POSTER #807

Pharmacokinetics of rilpivirine after switching from efavirenz in adolescents

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BACKGROUND

- Rilpivirine (RPV) has become a recommended non-nucleoside reverse transcriptase inhibitor (NNRTI), replacing efavirenz (EFV) due to fewer CNS effects.
- RPV pharmacokinetics (PK) data are limited among HIV-infected adolescents, particularly after switching from EFV, which potentially reduces rilpivirine exposure due to fading CYP3A inducing capacity.

OBJECTIVE

This study aims to describe the pharmacokinetic profile of RPV after switching from EFV in HIV-infected adolescents.

METHODS

Study design

- This was a substudy of treatment switch from efavirenz to rilpivirine in virologically-suppressed HIV-infected Thai adolescents study which was an open-label, single-arm study to describe the immunologic and virological outcome following switching regimen.
- Informed consent was obtained from each subject or his/her legally acceptable representatives.
- HIV-infected adolescents aged 12-18 years, weighing ≥ 25 kilograms, treated with EFV-based antiretroviral therapy for ≥ 3 months, HIV RNA (VL) < 50 copies/mL and ALT < 200 IU/L within the last 12 months were switched from EFV to RPV. Adolescents were excluded if, at screening, they had evidence of NNRTI-associated resistance mutation(s) from previous genotypic resistance testing, had PI(s) in the HAART regimen, active HIV-related infections, pregnancy and concomitant treatment with drugs known to affect the PK of RPV.
- This study was approved by the institutional review board of Faculty of Medicine, Chulalongkorn University

Pharmacokinetic evaluations

- RPV 25 mg was taken once daily with a solid meal in morning.
- At week 4, a PK profile was determined at 0 (pre-dose), 1, 2, 4, 5, 6, 9, 12 and 24 hours following an observed intake of RPV with a standardized meal (525 kcal).
- Plasma RPV concentrations were measured using a validated liquid chromatography-mass spectrometry (LC-MS) method (lower limit of quantification (LLQ) 4 ng/mL).
- Plasma EFV concentrations were measured at weeks 0 and 4, using a validate High Performance Liquid Chromatography (HPLC) method (LLQ 100 ng/mL).
- RPV PK parameters were calculated using a non-compartmental method (Winnonlin version 6.3) and compared with published data (the PAINT and pooled ECHO/THRIVE PK substudies).[1] The proposed target RPV C_{24h} was > 40 ng/mL, derived from ECHO and THRIVE studies.[2]

Antiviral activity and safety evaluations

- HIV RNA levels were performed at baseline, week 12 and 24.
- Safety and tolerability assessed by AE monitoring, physical examination and clinical laboratory evaluation. Blood chemistry included creatinine, alanine aminotransferase (ALT), fasting lipid profiles, total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) were collected at baseline and week 24, compared by Wilcoxon signed rank test
- Adherence was determined by pill count.

RESULT

Baseline characteristics

From January to June 2016, 20 adolescents were enrolled (**Table 1**).

Table 1. Baseline Characteristics of adolescents

	Total (N =20)
Demographics *	
Male sex, N (%)	12 (60%)
Age, years	15.7 (13.8-18.9)
Height, cm	159 (146-174)
Weight, kg	48 (31-93)
BMI, kg/m^2	19 (14-38)
% most severe WHO staging, stage I: II: III: IV	30:15:45:10
Baseline Absolute CD4+ count, cell/mm^3	726 (236-1145)
Pre-switching regimens	
- TDF/3TC/EFV, N (%)	18 (90%)
- AZT/3TC/EFV, N (%)	2 (10%)
Median (range) of duration on EFV before enrollment, months	40 (3-94)

* Data are presented as median (range)

RPV pharmacokinetics

- The PK parameters of RPV are shown in **Table 2** and mean (SD) plasma concentration-time curve of RPV as shown in **Figure 1**.
- All values from the present study are comparable with the PAINT and ECHO/THRIVE sub-studies.
- Four adolescents (20%) had RPV C_{24h} < 40 ng/mL, of which two reported poor adherence < 95%.
- Mean (SD) EFV plasma concentrations at week 0 was 2030 (1037) ng/ml which median (range) post-dose were 14 (2-16) hours, but none had detectable EFV levels at week 4.

