Switching efavirenz to rilpivirine in virologically suppressed adolescents with HIV: a multi-centre 48-week efficacy and safety study in Thailand

Wanatpreeya Phongsamart¹, Watsamon Jantarabenjakul²,³, Sasitorn Chantaratin⁴, Suvaporn Anugulruengkitt²,³, Piyarat Suntarattiwong⁵, Pakpen Sirikut⁵, Pope Kosalaraks⁶, Alan Maleesatharn¹ and Kulkanya Chokephaibulkit¹,§

§Corresponding author: Kulkanya Chokephaibulkit, Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkok 10700, Thailand. Tel: +66 24180544. (kulkanya.cho@mahidol.ac.th)

Introduction: Efavirenz (EFV) is commonly used for first-line antiretroviral therapy in children and adolescents with HIV, but is associated with neuropsychiatric and metabolic side effects. Rilpivirine (RPV) is better tolerated, and switching from EFV to RPV in virologically suppressed adults has been safe and efficacious, but data in adolescents are limited. Our primary objective was to describe the 48-week immunologic and virologic outcomes in virologically suppressed adolescents switching from EFV to RPV-based antiretroviral therapy. Secondary objectives included assessment of neuropsychiatric adverse events, quality of life (QOL) and metabolic profiles while on RPV.

Methods: We conducted an open-label, single-arm, multi-centre study in Thailand in virologically suppressed adolescents aged 12–18 years receiving EFV plus two nucleoside/tide reverse transcriptase inhibitors (NRTIs/NtRTI) for ≥3 months. Participants were switched to an RPV (25 mg) tablet once daily, with the same NRTIs. HIV RNA viral load, CD4 cell count, fasting total cholesterol (TC), triglyceride, glucose, neuropsychiatric adverse events, depression and QOL were assessed over 48 weeks. Data were collected between February 2016 and September 2018.

Results: One hundred and two (52% male) adolescents were enrolled. Median age at entry was 15.5 years (IQR 14.4–17.0), median CD4 count was 664 cells/mm³ (29.9%); 58% were receiving tenofovir-DF and emtricitabine. At weeks 24 and 48, 96 (94.1%) and 94 (92.2%) participants were virologically suppressed, respectively, with no significant change in CD4 cell counts from baseline. Six (5.9%) participants experienced virologic failure, two of whom had RPV-associated mutations (K101E and Y181C) and a lamivudine-associated mutation (M184V/I). There were significant decreases in TC, triglyceride, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) at weeks 24 and 48 and a significant increase in LDL/HDL ratio at week 48 compared to baseline. No substantial changes in EFV-related symptoms, depression score or health-related QOL were observed over time; however, there was significant improvement in performance-based assessments of executive function at week 24.

Conclusions: A high proportion of adolescents (>92%) remained virologically suppressed up to 48 weeks after switching from EFV to RPV along with no significant change in CD4 cell counts. RPV was well tolerated and associated with improvements in metabolic profiles and executive function.

Keywords: adolescents; efavirenz; HIV; rilpivirine; treatment switch

Additional information may be found under the Supporting Information tab of this article.

Received 17 March 2021; Accepted 7 December 2021

Copyright © 2021 The Authors. Journal of the International AIDS Society published by John Wiley & Sons Ltd on behalf of the International AIDS Society. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

1 | INTRODUCTION

Antiretroviral therapy (ART) has substantially reduced mortality and improved the long-term prognosis for infants and children living with HIV. Today, the majority of children living with HIV are surviving into adolescence [1] and optimizing therapy, primarily through regimen simplification and limiting drug-related side effects, which are valuable tools to facilitate drug adherence during this often-challenging period of child development.
Efavirenz (EFV)-based ART has been the cornerstone of first-line treatments in adults, adolescents and children older than 3 years in resource-limited settings since 2016 [2]. EFV has shown good virological efficacy, but has been associated with neuropsychiatric and metabolic side effects that can lead to the discontinuation of therapy [3]. Common central nervous system (CNS) side effects associated with EFV treatment include vivid dreams, dizziness, headache and depression, but in most individuals, these symptoms resolve over the first few weeks of treatment [4]. However, long-term neuropsychiatric effects can occur, with higher rates of suicidality (i.e. reported suicidal ideation and attempted/completed suicide) among individuals treated with EFV-based ART [5]. Elevations in total cholesterol (TC) and triglycerides have also been associated with EFV use [6]. Thus, alternative options to EFV are needed for those experiencing or at high risk of EFV-related side effects.

