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BRIEF REPORT

Switching Tenofovir/Emtricitabine/Efavirenz (TDF/FTC/EFV) to TDF/FTC/Rilpivirine vs Continuing TDF/FTC/EFV in HIV-Infected Patients With Virological Suppression: A Randomized Controlled Trial

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A randomized controlled noninferiority trial was conducted in HIV-infected patients receiving tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV) with virological suppression in a resource-limited setting. Switching to TDF/FTC/rilpivirine was noninferior to continuing TDF/FTC/EFV in terms of maintaining compete viral suppression at 24 weeks and provided better lipid profiles and fewer central nervous system adverse effects.

Keywords. efavirenz; rilpivirine; switching; antiretroviral therapy; randomized controlled trial.

According to the proven benefits of early initiation of antiretroviral therapy (ART) regardless of CD4 cell count, there has been a large increase in the use of ART, particularly in low- to middle-income countries. Scaling-up of ART programs with a goal of universal access and standardization of ART regimens in resource-limited settings is ongoing [1]. In 2017, approximately 21.7 million people globally were receiving ART [2]. In Thailand, the reported number of people receiving ART in 2017 was >300 000. The World Health Organization and national AIDS programs in many developing countries have recommended tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV) as a preferred firstline regimen [3, 4] due to its efficacy and tolerability. However, drug-related central nervous system (CNS) adverse effects and metabolic complications, especially dyslipidemia, are primary concerns among EFV users. CNS disturbance, the most frequent adverse event related to EFV, varies from 8% to 40% of patients and leads to interruption of treatment in 2% to 11% [5, 6]. In concerns of dyslipidemia, EFV is associated with increasing of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL) levels, with variable effects on high-density lipoprotein cholesterol (HDL) levels [7].

Rilpivirine (RPV), a newer non-nucleoside reverse transcriptase inhibitor (NNRTI), is claimed to have fewer adverse effects with comparable efficacy when compared with the forerunner NNRTIs. From previous randomized controlled studies, ECHO [8] and THRIVE [9], RPV-based regimens have shown noninferior efficacy when compared with EFV-based regimens in treatment-naïve HIV-infected patients, especially in the groups of patients with HIV RNA <100 000 copies/mL. CNS adverse events and dyslipidemia were less common in the RPV group compared with the EFV group [8, 9]. However, these clinical studies were conducted in treatment-naïve HIV-infected patients. A retrospective study evaluating the efficacy of switching to TDF/FTC/RPV from other ART regimens in virologically suppressed patients showed no significant difference in virological failure and a better safety outcome [10]. There has been no randomized controlled study that focused on switching TDF/FTC/EFV, the most commonly used regimen in resource-limited settings, to the regimen of TDF/FTC/RPV. Moreover, RPV is a smaller-sized pill and a more affordable NNRTI in low- to middle-income countries. This would be beyond benefit in terms of national health economics if we could demonstrate the equivalent efficacy of these 2 regimens. This study aimed to compare the efficacy and adverse events between switching from TDF/FTC/EFV to TDF/FTC/RPV and continuing TDF/FTC/EFV in HIV-infected patients with complete virological suppression.

METHODS

A randomized controlled, noninferiority, open-labeled study was conducted among HIV-infected patients who received a TDF/FTC/EFV regimen and had complete viral suppression. The primary objective was to determine the noninferiority in virological response of switching from TDF/FTC/EFV to a TDF/FTC/RPV regimen compared with continuing a TDF/FTC/EFV regimen, in terms of percentage of patients who had sustained complete virological suppression. The secondary objectives were to evaluate the mean changes of CD4 cell counts and lipid levels (including TC, LDL, HDL, and TG) and the frequency of CNS adverse events, along with other significant adverse events, between the 2 groups.

