Report of Project Results

Title

Pharmacokinetics of low- dose lopinavir/ ritonavir tablet formulation in HIV-1 infected children

Rachadapiseksompotch Fund

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Study team

Project Title Pharmacokinetics of low- dose lopinavir/ritonavir tablet formulation in HIV-1 infected children

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Abstracts

Background: Lopinavir/ritonavir (LPV/r) is the most commonly used protease inhibitor in HIV-infected children. Data showed high blood level of LPV in Thai HIV-infected adults and children. This study aimed to determine pharmacokinetic parameters (PK) of low dose LPV/r.

Methods: This was an open-label, cross-over study of 24 HIV-infected children with HIV RNA < 50 copies/ml comparing PK parameter of standard dose LPV/r and low dose of LPV/r for 4 weeks. LPV dosage was prescribed by body weight band; 25-35 kg: LPV/r 300/75 vs. 200/50 mg, > 35 kg 400/100 vs. 300/75 mg. Blood samples were drawn at 0 (pre-dose), 2, 4, 6, 8, 10 and 12 hours. Plasma concentrations of LPV and RTV were measured by HPLC method. The acceptable C_{12h} is > 1 mg/L. The HIV RNA was measured at week 12 after switch back to standard dose for 4 weeks.

Results: Twenty four children were included. Median (interquartile range) age, body weight, CD4 count were 13.5 (12-15) years, 33.4 (28.3-41.1) kg, 913(737-1,178) cells/ mm^3. Geometric mean (95% Confidence Interval) value with standard dose lopinavir $AUC_{0-12\,h}$, C_{max}, C_{12h} and T_{half} were 93.8 (82.9-106.3) mg.h/L, 10.8(9.6-12.0) mg/L, 3.7(3.0-4.6) mg/L, and 4.8 (4.0-5.8) h respectively. For low dose LPV these values were 83.1(72.2-95.6) mg.h/L, 10.7 (9.5-12.0) mg/L, 2.8 (2.1-3.6) mg/L, and 4.1 (3.5-4.8) h, respectively. In the multivariate analysis, there was no significant different in LPV AUC ($p=0.35$) and C_{12h} ($p=0.65$) between standard and low dose LPV. But the AUC of ritonavir is the strong predictor for LPV AUC and C_{12h} ($p<0.001$). One child (3%) had C_{12h} < 1 mg/L (0.82 mg/L) but still had undetectable HIV RNA. There were 2 children had HIV RNA = 52 and 99 copies/ml but C_{12h} >1 mg/L.

Conclusions: Low dose of LPV/r provide adequate pharmacokinetic parameters. Successful usage of low dose LPV/r could have a significant public health impact in reducing side effects and costs related to treating complications and procuring the drug. A larger randomized clinical

study to assess efficacy of low dose vs. standard dose of LPV/r among HIV-infected children should be explored.

Keywords HIV infected children, Lopinavir/ritonavir and Pharmacokinetics

บทคัดย่อ

ชื่อโครงการวิจัย โครงการวิจัยเพื่อศึกษาเปรียบเทียบเภสัชจลนศาสตร์ ระหว่างการใช้ยาต้านไวรัสโลพินาเวียร์/ริโทนาเวียร์ชนิดเม็ดในขนาดมาตรฐานและขนาดต่ำในเด็กติดเชื้อเอชไอวี

ชื่อผู้วิจัย รองศาสตราจารย์แพทย์หญิง ชันยวีร์ ภูชนกิจ

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หลักการและเหตุผล: ยาต้านไวรัสโลพินาเวียร์/ริโทนาเวียร์ เป็นยาต้านไวรัสกลุ่มโปรติเอสที่ใช้กันอย่างแพร่หลายและได้ผลดีในเด็ก มีข้อมูลว่าขนาดยาต้านไวรัสโลพินาเวียร์/ริโทนาเวียร์ที่ใช้ในเด็กไทยมีระดับยาสูงมากในเลือด การศึกษานี้จึงทำขึ้นเพื่อศึกษาเปรียบเทียบเภสัชจลนศาสตร์ของยาโลพินาเวียร์/ริโทนาเวียร์ชนิดเม็ดในขนาดมาตรฐานและขนาดต่ำในเด็ก

รูปแบบและวิธีการศึกษา: เป็นการศึกษาแบบ open-label, cross-over ทำในอาสาสมัครเด็กติดเชื้อเอชไอวี อายุ <18 ปี จำนวน 24 ราย ที่มีระดับปริมาณเชื้อไวรัสเอชไอวีในเลือด< 50 copies/ml เปรียบเทียบค่าเภสัชจลนศาสตร์ของยาต้านไวรัสโลพินาเวียร์/ริโทนาเวียร์ชนิดเม็ดขนาดมาตรฐานและขนาดต่ำหลังได้รับยานาน 4 สัปดาห์ ยาขนาดมาตรฐานและขนาดต่ำให้ตามช่วงน้ำหนักตัว คือ น้ำหนัก 25-35 กิโลกรัมให้ยาโลพินาเวียร์/ริโทนาเวียร์ 300/75 และ 200/50 มิลลิกรัม, น้ำหนัก>35 กิโลกรัม ให้ยา 400/100 และ300/75 มิลลิกรัม ตามลำดับ วัดระดับยา 7 ครั้ง ที่ก่อนกินยามื้อเช้า, 2, 4, 6, 8, 10 และ 12 ชั่วโมงหลังกินยา ระดับยาในเลือดวัดโดยวิธี high performance liquid chromatography นำมาคำนวณค่าเภสัชจลนศาสตร์โดยโปรแกรม STATA ซึ่งระดับยาในเลือดที่ 12 ชั่วโมงควร >1 มก/ล และติดตามผู้ป่วย 12 สัปดาห์จึงวัดปริมาณไวรัสเอชไอวีในเลือดอีกครั้ง