Rilpivirine (RPV) is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) available in Thailand for free through the national ART program. The efficacy and safety of RPV is well established in adults. Among ART-naive adults with a baseline RNA viral load (VL) <100,000 copies/ml, the virologic efficacy of RPV was non-inferior to EFV over 48 weeks, and RPV had a more favourable tolerability profile, with lower rates of CNS toxicity and lipid abnormalities compared to EFV [7–9]. Switching from EFV to RPV-based ART in virologically suppressed adults was also found to be safe and efficacious up to 48 weeks, with 93.9% remaining suppressed and no subjects stopping treatment due to adverse events [10]. A study in adolescents using adult doses revealed RPV plasma exposures comparable to adults along with good short-term safety and antiviral activity [11]. The PAINT study assessed the safety and efficacy of RPV-based ART in treatment-naive adolescents, and among those with a baseline VL ≤100,000 copies/ml, 79% achieved VL <50 copies/ml at week 48. RPV resistance-associated mutations (RAMs) were detected in five of eight subjects who experienced virologic failure, and adverse events considered possibly related to treatment were mostly somnolence and nausea but generally mild in this adolescent population [12].

Overall, RPV is a potential alternative to standard EFV-based ART for adolescents struggling with mild CNS side effects, or to help reduce the risk of metabolic side effects associated with long-term EFV use. Our primary objective was to describe the 48-week immunologic and virologic outcomes in virologically suppressed adolescents switching from EFV to RPV-based ART. Assessment of neuropsychiatric adverse events, quality of life (QOL) and metabolic profiles while on RPV were secondary objectives.

2 METHODS

We performed an open-label, single-arm, multi-centre study in adolescents with HIV aged 12–18 years old. This study was performed at four sites in Thailand: Siriraj Hospital, Queen Sirikit National Institute of Child Health, HIV-NAT Chulalongkorn University and Khon Kaen University. Data were collected between 10th February 2016 and 19th September 2018.

Prior to screening, caregivers provided written informed consent and adolescents who knew their HIV status provided written assent. Adolescents 12–18 years, with a body weight ≥25 kilograms and receiving ART composed of EFV plus two nucleoside or nucleotide reverse transcriptase inhibitors (N(Nt)RTI) for ≥3 months with virological suppression (HIV RNA ≤50 copies/ml within the last 12 months) were screened for eligibility. We excluded individuals with prior evidence of NNRTI-associated resistance mutations based on the IAS–USA HIV drug-resistance mutations list (2019) (V90I, A98G, L100I, K101E/H/P/Q/R/N, K103N/S, V106A/M/I, V108I, E138K/A/G/Q/R, V179D/F/L/T, Y181C/I/V, Y188L/C/H, G190A/S/E, H221Y, P225H, F227L/C/R, M230L/I and L234I) [13]. However, resistance genotyping was not always obtained and adolescents who may have failed on a prior NNRTI regimen were consequently also excluded if no historical genotype result was available. In addition, adolescents were excluded if they were currently receiving an HIV protease inhibitor, were pregnant, had an alanine aminotransferase (ALT) ≥200 IU/L over the last 12 months, active opportunistic infection(s) related to immunosuppression, or significant medical problems in the investigator’s opinion that would compromise participation, or concomitant treatment with drugs known to effect the pharmacokinetics of RPV (i.e. carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin, omeprazole, esomeprazole, lansoprazole, erythromycin, clarithromycin, azithromycin and roxithromycin).

