International Journal of Antimicrobial Agents 54 (2019) 35–42

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Effectiveness of switching from protease inhibitors to dolutegravir in combination with nucleoside reverse transcriptase inhibitors as maintenance antiretroviral therapy among HIV-positive patients

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ARTICLE INFO

Article history:
Received 2 November 2018
Accepted 16 March 2019

Editor: Professor Philippe Colson

Keywords:
Integrase strand transfer inhibitor
Virological failure
Genotypic resistance
Resistance-associated mutation
Metabolic complications

ABSTRACT

Prolonged exposure to regimens containing protease inhibitors (PIs) as second-line therapy for human immunodeficiency virus (HIV) infection may have a negative impact on metabolic profiles and increase the risk of cardiovascular diseases. Real-world experience with dolutegravir (DTG)-based regimens as alternatives to PI-based regimens is limited in antiretroviral-experienced patients with previous failure or intolerance to first-line therapy. The current study included HIV-positive patients receiving PI-containing regimens with viral suppression for ≥6 months. Virological response and lipid profiles were compared between patients who were subsequently switched to DTG-based therapy plus nucleoside reverse transcriptase inhibitors (NRTIs) and those remaining on their PI-containing regimen at Week 48. In total, 189 patients were switched to DTG-based regimens and 313 remained on PI-containing regimens during the observation period. Patients in the DTG group were younger (mean age 40.0 years vs. 44.6 years) and were more likely to have a previous history of virological failure (44.4% vs. 19.5%) than those in the PI group. At Week 48, 1.1% of the DTG group and 3.8% of the PI group had virological non-response (HIV-RNA load >50 copies/mL) (difference, −2.7%, 95% CI −5.5% to 0.5%). The presence of M184V/I mutation and other NRTI resistance-associated mutations (RAMs) did not increase the risk of virological failure in either group. Patients switched to DTG-based therapy had statistically significant improvement of lipid profiles. Among virally suppressed HIV-positive patients, a switch to DTG-based therapy was non-inferior to continuation of PI-based therapy in virological effectiveness at Week 48, even in the presence of NRTI RAMs.

1. Introduction

For human immunodeficiency virus (HIV)-positive patients who experience virological failure with first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral therapy (ART), protease inhibitors (PIs) are recommended in major HIV treatment guidelines to achieve re-suppression of viral replication and to improve clinical outcome [1–3], based on the results of several clinical trials in which combination of boosted PI and nucleoside reverse transcriptase inhibitors (NRTIs) demonstrated efficacy in achieving sustained viral suppression up to 96 weeks [4–6]. However, prolonged exposure to PIs has been shown to cause several metabolic complications, including hyperlipidaemia and insulin resistance [7]. Furthermore, a recent analysis from the D:A:D (Data collection on Adverse events of Anti-HIV Drugs) cohort also suggested that prolonged exposure to boosted darunavir might increase the risk of cardiovascular diseases [8]. As

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https://doi.org/10.1016/j.ijantimicag.2019.03.016
0924-8579/

HIV-positive patients receiving combination ART (cART) are aging, alternative regimens with better metabolic and safety profiles are becoming more and more desirable.

Compared with PIs, integrase strand transfer inhibitors (InSTIs) are associated with lower rates of metabolic complications and are therefore an attractive alternative for patients receiving PI-based therapy [7]. However, the efficacy of the first-generation InSTIs in maintaining viral suppression among HIV-positive patients with a prior history of virological failure has been questioned. In the SWITCHMRK study that assessed the efficacy of switching from a boosted PI-based regimen to a raltegravir-based regimen among virally suppressed patients, raltegravir-based therapy was associated with a higher rate of virological failure after 24 weeks [9]. Moreover, in a subgroup analysis, patients with a prior history of virological failure were more likely to experience viral rebound while on raltegravir-based cART [9]. One possible explanation is that the genetic barrier of raltegravir is lower than that of boosted PIs, which might be associated with failure to maintain suppression of resistant viruses [10].

Dolutegravir (DTG), a second-generation InSTI, has a high genetic barrier compared with first-generation InSTIs such as raltegravir or elvitegravir [11]. However, only a few clinical trials have investigated the role of DTG to replace boosted PIs in virally suppressed patients. In the NEAT022 study, Gatell et al. demonstrated that switching from a boosted PI-based ART regimen to a DTG-based regimen in virally suppressed HIV-positive patients with high cardiovascular risk led to an improvement of lipid profiles at Week 96 while maintaining viral suppression [12]. However, the study excluded patients with known archived genotypic resistance to NRTIs and the results could not be generalised to patients with a prior history of virological failure with emergent resistance-associated mutations (RAMs). In the DAWNING study, HIV-positive patients with virological failure with first-line NNRTI-based cART were randomised to receive either DTG-based or boosted lopinavir-based therapy, both combined with two NRTIs [13]. The study was terminated prematurely due to the superiority demonstrated in the DTG arm in the interim analysis. Owing to the early termination, long-term data are needed to confirm the durability of DTG-based regimens as salvage therapy for patients experiencing failure with first-line NNRTI-based cART.

