

Efficacy of Rilpivirine-Based Regimens as Switch Therapy From Nevirapine-Based Regimens in Human Immunodeficiency Virus-Infected Patients With Virological Suppression: A Randomized Controlled Trial

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Background. Nevirapine (NVP)-based antiretroviral therapy continues to be used in some human immunodeficiency virus (HIV)-infected patients. Rilpivirine (RPV) could be used as an alternative to NVP. We studied the efficacy of RPV-based regimens as switch therapy.

Methods. A randomized controlled noninferiority trial was conducted in HIV-infected patients who received NVP-based regimens and had undetectable plasma viral loads (VLs). Patients were randomized to a continuation arm (NVP was continued) or a switch arm (NVP was switched to RPV). Tenofovir disoproxil fumarate (TDF) plus lamivudine or emtricitabine were the backbone of the regimens. The primary endpoint was an HIV VL <40 copies/mL at week 48.

Results. A total of 106 patients were enrolled, 55 patients were in the continuation arm and 51 patients were in the switch arm. The mean (standard deviation) age was 49.1 (9.2) years and 51.9% were females. The median (interquartile range) baseline CD4 count was 561 (443–732) cells/mm³. At week 48, 52 patients (94.6%) in the continuation arm and 50 patients (98.0%) in the switch arm had an HIV VL <40 copies/mL, with an efficacy difference of 3.5% (95% confidence interval [CI], –13.0 to 5.6; *P* = .619). Decreases in total cholesterol and triglyceride were observed in the switch arm (–17.1 mg/dL, 95% CI = –29.7 to –4.4, *P* = .008 and –36.0 mg/dL, 95% CI = –71.0 to –1.1, *P* = .044, respectively).

Conclusions. Switching from NVP to RPV can maintain virological suppression and decrease total cholesterol and triglyceride at week 48. In patients virologically suppressed with NVP-based regimens, RPV-based regimens can be a switch option.

Keywords. efficacy; HIV; randomized controlled trial; rilpivirine; switch therapy.

In resource-limited settings, 2 nucleoside reverse-transcriptase inhibitors (NRTIs) in combination with efavirenz (EFV) is the preferred agent for initial treatment of human immunodeficiency virus (HIV)-1-infected patients [1]. However, some patients remain on nevirapine (NVP)-based antiretroviral therapy (ART), despite its twice-daily dosing, because the treatment was initiated before EFV availability and/or the presence of drug-related adverse effects due to EFV in the past [2].

Rilpivirine (RPV) is a second-generation nonnucleoside reverse-transcriptase inhibitor (NNRTI), given at a daily dose of 25 mg, which can be coformulated with 2 NRTIs [3]. Rilpivirine has noninferior efficacy compared with EFV in treatment-naive HIV-infected patients, especially in the groups of patients with either an HIV ribonucleic acid (RNA) <100 000 or 100 000–500 000 copies/mL, along with a favorable safety and tolerability profile [4, 5]. The ART regimen tenofovir/emtricitabine (FTC)/RPV is categorized as the recommended initial regimen for certain HIV-infected patients with pretreatment HIV RNA viral loads (VLs) <100 000 copies/mL and a CD4 count >200 cells/mm³ in both the United States and the European guidelines [3, 6]. However, in resource-limited settings, HIV VL is scarcely carried out before initiation of therapy, and many patients presented with late-stage HIV disease despite ART scale-up [7]. Consequently, RPV has seldom been used in treatment-naive HIV-infected patients in resource-limited settings.

Previous studies showed that RPV combined with 2 NRTIs, as a switch therapy in virologically suppressed HIV-infected patients, was a safe and efficacious option [8, 9]. A small, prospective, single-arm study of switching from tenofovir

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disoproxil fumarate (TDF)/FTC + NVP to a TDF/FTC/RPV single-tablet regimen in virologically suppressed, HIV-1-infected subjects demonstrated that all 32 patients remained virologically suppressed at weeks 12 and 24 [10]. A randomized controlled study in Rwandans revealed that a switch from NVP plus any 2 NRTIs to coformulated TDF/FTC/RPV was virologic effective, with few adverse events at week 24 [11].

Due to cost constraints, a fixed drug combination of TDF/FTC/RPV is not available in some resource-limited countries. However, RPV is available as a separate tablet to be combined with TDF/FTC or TDF plus lamivudine (3TC) as once-daily regimens. We aimed to investigate the efficacy and adverse events of ART switching from NVP to RPV, plus either TDF/FTC or TDF + 3TC in virologically suppressed HIV-infected patients. The primary endpoint was an HIV VL <40 copies/mL at week 48. The secondary endpoints were the changes in CD4 cell counts and lipid profiles from baseline at week 48.