At the study entry visit, EFV-based ART was discontinued and switched to RPV-based ART. Study participants were advised to take a single RPV 25 mg tablet once daily with a substantial meal to increase drug absorption. This food requirement was emphasized at each study visit. The choice of the NRTIs/NNRTI backbone was according to the standard of care in Thailand and inclusive of drugs and formulations provided for free through the national ART program. Study participants were also advised to report any adverse events (e.g. rash, insomnia, headache, etc.) that developed after switching to RPV. Due to the extended inductive effect of EFV on CYP3A4, there were initial questions around the potential for reduced RPV exposures immediately after switching from EFV; thus, at the start of this study, a pharmacokinetic sub-study was performed in 20 participants. We have previously reported that RPV exposures were adequate in this sub-cohort immediately after switching from EFV and study-related dosing was not altered [14]. The planned duration of follow-up for each study participant was 48 weeks. HIV-1 RNA VL was performed at entry, weeks 12, 24 and 48. Complete blood count, CD4 cell counts and percentage, ALT and creatinine were assessed at baseline, weeks 4, 24 and 48. Fasting TC, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride and glucose were tested at baseline, weeks 24 and 48. These laboratory tests were collected to monitor the safety of RPV. If a participant’s VL was found to be >50 copies/ml, the VL test was repeated within 4–8 weeks and adherence counselling provided. Virologic failure was defined as a confirmed VL >50 copies/ml during the 48-week follow-up. If a VL >1000 copies/ml was reported, an HIV genotypic-resistance test (GRT) was also performed. Resistance results were interpreted using the 2019 edition of the IAS–USA HIV drug-resistance mutations
list [13]. Modification of ART due to either drug resistance and/or safety considerations was at the discretion of the site investigators. Executive function and global cognition were evaluated by standard tests, including the non-verbal part of the Standard Progressive Matrices (SPM), digit symbol coding sub-test of the Wechsler Intelligence Scale for Children-Third Edition (WISC-III), Trail Making Test (TMT) part A and part B, and the Wisconsin Card Sorting Test (WCST) at baseline and week 24. Depression, QOL and EFV-related symptoms were assessed at baseline, weeks 4 and 24 by the Center for Epidemiologic Studies-Depression Scale (CES-D), PedsQL™ 4.0 [15,16] and a self-reported questionnaire, respectively.

This study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine Siriraj Hospital, Mahidol University, Queen Sirikit National Institute of Child Health Chulalongkorn University and Khon Kaen University.

The primary objective was to describe the 48-week virologic and immunologic outcomes in virologically suppressed adolescents switching from EFV- to RPV-based ART. Under the assumption that all study participants were virologically suppressed at the time of treatment switch, and that 10% would experience virological failure over 48 weeks [17], a sample size of 100 subjects would provide 90% power to detect a change of 10% from baseline based on McNemar’s test of paired proportions for a single group of subjects (two-sided, alpha of 0.05). The primary endpoints were the proportion of study participants with VL <50 copies/ml and change of CD4 cell count from baseline at 48 weeks. Analysis for virologic suppression was intention-to-treat, with study losses to follow-up or deaths imputed as failures. Both primary endpoints were analysed using the Wilcoxon signed-rank test. The secondary endpoints of change in TC, LDL, HDL, triglyceride, LDL/HDL ratio, TC/HDL ratio and glucose were compared between baseline and week 24, and baseline and week 48. In addition, depression, QOL and EFV-related symptom scores were compared between baseline and week 4, and baseline and week 24. Each of these comparisons were tested using a Wilcoxon signed-rank test. Changes in executive function and global cognition were compared between baseline and week 24 by a McNemar test. Participant data were collected from source documents onto Case Record Forms, and transferred to an electronic data capture program. All analyses were performed using STATA, version 11.2 (StataCorp, College Station, TX, USA).

3 RESULTS

A total of 105 adolescents were screened and 102 (52% male) were enrolled (Figure 1). The three adolescents who did not enrol had a VL >50 copies/ml at screening. All study participants were receiving first-line EFV-based ART at enrolment. Baseline demographic data of study participants are shown in Table 1. The median age at enrolment was 15.5 years [interquartile range (IQR) 14.4–17.0] with a median CD4 count of 664 cells/mm³ (IQR 553–862) (29.9%). Twenty-seven (26.5%) participants were receiving a single-tablet regimen of tenofovir-DF/emtricitabine/EFV (TDF/FTC/EFV) before switching ART. The majority of study participants...
Table 1. Baseline demographic data of study participants in switching efavirenz to rilpivirine in virologically suppressed adolescents with HIV: a 48-week efficacy and safety, multi-centre study in Thailand (n = 102)