ผลการศึกษา : ผู้เข้าร่วมการศึกษา 24 ราย โดยค่าเฉลี่ย (interquartile range) ของอายุ น้ำหนัก จำนวน CD4 คือ 13.5(12-15) ปี, 33.4(28.3-41.1) กิโลกรัม, และ 913 (737-1,178) เซลล์/มม.^{3} และค่าเฉลี่ย(ความเชื่อมั่นที่ร้อยละ 95) ค่าเภสัชจลนศาสตร์ยาโลพินาเวียร์ขนาดมาตรฐาน ได้แก่ $AUC_{0\text{-}12\,h}$, C_{max} ,C_{12h} และT_{half} คือ 93.8 (82.9-106.3) mg.h/L, 10.8(9.6-12.0) mg/L, 3.7(3.0-4.6) mg/L, และ 4.8 (4.0-5.8) h ตามลำดับ ค่าเภสัชจลนศาสตร์ยาโลพินาเวียร์ขนาดต่ำคือ 83.1(72.2-95.6) mg.h/L, 10.7 (9.5-12.0) mg/L, 2.8 (2.1-3.6) mg/L, and 4.1 (3.5-4.8) h ตามลำดับ โดยมีผู้ป่วย 1 ราย (ร้อยละ3) ที่มีระดับยาโลพินาเวียร์มีค่า C_{12h} น้อยกว่า 1 มก/ล (0.82 มก/ล) อย่างไรก็ตามปริมาณไวรัสเอชไอวีในเลือดต่ำกว่า 50 copies/ml ทั้งนี้มีผู้ป่วย 2 รายที่มีปริมาณไวรัสในเลือดวัดได้ 52 และ 99 copies/ml โดยที่มีค่า C_{12h} มากกว่า 1 มก/ล (1.61,1.66 ตามลำดับ)

สรุป : การใช้ยาโลพินาเวียร์และริโทนาเวียร์ขนาดต่ำในเด็กติดเชื้อเอชไอวีส่วนใหญ่ได้ค่าเภสัชจลนศาสตร์ที่เพียงพอ ทั้งนี้ควรมีการศึกษาวิจัยทางคลินิกในประชากรที่มากขึ้นและติดตามผลการรักษาในระยะยาว เพื่อนำไปสู่การใช้ยาในขนาดที่เหมาะสมในระดับประเทศ ซึ่งหากพบว่าการใช้ยาในขนาดต่ำสามารถใช้ได้ในทางคลินิก จะช่วยประหยัดงบประมาณในการซื้อยาต้านไวรัส และลดค่าใช้จ่ายในการรักษาผลข้างเคียงในระยะยาวจากการใช้ยาต้านไวรัสอีกด้วย

คำสำคัญ การติดเชื้อเอชไอวีในเด็ก,ยาต้านไวรัส และการศึกษาเภสัชจลศาสตร์

Table of Contents

page

List of tables and figures

page

The widespread use of antiretroviral therapy (ART) for the treatment of HIV-infected children improved the course of HIV disease with successful viral suppression and immune restoration leading to reductions in morbidity and mortality.[1-3] The preferred first-line ART regimen in resource limited settings includes two nucleoside reverse transcriptase inhibitors (NRTIs) with a non-nucleoside reverse transcriptase inhibitor (NNRTI).[4-5] The meta-analysis of 12-month ART outcome of 1457 children in resource limited settings showed that 70% of children had viral suppression.[6] Likewise, the report from Thai children cohort showed that 20% of children who received NNRTI-based ART met the criteria of virologic failure and subsequently need second line regimen.[7]

The recommended second-line regimen in children who failed first-line NNRTI-based ART is boosted protease inhibitor (PIs) with NRTIs. [4-5, 8-9] Lopinavir/ritonavir (LPV/r) is the most commonly used boosted PI due to its high efficacy and various formulation in form of syrup, soft gel capsule and heat stable tablet. [10] However, there is some discrepancy in currently recommended dose for heat stable tablet .The approved EMEA dose was based upon body surface area band, while US FDA based upon body weight band, of which in general resulting in higher dose. The suggested minimum target level trough concentration of lopinavir among patient who is naïve to protease inhibitor is 1.0 mg/L. [11] The pharmacokinetics of ARV drugs in Asians and Caucasians are difference. Asians have a significantly higher exposure to both NNRTIs and PIs compared to Caucasians. [12] There is evidence supported that the recommended dose according to the US or European guidelines resulting in much higher plasma blood level in both Thai adult and children. The data from Thai adult with low-dose LPV/r of soft gel capsule 266 /66 mg demonstrated the minimum concentration(C_{12h}) of 3.4 mg/L, while Thai adult with standard dose of tablet 400/100 mg had c_{12h} at 6.5 mg/L. [13] There were a few studies provide evidence support the low dose of LPV/r among Thai children. The pilot study from Thai children using 230/57.5 mg/m^2 lopinavir/ritonavir oral solution demonstrated Cmin of 5.9 mg/L compare to 3.4 mg/L in US children when use the same dose. [14] The therapeutic drug monitoring for lopinavir/ritonavir level among Thai children using US recommended dose lopinavir heat stable tablet demonstrated lopinavir C_{12h} as high as 6.7 mg/L. [15] The pilot study of 70% of standard dose lopinavir using syrup formulation among 12

