

## Generic lopinavir/ritonavir is bioequivalent to Aluvia<sup>®</sup> but neither result in adequate lopinavir exposure at 50% dose reduction: HIV-NAT 085

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# Background

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- ❑ Lopinavir (LPV) is used with ritonavir (RTV), RTV increases the plasma levels of LPV by inhibiting its cytochrome P-450 (CYP-450) mediated metabolism.
  
- ❑ The tablet formulation of LPV/r is heat stable and there is no food effect on the bioavailability. It proved to be bioequivalent to the soft gel capsule formulation<sup>1</sup>
  
- ❑ Due to compulsory license issue in Thailand only the pediatric formulation of Aluvia<sup>®</sup> is available (100/25 mg).
  
- ❑ A generic tablet formulation of LPV/r (200/50 mg) is available and used in the government program for drugs supply, but very little data exist in the public domain on generics.

1. Klein, et al. JAIDS 2007, 44: 401-410.

# Background

Comparison of Kaletra SGC and Generic Lopinavir/ritonavir tablet formulation within the same patients<sup>1</sup>

Parameter	LPV, Kaletra SGC 400/100 mg BID	LPV, generic 400/100 mg BID	P (value)
<b>N</b>	16	16	-
<b>Week</b>	0	4	NA
<b>Median, Cmin mg/L (IQR)</b>	5.6 (3.3-8.1)	7.1 (5.9-8.6)	0.234
<b>CV%</b>	54	25	NA
<b>Median Time of Sample Collection, hh:mm (±SD)</b>	11:49 (0.29)	11:36 (0.23)	NA

Generic RTV levels were significantly higher compared to Kaletra RTV levels

1. Van der lugt, et al. Antiv Ther 2009, 14: 1001-1004.

# Background

- Dose reductions of several Protease Inhibitors (PIs) in Thai HIV-1 infected patients result in adequate plasma concentrations, including lopinavir <sup>1,2,3</sup>

## Steady-state pharmacokinetic parameters of lopinavir for all study arms <sup>3</sup>

Parameters	LPV/RTV/SQV 400/100/1000 twice daily	LPV/RTV/SQV 400/100/600 twice daily	LPV/RTV/SQV 266/66/1000 twice daily	LPV/RTV/SQV 266/66/600 twice daily
<b>N</b>	11	9	10	13
<b>C<sub>min</sub> (mg/l)</b>	6.57 (5.44-8.18)	5.39 (4.58-10.91)	3.43 (1.34-4.31)	2.77 (1.55-3.76)
<b>C<sub>max</sub> (mg/l)</b>	14.98 (11.97-16.36)	13.06 (10.28-19.08)	8.74 (5.85-10.11)	8.86 (6.54-11.24)
<b>AUC (mg.h/L)</b>	128.20 (119.53-135.11)	119.20 (92.87-179.46)	66.10 (44.09-88.43)	68.47 (52.03-86.42)

