0%] in the 2-drug and 16 [5.9%] in the 3-drug group), only one patient who had no previous exposure to rilpivirine and had PVL >1000 copies/mL in 2-drug group and had one emergent RAM of M230L/I without concurrent PI RAM by genotypic resistance testing. Of the remainder 18 patients, resistance testing was not performed due to low-level viremia with PVL <1000 copies/mL.

Table 1 Baseline demographic and clinical characteristics of the included patients.

	Dual therapy group (N = 93)	Triple therapy group (N = 271)	*p* value
Male, n (%)	88 (94.6)	244 (90)	0.178
Age, (median, IQR), years	36 (31–42)	37 (32–44)	0.366
Risk group of HIV transmission			
MSM, n (%)	50 (53.7)	240 (88.5)	<0.001
IDU, n (%)	42 (45.1)	22 (8.1)	<0.001
Heterosexual, n (%)	1 (1.2)	9 (3.3)	0.252
Previous NRTIs before switch to dual therapy			
AZT/3TC, n (%)	73 (78.4)	NA	
TDF/FTC or 3TC, n (%)	13 (14.0)	NA	
ABC/3TC, n (%)	7 (7.5)	NA	
Concurrent NRTIs in triple therapy			
AZT/3TC, n (%)	NA	50 (18.5)	
TDF/FTC or 3TC, n (%)	NA	147 (54.2)	
ABC/3TC, n (%)	NA	74 (27.3)	
Current protease inhibitor			
LPV/r, n (%)	73 (78.5)	184 (67.9)	0.037
DRV/r, n (%)	20 (21.5)	87 (32.1)	0.037
Co-infection			
HBsAg-positive, n (%)	0	58 (21.4)	NA
Anti-HCV-positive	35 (37.6)	40 (14.8)	<0.001
Immunological and virological status before switch			
CD4, median (IQR), cells/μL	502 (389–693)	529 (400.5–675)	0.589
CD4/CD8 ratio, median (IQR)	0.58 (0.44–0.83)	0.57 (0.42–0.77)	0.645
PVL <50 copies/mL, n (%)	90 (96.7)	255 (94.1)	0.316
Lipid and glucose profile before switch			
Total cholesterol, median (IQR), mg/dL (n = 320)	178 (163–198)	177 (152–198)	0.477
TG, median (IQR), mg/dL, (n = 317)	173 (112–241)	165 (120–257)	0.518
LDL-C, median (IQR), mg/dL (n = 250)	97 (85–116)	98 (81–115)	0.941
HDL-C, median (IQR), mg/dL (n = 171)	48 (39–57)	46 (38–55)	0.759
HbA1c, median (IQR), % (n = 262)	4.9 (4.6–5.2)	5.3 (5.1–5.6)	<0.001

Abbreviations: 3TC, lamivudine; ABC, abacavir; AZT, zidovudine; DRV/r, ritonavir-boosted darunavir; FTC, emtricitabine; HbA1c, glycated hemoglobin; IDU, injecting drug user; LDL-C, low-density lipoprotein cholesterol HDL-C, high-density lipoprotein cholesterol; LPV/r, ritonavir-boosted lopinavir; MSM, men who have sex with men; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; PVL, plasma viral load; TDF, tenofovir disoproxil fumarate; TG, triglyceride.

