International Journal of Pharmacy
Journal Homepage: http://www.pharmascholars.com

Research Article **CODEN: IJPNL6**

PHARMACOKINETICS OF ATAZANAVIR IN RITONAVIR-BOOSTED COMBINATION IN ASIAN HEALTHY VOLUNTEERS: COMPARISONS BETWEEN THE STANDARD AND REDUCED DOSES OF BOTH AGENTS

Chankit Puttilerpong[1], Duangchit Panomvana[1*] and Kiat Ruxrungtham[2,3]

[1]Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand
[2]Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
[3]The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), Bangkok, Thailand

[*]**Corresponding author e-mail**: Duangchit.p@chula.ac.th

ABSTRACT

Atazanavir/ritonavir (ATV/r) 200/100 mg once-daily (OD) has been shown comparable in drug exposure to the standard dose in Asian study. We explored the pharmacokinetic profiles of the boosting effect of ritonavir at 50 mg to either atazanavir 300 or 200 mg in 32 adult Thai healthy volunteers. The geometric means (GM) of ATV AUC_{0-24} were 40.66, 25.50 and 24.97 mg-h/L and C_{min} were 0.53, 0.27 and 0.24 mg/L for 300/100, 300/50 and 200/50 mg OD doses, respectively. Subjects while taking ATV/r 300/50 and 200/50 mg OD had ATV AUC_{0-24} and C_{min} significantly lower than when 300/100 mg was taken ($P < 0.05$). The GM of bilirubin concentrations were significantly reduced 2.46 vs 1.48 mg/dL for 300/50 mg and 2.60 vs 1.36 mg/dL for 200/50 mg ($P = 0.001$). The reduced dose of ATV/r decreased in ATV AUC_{0-24}, C_{min} and the rate of hyperbilirubinaemia. However, one-third of subjects taken either ATV/r 300/50 or 200/50 had subtherapeutic ATV levels, boosted with 50 mg RTV is therefore not recommended.

Keywords: atazanavir, ritonavir, pharmacokinetics, hyperbilirubinaemia,

INTRODUCTION

The efficacy of highly active antiretroviral therapy (HAART) is well established and has provided benefits to many patients with HIV infection [1]. HAART has improved morbidity and mortality and has significantly increased the life expectancy [2-6]. Certain Protease inhibitors (PIs) are often boosted with a low dose of ritonavir (RTV) which can increase systemic exposure, prolong its half-life, reduce the risk of resistance and decrease the dose administration frequency of the main PI [3,4]. However, they can be associated with a number of adverse effects, such as gastrointestinal disturbances, liver toxicity and metabolic disorders, including alteration of lipid levels, insulin resistance and lipodystrophy [6].

Atazanavir (ATV) is approved for treating both naïve and experienced adult and paediatric patients of at least 6 years of age and has been established as the preferred initial regimen in published guidelines [1-5, 7-10]. Atazanavir benefits from once-daily dosing, low pill burden and also a favourable safety profile with less lipid abnormalities than other PIs. The optimal range for ATV trough concentration was determined between 0.15 and 0.85 mg/L which associated with the highest probability of virological response and the lowest probability of increase in serum bilirubin [4,5,8,11-13]. The standard boosting doses typically 100 or 200 mg of RTV can cause side effects including gastrointestinal symptoms and blood lipid abnormalities. Asians have significantly higher exposure to PIs compared to the Caucasians [14]. Appropriate dose-finding studies of boosted PIs have

demonstrated lower doses than those recommended in Caucasian populations. The pharmacokinetic (PK) parameters of ATV/r 300/100 mg in adult Thai HIV-infected patients showed 64% higher than therapeutic level of ATV which associated with higher risk of hyperbilirubinaemia [15]. Minimizing the boosting dose could potentially improve tolerability and lower the cost of therapy. Saquinavir, fosamprenavir and darunavir were boosted equally well by lower (50-100 mg) versus higher doses of ritonavir. Indinavir, tipranavir and lopinavir were boosted more by higher RTV doses but data on ATV was inconclusive [16]. We have been reported a lower dose ATV PK study in Thai HIV-infected patients that ATV 200 mg boosted with RTV 100 mg provided a similar ATV-exposure reported among Caucasians when treated with ATV/r 300/100 mg [15]. A small prove-of-concept study suggests that this ATV/r 200/100 mg dosing seems efficacious [17]. It is therefore warranted to further investigate whether RTV can be further reduced to 50 mg as a booster. This study, we investigated the pharmacokinetics of reduced dose of RTV to 50 mg and of ATV to 200 mg compared with standard dose of RTV-boosted ATV in Thai healthy volunteers.