The patients were enrolled between January and December of 2017 and followed up for 24 weeks in a medical school hospital

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in Bangkok, Thailand. All the study patients had documented HIV infection and met the following criteria: (1) >18 years of age, (2) receiving TDF/FTC/EFV for at least 6 months, (3) had undetectable HIV RNA (<50 copies/mL) within 3 months, and (4) able to sign an informed consent. Patients were excluded if they had a history of HIV drug resistance, used other drugs that might interact with RPV, or were pregnant or breastfeeding. Written informed consent was obtained from all eligible patients before randomization. The study was approved by the local institutional review board and registered with ClinicalTrials.gov, number NCT03251690.

All the enrolled patients were randomly assigned (1:1) to switch from TDF/FTC/EFV (300/200/600 mg) once daily to TDF/FTC/RPV (300/200/25 mg) once daily (switching group) or to continue TDF/FTC/EFV (300/200/600 mg) once daily (continuing group). RPV was taken with a regular meal, whereas EFV was required to be taken on an empty stomach before bedtime. All patients were prospectively followed up for 24 weeks. The definition for virological suppression in this study was an HIV RNA <50 copies/mL. Adherence was measured by patient self-report using a semistructured questionnaire, which was administered during a face-to-face interview.

Sample size was calculated from the proportional response rates from a previous trial [8]. A population of 122 in each group was required to establish the noninferiority of the switching group compared with the continuing group, at 0.8 power and a 0.05 significance level. The analysis was based on intention-to-treat (ITT) populations, with a prespecified noninferior margin of 12%. Baseline characteristics and clinical outcomes were compared using the *t* test or Mann-Whitney *U* test for continuous variables and the χ^2 or Fisher exact test for categorical variables.

RESULTS

A total of 246 patients were enrolled and analyzed in this study. There were 122 patients in the switching group and 124 patients in the continuing group. One hundred fifty-five (63.0%) were male, and the mean (SD) age was 44.6 (10.4) years. Seventy-four (30.1%) patients had previous AIDS-defining illness. The median (interquartile range [IQR]) duration of ART was 8.1 (5.3–12.1) years. At baseline, the mean (SD) CD4 cell count was 565 (229) cells/mm^3. The mean (SD) values of lipid profiles at baseline were as follows: TC 196 (23) mg/dL, LDL 117 (21) mg/dL, HDL 47 (15) mg/dL, and TG 148 (101) mg/dL. Forty-eight (11.3%) patients were on lipid-lowering agents at the time of recruitment. Twenty-four (9.8%) patients had CNS adverse effects at baseline—the most common symptom was dizziness. All baseline demographic data, duration of ART, CD4 cell count, lipid profiles, eGFR, liver function test, proportion of patients receiving lipid-lowering agents, and proportion of patients with CNS adverse effects were similar between the 2 groups ($P > .05$), as summarized in Table 1.

In an ITT analysis for the primary end point at week 24, 117 (95.9%) patients from the switching group and 121 (97.6%) patients from the continuing group maintained HIV RNA at <50 copies/mL (difference, 1.68%; 95% confidence interval, –7.06 to 3.35). This met the prespecified noninferiority criterion (Figure 1). The mean (SD) CD4 cell counts at week 24 were 564 (214) and 581 (231) cells/mm^3 in the switching group and the continuing group, respectively ($P = .604$). All patients had self-report adherence >95%. At week 24, there were significant differences in the mean changes of TC, LDL, HDL, and TG between the 2 treatment groups ($P < .05$); that is, the decreases of TC, LDL, HDL, and TG from baseline were significantly greater in the switching group when compared with the changes in the continuing group (Figure 1). At week 24, CNS adverse events were observed in 8 (6.5%) patients in the continuing group but were not observed in the switching group ($P = .007$). The most common CNS adverse effects in this study were dizziness and lightheadedness, usually a few hours after taking the TDF/FTC/EFV or in the morning upon waking up. No other appreciable clinical and laboratory adverse events were observed throughout the study. There was no patient lost to follow-up during the study.