METHODS

Study Design and Participants

A single-center, randomized, controlled, noninferiority trial to study 48-week treatment outcomes of RPV as a switch therapy was conducted at Ramathibodi Hospital, a 1300-bed university hospital in Bangkok, Thailand, from December 2016 to October 2017. Human immunodeficiency virus-1-infected adults over 18 years old were enrolled from the infectious disease clinic. Inclusion criteria were patients who had a recent plasma HIV-1 RNA VL within 6 months of the screening <40 copies/mL and had been treated with TDF/FTC + NVP or TDF + 3TC + NVP for at least 6 months. Exclusion criteria included patients with a history of any documented HIV drug resistance, patients who used drugs that interact with RPV (eg, proton pump inhibitors, histamine H₂-receptor antagonists, rifampin, and anticonvulsants), women during pregnancy or breastfeeding, patients with an estimated glomerular filtration rate (eGFR) of <60 mL/min per 1.73 m² (by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) [12], and patients who had depressive or psychiatric disorders.

The study was reviewed and ethically approved by the Committee of Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University (MURA2016/642). All participants provided written informed consent before enrollment. The trial was registered at ClinicalTrials.gov under registration number NCT03664440.

Procedures

Eligible patients who were on the regimens TDF + 3TC + NVP or TDF/FTC + NVP were blocks of 4 randomly assigned (1:1) by computer-generated random numbers, to continue their regimens of NVP 200 mg twice daily plus the previous backbone

NRTIs or to switch from NVP to RPV 25 mg once-daily plus the previous backbone NRTIs. Patients were advised to take RPV with a meal. Patient visits were scheduled at baseline, weeks 12, 24, 36, and 48. The laboratory assessment was performed at baseline, weeks 24 and 48. Laboratory tests included complete blood count, CD4 percentage, CD4 cell count, chemistry panel (eg, alanine aminotransferase [ALT], creatinine, fasting sugar, and lipid panel), and urinalysis. The HIV RNA VL was performed using the Amplicor HIV-1 Monitor Test, version 1.5 (Roche, Basel, Switzerland). We assessed safety and tolerability by self-adverse event reporting, history taking, and physical examination. Adherence counseling and routine standard of care were performed at each study visit to patients enrolled in the program (Figure 1). Depression was accessed by using Patient Health Questionnaire-2 at weeks 0, 24, and 48 [13].

Outcomes

The primary outcome was assessed at week 48. The proportion of patients with virological suppression (HIV VL <40 copies/mL) after switching treatment regimens from NVP-based regimens to RPV-based regimens (switch arm) were compared with those continuing the NVP-based regimens (continuation arm). The secondary outcomes were to evaluate changes in CD4 cell counts, lipid levels (including triglycerides level, total cholesterol level, low-density lipoprotein cholesterol level [LDL-C], and high-density lipoprotein cholesterol level [HDL-C]), and adverse events between the 2 groups during the study.

The definition of virological suppression was an HIV RNA VL <40 copies/mL. Virological failure was defined as the inability to maintain a suppression level of an HIV VL <200 copies/mL [3]. Adverse events were defined as any undesirable experience associated with the use of antiretroviral drugs include rash, gastrointestinal symptoms (nausea, vomiting, and epigastric pain), neurological symptoms, and psychiatric events [3, 5]. Serious adverse events included death, hospitalization, disability, or permanent impairment of body structure, physical activities, and quality of life [14].

Statistical Analyses

The sample size was calculated from the proportional response rate from the previous trial [11] using n4Studies program, version 1.4.0 [15]. A population of 53 in each group was required to establish the noninferiority of the switching group compared with the continuing group and allowing for a dropout rate of approximately 10% at 0.9 power and a 0.05 significance level. Baseline participant characteristics were compared using *t* test and Mann-Whitney *U* test for continuous variables and χ^2 or Fisher's exact tests for categorical variables. The primary analysis was based on intention-to-treat (ITT) populations (all who received a study drug). We did an additional analysis on per-protocol populations (as ITT but excluding dead patients or patients that discontinued study drug for any reason), with