The current study aimed to examine the virological effectiveness and metabolic impact of DTG in combination with NRTI(s) to substitute boosted PI-containing therapy in virally suppressed HIV-positive patients with a prior history of failure or intolerance to first-line cART in a real-world setting.

2. Methods

2.1. Study population

This was a single-centre, observational cohort study with retrospective data collection. HIV-positive individuals aged ≥20 years who received HIV care at National Taiwan University Hospital (NTUH) between 1 September 2016 and 30 April 2017 were eligible for inclusion in the study. To be included in further analysis, patients must have had a history of virological failure or intolerance to first-line NNRTI-based therapy. All included patients must have remained on boosted or unboosted PI-containing regimens with plasma HIV-RNA load (PVL) <200 copies/mL for ≥6 months. Exclusion criteria included those with a history of treatment failure while receiving raltegravir- or elvitegravir-based therapy, or with HIV-1 infection with archived mutations that are predicted to confer intermediate- to high-level resistance to DTG based on the Stanford HIV Drug Resistance Database [14]. Patients switched to DTG plus boosted PI or other agents were also excluded.

2.2. Study procedure

In Taiwan, DTG and its fixed-dose combination with abacavir and lamivudine (3TC) were introduced into clinical use in September 2016. Following their introduction, HIV-positive patients who were receiving PI-based regimens with viral suppression were switched to DTG-based therapy at the discretion of the treating physicians (DTG group). Meanwhile, patients who continued their PI-containing regimens were included as a control group (PI group). This study aimed to compare the virological effectiveness between these two groups: thus, the DTG group was followed for ≥48 weeks after switch to DTG-based therapy, and the PI group was followed for 48 weeks after their first clinic visit within the study period.

Medical records of all included patients were reviewed retrospectively to collect information on demographic and clinical characteristics. According to the national HIV treatment guidelines in Taiwan, all included HIV-positive individuals were followed at the hospital every 3 months, and laboratory tests were performed every 3–6 months including PVL, $CD4^+$ T-cell count, viral hepatitis serological testing, renal function, liver function, lipid profile and serum glucose level.

In Taiwan, genotypic resistance testing is performed by amplification of HIV-RNA and was either retrospectively conducted using stored blood samples collected before initiation of first-line therapy for the purpose of surveillance or at the time of virological failure on an as-needed basis [15,16]. These results might not be readily available before a decision to switch regimens was made. For patients with available genotypic resistance testing results, the genotypic susceptibility score (GSS) to the prescribed NRTIs was determined using the Stanford HIV Drug Resistance Database [14].

2.3. Study endpoint

The primary outcome was the proportion of patients with virological non-response at Week 48, which was defined as: (i) patients who remained on DTG- or PI-based regimens with PVL ≥ 50 copies/mL at Week 48; (ii) patients with two consecutive PVL > 400 copies/mL with DTG- or PI-based therapy during the observation period; and (iii) patients who discontinued DTG- or PI-based regimens owing to viral rebound before Week 48. For these patients with viral rebound, the decision to continue the current cART regimen or to change to other salvage regimens was made by the treating physicians. Patients who switched cART owing to adverse effects were also recorded accordingly. Those who died, were lost to follow-up for ≥12 weeks or remained on the same cART but had no virological data before or at 48 ± 4 weeks were classified as having 'no virological data'.

Secondary endpoints included (i) changes in lipid profile from baseline to Week 48 and (ii) change of estimated glomerular filtration rate (eGFR) (using the Modification of Diet in Renal Disease equation) from baseline to Week 48 [17]. To investigate the impact of NRTI RAMs on the virological effectiveness of DTG-based cART, a per-protocol analysis was performed to estimate the proportion of viral suppression at Week 48 among patients with HIV-1 harbouring M184V or M184I mutation and different GSS to NRTIs in both arms. The study was approved by the Research Ethics Committee of NTUH. Informed consent was waived due to the retrospective study design.

2.4. Statistical analysis

Comparison of demographic and clinical characteristics was made between patients in the DTG and PI groups. Non-categorical variables were compared using Student's *t*-test or Mann–Whitney *U*-test, and categorical variables were compared using χ^2 test or

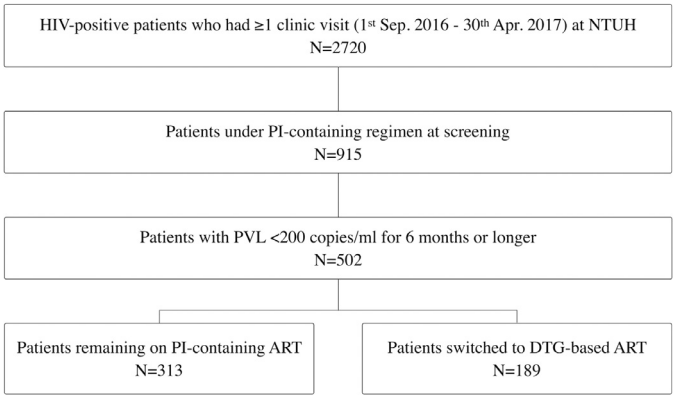

Fig. 1. Flow diagram of the study. ART, antiretroviral therapy; DTG, dolutegravir; HIV, human immunodeficiency virus; NTUH, National Taiwan University Hospital; PI, protease inhibitor.