MATERIALS AND METHODS

Study design This study was designed and conducted as a prospective, open-label, randomized and parallel pharmacokinetics study in Thai healthy volunteers at the Clinical Research Center (CRC), Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. The study protocol was approved by the Ethics Committee at the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (IRB No.210/53). Written inform consent was obtained from all subjects before enrolment.

Subjects: Male and non-pregnant, non-lactating females aged 18 to 60 years were eligible for enrolment if they met the following inclusion criteria: body mass index (BMI) 18.5-35 kg/m^2 and women of childbearing potential must be using an adequate method of contraception to avoid pregnancy throughout the study and for a period of at least 1 month after the study. Subjects were excluded if they had any significant acute or chronic medical illness, abnormal physical examination, vital signs or clinical laboratory determinations, current or recent (within 3 months) gastrointestinal disease, positive blood screen for HIV-antibodies, clinically relevant alcohol or drug use considered by the investigator to be sufficient to hinder compliance with study procedures, exposure to any investigational drug within 3 months of the first dose of study drug, use of any other drugs, including over-the-counter medications and herbal preparations, within 2 weeks prior to the first dose of study drug and previous allergy to any of the constituents of the pharmaceuticals administered in this study.

Study Methodology: At the screening period, healthy subjects as determined by their medical history, physical examination and laboratory screening were eligible to participate in the study. After the successful screening, subjects were randomly assigned by block size of 4 to 2 groups. At period 1, all subjects were received ATV/r 300/100 mg once daily for 11 days. At period 2, subjects whom were randomized to group 1 received ATV/r 300/50 mg while those who were randomized to group 2 received ATV/r 200/50 mg on day 12 through 22. Study medication was administered with 240 ml of water following a light meal or snack. Because 50 mg dosage form of RTV was not available in Thailand. Two tablets of paediatric Aluvia® (each tablet containing 100 mg lopinavir and 25 mg ritonavir) were used in place when 50 mg dose of RTV was required as booster. The safety and tolerability were assessed by monitoring adverse events using the subjects' interview, vital signs, physical examinations and laboratory tests performed throughout the study. The severity of adverse events and laboratory abnormalities were graded according to Common Toxicity Criteria (CTC), Common Terminology Criteria for Adverse Events (CTCAE) or a modified CTC of the National Institutes of Allergy and Infectious Diseases [18-20].

Analytical methods: The full PK studies of ATV and RTV will be assessed on days 10 and 21. Subjects were confined to stay in the unit on days of intensive PK study. Blood samples were collected at pre-dose (0 hr) and at 2, 3, 4, 8, 12, 24 and 26 hours after dosing on days 10, 11 in period 1 and days 21, 22 in period 2. Blood samples were centrifuged at 3,000 rpm for 10 minutes at 20ºC, and were kept at -20ºC until analysis. Plasma concentrations of ATV and RTV were measured by validated high-performance liquid chromatography (HPLC) methods with UV detection at The HIV Netherlands-Australia-Thailand (HIV-NAT) Clinical Research Laboratory. Protease Inhibitors and internal standard were detected at 215 nm. The method was linear over the range of 0.045-30.0 mg/L for both drugs. Within day and between-day precision coefficient of variation did not deviate more than 20% for both drugs. The assay of HIV-NAT Clinical Research Laboratory participates in an international quality control and quality assessment program was developed by the department of Clinical Pharmacology at the University Medical Centre

Nijmegen (Nijmegen, the Netherlands) [21] and has been cross-validated with other PK laboratories [22].

Pharmacokinetic and statistical analysis: Pharmacokinetic parameters of ATV and RTV were calculated by using non-compartmental techniques with WinNonlin® Professional version 6.2 (Pharsight Corporation, Mountain View, CA, USA) using the linear up/log down trapezoidal rule. AUC from time zero to the end of the dosing interval ($AUC_{0–24}$), C_{min}, C_{max}, T_{max}, terminal phase rate constant, $T_{1/2}$, apparent volume of distribution (V_d/F) and apparent oral clearance (CL/F) parameters will be determined.

All data were performed by using the SPSS for windows version 17.0 (SPSS, Inc.) and analyzed by descriptive statistics and inferential statistics. Paired t-test, Independent t-test or Wilcoxon signed-rank test will be used for comparison of pharmacokinetic parameters between the groups.

RESULTS

Demographic data: Thirty-two volunteers were enrolled and randomly assigned into two groups. Only thirty-one volunteers (22 males) had completed the study and included in the further analysis; one subject had finished the first phase of the study but had withdrew the consent and declined to participate in the next study phase. Mean (standard deviation) age, body weight, body mass index and baseline total bilirubin were 28.1 (5.5) years, 61.7 (10.3) kg, 21.8 (2.1) kg/m^2 and 0.8 (0.2) mg/dL.