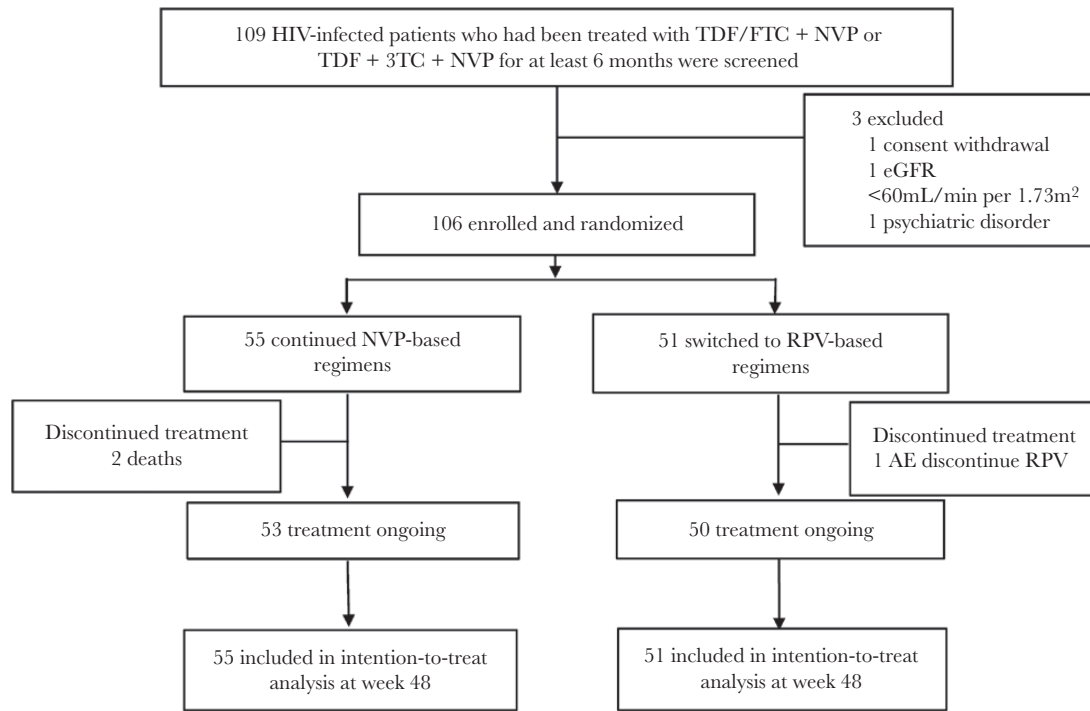


Figure 1. Study screening, enrollment, and follow-up through week 48. 3TC, lamivudine; AE, adverse events; eGFR, estimated glomerular filtration rate; FTC, emtricitabine; NVP, nevirapine; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate.

a prespecified noninferior margin of 12%. The noninferiority margin was chosen in accordance with the US Food and Drug Administration guidelines for HIV drug development, with the margin ranging from 10% to 12% [16]. Secondary outcomes were compared using Mann-Whitney *U* test for nonparametric continuous variables and multilevel mixed-effects linear regression for repeated measurements of continuous variables. All statistical analyses were performed using Stata statistical software, version 14.0.

RESULTS

Participants and Baseline Characteristics

During the study period, 109 HIV-infected individuals were screened for study enrollment with 106 enrolled and randomized. Three individuals were excluded: 1 had an eGFR <60 mL/min per 1.73 m², 1 withdrew consent, and 1 suffered from a psychiatric disorder. A total of 106 patients were enrolled: 55 and 51 patients were randomly assigned to the continuation arm and the switch arm, respectively. Of all patients, 55 (51.9%) were females. The mean age was 49.1 (standard deviation [SD] = 9.2) years. The median baseline CD4 cell count was 561 (interquartile range [IQR], 443–732) cells/mm³. Pretreatment HIV VL was performed in 40 patients (36.7%). The median pretreatment HIV VL was 105 600 (IQR, 17 345–252 378) copies/mL. The median nadir CD4 cell count was 157.5 (IQR, 39–305) cells/mm³. Of all patients, 57 (53.8%) had a history of opportunistic infection, and the most common opportunistic

infection was tuberculosis. The mean duration of ART was 10.9 (SD = 4.1) years. Baseline characteristics including age, gender, CD4 percentage, CD4 cell count, and ART duration were comparable between the 2 groups (*P* > .05) (Table 1).

There were 2 deaths in the continuation arm, from hematologic malignancy and dilated cardiomyopathy, which occurred at weeks 12 and 20 after enrollment, respectively. One patient in the switch arm developed nausea and vomiting, which occurred at week 8 of enrollment. She discontinued RPV and chose to resume TDF/FTC + NVP. At week 48, 53 patients in the continuation arm and 50 patients in the switch arm remained in the study (Figure 1).

Efficacy

At week 48, by ITT analysis, 52 patients (94.6%) in the continuation arm and 50 patients (98.0%) in the switch arm achieved the primary outcome of an HIV VL <40 copies/mL. The difference in the proportions was 3.5% (95% confidence interval [CI], –13.0 to 5.6; *P* = .619), thus meeting the prespecified noninferiority criterion. By per-protocol analysis, the difference in the proportions was 1.9% (95% CI, –9.9 to +5.4; *P* > .999) (Figure 2). During the study, one patient had an HIV VL of 593 copies/mL at week 24 under RPV therapy. This patient reported poor compliance to the ART regimen at approximately 3 weeks after enrollment because of family matters. After assessment and discussion on the adherence issue with the patient, HIV VL was followed at week 32 and week 48 in which the level