| Characteristics                          | N = 102 |
|------------------------------------------|---------|
| Enrolment by site; n (%)                 |         |
| The HIV Netherlands Australia Thailand   | 23 (22.5)|
| Research Collaboration                   |         |
| Khon Kaen University                     | 11 (10.8)|
| Queen Sirikit National Institute of Child| 26 (25.5)|
| Health                                   |         |
| Siriraj Hospital                         | 42 (41.2)|
| (%)                                      |         |
| Sex; n (%)                               |         |
| Female                                   | 49 (48.0)|
| Male                                     | 53 (52.0)|
| Age (years); median (IQR)                | 15.6 (14.4–17.0)|
| WHO Stage; n (%)                         |         |
| Stage 1                                  | 22 (21.6)|
| Stage 2                                  | 18 (17.7)|
| Stage 3                                  | 46 (45.1)|
| Stage 4                                  | 16 (15.6)|
| CDC Stage; n (%)                         |         |
| N                                        | 12 (11.8)|
| A                                        | 21 (20.6)|
| B                                        | 33 (32.4)|
| C                                        | 36 (35.3)|
| Nadir CD4 cells/mm³; median (IQR)        | 12.3 (3.0–20.0)|
| Nadir CD4 percentage; median (IQR)       | 289 (46–493)|

Abbreviations: CDC, Centers for Disease Control and Prevention; IQR, interquartile range; WHO, World Health Organization.

We found that a high proportion of virologically suppressed adolescents switching from EFV- to RPV-based ART maintained virologic suppression after 48 weeks. This finding is important as there is a paucity of data about RPV in adolescents. Over 92% of the adolescents maintained virologic suppression up to 48 weeks. Our results are comparable to a 48-week, phase 2b study in adults switching from EFV/TDF/FTC to RPV/TDF/FTC, which reported 93.9% of participants remaining virologically suppressed [10]. While no emergence of RPV resistance was observed in the 4.1% of study participants with virologic failure in the adult study, two of six adolescents with virologic failure in our study developed RPV RAMs (K101E and Y181C) and a lamivudine-associated mutation (M184V/I). In ART-naïve adults initiating RPV/FTC/TDF, resistance mutations to RPV development were more frequent in subjects with baseline HIV-1 RNA >100,000 copies/ml compared to baseline HIV-1 RNA ≤100,000 copies/ml [18]. Resistance analyses of RPV from the ECHO and THRIVE Phase III trials found that 6.7% of subjects on RPV developed treatment-emergent NNRTI RAMs, with E138K+M184I being the most frequent combination [19].

Consistent with studies in adults, an important aspect of the current study is that switching from EFV- to RPV-based...
### Table 2. Comparison of virologic, immunologic and metabolic outcomes between baseline versus week 24, and baseline versus week 48 after switching from efavirenz to rilpivirine in virologically suppressed adolescents with HIV in Thailand ($n = 102$)

| Laboratory results | Week 0 | Week 12 | Week 24 | Week 48 | $p$-Value Week 0 versus Week 24 | $p$-Value Week 0 versus Week 48 |
|--------------------|--------|---------|---------|---------|-------------------------------|-------------------------------|
| **Virology**       |        |         |         |         |                               |                               |
| Virological suppression (HIV RNA <50 copies/ml); n (%) | 102 (100.0) | 94 (92.2) | 96 (94.1) | 94 (92.2) | 0.031                         | 0.008                         |
| **Immunology**     |        |         |         |         |                               |                               |
| CD4 cells/mm$^3$; median (IQR) | 664 (553-862) | – | 689 (565-859) | 667 (553-920) | 0.219                         | 0.866                         |
| **Lipid profile; median (IQR)** |         |         |         |         |                               |                               |
| Cholesterol        | 159 (144–176) | – | 140 (123–156) | 139 (126–159) | <0.001                        | <0.001                        |
| Triglycerides      | 83 (68–110) | – | 70 (59–87) | 74 (60–85) | <0.001                        | <0.001                        |
| HDL                | 52 (41–62) | – | 43 (37–54) | 44 (38–52) | <0.001                        | <0.001                        |
| LDL                | 89 (74–104) | – | 79 (64–92) | 81 (68–95) | <0.001                        | <0.001                        |
| LDL/HDL ratio      | 1.8 (1.3–2.2) | – | 1.8 (1.4–2.4) | 1.9 (1.5–2.3) | 0.409                         | 0.016                         |
| Cholesterol/HDL ratio | 3.2 (2.7–3.7) | – | 3.2 (2.6–3.7) | 3.3 (2.8–3.7) | 0.617                         | 0.249                         |
| Glucose            | 86 (81–91) | – | 85 (81–91) | 85 (80–91) | 0.721                         | 0.166                         |