DISCUSSION

The once-daily regimen of TDF/FTC/RPV provides a simplified treatment option for ART-naïve patients with baseline HIV RNA ≤100 000 copies/mL [8, 9]. The pooled 96-week data from the ECHO and THRIVE studies in treatment-naïve patients demonstrated a noninferiority of TDF/FTC/RPV when compared with a TDF/FTC/EFV regimen. However, the virologic failure rate was higher in the TDF/FTC/RPV group, and this was balanced with higher rates of discontinuations due to adverse events in the TDF/FTC/EFV group [11]. Baseline HIV RNA ≤100 000 copies/mL was associated with a higher virological success rate when compared with those with a baseline HIV RNA >100 000 copies/mL [8, 9]. However, baseline HIV RNA is not routinely tested before ART initiation in resource-limited settings, and use of RPV as an initial ART regimen in this setting may be difficult. Thus, using TDF/FTC/RPV as a switching therapy in patients with complete virological suppression may result in a higher success rate and is more practical in resource-limited settings.

The present study has demonstrated that in HIV-infected patients taking once-daily TDF/FTC/EFV with complete virological suppression, switching to a once-daily TDF/FTC/RPV regimen was not inferior to continuing TDF/FTC/EFV, in term of maintained virological suppression at 24 weeks. Immunological responses were also similar between the 2 treatment groups. The rates of sustained virological response in both treatment groups in our study were quite high, and higher than rates that have been reported in treatment-naïve studies [8, 9]. In this study, all patients had complete virological suppression,

Table 1. Demographic Data and Baseline Characteristics of Study Patients Between Switching and Continuing Groups

Characteristics	Switching Group (n = 122)	Continuing Group (n = 124)	*P* Value
Sex, No. (%)			.998
Male	77 (63.1)	78 (62.9)	
Female	45 (36.9)	46 (37.1)	
Age range, No. (%)			.064
<35 y	21 (17.2)	29 (23.4)	
35–44.9 y	32 (26.2)	43 (43.7)	
45–54.9 y	41 (33.6)	38 (30.6)	
≥55 y	28 (23.0)	14 (11.3)	
HIV risk, No. (%)			.215
Heterosexual	98 (80.4)	87 (70.2)	
Homosexual	21 (17.2)	35 (28.2)	
Blood transfusion	-	1 (0.8)	
Intravenous drug use	2 (1.6)	1 (0.8)	
Vertical transmission	1 (0.8)	-	
Duration of HIV diagnosis, median (IQR), y	9.0 (6.0–13.8)	7.3 (6.3–12.9)	.140
Duration of ART, median (IQR), ye	8.0 (5.1–11.8)	8.2 (5.4–12.3)	.760
Body weight, mean (SD), kg	61.4 (3.8)	62.4 (4.1)	.537
CD4 cell counts, mean (SD), cells/mm^3	549 (224)	579 (233)	.390
Serum lipid levels, mean (SD), mg/dL			
Total cholesterol	197 (24)	195 (22)	.726
LDL cholesterol	115 (20)	118 (21)	.968
HDL cholesterol	47 (14)	47 (16)	.439
Triglycerides	161 (104)	135 (98)	.089
Serum creatinine, mean (SD), mg/dL	0.81 (0.18)	0.82 (0.21)	.428
eGFR, mean (SD), mL/min/1.73 m^2	101.0 (15.2)	102.7 (14.6)	.411
Presence of CNS adverse effects, No. (%)	13 (10.7)	11 (8.9)	.637
Taking lipid lowering agents, No. (%)			
Atorvastatin	7 (5.7)	9 (7.3)	.749
Rosuvastatin	5 (4.1)	4 (3.2)	
Simvastatin	10 (8.3)	7 (5.6)	
Others	3 (2.4)	3 (2.4)	

Abbreviations: ART, antiretroviral therapy; CNS, central nervous system; eGFR, estimated glomerular filtration rate; IQR, interquartile range; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