Table 1. Baseline Characteristics

Characteristics	Continuation Arm	Switch Arm	P Value
	(Group A)	(Group B)	
	N = 55	N = 51	
Female sex, n (%)	29 (52.7)	26 (47.3)	.857
Mean age, years (SD)	50.0 (9.6)	48.2 (8.9)	.325
Mean body weight, kilograms (SD)	58.4 (10.6)	58.8 (9.9)	.849
Route of HIV transmission, (%)			.123
Heterosexual	52 (94.6)	42 (82.4)	
Homosexual	3 (5.5)	8 (15.7)	
Intravenous drug user	0 (0.0)	1 (2.0)	
Mean duration of ART, years (SD)	10.84 (4.3)	10.96 (4.0)	.877
Prior NRTI and NNRTI use, n (%)			.662
Stavudine	26 (47.3)	23 (45.1)	
Zidovudine	19 (34.6)	22 (43.1)	
Efavirenz	7 (12.7)	5 (9.2)	
Reason for efavirenz discontinuation			.332
CNS adverse effects	3 (42.9)	4 (80.0)	
Rash	2 (28.6)	1 (20.0)	
Gynecomastia	2 (28.6)	0 (0.0)	
Underlying diseases, n (%)			.053
No underlying diseases	35 (63.6)	41 (80.4)	
Diabetes mellitus	2 (3.6)	0 (0.0)	
Hypertension	11 (20.0)	2 (3.9)	
Dyslipidemia	2 (3.6)	4 (7.8)	
Others ^a	5 (9.1)	4 (7.8)	
Median CD4 cell count at entry, cells/mm ³ (IQR)	552 (434–733)	563 (457–727)	.912 ^b
Median CD4 at entry, % (IQR)	27 (22–33)	27 (22–32)	.995 ^b
Median nadir CD4 cell count, cell/mm ³ (IQR)	190 (40–368)	145 (30–297)	.479
Median pretreatment HIV VL, copies/mL (IQR)	125 000 (21 200–31 200)	81 900 (15 000–211 000)	.303 ^b
History of opportunistic infection, n (%)	31 (56.4)	26 (51.0)	.579
Tuberculosis	19 (34.6)	14 (27.5)	.431
Pneumocystis pneumonia	4 (7.3)	6 (11.8)	.429
Cryptococcal infection	1 (1.8)	1 (2.0)	.957
Herpes virus infection	4 (7.3)	3 (5.9)	.773
CMV infection	1 (1.8)	2 (3.9)	.514
Histoplasmosis	1 (1.8)	0 (0.0)	.333
Toxoplasmosis	1 (1.8)	0 (0.0)	.333
HBsAg positive	3 (5.5)	5 (5.9)	.924
Anti-HCV IgG positive	2 (3.6)	1 (2.0)	.603
Mean fasting plasma glucose, mg/dL (SD)	92.7 (9.7)	94.7 (11.6)	.302
Mean lipid levels, mg/dL (SD)			
Total cholesterol	198.7 (36.5)	198.6 (25.0)	.930
HDL-C	50.4 (15.8)	52.9 (11.7)	.389
LDL-C	114.9 (34.1)	116.9 (25.7)	.716
Triglycerides	155.8 (98.3)	128.1 (82.0)	.130
Total cholesterol/HDL-C ratio, (SD)	4.2 (1.2)	4.0 (1.0)	.238
Mean alanine aminotransferase, U/L (SD)	40.4 (25.8)	44.8 (27.1)	.057
Mean serum creatinine, mg/dL (SD)	0.9 (0.2)	0.9 (0.2)	.810
Mean eGFR, mL/min per 1.73 m ² (SD)	91.8 (18.6)	92.6 (16.0)	.912

Abbreviations: ART, antiretroviral therapy; CMV, cytomegalovirus; CNS, central nervous system; eGFR, estimated glomerular filtration rate; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDL-C, high-density lipoprotein cholesterol level; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol level; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleos(t)ide reverse-transcriptase inhibitor; SD, standard deviation; VL, viral load.

^aThyroid disease, anal cancer, liver cirrhosis, chronic kidney disease, cardiovascular disease.

^bMann-Whitney *U* test.

was <40 copies/mL. Another patient in the continuation arm had an HIV VL of 42 copies/mL at week 48. He reported low

compliance to the ART regimen at week 40 after enrollment because of a change of his work and financial problems.