Fisher's exact test. When comparison of categorical variables was required for more than two groups, Kruskal–Wallis test was used and post-hoc analysis with Dunn's test was applied for pairwise comparisons if needed [18]. For the primary endpoint, a US Food and Drug Administration (FDA) snapshot analysis was performed at Week 48 and the proportions of virological non-response between the two groups were compared at Week 48 with a non-inferiority margin of 4%. Multivariate analyses were then performed to identify factors associated with virological non-response during the study period. Multivariate analysis was performed using a logistic regression model. A backward elimination process was used during the multivariate analysis in which all possible associated factors were included in the model initially and factors were removed from the model starting with factors with the largest *P*-value. The process was repeated until all factors in the model had a *P*-value of <0.2. Statistical analyses were performed using STATA software v.14.0 S/E (StataCorp LP, College Station, TX). All *P*-values were two-sided.

3. Results

3.1. Study population

During the study period, 2720 HIV-positive patients had at least one clinic visit for HIV care at NTUH. After excluding patients receiving non-PI-containing regimens and patients failing to achieve viral suppression for ≥6 months, a total of 502 HIV-positive patients were eligible for further analysis. Among these 502 patients, 189 were switched to DTG-based therapy during subsequent clinic visits within the study period (Fig. 1). Among the patients switched from PI-containing regimens to DTG-based regimens, 75.1% (142/189) were switched for drug simplification, 15.3% (29/189) for adverse effects and 9.5% (18/189) owing to metabolic concerns.

The baseline characteristics of the DTG and PI groups are shown in Table 1. Compared with patients in the PI group, those in the DTG group were younger (mean age 40.0 years vs. 44.6 years), had a shorter duration of viral suppression before inclusion in this study (median 5 years vs. 6 years) and were more likely to be seropositive for hepatitis C virus (17.6% vs. 10.5%). Previous virological failure had occurred in 44.4% of patients before the switch to a DTG-based regimen compared with 19.5% in the PI group. Therefore, significantly more patients in the DTG group had available results of HIV genotypic resistance testing (54.0% vs. 20.1%). Among the patients with available data for genotypic resistance testing, the proportion of patients with HIV-1 harbouring M184V or M184I mutation was similar for both groups (45.1% vs. 47.6%).

The cART regimens in this study are listed in Table 1. More patients in the DTG group had been receiving boosted lopinavir-based therapy (43.9% vs. 10.2%). Meanwhile, the majority of patients in the PI group had been receiving unboosted atazanavir-based therapy on inclusion in this study. Regarding the NRTIs, most patients had been receiving emtricitabine (FTC) or lamivudine (3TC), followed by tenofovir disoproxil fumarate (TDF) as one of the NRTI backbone agents in 65.4% and 77.6% of the DTG and PI groups, respectively.

3.2. Virological effectiveness

Analysis of virological effectiveness at Week 48 using the FDA snapshot algorithm is shown in Fig. 2. Overall, 85.2% of patients in the DTG group and 85.3% in the PI group achieved viral suppression at Week 48, whilst 2 patients (1.1%) in the DTG group and 12 patients (3.8%) in the PI group had virological non-response, with a difference in virological non-response of –2.7% [95% confidence interval (CI) –5.5% to 0.5%]. Among the 189 patients in the DTG group, 84 (44.4%) had a previous history of virological failure prior to the switch, and 105 (55.6%) were receiving a PI-based regimen owing to previous intolerance to NNRTIs. Among those with a history of virological failure, 1.2% (1/84) had a PVL ≥ 50 copies/mL at Week 48 compared with 1.0% (1/105) among patients without prior failure. The rate of virological non-response was not statistically significantly different between these two subgroups. In the DTG group, the PVL of the two patients with virological non-response at Week 48 was 173 copies/mL and 432 copies/mL, respectively. In the PI group, the PVL of the 12 patients (6 receiving boosted darunavir, 4 unboosted atazanavir, 1 boosted atazanavir and 1 boosted lopinavir) with virological non-response ranged from 50 copies/mL to 102 000 copies/mL, and 4 patients (2 receiving boosted darunavir and 2 unboosted atazanavir) had PVL > 1000 copies/mL at Week 48. Two of the latter four patients in the PI group were successfully genotyped for HIV drug resistance; however, no emergent RAMs were detected.

In the DTG group, 26 patients (13.8%) had no virological data at Week 48 (Fig. 2), including 7 with early treatment discontinuation due to adverse effects (Supplementary Table S1), 7 being lost to follow-up during the observation period (including 1 patient who was incarcerated and 1 who died of lung cancer) and 12 remaining on their DTG-based cART but without undergoing blood testing during the study window. In the PI group, 34 patients (10.9%) continued their PI-based cART at Week 48 but did not undergo blood testing.