Abbreviations: HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

### Table 3. Comparison of health-related quality of life evaluated by self-report, PedsQL, and depression evaluated by CES-D at baseline and week 24 after switching from efavirenz to rilpivirine in virologically suppressed adolescents with HIV in Thailand ($n = 102$)

| Tests                        | Week 0 | Week 4 | Week 24 | $p$-Value Week 0 versus Week 4 | $p$-Value Week 0 versus Week 24 |
|------------------------------|--------|--------|---------|-------------------------------|-------------------------------|
| **Self-report, median (IQR)** |        |        |         |                               |                               |
| Sleep                        | 3 (1–6) | 4 (1–7) | 4 (1–7) | 0.152                         | 0.237                         |
| Dizziness/headache           | 1 (0–3) | 2 (0–3) | 2 (0–3) | 0.797                         | 0.638                         |
| Concentration                | 2 (1–2) | 2 (1–3) | 2 (1–3) | 0.146                         | 0.225                         |
| Mood/emotion                 | 5 (4–7) | 5 (4–7) | 5 (4–8) | 0.617                         | 0.522                         |
| **PedsQL**                   |        |        |         |                               |                               |
| Health problem               | 4 (0–15) | 4 (0–14) | 6 (0–17) | 0.688                         | 0.577                         |
| Emotional problem            | 3 (0–6) | 3 (0–8) | 4 (0–7) | 0.843                         | 0.952                         |
| Social problem               | 1 (0–4) | 1 (0–5) | 2 (0–4) | 0.358                         | 0.717                         |
| School problem               | 6 (2–9) | 4 (2–9) | 7 (2–9) | 0.231                         | 0.816                         |
| **Child report, median (IQR)** |        |        |         |                               |                               |
| Health problem               | 4 (1–9) | 3 (0–8) | 3 (0–7) | 0.152                         | 0.246                         |
| Emotional problem            | 4 (1–7) | 3 (1–8) | 4 (1–7) | 0.216                         | 0.999                         |
| Social problem               | 0 (0–4) | 1 (0–3) | 0 (0–2) | 0.510                         | 0.279                         |
| School problem               | 6 (3–8) | 6 (3–9) | 5 (3–8) | 0.717                         | 0.253                         |
| **CES-D**                    |        |        |         |                               |                               |
| Total score                  | 15 (11–18) | 15 (11–19) | 14 (11–19) | 0.779                         | 0.767                         |
| Normal ($\leq 22$); n (%)    | 87 (85.3) | 84 (83.2) | 85 (85.0) |                               |                               |
| Abnormal ($>22$); n (%)       | 15 (14.7) | 17 (16.8) | 15 (15.0) |                               |                               |

Abbreviations:
- CES-D, Center for Epidemiologic Studies-Depression Scale;
- IQR, interquartile range; PedsQL™, Pediatric Quality of Life Inventory™ 4.0.
Table 4. Comparison of executive and cognitive function at baseline and week 24 after switching from efavirenz to rilpivirine in virologically suppressed adolescents with HIV in Thailand

|                          | Week 0 n (%)a | Week 24 n (%)a | p-Value |
|--------------------------|---------------|---------------|---------|
| **Standard Progressive Matrices** |               |               |         |
| Total                    |               | Normal        | Abnormal | 0.549   |
| Normal                   | 78 (100.0)    | 74 (94.9)     | 4 (5.1)  |
| Abnormal                 | 19 (100.0)    | 7 (36.8)      | 12 (63.2)|         |
| Total                    | 97            | 81            | 16       |
| **Coding**               |               | Average to superior | Below average | 0.049   |
| Total                    |               | 57 (100.0)    | 53 (93.0) |         |
| Average to superior      |               | 4 (8.9)       | 7 (36.8)  |
| Below average            |               | 12 (63.2)     | 27 (67.5)|         |
| Total                    | 97            | 66            | 31       |
| **Trail Making Test: part A** |               | Average to fast | Slow | <0.001   |
| Total                    |               | 45 (100.0)    | 41 (91.1) |         |
| Average to fast          |               | 30 (57.7)     | 22 (42.3)|         |
| Slow                     | 52 (100.0)    | 7 (13.5)      | 49 (93.0)|         |
| Total                    | 97            | 71            | 26       |
| **Trail Making Test: part B** |               | Average to fast | Slow | 0.001    |
| Total                    |               | 31 (100.0)    | 25 (80.6) |         |
| Average to fast          |               | 24 (77.4)     | 41 (63.1)|         |
| Slow                     | 65 (100.0)    | 49 (75.8)     | 47       |
| Total                    | 96            | 49            | 47       |
| **WCST: total number of errors** |               | Average to fast | Slow | 0.103    |
| Total                    |               | 48 (100.0)    | 40 (83.3) |         |
| Average to above         |               | 16 (35.6)     | 29 (64.4)|         |
| Below average to impairment |           | 56            | 37       |
| Total                    | 93            |               |         |