children displayed good pharmacokinetic parameters and efficacy at 48 weeks as compared with standard-dose lopinavir in Thai children. [18]

Therefore, this study was aimed to evaluate the pharmacokinetics of low-dose (70% of standard dose) LPV/r heat-stable tablet formulation compared with standard dose in viral suppressed HIV-infected Thai children. If the result showed that the low dose is optimum for Thai children, it could have significant impact in reducing side effects and costs related to procuring the drug.

Material and methods

Study population

This is an open-label, prospective cross-over study comparing standard dose with low dose (70% of standard dose) of LPV/r pharmacokinetic performed at the Department of Pediatrics, Chulalongkorn University, Bangkok, Thailand and the HIV Netherlands Australia Thailand Research collaboration (HIV-NAT). The study aimed to enroll 24 HIV-infected children who were stable with LPV/r containing regimen. Eligibility criteria were aged under 18 years old, weighing over 25 kg, confirmed HIV infection and plasma HIV-1 RNA < 50 copies/ml within 6 months of study entry. The exclusion criteria were taking any medication that has been reported to have a drug interaction with lopinavir, such as rifampicin, efavirenz and nevirapine, having active opportunistic infection or had any serious illness that may be interfere LPV/r pharmacokinetics. The study was approved by the Institutional Review Board of Chulalongkorn University. Written informed consent was obtained from each child's legal guardian and also written assent from child before performing any study-specific procedure. The clinical trial number of the study is NCT01139905.

Study procedure

The study drugs is a lopinavir/ritonavir 100/25 mg pediatric tablet (Aluvia® Abbott laboratories). The LPV/r dosage was prescribed by body weight band as a standard dose and low dose orally every 12 hours as follow; Group 1; 25-35 kg, the patients received 300/75 mg (3 tablets) and 200/50 mg(2 tablets) for standard and low dose respectively.Group2; over 35 kg, the

patients received 400/100 mg (4 tablets) and 300/75 mg(3 tablets) for standard and low dose respectively. The study period was 12 weeks, started with 4 weeks of standard dose, followed by 4 weeks of low dose and then switched back to 4 week of standard dose. The 12 hours pharmacokinetic study was performed at week 4 and week 8. The patients were evaluated at the screening visit and at study entry prior to receipt of any treatment, at 4, 8 and 12 weeks. Physical examination and ARV adherence will be evaluated by pill count on every visit. Complete blood count with differential and platelets, CD4 cell count, CD4 percentage were performed during screening and at week 12 visit. Toxicity was classified using the Division of AIDS (DAIDS) toxicity tables for grading severity of pediatric adverse experiences. [17]

Pharmacokinetic

The intensive pharmacokinetic study at week 4 of LPV/r standard dose and 70% reduction dose therapy consisted of blood samples obtained prior to the morning dose (t=0) and at 2, 4, 6, 8, 10 and 12 h following an observed dose. Blood samples were centrifuged at 3,000 rpm for 10 minutes at 20°C. The samples were kept at -20 °C until analysis (no more than 2 months), after which all the samples are transferred to -80 °C. Plasma concentrations of lopinavir and ritonavir were measured by a validated HPLC method. [18] The lopinavir level was linear over the range of 0.1–30.0 mg/L. The percentage accuracy was found to be 104% at 0.15 mg/L, 102% at 1.5 mg/L and 101% at 7.5 mg/L. The with-in day precision are 3.34% at 0.15 mg/L, 1.37% at 1.5 mg/L and 1.42% at 7.5 mg/L, and the between day precision are 1.22% at 0.15 mg/L, 1.30% at 1.5 mg/L and 1.18% at 7.5 mg/. The % extraction of recovery in plasma is 95%. The lower limit of quantification for lopinavir is 0.105 mg/L. The ritonavir level was linear over the range of 0.045–30.0 mg/L. The percentage accuracy was found to be 101% at 0.15 mg/L, 104% at 1.5 mg/L and 103% at 7.5 mg/L. The with-in day precision are 3.22% at 0.15 mg/L, 1.70% at 1.5 mg/L and 0.89% at 7.5 mg/L, and the between day precision are 3.64% at 0.15 mg/L, 1.17% at 1.5 mg/L and 1.10% at 7.5 mg/. The % extraction of recovery in plasma is 94%. The lower limit of quantification for ritonavir is 0.045 mg/L. The HIV-NAT laboratory participates in an international quality control and quality assessment program and has been cross-validated with other pharmacokinetic laboratories. [19]