In the per-protocol analysis to evaluate the impact of NRTI resistance on the virological effectiveness at Week 48, 97.1% (34/35) of patients in the DTG group with an archived mutation of M184V or M184I achieved viral suppression at Week 48, which was similar to that of patients without M184V/I mutation (98.1%; 51/52) ($P = 0.56$) (Fig. 3a). However, in the PI group only 76.7% (23/30) of patients without M184V/I mutations achieved viral suppression at Week 48 compared with those with archived M184V/I mutation (96.2%; 25/26) ($P = 0.06$). Similar results could be observed after stratifying patients by their GSS to NRTIs (Fig. 3b). In the DTG group, the proportion of viral suppression at Week 48 for patients with a GSS of 2.0, 1.0–1.75 and 0–0.75 was 98.0%, 95.8% and 100%, respectively ($P = 0.31$). In the PI group, only 74.1% (20/27) of patients receiving PI-based regimens with a GSS of 2.0 achieved viral suppression at Week 48, which was lower than that of those with a GSS of 1.0–1.75 or 0–0.75 (96.2% and 100%, respectively).

In the multivariate analysis, older age was associated with a higher risk of virological non-response at Week 48 [relative risk (RR) = 1.05 per 1-year increase, 95% CI 1.00–1.10], whilst a longer duration on suppressive cART before inclusion in the study had

Table 1
Baseline characteristics of the included patient cohort

Characteristic	DTG group ($N = 189$)	PI group ($N = 313$)	P-value
Age (years) (mean ± S.D.)	40.0 ± 10.2	44.6 ± 10.7	**<0.001**
Male sex [n (%)]	185 (97.9)	302 (96.5)	0.43
Men who have sex with men [n (%)]	176 (93.1)	282 (90.1)	0.26
PVL at inclusion ($\log_{10}$ copies/mL) [median (IQR)]	1.3 (1.3–1.3)	1.3 (1.3–1.3)	0.82
PVL <50 copies/mL at inclusion [n (%)]	183 (96.8)	305 (97.4)	0.78
$CD4^+$ T-cell count at inclusion (cells/mL) (mean ± S.D.)	619.8 ± 259.9	630.2 ± 270.1	0.68
HBsAg seropositivity [n (%)]	27/175 (15.4)	56/313 (17.9)	0.49
Anti-HCV Ab seropositivity [n (%)]	33/188 (17.6)	33/313 (10.5)	**0.03**
Patients with previous virological failure [n (%)]	84 (44.4)	61 (19.5)	**<0.001**
Duration of viral suppression before inclusion (years) [median (IQR)]	5 (3–7)	6 (4–9)	**<0.001**
Patients with available genotypic resistance results [n (%)]	102 (54.0)	63 (20.1)	**<0.001**
Patients with M184I/V mutations	46/102 (45.1)	30/63 (47.6)	0.75
Lipid profile at baseline			
LDL-C (mg/dL) (mean ± S.D.)	100.5 ± 32.3	99.9 ± 29.6	0.85
Triglyceride (mg/dL) (mean ± S.D.)	170.7 ± 93.2	155.6 ± 122.8	0.17
Total cholesterol (mg/dL) [median (S.D.)]	174.5 (43.3)	166.2 (35.6)	**0.03**
HDL-C-to-total cholesterol ratio [median (IQR)]	4.0 (3.3–4.7)	3.8 (3.3–4.6)	0.39
eGFR at baseline (mL/min) [median (S.D.)]	103.3 (34.1)	99.3 (23.0)	0.16
Reason for switching to DTG-based therapy [n (%)]			
Simplification	142 (75.1)	–	
Adverse effects/intolerance	29 (15.3)	–	
Metabolic syndrome	18 (9.5)	–	
Antiretroviral agents used at inclusion [n (%)]			
Boosted darunavir	49 (25.9)	54 (17.3)	
Boosted atazanavir	13 (6.9)	12 (3.8)	
Unboosted atazanavir	44 (23.3)	215 (68.1)	
Boosted lopinavir	83 (43.9)	32 (10.2)	
3TC or FTC	182 (96.3)	312 (99.7)	
TDF	119 (63.0)	243 (77.6)	
Abacavir	43 (22.8)	38 (12.1)	
Zidovudine	23 (12.2)	32 (10.2)	
Others[a]	9 (4.8)	0 (0)	
NRTI(s) used after switch to DTG [n (%)]			
TDF plus FTC	103 (54.5)	–	
Abacavir plus 3TC	83 (43.9)	–	
Zidovudine plus 3TC	1 (0.5)	–	
3TC alone	2 (1.1)	–	

[a] Including 1 patient receiving etravirine, 7 receiving raltegravir and 1 receiving dolutegravir.
3TC, lamivudine; anti-HCV Ab, anti-hepatitis C antibody; DTG, dolutegravir; eGFR, estimated glomerular filtration rate; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PVL, plasma HIV-RNA load; S.D., standard deviation; TDF, tenofovir disoproxil fumarate.