Abbreviation: WCST, Wisconsin Card Sorting Test.

aPercentage by row.
bOnly those with available test results at baseline and week 24 were included in the analysis.

ART was extremely well tolerated with no treatment discontinuations due to adverse events. Among virologically suppressed adults switching from EFV/FTC/TDF to RPV/FTC/TDF, there were significant decreases in fasting TC, direct LDL cholesterol and triglycerides at week 12, and these changes persisted through week 48 [10]. Switching from EFV-based to RPV-based ART among virologically suppressed adolescents in our study was associated with improvements in metabolic profiles with significant decreases in TC, triglyceride and LDL at weeks 24 and 48. There was a significant decrease in HDL at weeks 24 and 48. However, the median (IQR) HDL at weeks 24 and 48 was 43 (37–54) and 44 (38–52) mg/dl, respectively, which was in the range of borderline level of HDL (35–45 mg/dl), as defined by the National Cholesterol Education Program [20]. While there was a statistically significant increase in the LDL/HDL ratio at week 48, the magnitude of the increase was small and not considered clinically significant. The change in TC/HDL ratio was not statistically significant, and the median ratio was below the cut-off associated with development of metabolic syndrome reported in Korean adolescents; in which a high risk of metabolic syndrome was associated with a TC/HDL ratio ≥ 3.8 [OR: 14.8 (95% CI 2.8–77.4)] and those with a TG/HDL ratio ≥ 3.3 [OR: 30.6 (95% CI, 6.0–157.6)] [21]. When TC/HDL and TG/HDL were both above the cut-off values, the risk of metabolic syndrome further increased [OR: 36.2 (95%, 7.2–186.2)]. The significance and long-term effects of these findings need further study.

Perhaps unexpectedly, we did not demonstrate a significant change in EFV-related side effects evaluated by self-report (i.e., sleep, dizziness/headache, concentration, mood/emotion and total scores). An observational study in Tanzania compared the competence (social involvement, activities and school performance), psychopathology (internalizing and externalizing problems) and cognitive performance (intelligence and working memory) of children with HIV aged 6–12 years receiving an EFV-based versus non-EFV-based regimens, and found that EFV use in children was associated with a mild increase in neuropsychiatric symptoms [21]. The lack of a difference in our study could be explained by selection bias, as the study participants enrolled were stable on EFV-based ART (for ≥ 3 months) and therefore somewhat tolerant of EFV, while those who did not tolerate EFV may have already been switched to an alternative regimen. Furthermore, it is possible that children and adolescents may tolerate EFV better than adults and report fewer neuropsychiatric side effects. Improvements in neuropsychiatric symptoms, sleep quality and self-perceived cognition were observed in a randomized study in adults who already had altered neurocognitive assessment, depression, anxiety or low sleep-quality, switching either immediately or delayed to RPV- from EFV-based ART [23]. Interestingly, switching to RPV was not found to improve cognitive function in these adults. In our study, 20.0–68.7% of adolescents had some degree of impairment of executive and cognitive function at baseline, and significant improvement in executive function was observed. A study on
executive function and emotional behavioural problems in a cohort of Asian adolescents living with HIV, in which 86.4% had virologic suppression, found that there were significantly higher rates of impairment in all assessed measures of executive function and behavioural problems in adolescents living with HIV, compared with HIV-unexposed, uninfected youth, after adjustment for relevant socio-demographic factors [24]. Thai adolescents living with HIV on ART (with 93% achieving virologic suppression) had significantly lower scores on the measures of executive function compared to HIV-uninfected controls across multiple neuropsychological tests [25]. These findings are consistent with prior studies in the U.S.-based Pediatric HIV/AIDS Cohort [26]. Individual differences in executive function are associated with multiple important aspects of human health, including academic and occupational functioning, interpersonal problems, substance use, physical health and mental health. Of critical importance, executive function impairments are associated with poor academic performance as well as emotional and behavioural problems [27]. A key finding of our study is the significant improvement in performance-based assessments of executive and cognitive function at week 24 after switching to RPV from EFV.