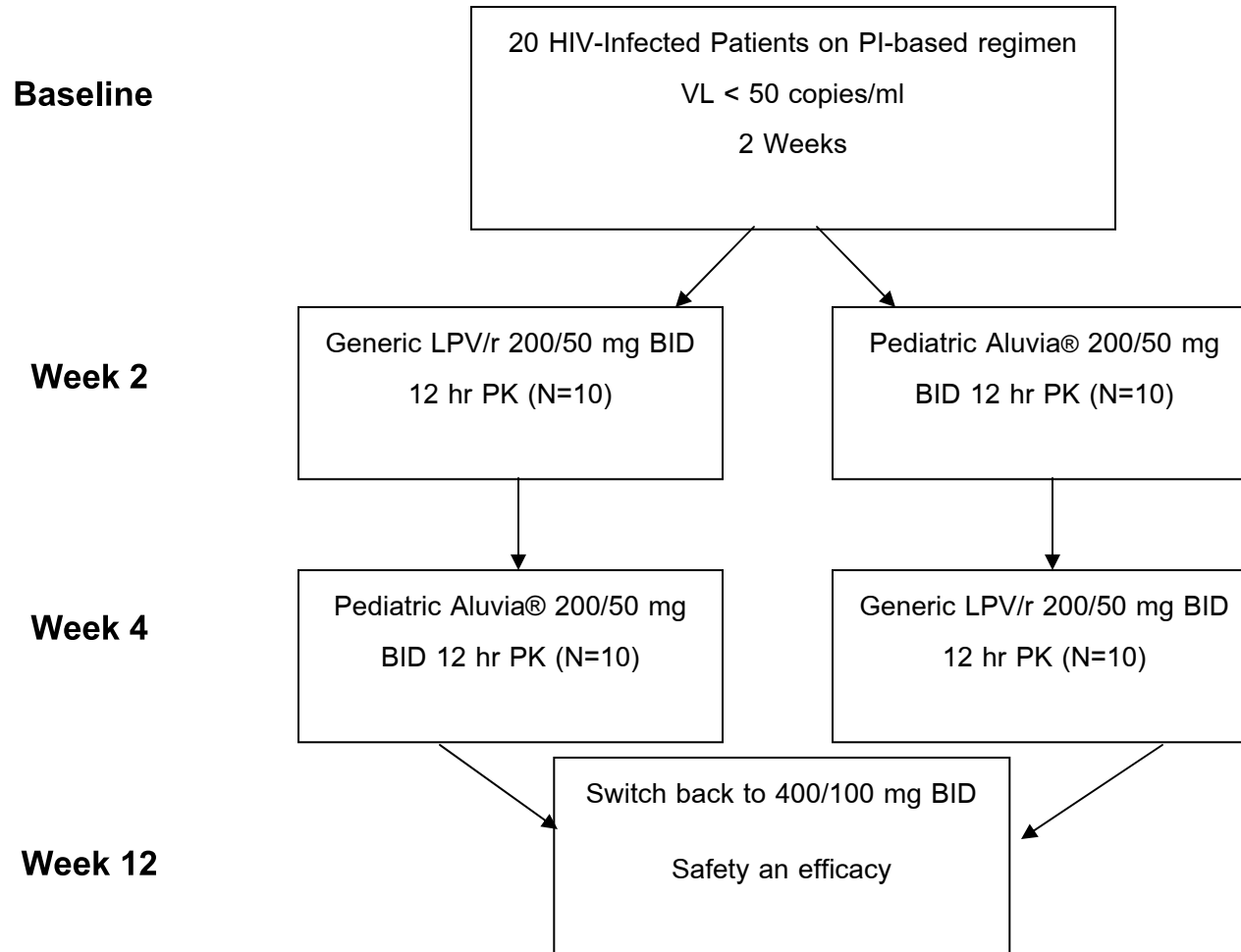
1. Avihingsanon et al, Clin Pharm Ther 2008
2. Boyd et al, Antiviral Therapy, 2005
3. Van der Lugt et al JAC 2008

# Objectives

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- Study the pharmacokinetics profiles of generic lopinavir/ritonavir and Pediatric Aluvia<sup>®</sup> at a dose reduction of 50% in Thai HIV-infected patients
- To compare the PK parameters of generic LPV/r with the original product (being the pediatric Aluvia<sup>®</sup> formulation)
- To assess short term safety and tolerability

# Study Design



## Methods

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- ❑ Plasma levels of lopinavir and ritonavir were determined by a validated HPLC method, with a lower limit of quantification of 0.1 mg/l for lopinavir and 0.045 mg/l for ritonavir.
- ❑ The HIV-NAT pharmacokinetic laboratory participates in an international quality control and quality assessment program (KKGIT).
- ❑ PK parameter calculation and statistical analysis was conducted using STATA version 1.0
- ❑ ANOVA was used to compare PK parameters of both groups