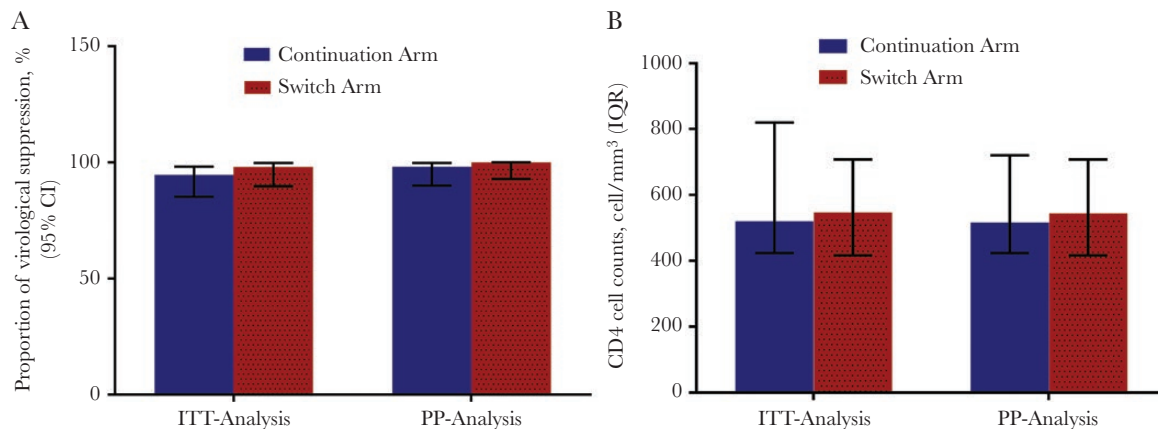


Figure 2. Proportion of patients with virological suppression (A), and median CD4 cell counts (B) at week 48. CI, confidence interval; ITT-analysis, intention to treat analysis; IQR, interquartile range; PP-analysis, per protocol analysis.

For the secondary outcomes, by ITT analysis, the median CD4 cell count at week 48 was 520 (424–720) cells/mm³ in the continuation arm and 547 (417–708) cells/mm³ in the switch arm ($P = .911$) (Figure 2). Significant decreases in the means total cholesterol and triglyceride were observed in the switch arm (–17.1 mg/dL, 95% CI = –29.7 to –4.4, $P = .008$ and –36.0 mg/dL, 95% CI = –71.0 to –1.1, $P = .044$, respectively). In the continuation arm, significant increases in the means HDL-C and LDL-C were observed (5.2 mg/dL, 95% CI = 2.5 to 7.9, $P < .001$ and 8.5 mg/dL, 95% CI = 1.6 to 15.4, $P = .015$, respectively). However, there were no significant changes in means of the total cholesterol to HDL-C ratio, alanine aminotransferase, serum creatinine, eGFR, or fasting plasma glucose in both arms (Figure 3 and Table 2).

Three patients (5.9%) in the switch arm reported adverse events. Two patients developed nausea, vomiting, and abdominal discomfort. One patient discontinued RPV and chose to resume TDF/FTC + NVP, whereas the symptoms improved after week 10 in another patient in which RPV was continued. Another patient complained of numbness in both hands at week 3, but the symptom later subsided, and RPV was continued. No patient developed a rash or central nervous system adverse effects. None of the patients in the switch arm complained of RPV-associated food constraints or reported serious adverse events. In the continuation arm, 2 deaths (3.6%) occurred from hematologic malignancy and dilated cardiomyopathy. There was no statistically significant difference in adverse events between both arms ($P = .670$).

DISCUSSION

Our study demonstrated that in HIV-infected patients virologically suppressed with NVP-based regimens, the switch to once-daily RPV-based regimens was not inferior to the continuation of TDF + 3TC + NVP or TDF/FTC + NVP after 48 weeks, with a few adverse events. Our results agreed with the previous study

in Rwanda, which showed that switching from an NVP-based regimen to coformulated TDF/FTC/RPV was noninferior to a continuation of NVP-based regimens at week 24. However, the switching strategies were different between that study and our study. The NRTI backbones before switching to TDF/FTC/RPV in the Rwandan study included TDF (63%), azidothymidine (35%), and abacavir (1%) combined with 3TC [11]. In our study, 70% used TDF + 3TC and 30% used TDF/FTC as backbones. The NRTI backbones were fixed, and only RPV was switched from NVP. Despite FTC and 3TC being closely structurally related NRTIs, in vitro study showed differing resistance profiles when administered in combination with TDF and either EFV or ritonavir-boosted protease inhibitors [17]. The prevalence of the M184V/I resistance mutation was significantly lower in patients who received FTC and TDF than in those who received 3TC and TDF [17, 18]. In an observational study using data from the AIDS Therapy Evaluation in the Netherlands (ATHENA), the nationwide HIV cohort revealed that the use of FTC instead of 3TC as part of combination ART was associated with better virological responses [19]. Therefore, by reducing the effect of different NRTIs in the backbone, our study demonstrated the efficacy of RPV per se in the switch regimens.