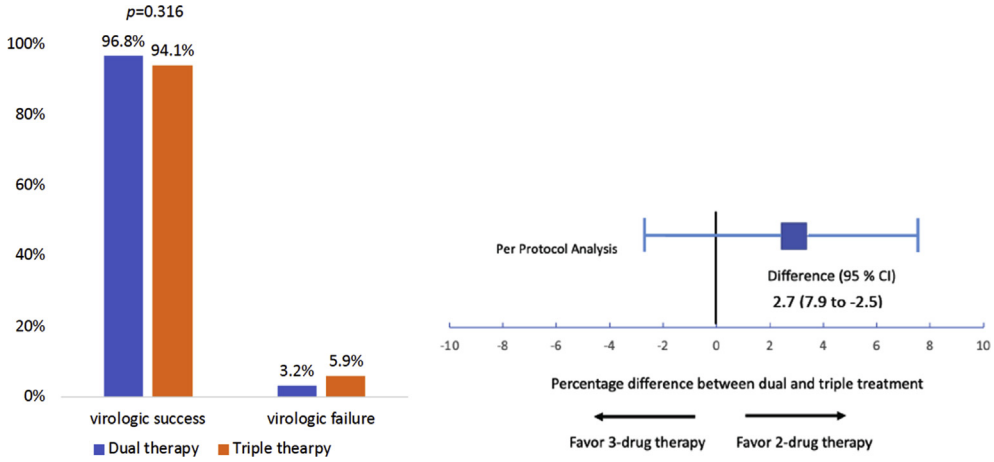

Figure 2. Comparison of virological outcomes of patients receiving dual therapy and those receiving triple therapy in per-protocol analysis.

Regarding to lipid parameters after 48 weeks of follow-up, the increase in T-CHOL level was higher in 2-drug group than 3-drug group (median, 13 mg/dL vs 2 mg/dL; $p = 0.003$). HDL level was also higher in 2-drug group (3 mg/dL in 2-drug group and −2 mg/dL in 3-drug group, $p = 0.019$). The changes of LDL-C level (2.5 mg/dL in 2-drug group vs 3 mg/dL in 3-drug group; $p = 0.304$), TG level (2.5 mg/dL in 2-drug group vs 3.5 mg/dL in 3-drug group; $p = 0.648$) were of no statistically significant differences (Fig. 3).

Discussion

In the 2.5-year retrospective observational study, we found that 2-drug regimens consisting of boosted PI plus lamivudine demonstrated non-inferior effectiveness in maintaining viral suppression after 48-week treatment compared with 3-drug regimen consisting of boosted PI plus 2 NRTIs in PP analysis (96.8% vs 94.1%; difference 2.7% [95% CI -2.5%—7.9%]) as well as in ITT analysis, (80.4% vs 85.9%; difference −5.5% [95% CI -13.3%—2.4%]). The 2-drug regimens were well tolerated with few discontinuations because of tolerance or safety issues.

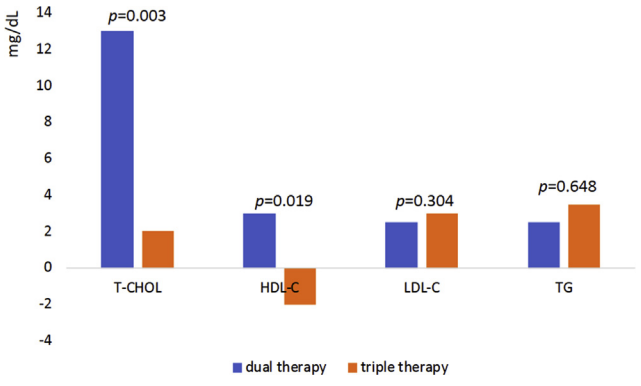

Figure 3. Interval changes of metabolic profiles after 48 weeks. T-CHOL: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride.

Nine patients in two-drug regimen group could not complete protocol due to being switched to dolutegravir-containing single-tablet regimen (STR) when it was available in Taiwan, but all of them remained virally suppressed before being switched to STR. Overall, the percentage of patients being lost to follow-up was nearly identical in these two groups (8.9% in two-drug group and 8.7% in 3-drug group). Also, we did not observe difference of virological failure between two groups.

In our study, only one out of 19 patients who had virological failure had emergent RAM of M230L/I, which is an extremely rare RAM selected by rilpivirine[30]; however, this patient had no exposure to rilpivirine; and no RAMs to PIs or NRTI were detected, though only one patient met criteria of resistance testing in our study. The majority of the patients with virological failure presented with low-level viremia with PVL<1000 copies/mL. These results were in line with those of the OLE study in that, despite low genetic barrier of lamivudine, dual therapy with boosted PI and lamivudine did not significantly increase the risk of virological failure, and the only RAM in our study was not associated with lamivudine. In terms of immunological profile, since all included patients had stable viral suppression for more than 6 months before switch, and CD4 counts were similar at baseline between both groups. After 48 weeks of treatment, the two groups of patients had similar changes of CD4 counts.