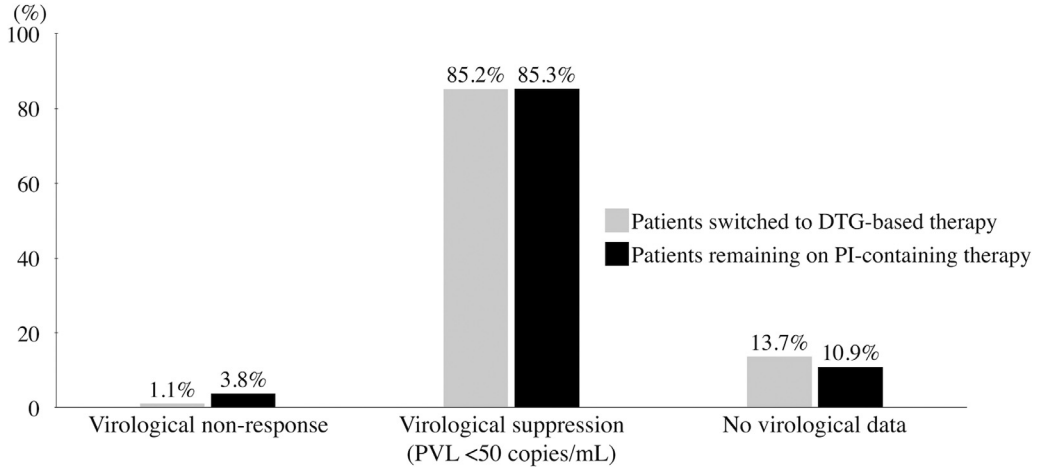

Fig. 2. FDA snapshot analysis results at Week 48. DTG, dolutegravir; PI, protease inhibitor; PVL, plasma HIV-RNA load.

a significantly lower risk of virological non-response at Week 48 (RR = 0.76 per 1-year increase, 95% CI 0.63–0.93) (Table 2).

3.3. Lipid profile and renal function

Changes in lipid profiles from baseline to Week 48 for both groups are shown in Fig. 4. Whilst changes in low-density lipoprotein cholesterol (LDL-C) and in total cholesterol (TC) to high-density lipoprotein cholesterol (HDL-C) ratio were similar between the DTG and PI groups, the DTG group had statistically significant decreases in triglyceride (TG) and TC levels compared with the PI group. Patients in the DTG group experienced a more significant decline in eGFR than those in the PI group at Week 24 (–15.3 mL/min vs. –0.4 mL/min; $P < 0.001$) and Week 48 (–18.2 mL/min vs. –0.7 mL/min; $P < 0.001$) (Fig. 5).