Statistical Analyses

Non-compartmental pharmacokinetic parameters were calculated using standard method by STATA® software version 11.0 (Statacorp, College Station, TX, USA) to determine the $AUC_{0\text{-}12h}$, maximum concentration (C_{max}), clearance time (CL), half-life (T_{half}) and the plasma concentration at 12 hours (C_{12h}). Geometric mean of each pharmacokinetic parameter was used as the outcome variable, coefficients and 95% confidence intervals were exponentiated to give the results. Descriptive statistic calculated for the patient characteristic. Comparison of PK parameters was done using a random effects longitudinal regression model adjusting for patient and timing of regimen, with maximum likelihood estimation. Parameters significant in univariate analysis at a level of $P \leq 0.1$ were adjusted for in multivariate models.

Results

From March to May 2010, 24 children were enrolled. The baseline characteristics data was presented in Table 1. The overall median age, weight, %CD4 and CD4 count were 13.5 years (IQR 9-17), 33.4 Kg (SD 8.8), 27.0% (SD 6.8) and 990 cell/mm^3 (SD 349.6) respectively. The half of patient had the Centers for Disease Control and Prevention clinical categories at entry at class N or A. The other ARVs in regimen are zidovudine plus lamivudine (12), didanosine plus lamivudine (8), only lamivudine (2), tenofovir plus lamivudine (1) and only saquinavir (1). One patient discontinued study prior to low dose pharmacokinetics study because of developed upper GI bleeding from non-cirrhotic portal hypertension.

Table 1.Subject Characteristics of 24 HIV-infected children at enrollment

Parameter	Group1:25-35 Kg (N=12)	Group2:over 35 Kg (N=12)	Total (N=24)
Median age(IQR), years	11.9(9-14)	14.8(12-17)	13.5(9-17)
Gender (male/female), N	7/5	7/5	24
CDC clinical stage, N (%)			
N	0(0.0)	3(25.0)	3(12.5)
A	5(41.7)	4(33.3)	9(37.5)
B	5(41.7)	2(16.7)	7(29.2)
C	2(16.7)	3(25.0)	5(20.8)
Median height, cm(SD)	137.1(4.8)	153.4(9.6)	142.7(11.2)
Median weight, kg(SD)	28.2(2.1)	43.1(6.2)	33.4(8.8)
Mean body surface area, m^2(SD)	1.03(0.04)	1.30(0.12)	1.14(0.2)
Mean CD4% (SD)	28.3(9.0)	26.7(5.8)	27.0(6.8)
Mean CD4 count(SD)	1093(422)	886(231)	990(349)
Mean duration LPV/r, month(SD)	33.6(17.4)	28.0(10.2)	31.0(14.3)

IQR: interquartile range

SD: standard deviation

Pharmacokinetics results

The pharmacokinetic parameters of 24 patients with standard dose and 23 patients with low dose lopinavir/ritonavir were shown in Table 2. The values of C_{12h} were highly variable, having within subject coefficients of variation ranging from 55 to 66%. The geometric mean of the LPV C_{12h} values of low dose and standard dose were 2.7 and 3.7 mg/L, respectively. The LPV AUC_{0-12h} and C_{12h} while received low dose were reduced by 11% (83.1 versus 93.8mg.h/L) and 27% (2.7 versus 3.7 mg/L) comparing to standard dose . The plasma lopinavir concentration–time curves among standard and low-dose lopinavir were shown in Figure 1. Among children who received low dose LPV/r, one child (3%) had C_{12h}< 1 mg/L (0.82 mg/L) but had no viral rebound.

Table 2 Pharmacokinetic parameters of lopinavir and ritonavir standard and low dose.

Parameters	Lopinavir		Ritonavir	
	Standard dose	Low dose	Standard dose	Low dose
	(N=24)	(N=23)	(N=24)	(N=23)
AUC_{0-12h}	93.8	83.1	4.1	3.0
(mg.h/L)	(82.9-106.3)	(72.2-95.6)	(4.9-5.8)	(3.5-4.1)
%CV	30.1	33.3	41.2	38.2
C_{max} (mg/L)	10.8(9.6-12.8)	10.6(9.4-11.9)	0.6(0.7-0.8)	0.4(0.5-0.6)
%CV	26.7	27.7	42.8	41.2
T_{half} (h)	4.8(4.0-5.8)	4.1(3.5-4.7)	2.9(3.3-3.7)	3.16(3.5-3.9)
%CV	45.7	34.4	27.4	25.4
C_{12h}(mg/L)	3.7(3.0-4.6)	2.7(2.1-3.5)	0.11(0.14 0.17)	0.07(0.09-0.12)
%CV	55.9	66.1	56.4	58.9
CL (L/h)	4.2(3.7-4.8)	4.8(4.1-5.5)	17.2(20.3-24.0)	23.9(28.0-32.9)
%CV	30.1	33.3	27.4	38.2