Pharmacokinetics: The mean plasma concentration-time profiles of ATV and RTV, compared between subjected receiving the different doses of ATV/r, are illustrated in Figure 1. The geometric means (90%CI) of PK parameters of both drugs and the analyses results were summarized in Table 1.

Comparisons of ATV PK parameters between subjects in group 1 period 1; G1P1 (ATV/RTV 300/100) and group 1 period 2; G1P2 (ATV/RTV 300/50), the reduction of the RTV dose was associated with a significantly decrease in the area under the plasma concentration-time curve (AUC) from the time 0 to 24 hours (AUC_{0-24}), the maximum concentration (C_{max}), the minimum concentration (C_{min}) while the V_d/F and CL/F were significantly increase and half-life ($T_{1/2}$) was not significantly different between the two periods. There were approximately 36%, 30% and 53% decrease in the geometric mean of ATV AUC_{0-24}, C_{max} and C_{min}, respectively when the dose of RTV was reduced from 100 mg to 50 mg ($P < 0.05$). Subjects administered with reduced dose of both ATV and RTV to 200/50 mg OD showed statistically significant decrease in the AUC_{0-24}, C_{max}, C_{min} of ATV while the $T_{1/2}$, V_d/F and CL/F were not significantly different when compared with those taken the standard dose of 300/100 mg OD. There was a 40% reduction of ATV $AUC_{0-24,}$ 39% and 51% of C_{max} and C_{min}, respectively. Comparisons of RTV PK parameters between 300/100 versus 300/50 and between 300/100 versus 200/50, the results from both groups revealed that AUC_{0-24}, C_{max} and C_{ave} of RTV were significantly decrease while the V_d/F and CL/F were significantly increase and $T_{1/2}$ showed no significantly different. Neither ATV nor RTV PK parameter was statistically significantly different between the ATV/r 300/50 mg and 200/50 mg groups. In this study, due to the 50 mg tablet of RTV was not available by the time the study conducted, 2 tablets of paediatric Aluvia® (each tablet containing lopinavir/ritonavir 100/25 mg) were used for the 50 mg RTV boosted PK studies. There were no significant differences of all lopinavir (LPV) PK parameters when combined with either 300 or 200 mg ATV.

A comparison of the distribution of C_{min} values among different dosage regimens was shown in Figure 2. While taking ATV/r 300/100, 300/50 and 200/50 mg OD, 74.20%, 56.25% and 66.67% of ATV C_{min} was within the therapeutic range, respectively. While administered with ATV 300 mg, 25.80% and 12.50% of their ATV C_{min} was above the therapeutic range when boosted with 100 and 50 mg of RTV, respectively. While dosing with ATV/r 300/50 and 200/50 mg, 31.25% and 33.33% of their ATV C_{min} was below the therapeutic range, respectively and these differences were not statistically significant.

Safety and tolerability: All regimens were generally well tolerated. No serious adverse events were reported. The most common adverse events related to ATV were hyperbilirubinaemia and jaundice. Most of the subjects receiving ATV/r 300/100 mg had hyperbilirubinaemia which had severity in grade 2 (total bilirubin > 1.5 - 3 times the upper limit of normal [ULN]), or 3 (> 3-10 ULN) as shown in Figure 3A. The GM of total bilirubin levels were decreased significantly by 40% (2.46 versus 1.48 mg/dL; $P = 0.001$) and 48% (2.60 versus 1.36 mg/dL; $P = 0.001$) when the dose of ATV and/or RTV was reduced from 300/100 mg to 300/50 mg and 200/50 mg, respectively as presented in Figure 3B. Comparisons of hyperbilirubinaemia and the GM of total bilirubin concentrations classified by therapeutic ranges were illustrated in Figure 4. All subjects whose ATV C_{min} was classified as above therapeutic range had hyperbilirubinaemia grade 2 or 3 and their

mean total bilirubin concentration (3.27 mg/dL) was significantly higher than subjects whose ATV C_{min} was classified to be within therapeutic range or subtherapeutic range (1.93 and 1.02 mg/dL; *P* = 0.000). Jaundice occurred higher in subjects receiving the standard dose of ATV boosted with RTV. Loose stool or diarrhoea was reported to be 32% which might be caused by LPV that was combined with RTV in Aluvia® tablet. All adverse events and laboratory abnormalities were reversible.