In our study, we found significantly greater increases of T-CHOL and HDL-C level in 2-drug group after 48 weeks of treatment, while no statistically significant differences in other metabolic profiles, including LDL-C, TG and HbA1c, were observed. In the OLE study, T-CHOL, LDL-C and TG showed significantly higher in 2-drug group than 3-drug group, while HDL-C was not statistically significantly different. In contrast, a higher HDL-C level was observed in 2-drug group in our study.[11] In the GARDEL study, more patients in the 2-drug group than in the 3-drug group had hyperlipidemia, and the difference might have been driven by the use of TDF.[20] In week 48 analysis of the ANDES study, an increase of T-CHOL level was observed in 19% of patients receiving 2-drug therapy, while only 4% of patients receiving 3-drug therapy ($p = 0.01$). The other lipid profiles

showed trends of elevation in 2-drug group, but the differences did not reach statistical significance.[21] In the OLE trial, 60% of the patients concurrently took TDF in 3-drug group, while in our study, 54% of patients in 3-drug group took TDF. Similar findings were also observed in another randomized, open-label, 72-week trial (KALEAD trial) that compared LPV/r plus TDF versus LPV/r plus two (non-TDF) NRTIs in HIV-positive adults.[31] In patients receiving 2-drug therapy with LPV/r plus TDF, the proportions of dyslipidemia and hypertriglyceridemia were also significantly lower than those receiving 3-drug therapy. Moreover, in one randomized study, reductions of T-CHOL and LDL-C were observed after 2 weeks of TDF administration.[32] Regarding glycated hemoglobin, a higher level was observed in 3-drug group at baseline; however, there was no significant difference between the two groups after 48 weeks of treatment. In the 2-drug group, 77.8% of patients were concurrently taking zidovudine before switch, compared with 18.5% of patients in the 3-drug group. Zidovudine may cause anemia and underestimate the value of glycated hemoglobin.[33,34] In our study, eight patients were shifted to dual therapy due to intolerance or toxicity. All 8 patients were taking zidovudine, five were shifted to dual therapy due to lipoatrophy; two were due to peripheral neuropathy, one was anemia, and the rest were due to simplification of regimen to avoid adverse effects of zidovudine.

This study has several limitations. First, this is a retrospective study with unbalanced patient numbers and clinical characteristics in the two treatment groups. The decision to switch the patients taking 3-drug regimens to 2-drug regimens was made by the treating physicians, which might have introduced significant bias. Second, we used convenient samples from patients receiving cART at two different hospitals designated for HIV care and did not estimate the appropriate case numbers of patients required to demonstrate the non-inferiority of 2-drug regimens to 3-drug regimens. Third, the analyses were conducted in the PP population and we might have overestimated the treatment responses for the two groups because we excluded the patients, particularly injecting drug users, who failed to complete the 48-week follow-up. Fourth, the information on time since HIV diagnosis, duration on cART before study recruitment and taking concurrent lipid-lowering agents or oral antidiabetic drugs was not available, and therefore, the impact of add-on lipid-lowering agents and antidiabetic drugs on the changes of lipid profiles and glycated hemoglobin, respectively, could not be assessed. Also, limited by the retrospective study design, no all of the included patients had complete lipid profiles for assessment of the evolution with treatment.

In conclusion, we found that dual therapy with lamivudine plus ritonavir-boosted lopinavir or darunavir could be an effective option to 3-drug regimens with two NRTIs and boosted PI in maintaining viral suppression at 48 weeks of follow-up.

Conflicts of interest

C.-C. H. has received research support from Gilead Sciences, Merck, and ViiV and speaker honoraria from Gilead Sciences and ViiV, and served on advisory boards for Gilead Sciences and ViiV.

Other authors report no conflicts of interest.

Acknowledgements

The authors would like to thank all the case managers for supporting the patients in the participating hospitals.

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