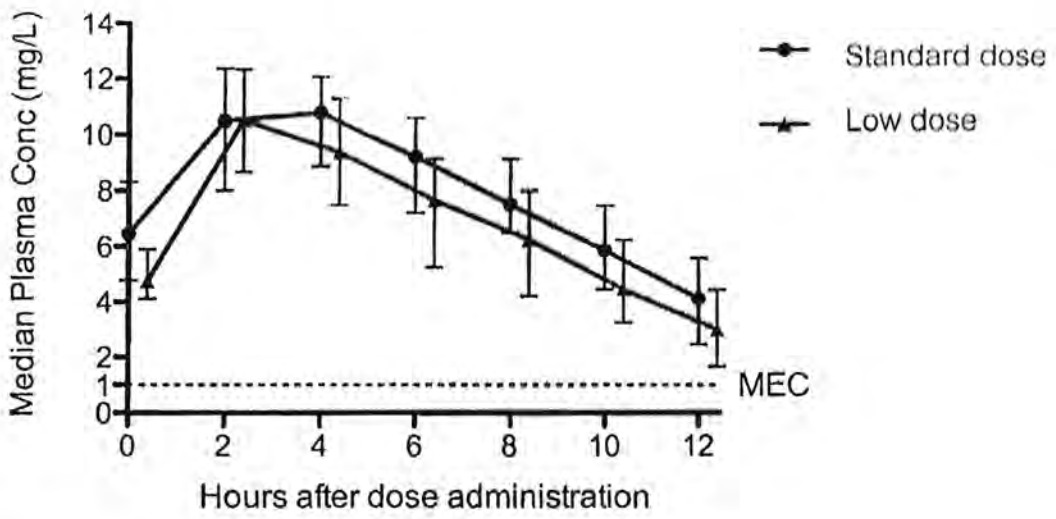
Data show in geometric mean (95% confidence interval)

CV (%): coefficient of variation as a % measure of the intra-subject variability

AUC: area under the concentration–time curve, CL: apparent clearance

C_{max}: maximum concentration, C_{12h}: plasma concentration at 12 hours

Figure 1 Plasma lopinavir (LPV) concentration time curves of standard and low dose LPV/r



MEC = minimum effective concentration

The data are presented as medians (Interquartile range).

The correlation between the LPV AUC $_{0\text{-}12h}$ and C $_{12h}$ by body weight are shown in Figure 2 and 3. There is a trend of lower the LPV AUC $_{0\text{-}12h}$ and C $_{12h}$ among children with high body weight.

Figure 2 Scatter-plot of the LPV AUC $_{0\text{-}12h}$ and body weight.

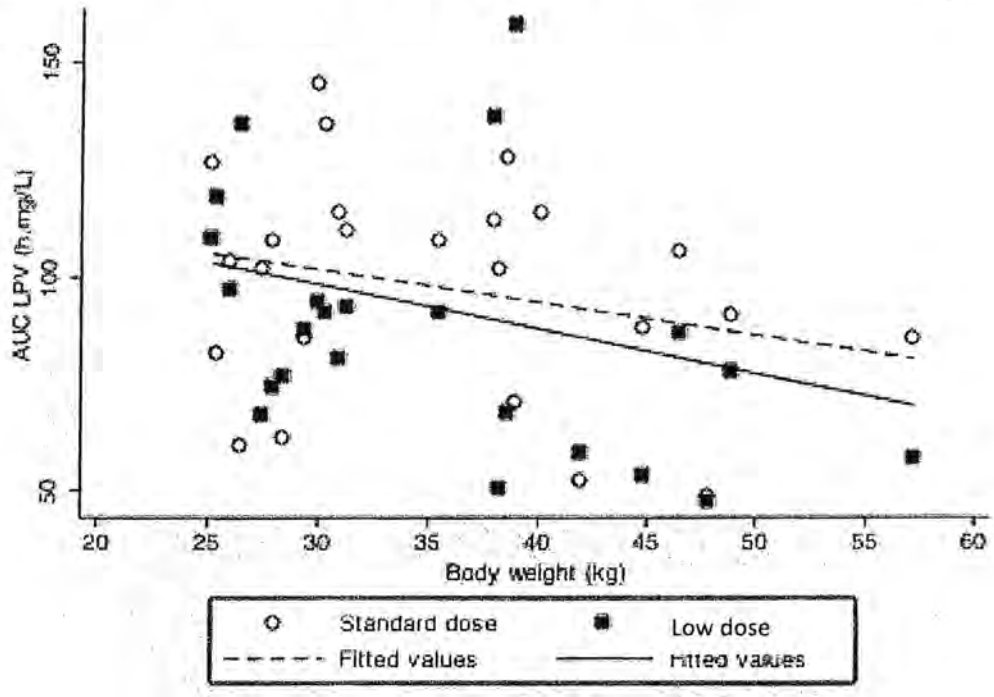
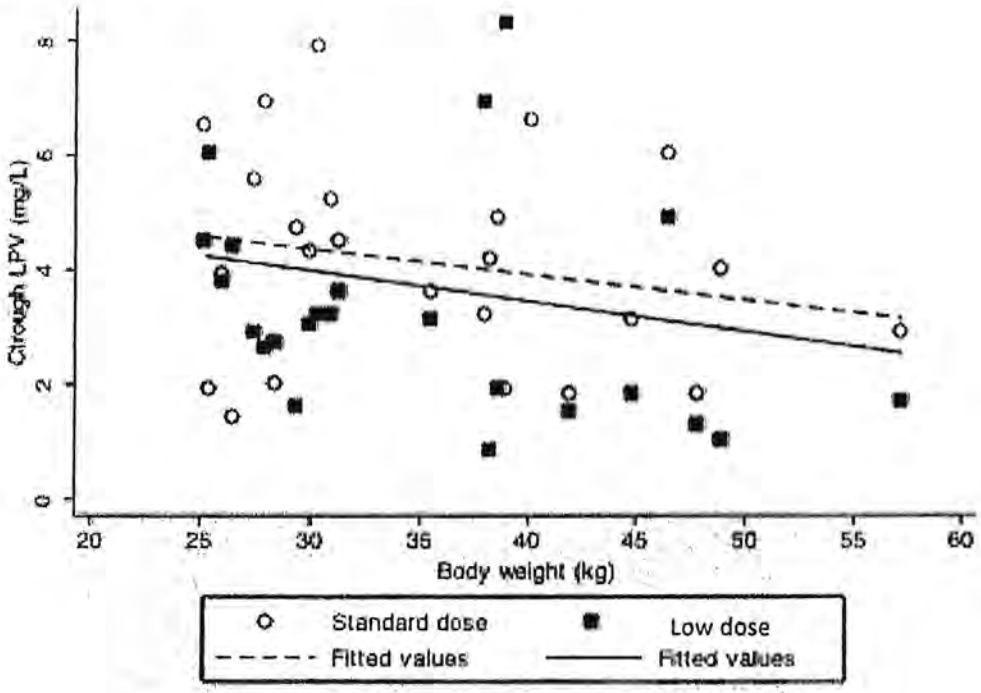