DISCUSSION

The reduced boosting dose of RTV with other PIs could complete virological suppression while potentially decreasing adverse effects, improve patient adherence and lower the cost of therapy. Our study investigated the PK parameters of standard dose and reduced doses of RTV or both RTV and ATV in Thai healthy volunteers. We found that when the doses of RTV was reduced to 50 mg to boost ATV either at 300 mg or 200 mg, ATV AUC_{0-24}, C_{max} and C_{min} were significantly decreased when compared to the standard dose. In this study ATV PK parameters were significantly different when Thai healthy volunteers received ATV 300 mg with RTV 100 mg compared to 50 mg. Our results were different from Estevez JA, et al [23] who demonstrated the equivalent in ATV PK profiles when boosted with 100 or 50 mg of RTV. The reason for the difference in pharmacokinetics between Thai and Spanish studies was most likely due to the difference in dosage form of RTV 50 mg used in the studies. Different ritonavir's dosage form between 100 mg soft gelatin capsule and 50 mg solution (using 0.63 ml of 80 mg/ml of Norvir® oral solution) or 50 mg tablet (using 2 tablets of Aluvia® which is the combination of LPV 200 mg and RTV 50 mg) resulted in difference in bioavailability of RTV, PK parameters of RTV and in turn affect the boosting and PK of ATV [15,24,25]. Even though it was very unlikely, a suboptimal dose of LPV may introduce some significant confounding variable.

Ritonavir can increase the plasma concentration of ATV either by improving bioavailability or increasing their eliminate half-life in plasma. We would like to investigate whether 50 mg of RTV could boost 300 mg of ATV to the same extent as 100 mg RTV, however, since the bioavailability of the two dosage forms used in our study were much difference and bioavailability from Aluvia® tablet was much lower, we could not conclude whether 50 mg of RTV in the dosage form with good bioavailability could provide enough boosting effect on ATV, we can only conclude that 50 mg of RTV from 2 tablets of Aluvia® could not provide enough boosting effect on ATV. In general practice, ATV is often used in boosted with RTV which can increase systemic exposure of ATV by inhibition of gut metabolism through both CYP 3A4 and P-glycoprotein (P-gp) activity. When the oral bioavailability of RTV was lower, RTV concentration was decreased in company with the overall boosting effect to ATV. The available of RTV in the systemic circulation from two tablets of Aluvia® was low, the boosting activity on ATV had come to its full capacity at 200 mg or even lower of ATV, therefore, it could boost 300 mg of ATV to nearly the same extent as 200 mg of ATV resulted in no significant difference in either observed PK parameters of ATV between ATV/r 300/50 and ATV/r 200/50 groups. Approximately one third of the patients while using reduced dose of RTV, either taken 300 or 200 mg of ATV, had suboptimal ATV C_{min} concentrations. In contrast, one-fourth of patients taken the standard dose of ATV/r 300/100 daily had their ATV concentration > 0.85 mg/L and had severity in grade 2 or 3 of hyperbilirubinaemia. While only 13% and none of the patients who were taking the reduced doses of ATV/r 300/50 mg and 200/50 mg, had their ATV C_{min} levels over the therapeutic ranges, respectively.

Of note, the ATV of AUC_{0-24}, C_{max} and C_{min} in Thai healthy volunteers from this study were lower than those reported in the previous study of Avihingsanon A and colleagues [15] in Thai HIV-infected patients receiving the equally dose of ATV/r 300/100 mg (72.01 mg.h/L, 6.67 and 1.36 mg/L). The ratios of mean ATV AUC_{0-24}, C_{max} and C_{min} in Thai HIV-infected patients compared with Thai healthy volunteers in this study were higher 1.58, 1.47 and 2.03, respectively. If we calculated and estimated the mean of ATV AUC_{0-24}, C_{max} and C_{min} for Thai HIV-infected patients by using these ratios, patients who are taking the ATV/r 300/50 mg and 200/50 mg may have the ATV AUC_{0-24}, C_{max} including C_{min} which are higher than those obtained in healthy volunteers and possibly will result in higher percentage of ATV level which is within the therapeutic range and lesser percentage which is under therapeutic range. This observation was consistent with comparisons between the results reported by Taburet A, et al [26] and Hill A, et al [27] which demonstrated that Caucasian HIV-infected patients had higher ATV of AUC_{0-24}, C_{max} and C_{min} than Caucasian healthy volunteers when consuming the same amount of ATV/r standard dose. However, disagreement results had also been reported when compared the data reported by Bristol-Myers Squibb Company [9] and Taburet A, et al [26], Giambenedetto S, et al [28] which

demonstrated higher ATV AUC_{0-24}, C_{max} and C_{min} in Caucasian healthy volunteers than in the Caucasian HIV-infected patients. The higher levels in HIV-infected patients might be explained by the decreasing in cytochrome P450 3A4 activity (50%) and P-glycoprotein (22-30%) [29]. Several of our previous studies have also shown that the indinavir and saquinavir PK parameters in Thai HIV-infected patients were higher than those of Caucasian HIV-infected patients [24,30-36]. The reason for the difference in pharmacokinetics between Thai and Caucasian populations is unclear, it may be related to difference in activity of CYP 3A4, activity of P-glycoprotein, lower body weight, racial and food intake [17,26,37,38].