We demonstrated that RPV was well tolerated and was associated with improvement in metabolic profiles, executive and cognitive function, and is a reasonable alternative for adolescents experiencing EFV-associated side effects. Of note, adolescents must be able to take RPV following a regular schedule with a full meal to assure adequate RPV concentrations, which may limit its usefulness for adolescents with irregular eating schedules. Importantly, our findings support the use of RPV as a part of a long-acting injectable treatment regimen, which would be an ideal option for adolescents [28].

Our study had several limitations. Firstly, an HIV GRT was not performed prior to initiation of ART. This is consistent with the national antiretroviral treatment guidelines in Thailand. Although GRT could have identified those less likely to respond to RPV, we only enrolled participants who had not previously failed NNRTI-based ART (based on virologic criteria). Therefore, the presence of NNRTI mutations was expected to be very low and not anticipated to affect treatment outcomes. Secondly, we did not record participant adherence to ART – whether by self-report or other means (e.g. pill count), which could have been a primary contributor to virologic failure. Thirdly, improvement on repetition of neuropsychological testing could have been due to learning the skills of the test over time. Furthermore, there were many potential psychosocial issues among adolescents living with HIV, which may have influenced the results of the QOL and depression scores while on RPV.

Recently, the World Health Organization revised its recommendations for preferred first- and second-line regimens for adolescents and adults to include dolutegravir (DTG)-based ART [29]. The Thailand National Guidelines on HIV/AIDS Diagnosis, Treatment and Prevention 2020/2021 also revised its recommendations accordingly. RPV is now recommended as an alternative first-line regimen for those with VL <500,000 copies/ml or CD4 >350 cells/mm³ if the HIV RNA VL is not available. Furthermore, RPV can be used for a treatment switch for those individuals who have had an undetectable VL for 6–12 months and do not have prior NNRTI resistance, or those who cannot tolerate EFV within 2 weeks after initiation [30]. Although our data were collected between 2016 and 2018, they remain relevant more broadly in Asia today. To date, access to DTG remains limited in many countries in the region, and rollout has been slower overall than in African countries – a challenge that has been exacerbated by the impact of the COVID-19 pandemic on drug production and supply chains [31]. Until DTG is widely available, alternatives to EFV, such as RPV, are still needed.

5 | CONCLUSIONS

Overall, the majority of adolescents on EFV-based ART with HIV-VL <50 copies/ml who switched to RPV remained virologically suppressed up to 48 weeks, along with no significant change in CD4 cell counts. Among the few participants with virologic failure, development of RPV-RAMs (K101E and Y181C) was infrequent. RPV was well tolerated and was associated with improvement in metabolic profiles, executive and cognitive function and is a reasonable alternative for adolescents experiencing EFV-associated side effects.

AUTHORS’ AFFILIATIONS

1Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; 2Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; 3Thai Red Cross AIDS Research Center (TRCARC), HIVNET, Bangkok, Thailand; 4Division of Child and Adolescent Psychiatry, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; 5Queen Sirikit National Institute of Child Health, Bangkok, Thailand; 6Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.

5Queen Sirikit National Institute of Child Health, Bangkok, Thailand; 6Department

DATA AVAILABILITY STATEMENT

The data are available upon request to the corresponding author.
REFERENCES

1. Mofenson LM, Cotton MF. The challenges of success: adolescents with perinatal HIV infection. J Int AIDS Soc. 2013;16:18450.

2. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. 2nd ed. 2016. Available from https://www.who.int/hiv/pub/arv/arv-2016/en/.