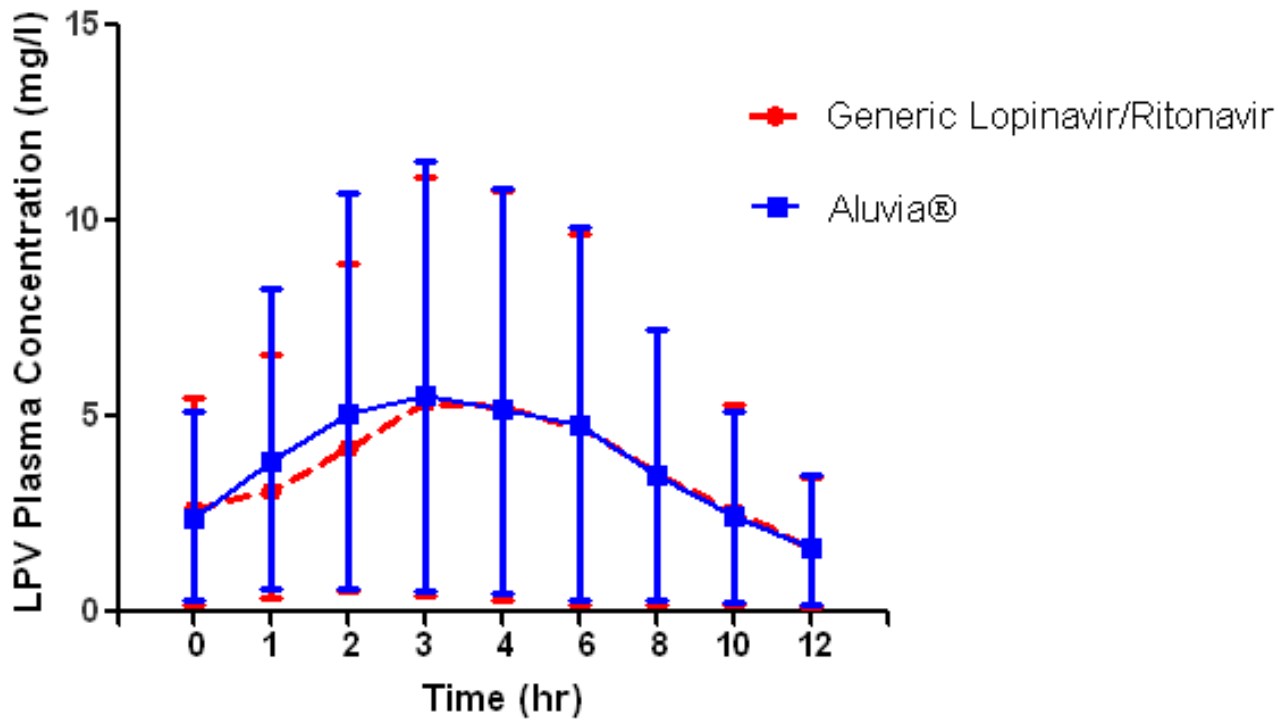
# Results

- 20 patients were included in the analysis, ten in each arm
- Baseline Characteristics

Baseline characteristics	
<b>Patients, <i>n</i></b>	<b>20</b>
<b>Gender (M:F)</b>	<b>12:8</b>
<b>Median (IQR) age, years at baseline</b>	<b>38.6 (34.4-47.5)</b>
<b>Median (IQR) weight at baseline</b>	<b>59.8 (52.9-62.0)</b>
<b>Median (IQR) height at baseline</b>	<b>160 (155-165)</b>
<b>Median (IQR) BMI at baseline</b>	<b>23.0 (19.7-24.5)</b>
<b>Viral load at Baseline</b>	<b>&lt; 50</b>
<b>Median (IQR) CD4 cell count Baseline</b>	<b>577 (476-795)</b>
<b>Median (IQR) years on LPV/r tablets (n=17)</b>	<b>1.5 (1.2-3.9)</b>
<b>Median (IQR) years on other PIs (n=3)</b>	<b>2.5(2.4-2.6)</b>