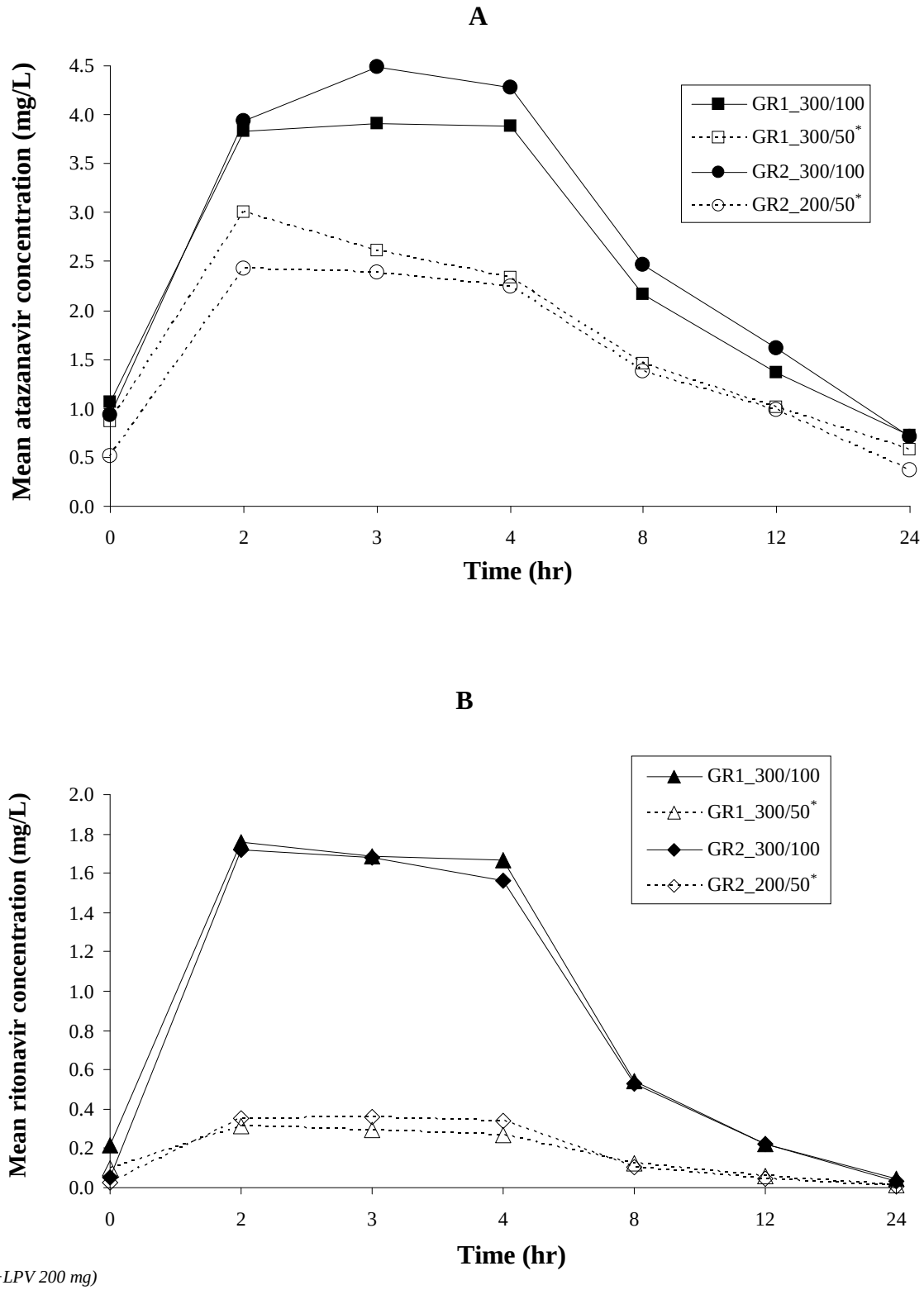
Hyperbilirubinaemia was the most common adverse events related to ATV and was found in all study groups. Hyperbilirubinaemia grades 2 or 3 were found higher in subjects taking the standard dose than the reduced dose (45% versus 13%). Previous studies in HIV patients reported severe hyperbilirubinaemia with a prevalence ranging from less than 20% to 60% in Caucasian and 36% in Thai [4,5,9,15,39,40]. Several studies have found an association between plasma ATV C_{min} and serum bilirubin level [41-46]. Our study showed that subjects with ATV C_{min} higher than 0.85 mg/dL had 2-3 fold higher risk of bilirubin elevation than subjects with ATV C_{min} lower than this level. There was a significant decrease in the total bilirubin concentrations after the reduction of ATV/r once daily from standard dose (300/100 mg) to reduced dose (300/50 or 200/50 mg). This result is consistent with previous study by Colombo S, et al [47] and Gonzalez de Requena D, et al [43]. However, we observed 6%, 65% and 16% of subjects presented with elevated bilirubin when their ATV C_{min} levels were lower than, within and higher than therapeutic ranges, respectively. This weak correlation between ATV C_{min} and bilirubin concentration has also been reported by previous observations [43]. Bilirubin elevation was influenced by the genetic polymorphisms had recently been reported by Rodriguez-Novoa S, et al [45,46]. Polymorphisms at MDR 1-3435 significantly influence ATV levels; Caucasian patients with CT/TT genotypes were associated with lower ATV levels. They also found that ATV concentration was directly correlated with bilirubin level and the severe hyperbilirubinaemia was associated with the presence of the UGT1A1-TA7 allele. This polymorphism is much lower in Asians (13-16%) compared with Caucasians (36-39%) and African Americans (43%) population. High prevalence of severe ATV-associated hyperbilirubinaemia in Asians with low prevalence of this polymorphism may be due to the frequent of other polymorphism in these population such as MDR1 G2677T/A [47,48].