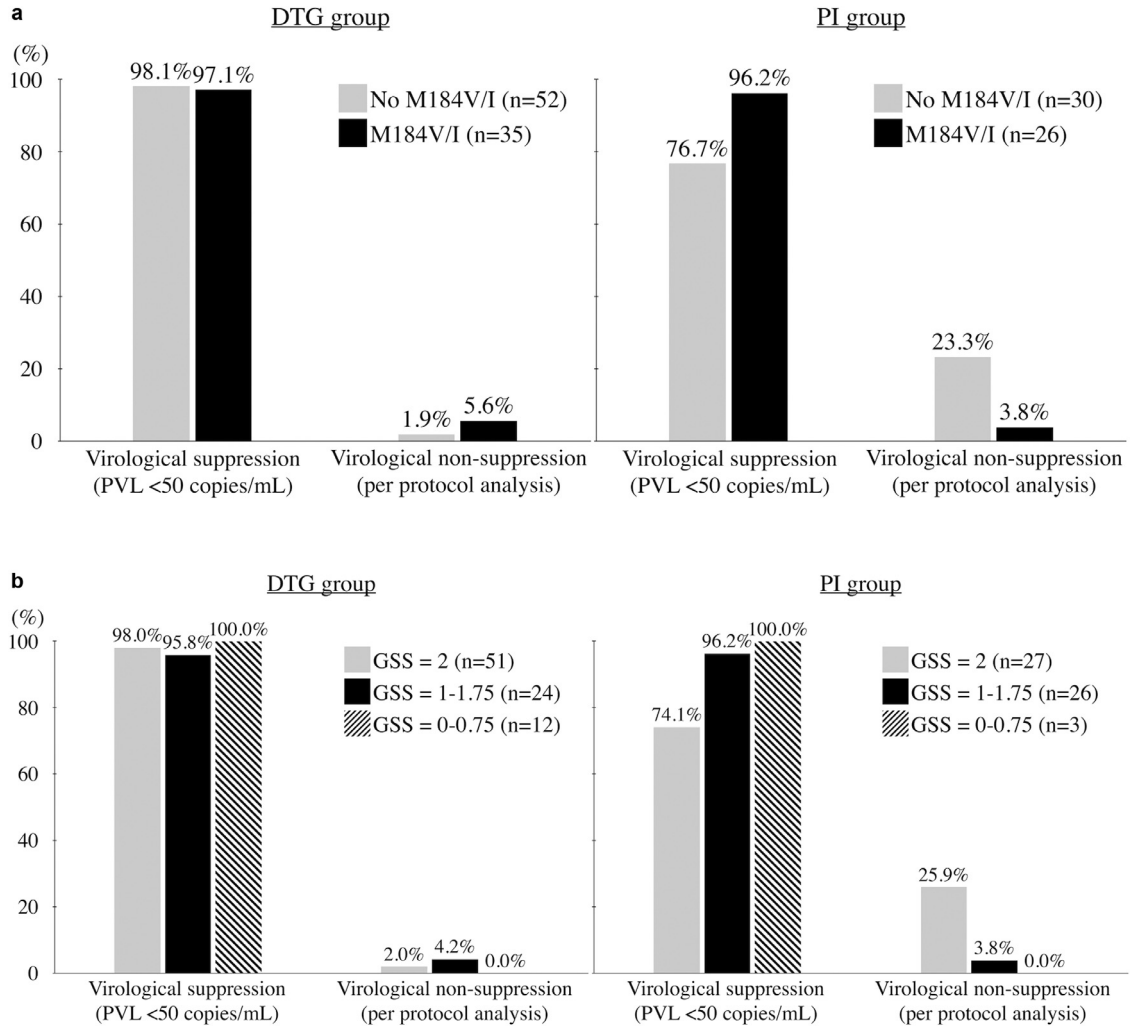

Fig. 3. Probability of maintaining viral suppression at Week 48 in the per-protocol analysis stratified by (a) the presence of archived M184V/I mutation and (b) the genotypic susceptibility score (GSS) of nucleoside reverse transcriptase inhibitors. DTG, dolutegravir; PI, protease inhibitor; PVL, plasma HIV-RNA load.

Table 2
Univariate and multivariate analyses of factors associated with virological failure

Factor	RR (95% CI)	
	Univariate analysis	Multivariate analysis
Age, per 1-year increase	1.04 (0.99–1.09)	1.05 (1.00–1.10)
Positive HBsAg	2.04 (0.62–6.68)	–
Anti-HCV Ab seropositivity	0.48 (0.06–3.74)	–
Prior history of virological failure	1.80 (0.61–5.29)	–
Duration of viral suppression before inclusion, per 1-year increase	0.82 (0.68–1.00)	0.76 (0.63–0.93)
$CD4^+$ T-cell count, per 50 cells/mm^3 increase	1.00 (0.90–1.10)	–
Switch to DTG therapy	0.27 (0.06–1.25)	0.25 (0.05–1.14)

anti-HCV Ab, anti-hepatitis C antibody; CI, confidence interval; DTG, dolutegravir; HBsAg, hepatitis B surface antigen; RR, relative risk.

4. Discussion

In this cohort study evaluating the virological effectiveness of switching from PI-containing cART to DTG in combination with one or two NRTIs among ART-experienced HIV-positive patients, it was found that a switch to DTG-based therapy was non-inferior to continuation of PI-containing regimens in terms of the risk of virological non-responses at Week 48 (1.1% vs. 3.8%). It was also found that the presence of an archived M184V mutation or other NRTI RAMs with lower GSS had little impact on the virological effectiveness of a switch to DTG-based therapy.

The efficacy of InSTI-based regimens as maintenance or salvage ART has been evaluated in several studies [9,13,19,20]. In the SWITCHMRK and SPIRAL studies, patients who had achieved viral suppression while receiving boosted PI-based therapy were randomised to either continue their PI-based regimen or to change to raltegravir-based ART, both in combination with NRTIs [9,19]. However, the results of these two clinical trials are conflicting. In the SWITCHMRK study, patients switched to raltegravir were more likely to experience viral rebound [9]. In the subgroup analysis, patients with a prior history of virological failure were at higher risk of virological failure compared with those without prior