# Results

## Lopinavir Plasma Concentration

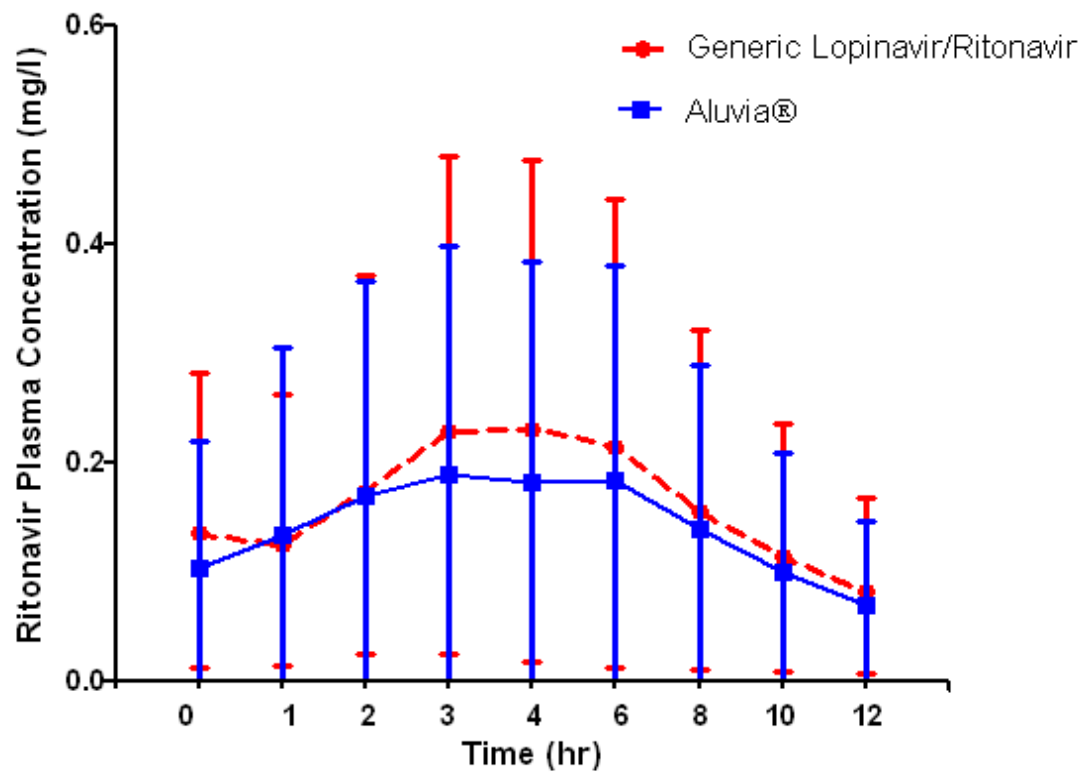


**Figure 1.** Mean and SD of Lopinavir plasma concentrations and time for Generic Aluvia®

Lopinavir/ritonavir and Pediatric

# Results

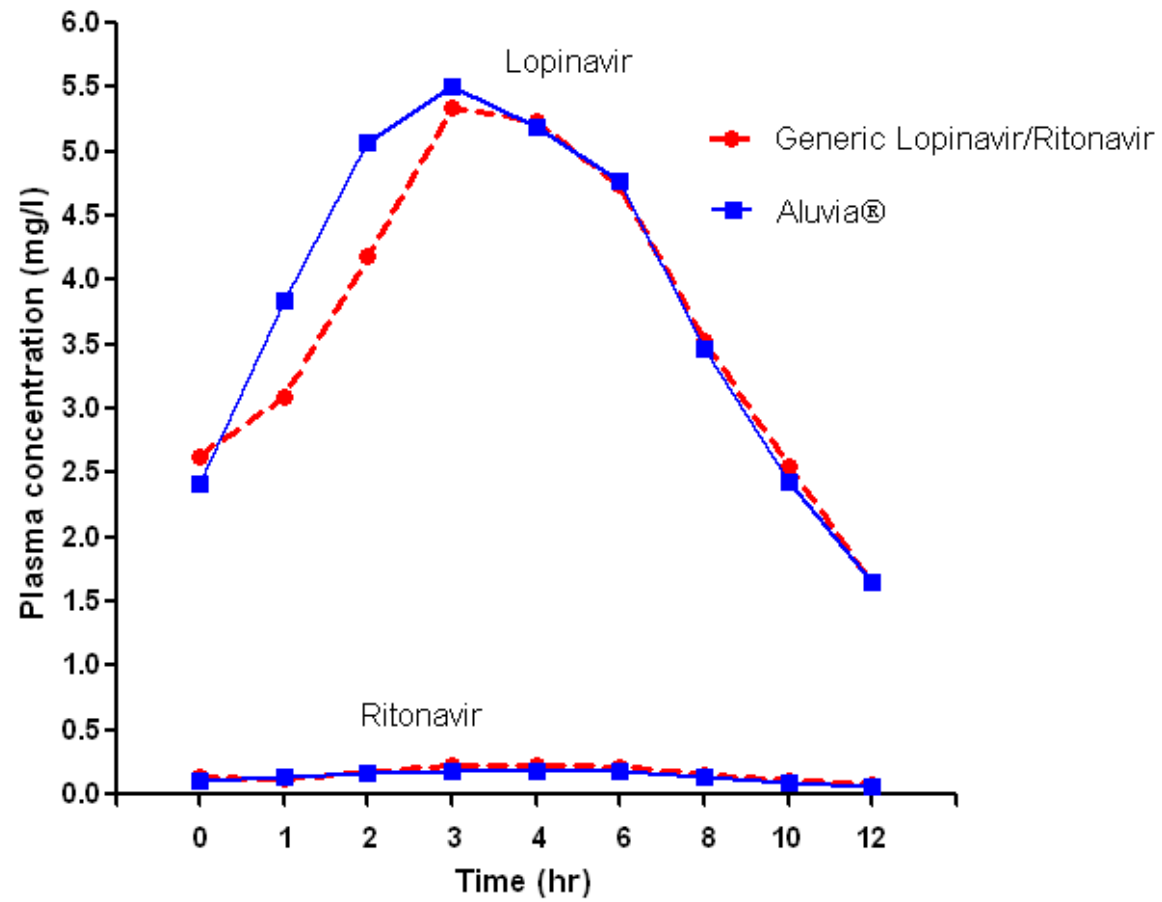
## Ritonavir Plasma Concentration



**Figure 2.** Mean and SD of Ritonavir plasma concentrations and time for Generic Aluvia®

Lopinavir/ritonavir and Pediatric

# Results



**Figure 3.** Mean of both Lopinavir and Ritonavir plasma concentrations and time for Generic Lopinavir/ritonavir and Pediatric Aluvia®