CONCLUSION

This study indicated the reduced doses of RTV and/or ATV in Thai healthy volunteers provided significantly lower the levels of ATV AUC_{0-24}, C_{max} and C_{min} than the standard dose and with a significant decrease of total bilirubin levels which related to hyperbilirubinaemia. Minimizing the dose of RTV could improve tolerability and patient adherence while lowering costs and pill burden. However, because one-third of subjects taken either ATV/r 300/50 or 200/50 had subtherapeutic ATV levels, therefore boosted with 50 mg RTV by using Aluvia® is not recommended. Further study using the high bioavailability dosage form of 50 mg RTV and/or in HIV-infected patients may result in different recommendation.

ACKNOWLEDGEMENTS

We would like to thank all of the staffs at the Chula Clinical Research Center of the Faculty of Medicine, Chulalongkorn University and The HIV Netherlands-Australia-Thailand (HIV-NAT) Clinical Research Laboratory for their helpful cooperation and support in the laboratory and many facilities through the sample analysis. This study was funded by a grant from the Strategic Scholarships Fellowships Frontier Research Networks, Commission on Higher Education and the Senior Researcher Scholar, Thai Research Fund (TRF). KR is supported by the grants from the National Research University Project of CHE and the Ratchadaphiseksomphot Endowment Fund (HR1161A); the Senior Researcher Scholar, Thai Research Fund (TRF); and the Professional Research Team Strengthening Fund, BIOTEC; Thailand.



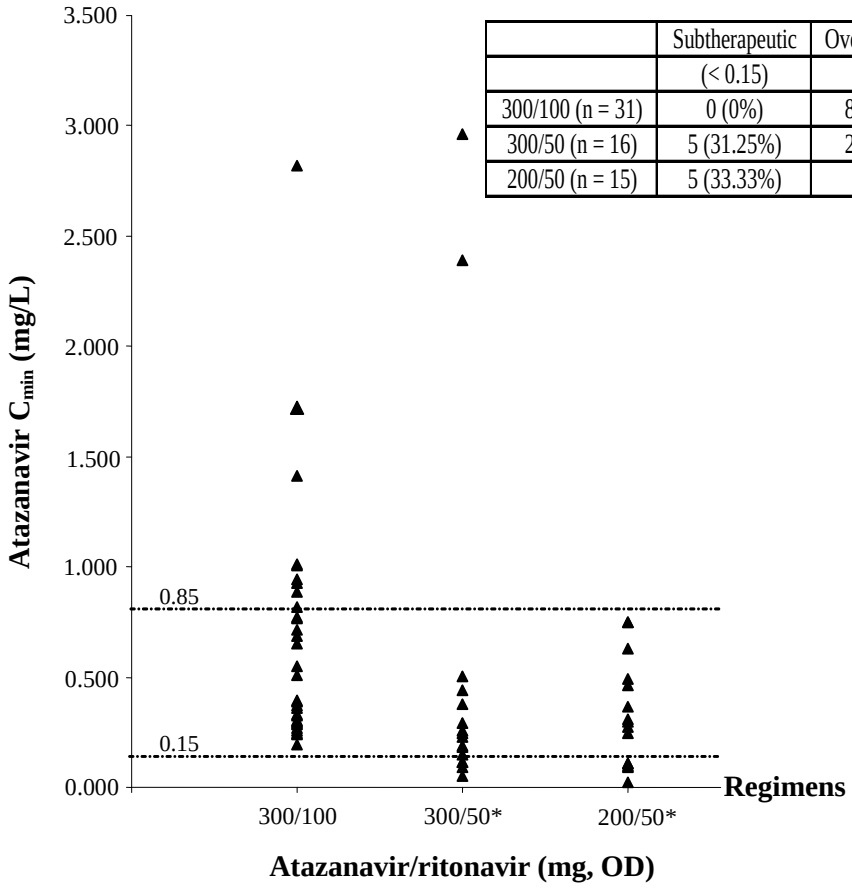
* *(+LPV 200 mg)*

Figure 1. Mean plasma (A) atazanavir (B) ritonavir concentration-time curves at steady state between subjects both groups receiving 300/100 mg versus 300/50 mg and 200/50 mg.