In our study, patients had been on ART for approximately 10 years and had good baseline CD4 at study entry. However, they had low nadir CD4, and more than half of the patients had a history of opportunistic infections. The median of known pretreatment HIV VL was more than >100 000 copies/mL. These demonstrated the efficacy of the RPV switch regimens in populations with a history of opportunistic infection, high baseline pretreatment VL, and/or low nadir CD4. We also showed the durability of the switch regimens through week 48.

Other than efficacy, the switch to RPV-based regimens in our study demonstrated a beneficial effect on total cholesterol and triglyceride. The switch trial in Rwanda also showed a trend toward a reduction in total cholesterol and HDL-C in the RPV

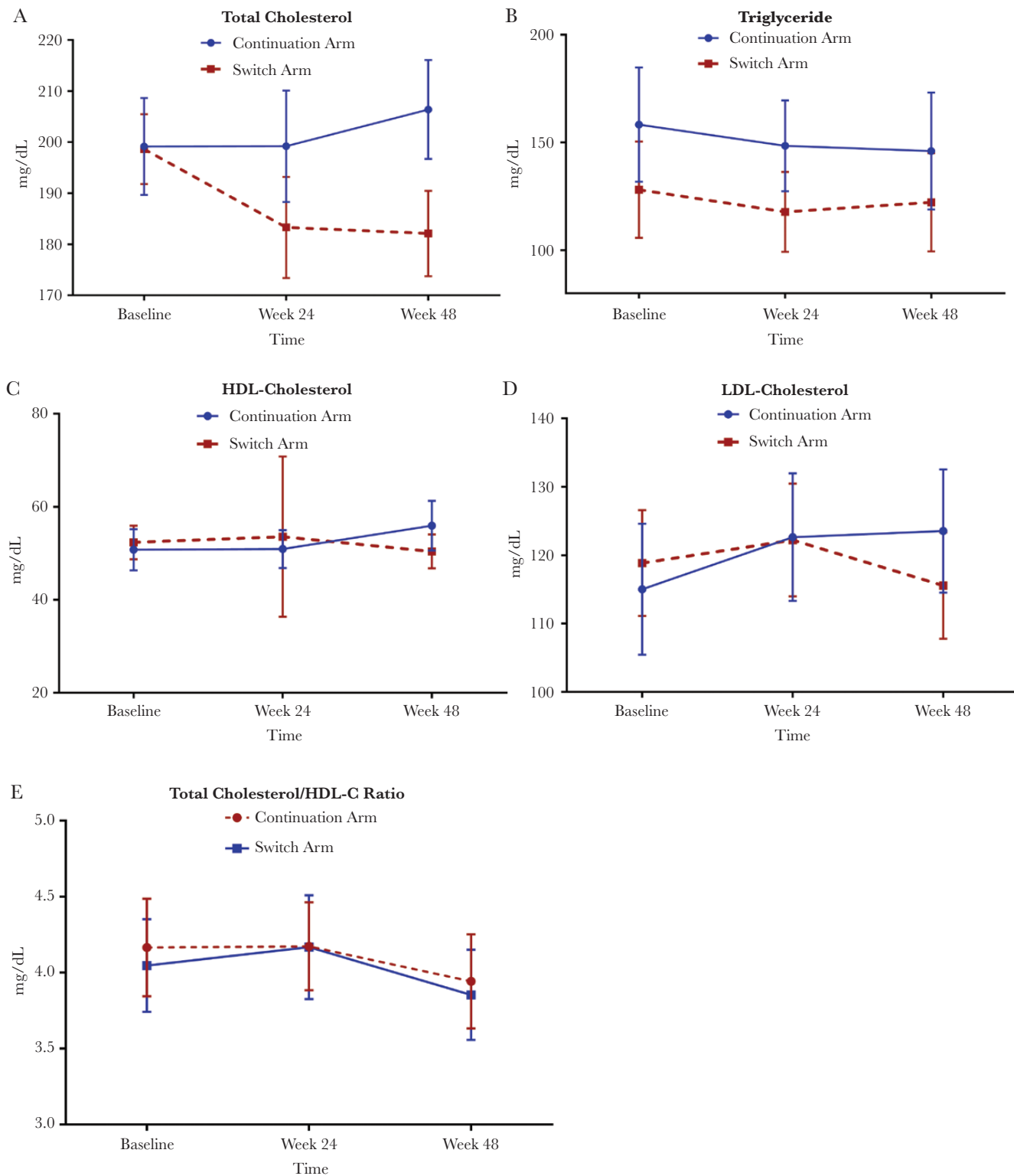


Figure 3. Changes in levels of lipid profiles from baseline through week 48: (A) total cholesterol, (B) triglyceride, (C) high-density lipoprotein cholesterol (HDL-C), (D) low-density lipoprotein cholesterol (LDL-C), and (E) total cholesterol/HDL-C ratio.