# Results

□ The generic LPV/r and Aluvia<sup>®</sup> showed no differences in the Lopinavir PK parameters, mean and SD

Pharmacokinetic parameters	Generic Lopinavir/Ritonavir		Pediatric Aluvia <sup>®</sup>		p-value
	Mean	SD	Mean	SD	
<b>Lopinavir</b>					
AUC <sub>0-12</sub> (mg.h/l)	46.6	10.7	45.1	16.9	0.98
C <sub>max</sub> (mg/l)	6.2	1.4	6.1	2.2	0.91
C <sub>min</sub> (mg/l)	1.5	0.6	1.6	0.9	0.92
T <sub>1/2</sub>	3.6	0.9	3.7	1.2	-
T <sub>max</sub>	3.3	1.4	3.9	1.5	-
<b>Ritonavir</b>					
AUC <sub>0-12</sub> (mg.h/l)	1.98	0.5	1.93	0.7	0.77
C <sub>max</sub> (mg/l)	0.28	0.08	0.26	0.1	0.46
C <sub>min</sub> (mg/l)	0.07	0.02	0.07	0.03	0.34
T <sub>1/2</sub>	4.8	2	4.2	1.3	-
T <sub>max</sub>	3.9	1.5	4.1	1.6	-

# Results

- Relative bioavailability and 90% confidence intervals for the geometric mean ratio for LPV and RTV

PK parameters	Mean		Relative Bioavailability		FDA Acceptable range
	Generic Lopinavir/Ritonavir	Pediatric Aluvia®	Point estimate	90% CI	
<b>Lopinavir</b>					
Log <sub>10</sub> AUC <sub>0-12</sub> (mg)	1.64	1.64	1.00	0.92-1.09	0.80-1.25
Log <sub>10</sub> Cmax (mg)	0.76	0.75	1.01	0.90-1.07	0.80-1.25
Log <sub>10</sub> Cmin (mg)	0.19	0.22	0.87	0.76-1.31	0.80-1.25
<b>Ritonavir</b>					
Log <sub>10</sub> AUC <sub>0-12</sub> (mg)	0.25	0.23	1.07	0.93-1.18	0.80-1.25
Log <sub>10</sub> Cmax (µg)	2.41	2.36	1.02	0.92-1.24	0.80-1.25
Log <sub>10</sub> Cmin (µg)	1.85	1.80	1.03	0.88-1.13	0.80-1.25

## Results

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- ❑ Ten curves (25%) had subtherapeutic levels (C<sub>min</sub> of LPV < 1.0 mg/l); four with generic LPV/r and six with Aluvia<sup>®</sup>.
- ❑ At week 12, all patients had plasma viral load below 50 copies/ml.
- ❑ 1 patient had ALT and AST elevation (grade IV) during the study(week 12); this was not related to study drugs, but due to acute hepatitis-C co-infection.
- ❑ The median (IQR) triglycerides decreased from **175.0** (131.0-284.5) at baseline to **115.0** (83.5-216.5) at week 12, *p*-value <0.001. Decreases in total cholesterol and LDL-cholesterol were not significant
- ❑ All patients completed the full study period.

# Conclusion - discussion

- Decreasing the lopinavir and ritonavir dose by half, resulted in inadequate plasma concentration in 50% HIV-infected individuals in contrast to other PIs<sup>1</sup>

Drug	Mean	Difference	P-value
<b>Lopinavir</b>			
Lopinavir/ritonavir 400/100 mg BID	7.1		
Generic Lopinavir/ritonavir 200/50 mg BID	1.5	5.6	< 0.01
Pediatric Aluvia® 200/50 mg BID	1.6	5.5	< 0.01
<b>Ritonavir</b>			
Lopinavir/Ritonavir 400/100	0.44		
Generic Lopinavir/Ritonavir 200/50 mg BID	0.07	0.37	< 0.01
Pediatric Aluvia® 200/50 mg BID	0.07	0.37	< 0.01

## Conclusion - discussion

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- ❑ The generic LPV/r tablet formulation (200/50mg) used in Thailand is bioequivalent to Aluvia<sup>®</sup>.
- ❑ Dose reduction to 200/50 mg twice daily does not result in adequate pharmacokinetic parameters in Thai HIV-1 infected patients.
- ❑ Lopinavir concentrations are ritonavir-dose dependent and 50% reduction of ritonavir dose leads to insufficient boosting of lopinavir.
- ❑ Increasing the boosting only, may result in adequate lopinavir concentrations

# Acknowledgements

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