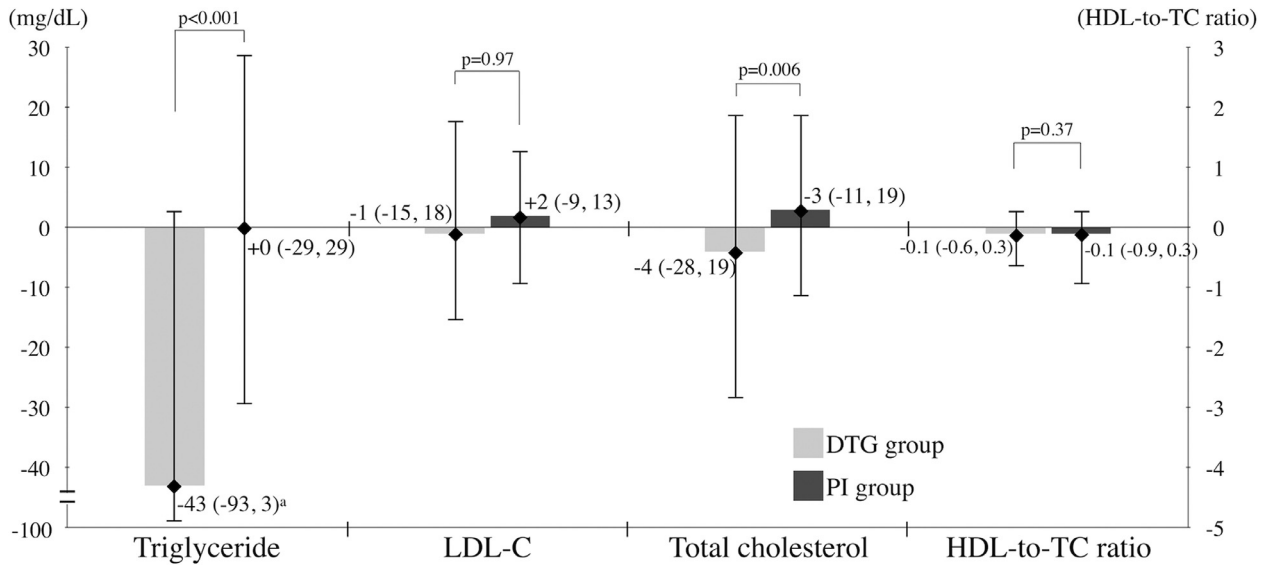

Fig. 4. Changes in lipid profile from baseline to Week 48. DTG, dolutegravir; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PI, protease inhibitor; TC, total cholesterol. [a] Change from baseline [median (interquartile range)].

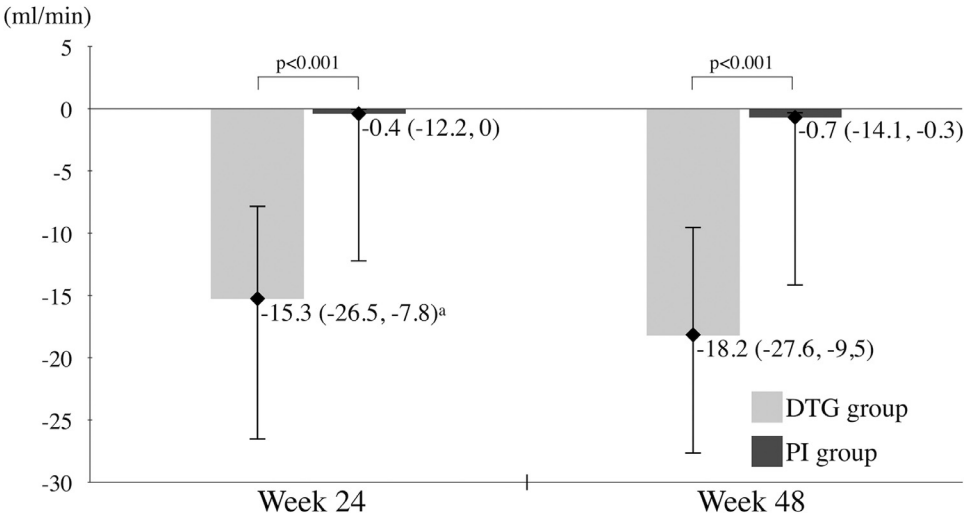

Fig. 5. Changes in estimate glomerular filtration rate from baseline to Weeks 24 and 48. DTG, dolutegravir; PI, protease inhibitor. [a] Change from baseline [median (95% confidence interval)].

failure. However, this finding was not observed in the SPIRAL study, which demonstrated non-inferior virological efficacy of raltegravir-based therapy compared with PI-based regimens [19]. Such a discrepancy between these two studies might be explained by the difference in patients' prior duration of viral suppression before switch of ART. Patients in the SPIRAL study had a median duration of 6 years of viral suppression before switch to raltegravir-based therapy, which was much longer than that in the SWITCHMRK study which enrolled patients with a median duration of 3.4 years of viral suppression before the switch. However, both studies did not report on the accumulation of archived HIV RAMs before randomisation and therefore direct comparison of the results is not possible. Nevertheless, switching ART-experienced HIV-positive patients from PI-based therapy to regimens containing a core agent with a lower genetic barrier, such as raltegravir, should always be done cautiously. Recently, Perez-Valero et al. reported 24-week results of switching virally suppressed patients to a single-tablet regimen with cobicistat-boosted elvitegravir, emtricitabine and tenofovir alafenamide, in which all of the patients remained virally suppressed at Week 24 [20]. However, the study only included patients with HIV-1 harbouring M184V and/or M184I mutations without other RAMs to NRTIs. Therefore, the efficacy of first-generation InSTIs among patients with more extensive NRTI resistance remains unclear.