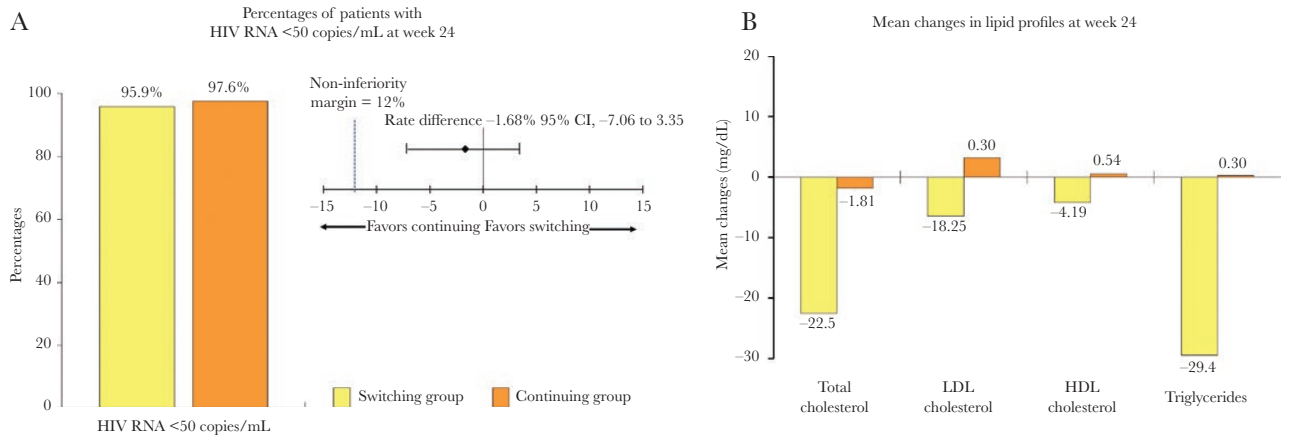

Figure 1. Intention-to-treat analysis for percentages of patients with virological suppression (A) and mean change in lipid profile (B) between the switching and continuing groups at week 24. Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

with a median duration of their firstline ART of 8 years and high CD4 cell counts at enrollment. This reflects good adherence on ART among these study patients. It has been established that good adherence on ART is associated with long-term prolonged virological suppression [12, 13].

Due to information from clinical studies and real-world practice, many physicians have concerns about the safety issues of EFV-based regimens, especially dyslipidemia and CNS adverse effects, which may lead to the consequences of cardiovascular events and treatment noncompliance. Our study demonstrated that the switching group had better lipid profiles and fewer CNS adverse effects. Switching to an RPV-based regimen was associated with improvement of TC and LDL, which could minimize some risks of cardiovascular diseases, one of leading causes of death in HIV-infected patients in the ART era [14]. Improvement of CNS adverse effects after switching to TDF/FTC/RPV was also shown in our study. At the end of the 24-week follow-up period, all patients who switched from TDF/FTC/EFV to a TDF/FTC/RPV regimen had their CNS symptoms disappear. Additionally, the lower cost after switching the treatment regimen would be above and beyond the initial benefit of this switching strategy, particularly in resource-limited countries.

To our knowledge, this is the first randomized controlled noninferiority trial regarding switching ART from the most commonly used regimen in resource-limited settings, TDF/FTC/EFV, to TDF/FTC/RPV. The strengths of our study were the study design of a randomized controlled trial and that RPV was the only antiretroviral agent in the regimen that was switched. Therefore, the efficacy of RPV as a switch therapy has been demonstrated. However, there were some limitations. The duration of the study was 24 weeks, which is relatively short; further study regarding the long-term durability of this switching strategy is needed. A long-term follow-up study may be needed to demonstrate whether the benefit of lipid profile changes will translate into benefits for cardiovascular disease. This was a single-center study, and the study was not blinded to investigators and participants. However, the open-label design may reflect the real adherence of each particular regimen, because TDF/FTC/EFV and TDF/FTC/RPV have differences in terms of drug and food interactions and directions.

In conclusion, switching TDF/FTC/EFV to a TDF/FTC/RPV regimen is noninferior to continuing TDF/FFTC/EFV in maintaining virological suppression at 24 weeks and yields similar immunological responses. This switching strategy provides better lipid profiles and fewer CNS adverse events. Switching to TDF/FTC/RPV should be considered in HIV-infected patients in resource-limited settings who are on a TDF/FTC/EFV regimen with complete virological suppression.

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