Figure 3 Scatter-plot of the LPV C_{12h} and body weight.



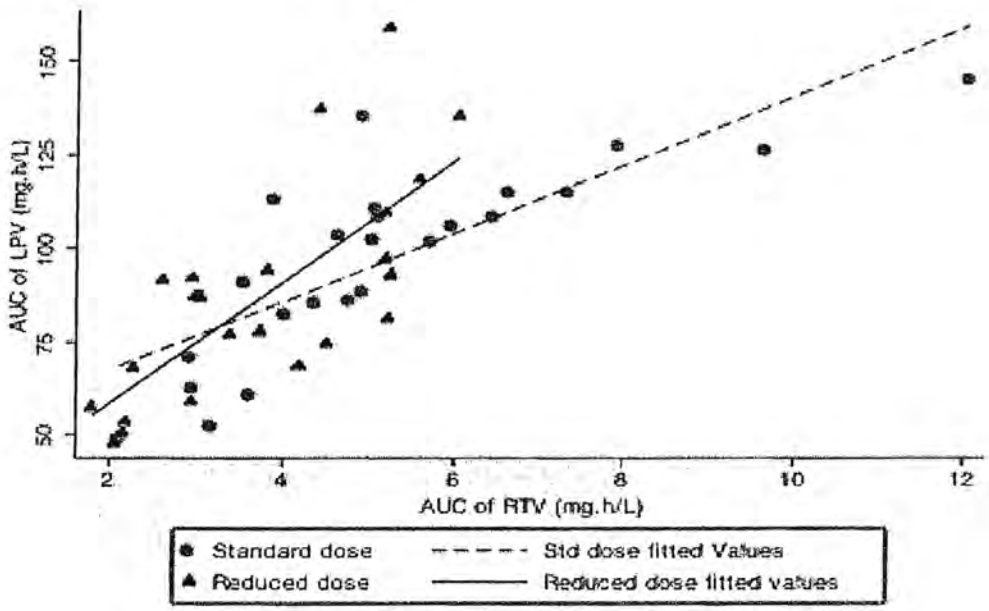
There is a strong correlation between the LPV AUC $_{0\text{-}12h}$ and the RTV AUC $_{0\text{-}12h}$ as shown in Figure 4. From the multivariate regression analysis adjusted for body surface area (BSA), standard or low dose LPV and RTV AUC $_{0\text{-}12h}$ to the LPV pharmacokinetic parameters, RTV AUC $_{0\text{-}12h}$ is the strong factor influenced the LPV pharmacokinetic parameters (Table 3).

Table 3 The multivariate regression analysis of LPV pharmacokinetic parameters at low dose compared to standard dose

Parameters	Multivariate			
	Coefficient	LCI	UCI	p
AUC_{0-12h}				
Dose (low vs. standard)	1.06	0.94	1.18	0.35
BSA (m^2)	0.80	0.54	1.18	0.26
AUC of RTV (h.mg/L)	1.12	1.08	1.16	<0.001
C_{max}				
Dose (low vs. standard)	1.12	1.00	1.26	0.05
BSA (m^2)	0.86	0.59	1.26	0.44
AUC of RTV (h.mg/L)	1.09	1.05	1.13	<0.001
C_{12h} (mg/L)				
Dose (low vs. standard)	0.93	0.70	1.25	0.65
BSA (m^2)	0.62	0.30	1.30	0.21
AUC of RTV (h.mg/L)	1.16	1.08	1.25	<0.001
Clearance (h)				
Dose (low vs. standard)	0.95	0.85	1.06	0.35
BSA (m^2)	1.25	0.85	1.85	0.26
AUC of RTV (h.mg/L)	0.89	0.86	0.92	<0.001
T_{half} (h)				
Dose (low vs. standard)	0.96	0.78	1.18	0.72
BSA (m^2)	0.97	0.55	1.72	0.91
AUC of RTV (h.mg/L)	1.07	1.01	1.12	0.02