3. Mbuagbaw L, Murseleen S, Irimajer JH, Spoobling AB, Rutherford GW, Siegfried N. Efavirenz or nevirapine in three-drug combination therapy with two-nucleoside or nucleotide-reverse transcriptase inhibitors for initial treatment of HIV infection in antiretroviral-naive individuals. Cochrane Database Syst Rev. 2016;12:CD004246.

4. Kenedi CA, Goforth HW. A systematic review of the psychiatric side-effects of efavirenz. AIDS Behav. 2011;15:1803–18.

5. Mollan KR, Smurzynski M, Enor JJ, Daar ES, Campbell TB, Sax PE, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. Ann Intern Med. 2014;161:1–10.

6. Ward DJ, Curtin JM. Switch from efavirenz to nevirapine associated with resolution of efavirenz-related neuropsychiatric adverse events and improvement in cognitive approaches. Front Psychol. 2015;6:328.

7. Cohen CJ, Molina JM, Cahn P, Ciotet B, Fourie J, Grinsztejn B, et al. Efficacy and safety of rilpivirine (TMC278) versus efavirenz at 48 weeks in treatment-naive HIV-1-infected patients: pooled results from the phase 3 double-blind randomized ECHO and THRIVE Trials. J Acquir Immune Defic Syndr. 2012;60:33–42.

8. Molina JM, Clumeneck N, Redant K, Rimsyk L, Vanvelk G, Stevens M, et al. Rilpivirine vs. efavirenz in HIV-1 patients with baseline viral load 100,000 copies/ml or less: week 48 phase III analysis. AIDS. 2013;27:889–97.

9. Cohen CJ, Molina JM, Cassetti I, Chetchotisakd P, Lazarrin A, Orkin C, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two phase III randomized trials. AIDS. 2013;27:939–50.

10. Mills AM, Cohen C, Dejesus E, Brinson C, Williams S, Yale KL, 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;14:216–27.

11. Crauwels H, Hoogstool A, Vanvelk G, Sarnall W, Stevens M, Boen K, et al. Rilpivirine pharmacokinetics in HIV-1-infected adolescents: a substudy of PAINT (Phase II trial). In: 21st Conference on Retroviruses and Opportunistic Infections, March 3–6, 2014. Boston, MA.

12. Lombard J, Bunupuradah T, Flynn PM, Ramapuram J, Sali F, Crauwels H, et al. Rilpivirine as a treatment for HIV-infected antiretroviral-naive adolescents: week 48 safety, efficacy, virology and pharmacokinetics. Pediatr Infect Dis J. 2016;35:1915–21.

13. Wensing AM, Calvez V, Ceccherini-Silberstein F, Charpentier C, Günthard HF, Paredes R, et al. 2019 Update of the drug resistance mutations in HIV-1. Top Antivir Med. 2019;27:111–1.

14. Jantarabenjakul W, Anugulruengkitt S, Kasipong N, Thammajaruk N, Sophon-Jitt A, Hinkin BL. Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. Front Psychol. 2016;5:628.

15. Rajoli RKR, Back DJ, Rannard S, Meyers CF, Flexner C, Owen A, et al. In silico dose prediction for long-acting rilpivirine and cabotegravir administration to children and adolescents. Clin Pharmacokinet. 2018;57:255–66.

16. Porter DP, Kulkarni R, Frailich T, Miller MD, White KL. 96-Week resistance analyses of the START study: rilpivirine/emtricitabine/tenofovir DF versus efavirenz/emtricitabine/tenofovir DF in antiretroviral-naive, HIV-1-infected subjects. HIV Clin Trials. 2015;16:30–8.

17. Chi S, Jung J, Park M, Kim S. Risk assessment of metabolic syndrome in adolescents using the triglyceride/high-density lipoprotein cholesterol ratio and the total cholesterol/high-density lipoprotein cholesterol ratio. Ann Pediatr Endocrinol Metab. 2019;24:41–8.

18. Van de Wijer L, McHaiie DN, de Mast Q, Mmbaga BT, Rommelse NNN, Duijmajer A, et al. Neuropsychiatric symptoms in Tanzanian HIV-infected children receiving long-term efavirenz treatment: a multicentre, cross-sectional, observational study. Lancet HIV. 2019;6:250–8.

19. Jantarabenjakul W, Anugulruengkitt S, Kasipong N, Thammajaruk N, Sophon-Jitt A, Hinkin BL. Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. Front Psychol. 2016;5:628.

SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article.