switch arm compared with the NVP continuation arm, but no significant differences were detected in other fasting lipid measurements at week 24 [11]. A prospective, open-label,

controlled trial in the Netherlands showed significant decreases in total cholesterol, HDL-C, and LDL-C over 24 weeks after switching from NVP to RPV [20]. Previous studies comparing

Table 2. Mean Change in Blood Chemistry Parameters From Baseline

Blood Chemistry Parameters	Change ^a (95% CI)		
	Continuation Arm at Week 24	Continuation Arm at Week 48	Switch Arm at Week 48
Total cholesterol, mg/dL	0.06 (-8.76 to 8.89)	725 (-0.87 to 15.38)	-15.88 ^b (-29.57 to -2.14)
Triglyceride, mg/dL	-9.83 (-33.68 to 14.01)	-12.25 (-40.93 to 16.43)	-40.45 ^b (-72.82 to -8.08)
HDL-cholesterol, mg/dL	0.13 (-2.70 to 2.97)	5.16 ^c (2.46 to 7.86)	2.80 (-14.98 to 20.57)
LDL-cholesterol, mg/dL	762 ^b (0.88 to 14.38)	8.52 ^b (1.63 to 15.41)	720 (-5.45 to 19.83)
TC/HDL-C ratio, mg/dL	0.01 (-0.20 to 0.22)	-0.22 (-0.47 to 0.03)	0.00 (-0.47 to 0.47)
Alanine aminotransferase, U/L	2.91 (-0.86 to 6.68)	-2.13 (-760 to 3.35)	-3.53 (-12.68 to 5.62)
Serum creatinine, mg/dL	-0.01 (-0.03 to 0.02)	-0.01 (-0.04 to 0.02)	0.51 (-0.42 to 1.43)
eGFR, mL/min per 1.73 m ²	0.13 (-2.30 to 2.56)	2.25 (-1.24 to 5.73)	-2.50 (-9.14 to 4.15)
Fasting plasma glucose, mg/dL	-1.56 (-3.61 to 0.50)	-0.40 (-2.76 to 1.95)	7.69 (-3.21 to 18.59)

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol level.

^a Multilevel mixed-effects linear regression, reference is blood chemistry levels at baseline of continuation arm

^b *P* < .05

^c *P* < .01

RPV to EFV showed improvement of lipid profiles in the RPV switch arm [4, 5, 21]. Nevirapine was demonstrated to have less atherogenic lipid profiles compared with EFV [22]. Our results agreed with the previous study, which demonstrated (1) small increases in HDL-C and (2) non-HDL-C in patients taking an NVP-containing ART [22]. Without significant changes of LDL-C and the total cholesterol to HDL-C ratio after ART switching, this suggested that RPV might be suitable for switching in patients with risk factors of cardiovascular diseases.

Although the switch to RPV in treatment-experienced patients did not show higher virological failure [8, 11, 21], this switching strategy had some concerns on pharmacokinetics. Rilpivirine should always be taken with a meal to enhance its bioavailability. Administration of RPV under fasting conditions lowered the oral bioavailability when compared with the administration with a normal-fat and high-fat breakfast [23]. Rilpivirine is predominantly metabolized by cytochrome P450 3A4 (CYP3A4), sharing this metabolic pathway with the first-generation NNRTIs and CYP3A4 inducers NVP and EFV [24]. In a previous prospective study, RPV concentrations were therapeutic at day 7 after NVP to RPV switching in most subjects [25]. Substituting NVP for RPV did not have clinically relevant pharmacokinetic effects by cytochrome P450 interactions [25]. In our study, substituting NVP for RPV can maintain virological suppression. Only 1 patient who had a compliance problem had a virological rebound.

The strengths of our study included the following: the study was a randomized control trial, and RPV was the only drug in the regimens that was switched. Therefore, the efficacy of RPV per se as a switch therapy can be demonstrated. Moreover, the duration of the study was 48 weeks, which showed the durability of the switch regimens. However, there were some limitations. This study was a single-center study, and the study was not blinded to investigators and participants.

CONCLUSIONS

In conclusion, our findings show that in virologically suppressed HIV-infected patients with NVP-based regimens, switching to once-daily RPV-based regimens can maintain virological suppression and decrease total cholesterol and triglyceride. A few adverse events were observed with this switching strategy. Further study on long-term efficacy and durability of this switching strategy should be pursued.