Table 1. Comparison of the pharmacokinetic (PK) parameters of atazanavir and ritonavir between subjects receiving different doses of atazanavir/ritonavir (300/100 vs. 300/50 and 300/100 vs. 200/50)

PK parameters	Geometric Mean (90% CI)		Ratio of Geometric Mean (G1P2/G1P1)	G1P2 versus G1P1 (*P* value)	G1P1 versus G2P1 (*P* value)
	ATV/RTV 300/100 G1P1 (N=16)	ATV/RTV 300/50* G1P2 (N=16)			
Atazanavir					
AUC $_{0-24}$ (mg.h/L)	39.80 (33.21 - 47.71)	25.50 (19.85 - 32.76)	0.64	0.000	0.802
C_{max} (mg/L)	4.03 (3.43 - 4.73)	2.83 (2.29 - 3.50)	0.70	0.001	0.761
C_{min} (mg/L)	0.58 (0.44 - 0.76)	0.27 (0.17 - 0.43)	0.47	0.000	0.490
$T_{1/2}$ (hr)	12.33 (10.85 - 14.02)	11.10 (9.29 - 13.26)	0.90	0.090	0.733
CL/F (L/hr)	7.54 (6.29 - 9.03)	11.76 (9.16 - 15.11)	1.56	0.000	0.802
V_d/F (L)	134.09 (114.14 - 157.53)	188.40 (164.70 - 215.50)	1.41	0.000	0.952
Ritonavir					
AUC $_{0-24}$ (mg.h/L)	9.15 (6.77 - 12.39)	1.58 (1.11 - 2.25)	0.17	0.000	0.705
C_{max} (mg/L)	1.53 (1.15 - 2.04)	0.25 (0.19 - 0.34)	0.16	0.000	0.868
C_{ave} (mg/L)	0.38 (0.28 - 0.52)	0.07 (0.05 - 0.09)	0.17	0.000	0.705
$T_{1/2}$ (hr)	5.78 (4.95 - 6.71)	6.24 (5.24 - 7.43)	1.08	0.416	0.992
CL/F (L/hr)	10.92 (8.07 - 14.77)	31.56 (22.20 - 44.86)	2.89	0.000	0.695
V_d/F (L)	90.80 (67.59 - 125.29)	284.23 (196.86 - 410.38)	3.13	0.000	0.722
	ATV/RTV 300/100 G2P1 (N=15)	**ATV/RTV 200/50* G2P2 (N=15)**	**Ratio of Geometric Mean (G2P2/G2P1)**	**G2P2 versus G2P1 (*P* value)**	**G1P2 versus G2P2 (*P* value)**
Atazanavir					
AUC $_{0-24}$ (mg.h/L)	41.60 (32.37 - 53.45)	24.97 (20.92 - 29.81)	0.60	0.000	0.907
C_{max} (mg/L)	4.23 (3.36 - 5.32)	2.58 (2.23 - 2.98)	0.61	0.001	0.533
C_{min} (mg/L)	0.49 (0.35 - 0.67)	0.24 (0.15 - 0.37)	0.49	0.004	0.734
$T_{1/2}$ (hr)	12.78 (11.25 - 14.51)	11.18 (9.78 - 12.78)	0.88	0.155	0.956
CL/F (L/hr)	7.21 (5.61 - 9.27)	8.01 (6.71 - 9.56)	1.11	0.295	0.038
V_d/F (L)	132.94 (110.06 - 160.58)	129.17 (110.49 - 151.01)	0.97	0.830	0.003
Ritonavir					
AUC $_{0-24}$ (mg.h/L)	9.98 (7.75 - 12.87)	1.94 (1.47 - 2.55)	0.19	0.000	0.438
C_{max} (mg/L)	1.59 (1.26 - 2.00)	0.32 (0.24 - 0.42)	0.20	0.000	0.294
C_{ave} (mg/L)	0.42 (0.32 - 0.54)	0.08 (0.06 - 0.11)	0.20	0.000	0.393
$T_{1/2}$ (hr)	5.77 (5.01 - 6.65)	7.11 (4.87 - 10.39)	1.23	0.355	0.578
CL/F (L/hr)	10.02 (7.77 - 12.91)	25.31 (19.36 - 33.08)	2.53	0.000	0.393
V_d/F (L)	83.38 (64.34 - 108.06)	259.72 (162.96 - 450.81)	3.11	0.001	0.790