LCI: lower 95% confidence interval; UCI: upper 95% confidence interval

Figure 4 Scatter-plot of the LPV AUC_{0-12h} and RTV AUC_{0-12h} at standard and low doses.



Discussion

This is the first study on the pharmacokinetics of low dose lopinavir/ritonavir pediatric heat stable tablet formulation (Aluvia®) in Thai children. The study showed that the 70% of standard dose of LPV/r was provided adequate pharmacokinetic parameters in Thai children. The lopinavir $AUC_{0\ 12\ h}$ and C_{12h} while taking LPV/r low dose were reduced by 11% and 27% compared to standard dose. The median LPV C_{12h} of low dose and standard dose were 2.7 and 3.7 mg/ml, respectively. The apparent drug exposure at the steady-state 12 h sampling showed all but one had lopinavir plasma concentrations above the recommended efficacy threshold of >1.0 mg/L throughout the dosing interval.

The pharmacokinetic parameters of LPV among children received low dose was similar to the previous published study.[14] The children who recieved syrup formulation achieved the $AUC_{0\text{-}12h}$ of 117 and 83 mg.h/L for standard and low dose compared with 93.8 and 83.1 mg.h/L in this study. The Thai adults study with standard dose of generic LPV/r 400/100 mg (Kaletra®) showed the AUC $_{0\text{-}12h}$ of 117mg.h/L [13] compared with 93.8 mg.h/L in standard dose of this study. From the therapeutic monitoring study in Thai children receiving standard dose of adult tablet showed the LPV C_{12h} at 6.7 mg/L [15] that significantly higher than this study. It may be due to the plasma concentration of the therapeutic monitoring study measured concentration at morning predose as the C_{12h} that may not represent the exactly 12 hours

The strength of this study is that it was done in a real situation in a resource limited setting that can be direct applicability of the results to clinical practice. The well-designed, good laboratory practice certificated and good adherence to the ARV. There are some limitations. First, the study was focus on maintenance therapy of the patient with viral suppression and never had protease inhibitor failed, therefore it is generalizable only to this population. Second, this is a cross-sectional study where no data were obtained on long-term adverse events of LPV, such as lipid toxicity. Long term study in large scale and compared the metabolic complications before implement in the national program was necessary. More studies are warranted to investigate the efficacy of low dose LPV will have an impact on costs and reduce long term toxicity.

Conclusion and suggestion for further work

This study demonstrated adequate pharmacokinetic parameters of low dose LPV/r in Thai children. A larger randomized clinical study to assess efficacy of low dose vs. standard dose of LPV/r among HIV-infected children should be explored. The successful usage of low dose LPV/r could have a significant public health impact in reducing side effects and costs related to treating complications and procuring the drug.

References:

1. Puthanakit T, Aurpibul L, Oberdorfer P, Akarathum N, Kanjananit S, Wannarit P, et al. Hospitalization and mortality among HIV-infected children after receiving highly active antiretroviral therapy. Clin Infect Dis 2007; 44(4): 599-604.

2. Viani RM, Araneta MR, Deville JG, Spector SA. Decrease in hospitalization and mortality rates among children with perinatally acquired HIV type 1 infection receiving highly active antiretroviral therapy. Clin Infect Dis 2004 Sep 1;39(5):725-31.

3.Sanchez JM, Ramos Amador JT, Fernandez de Miguel S, Gonzalez Tomee MI, Rojo Conejo P, Ferrnado Vivas P, et al. Impact of highly active antiretroviral therapy on the morbidity and mortality in Spanish human immunodeficiency virus-infected children. Pediatr Infect Dis J 2003; 22(10):863-7.

4. Thai national guidelines for the use of antiretroviral therapy in pediatric HIV infection 2010. Available at:http://gfaidscare.com/2010hivtreatmentguideline.pdf.

5. WHO 2010 guideline for antiretroviral therapy for HIV infection in infants and children. Available at:http://www.who.int/hiv/pub/paediatric/infants2010/en/

6. Ciaranello AL, Chang Y, Margulis AV, et al. Effectiveness of pediatric antiretroviral therapy in resource-limited settings: a systematic review and meta-analysis. Clin Infect Dis 2009; 49:1915-27.

7. Jittamala P, Puthanakit T, Chaiinseeard S, Sirisanthana V. Predictors of virologic failure and genotypic resistance mutation patterns in Thai children receiving non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy .Paediatr Infect Dis J. 2009; 28: 826-30.

8. Working Group on Antiretroviral Therapy and Medical Managment of HIV-infected children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, February 23, 2009. US Department of Health and Human Services. Access 14 April 2009, Available at: http://AIDSinfo.nih.gov/.

9. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. Available at: http://www.pentatrials.org/guide09.pdf.

10. Klein, CE, Chiu YL, Awni W et al. The tablet formulation of lopinavir/ritonavir provides similar bioavailability to the soft-gelatin capsule formulation with less pharmacokinetic variability and diminished food effect. J Acquir Immune Defic Synr 2007; 44: 401-10.

11. Saex-Llorens X, Violari A, Deetz Co et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor in human immunodeficiency virus-infected children. Pediatr Infect Dis J 2003; 22:216-23.

12. Jasper van der Lugt, Anchalee Avihingsanon. Clinical pharmacology and pharmacokinetics of antiretrovirals in Asia. Asian Biomedicine 2009; 3(1):53-62

13. Jasper van der Lugt, Reshma Saskia Autar.et al. Pharmacokinetics and short-term efficacy of a double-boosted protease inhibitor regimen in treatment-naive HIV-1-infected adults. J Antimicrob Chemother 2008; 61:1145–53.

14. Ananworanich J, Kosalaraksa P, Hill A. et al. Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/rtitonavir in nucleoside-pretreated children. Pediatr Infect Dis J 2005; 24:874-9.

15. Puthanakit T, Chokephaibulkit K, Suntarattiwong P. Therapeutic drug monitoring of lopinavir in human immunodeficiency virus-infected children receive adult tablets. Pediatr Infect Dis J. 2010 Jan; 29(1):826-30.

16. Van der Lugt J, Puthanakit T, Gorawara M, et al. Pharmacokinetics and 48 week efficacy of low-dose lopinavir/ritonavir in HIV-infected children. J Antimicrob Chemother 2009; 64(5):1080-1086.

17. National Institute for Allergy and Infectious Disease (NIAID). Division of AIDS toxicity table for grading the severity of Adult and Pediatric adverse experiences publish date December 2004.Available at:
http://rcc.techres.com/Document/safetyandpharmacovigilance/DAIDS_AE_GradingTable_Clarification_August2009_Final.doc. Accessed January 18, 2009.

18. Droste JA, Verweij-Van Wissen CP, Burger DM. Simultaneous determination of the HIV drugs indinavir, amprenavir, saquinavir, ritonavir, lopinavir, nelfinavir, the nelfinavir hydroxymetabolite M8, and nevirapine in human plasma by reversed-phase high-performance liquid chromatography. Ther Drug Monit 2003; 25: 393–9.

19. Droste JA, Aarnoutse RE, Koopmans PP et al. Evaluation of antiretroviral drug measurements by an inter-laboratory quality control program. J Acquir Immune Defic Syndr 2003; 32: 287–91.

สัญญาเลขที่ CU-CLUSTER-Emerging H -๑๖-๑๑-๕๓

โครงการวิจัยร่วมเพื่อศึกษาเปรียบเทียบเภสัชจลนศาสตร์ระหว่างการใช้ยาต้านไวรัสไลพินาเวียร์/

ริโทนาเวียร์ชนิดเม็ดในขนาดมาตรฐานและขนาดต่ำในเด็กติดเชื้อเอชไอวี

รายงานการรับ – จ่ายเงิน

	ประมาณการ	งบที่เกิดขึ้นจริง
รายได้		
เงินอุดหนุนงบประมาณแผ่นดิน	400,000.00	280,000.00
รวมรายได้	400,000.00	280,000.00
รายจ่าย		
หมวดค่าจ้างชั่วคราว		
- ค่าตอบแทนพยาบาลวิจัย ตลอดโครงการ	5,000.00	5,000.00
- ค่าตอบแทนเภสัชจลนศาสตร์ ตลอดโครงการ	5,000.00	5,000.00
- ค่าตอบแทนแพทย์วิจัย ตลอดโครงการ	7,000.00	7,000.00
หมวดค่าใช้สอย		
- ค่าตรวจทางห้องปฏิบัติการ	307,200.00	317,400.00
- ค่าตอบแทนอาสาสมัคร	48,000.00	48,000.00
หมวดค่าวัสดุภัณฑ์		
- ค่าวัสดุวิทยาศาสตร์	26,000.00	20,009.00
- ค่าวัสดุสำนักงาน	1,800.00	00.00
รวมรายจ่าย	400,000.00	402,409.00
รายรับสูงกว่ารายจ่าย นำส่งส่วนการคลังจุฬาลงกรณ์มหาวิทยาลัย (เอกสารแนบ)		00.00
ดอกเบี้ย (ถ้ามี)		00.00
รวมจำนวนเงินที่นำส่งส่วนการคลังทั้งสิ้น		00.00

ขอรับรองว่ารายงานการรับ-จ่ายเงินข้างต้นเป็นความจริงทุกประการ

.....ธันย์ ภูธนกิจ.....

(รองศาสตราจารย์แพทย์หญิงธันยวีร์ ภูธนกิจ)

(หัวหน้าโครงการวิจัย)

.....29 / พ.ย / 2553.....

หมายเหตุ : รายงานตลอดโครงการเมื่อสิ้นสุดโครงการ/ปิดโครงการ