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Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. The Bureau of AIDS, TB and STI, Department of Disease Control, Thailand. Thailand national guidelines on HIV/AIDS treatment and prevention. 2017. Available at: http://www.thaiidsociety.org/index.php?option=com_content&view=article&id=79&Itemid=86. Accessed 5 March 2019.
2. Ford N, Shubber Z, Pozniak A, et al. Comparative safety and neuropsychiatric adverse events associated with efavirenz use in first-line antiretroviral therapy: A systematic review and meta-analysis of randomized trials. *J Acquir Immune Defic Syndr* 2015; 69:422–9.
3. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services. 2018. Available at: <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed 2 March 2019.
4. Cohen CJ, Andrade-Villanueva J, Clotet B, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naïve adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. *Lancet* 2011; 378:229–37.
5. Molina JM, Cahn P, Grinsztejn B, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naïve adults infected with HIV-1 (ECHO): A phase 3 randomised double-blind active-controlled trial. *Lancet* 2011; 378:238–46.
6. EACS: European AIDS Clinical Society. EACS Guidelines Version 9.1 - October 2018. European AIDS Clinical Society (EACS); 2018. Available at: <http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html>. Accessed 2 March 2019.
7. Kiertiburanakul S, Boettiger D, Lee MP, et al. Trends of CD4 cell count levels at the initiation of antiretroviral therapy over time and factors associated with late initiation of antiretroviral therapy among Asian HIV-positive patients. *J Int AIDS Soc* 2014; 17:18804.
8. Mills AM, Cohen C, Dejesus E, et al. Efficacy and safety 48 weeks after switching from efavirenz to rilpivirine using emtricitabine/tenofovir disoproxil fumarate-based single-tablet regimens. *HIV Clin Trials* 2013; 14:216–23.
9. Palella FJ Jr, Fisher M, Tebas P, et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. *AIDS* 2014; 28:335–44.
10. Allavena C, Dailly E, Reliquet V, et al. Switching from tenofovir/emtricitabine and nevirapine to a tenofovir/emtricitabine/rilpivirine single-tablet regimen in virologically suppressed, HIV-1-infected subjects. *J Antimicrob Chemother* 2014; 69:2804–8.
11. Collins SE, Grant PM, Uwinkindi F, et al. A randomized switch from nevirapine-based antiretroviral therapy to single tablet rilpivirine/emtricitabine/tenofovir disoproxil fumarate in virologically suppressed human immunodeficiency virus-1-infected Rwandans. *Open Forum Infect Dis* 2016; 3:ofw141.
12. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130:461–70.
13. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. *Med Care* 2003; 41:1284–92.
14. US Department of Health and Human Services. The FDA safety information and adverse event reporting program. Available at: <https://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm>. Accessed 5 October 2018.
15. Ngamjarus C, Chongsuvivatwong V, McNeil E. n4Studies: Sample size calculation for an epidemiological study on a smart device. *Siriraj Med J* 2016; 68:160–170.
16. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Human immunodeficiency virus-1 infection: developing antiretroviral drugs for treatment guidance for industry. 2015. Available at: <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf>. Accessed 5 October 2018.
17. Marcelin AG, Charpentier C, Wirden M, et al. Resistance profiles of emtricitabine and lamivudine in tenofovir-containing regimens. *J Antimicrob Chemother* 2012; 67:1475–8.
18. Llibre JM, Bravo I, Ornelas A, et al. Effectiveness of a treatment switch to nevirapine plus tenofovir and emtricitabine (or Lamivudine) in adults with HIV-1 suppressed viremia. *PLoS One* 2015; 10:e0128131.
19. Rokx C, Fibriani A, van de Vijver DA, et al. Increased virological failure in naïve HIV-1-infected patients taking lamivudine compared with emtricitabine in combination with tenofovir and efavirenz or nevirapine in the Dutch nationwide ATHENA cohort. *Clin Infect Dis* 2015; 60:143–53.
20. Rokx C, Blonk M, Verbon A, et al. The efficacy, pharmacokinetics, safety and cardiovascular risks of switching nevirapine to rilpivirine in HIV-1 patients: the RPV switch study. *J Int AIDS Soc* 2014; 17:19789.
21. Thamrongwongler P, Chetchoisakd P, Anunnatsiri S, Mootsikapun P. Improvement of lipid profiles when switching from efavirenz to rilpivirine in HIV-infected patients with dyslipidemia. *HIV Clin Trials* 2016; 17:12–6.
22. van Leth F, Phanuphak P, Stroes E, et al. Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naïve patients infected with HIV-1. *PLoS Med* 2004; 1:e19.
23. Crauwels HM, van Heeswijk RP, Buelens A, et al. Impact of food and different meal types on the pharmacokinetics of rilpivirine. *J Clin Pharmacol* 2013; 53:834–40.
24. Usach I, Melis V, Peris JE. Non-nucleoside reverse transcriptase inhibitors: a review on pharmacokinetics, pharmacodynamics, safety and tolerability. *J Int AIDS Soc* 2013; 16:1–14.
25. Rokx C, Blonk M, Verbon A, et al. The efficacy, pharmacokinetics, and safety of a nevirapine to rilpivirine switch in virologically suppressed HIV-1-infected patients. *J Acquir Immune Defic Syndr* 2015; 68:36–9.