In our study, both patients with and without M184V/I in the DTG group had a high rate of maintaining viral suppression at Week 48 (97.1% vs. 98.1%; Fig. 3a). This study is not the first to describe the satisfactory viral effectiveness among patients with HIV-1 harbouring NRTI RAMs while receiving cART with a lower GSS. In the DAWNING study, in which viraemic HIV-positive patients were switched to DTG-based or boosted lopinavir-based therapy after failing first-line NNRTI-based therapy, patients taking less than two fully active NRTIs had a higher rate of achieving viral suppression at Week 24 compared with those taking two fully active NRTIs [13]. In the EARNEST study, 89% of patients switched to boosted PI in combination with NRTIs that had no predictive activity remained virally suppressed by Week 144 [21]. Reduced fitness observed in HIV-1 harbouring M184V mutation might have contributed to these observations. In a study including patients with HIV-1 harbouring M184V mutation, Castagna et al. demonstrated

that monotherapy with lamivudine reduced the PVL by 0.5 $\log_{10}$ copies/mL and delayed both immunological and clinical progression to acquired immune deficiency syndrome (AIDS) compared with patients receiving no ART [22]. In the MOBIDIP study, whilst switch to boosted PI monotherapy was associated with a higher risk of viral rebound, addition of lamivudine only to boosted PI resulted in good viral suppression despite the fact that >95% of participants had archived M184V mutation [23]. Furthermore, among HIV-1 harbouring other NRTI RAMs, the presence of M184V mutation will decrease the fold-change of phenotypic resistance to other NRTIs such as zidovudine or tenofovir [24]. Moreover, boosted PIs and DTG are known to possess a higher genetic barrier to emergent resistance mutations and might also contribute to the sustained viral effectiveness observed [25,26]. On the other hand, in the PI group in the current study, the absence of RAMs is paradoxically associated with poor virological outcome. This is likely related to the adherence issue of patients, as has been shown in the DAWNING and EARNEST studies [13,21].

Replacing a PI with an InSTI has been shown to result in improvement of metabolic profiles in several clinical studies [9,12,19]. Gatell et al. recently evaluated the benefits among HIV-positive patients with high cardiovascular risk of switching from boosted PI-based therapy to DTG-based therapy [12]. Patients who were switched to DTG-based therapy had significant decreases of TC, LDL-C and TG levels as well as TC-to-HDL-C ratio, which supports the strategy of switching to a more lipid-friendly regimen in high-risk patients to reduce the risk of cardiovascular disease in the long-term. In the current study, the reductions of TC and TG from baseline to Week 48 were also more significant in the DTG group. However, the reduction of TC from baseline appeared more modest compared with the observation in the study by Gatell et al. (0.5% vs. 8.7%) and there was no significant decrease of LDL-C or TC-to-HDL-C ratio in the current study. The difference might be explained by the fact that a high proportion of patients in the current study had been receiving unboosted atazanavir-based regimens in both groups (23.3% in the DTG group and 68.1% in the PI group), which might be associated with a less significant impact on lipid profiles [7,27]. Patients who were switched to DTG-based therapy also experienced a decline in the eGFR in the current study, which was similar to the findings of other clinical trials and was likely related to direct inhibition of creatinine excretion in the kidney rather than deterioration of renal function [28].

This retrospective cohort study has several limitations and interpretation of the results should be cautious. First, the switch of regimen was not randomised and the baseline characteristics were not balanced between the two groups. Patients in the PI group were older and significantly fewer patients had previous virological failure. More patients in the PI group were able to maintain viral suppression while receiving unboosted atazanavir-based regimens, suggesting good adherence to cART. However, most of the unbalanced factors in this study favoured the PI group and we believe that this bias would make the finding of non-inferiority of a switch to DTG-based therapy to continuation of PI-based regimens more robust. Second, most of the patients had remained virally suppressed for a long duration (median 6 years) before switch in this study. Therefore, switching patients who have recently achieved viral suppression while on boosted PI therapy after prior virological failures to NNRTI-containing regimens should be cautious. Third, only 44.4% of the patients in the DTG group had a prior history of virological failure, and the results of archived genotypic resistance were not available for each patient. Fourth, therapeutic drug monitoring of ART was not available for assessment of adherence of the patients who experienced viral rebound during the study period. Finally, this was a retrospective study conducted when DTG was introduced into Taiwan, which made an a priori estimation of sample size not possible. A prospectively designed, properly controlled clinical trial is warranted to confirm these findings.

In conclusion, this study demonstrates that switch to DTG-based cART is non-inferior to remaining on PI-based cART among virally suppressed patients receiving PI-based therapy due to prior virological failure or intolerance to first-line NNRTI-based therapy, and the presence of M184V or other archived NRTI RAMs does not reduce the effectiveness of DTG-based therapy.

Acknowledgment

The authors would like to thank Prof. Charles Boucher (Department of Virology, Erasmus Medical Center, University Medical Center, Rotterdam, the Netherlands) for the critical review of the manuscript and the staff of the Department of Medical Research, National Taiwan University Hospital for the Integrated Medical Database (NTUH-iMD).

Funding

None.

Competing interests

C-CH has received research support from Janssen, AbbVie, Bristol-Myers Squibb, Merck, Gilead Sciences and ViiV, has received speaker's honoraria from Gilead Sciences, and has served on advisory boards for Gilead Sciences, ViiV, AbbVie and Janssen. All other authors declare no competing interests.

Ethical approval

This study was approved by the Research Ethics Committee of the National Taiwan University Hospital [registration no. 201003112R].

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.03.016.

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