Table 2. Steady-state RPV pharmacokinetic profiles in adolescents of this study compared to data from naïve adolescents (PAINT substudy) and adults (pooled ECHO/THRIVES substudy).

PK parameter of Rilpivirine*	This study Adolescents switched from EFV (n=20)	PAINT study Treatment naïve Adolescents[1] (n=23)	P-value**	Pooled ECHO/THRIVE Treatment naïve Adults[1] (n=44)	P-value**
AUC_{24h}, ng.h/mL	2041 (745)	1872 (717)	0.45	2005 (970)	0.88
C_{24h}, ng/mL	69 (29)	81 (40)	0.28	68 (39)	0.90
C_{max}, ng/mL	143 (65)	109 (38)	0.04	134 (72)	0.65
T_{max}, hours	5 (0-9)	5 (2-9)	-	4 (1-12)	-

*Data shown are: mean (SD), except T_{max} as median (range)
** P-value was compared by an independent two sample T-test

Pharmacokinetics analysis by subgroup

- No apparent relationship between RPV AUC_{24h} and age (>12 to ≤ 15 and > 15 to 18 years), weight (< 50 kg and ≥ 50 kg), or BMI (< 18 kg/m^2 and ≥ 18 kg/m^2) was found.
- Also, there are no apparent relationships between RPV C_{24h} or C_{max} and age, weight or BMI.

Antiviral activity at week 12 and 24

- The majority of adolescents (16/20) had > 95% adherence at their PK visit by pill count.
- All adolescents had HIV RNA < 50 copies/ml at weeks 12 and 24.

Safety and tolerability at week 24

- Overall, no patients discontinued study drugs due to adverse effects and no report of majority adverse effects.
- From baseline to week 24, there were significant decreases in fasting TC, TG and LDL (P-value 0.002, 0.01 and 0.02, respectively). However, HDL level were also significant decrease (P-value 0.002), whereas TC/HDL ratio and LDL/HDL ratio remained stable (P-value 0.28 and 0.13, respectively).
- There were no significant change in ALT, creatinine and eGFR by Schwartz equation (P-value 0.13, 0.15, and 0.39, respectively).

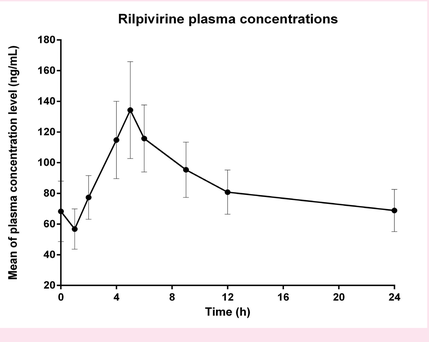

Figure 1. Mean (SD) plasma concentration-time curve of RPV 25 mg once daily at week 4 after switching from EFV

DISCUSSION

- Pharmacokinetic profiles of RPV after switching from EFV in adolescent were comparable with naïve HIV-1 infected adolescent and adult as well as switching in healthy subjects[1,3].
- Long-term safety, tolerability, and change of neuropsychiatric events in larger group of adolescents (N=100) are being evaluated.

CONCLUSIONS

HIV-infected adolescents switching from EFV to RPV had adequate RPV pharmacokinetic profiles and there was no virological failure detected at 24 weeks following switching.

REFERENCES

1. European Medicines Agency. Assessment Report Edurant International non-proprietary name: Rilpivirine. United Kingdom: European Medicines Agency Science Medicines Health, 2015.
2. Mills AM, Cohen C, Dejessus 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;14:216-223
3. Crauwels H, Vingerhoets J, Ryan R, et al. Pharmacokinetic parameters of once-daily rilpivirine following administration of efavirenz in healthy subjects. Antiviral Therapy 2012;17:439-446

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