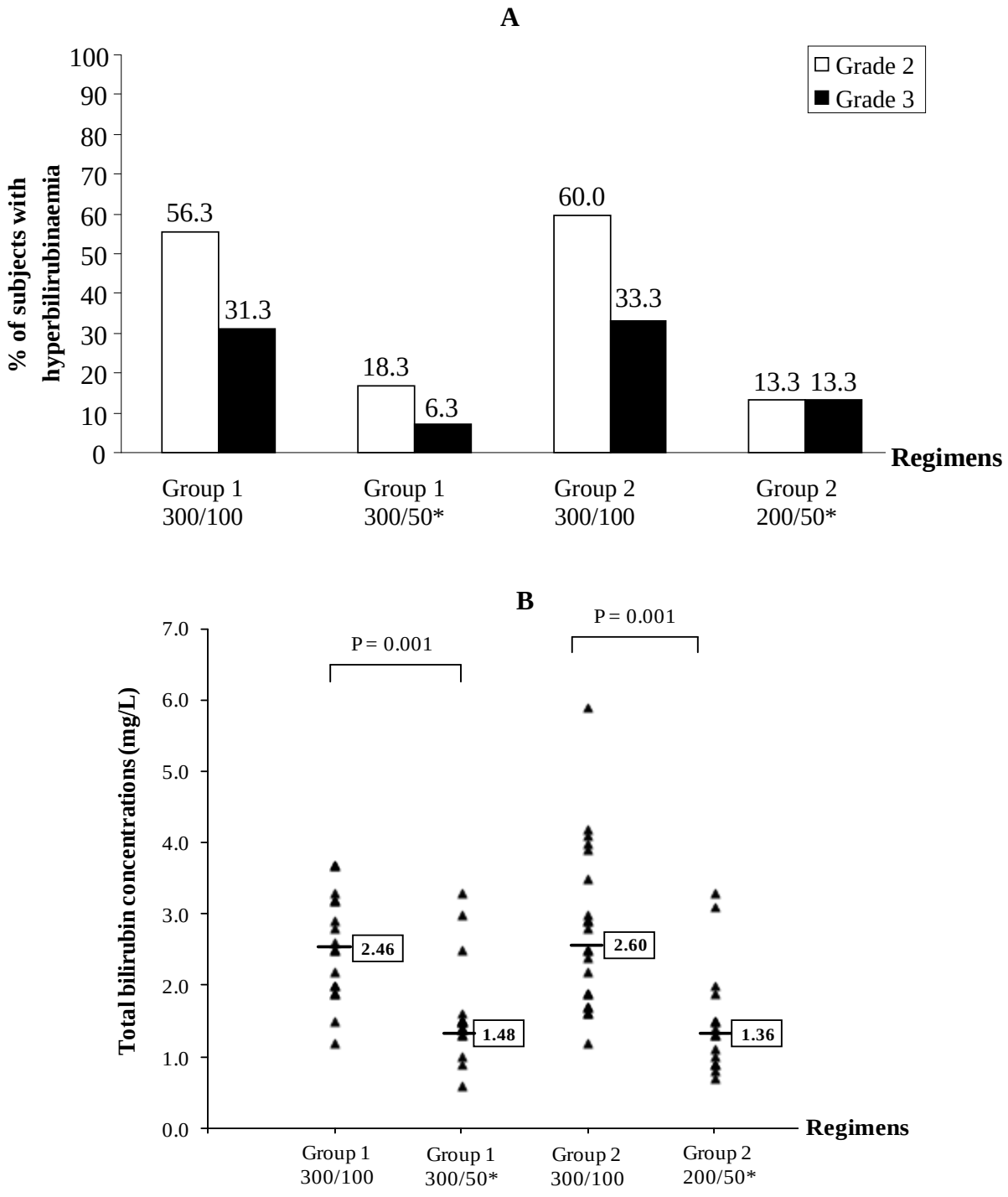
** (+LPV 200 mg)*



	Subtherapeutic (< 0.15)	Overtherapeutic (> 0.85)
300/100 (n = 31)	0 (0%)	8 (25.80%)
300/50 (n = 16)	5 (31.25%)	2 (12.50%)
200/50 (n = 15)	5 (33.33%)	0 (0%)

** (+LPV 200 mg)*

Figure 2. Comparison of the distribution of C_{min} values between subjects receiving different dosage regimens of atazanavir with ritonavir.



** (+LPV 200 mg)*

Figure 3. Comparison of (A) hyperbilirubinaemia grade 2 and 3 (B) the geometric mean total bilirubin values between subjects receiving different doses of atazanavir with ritonavir.

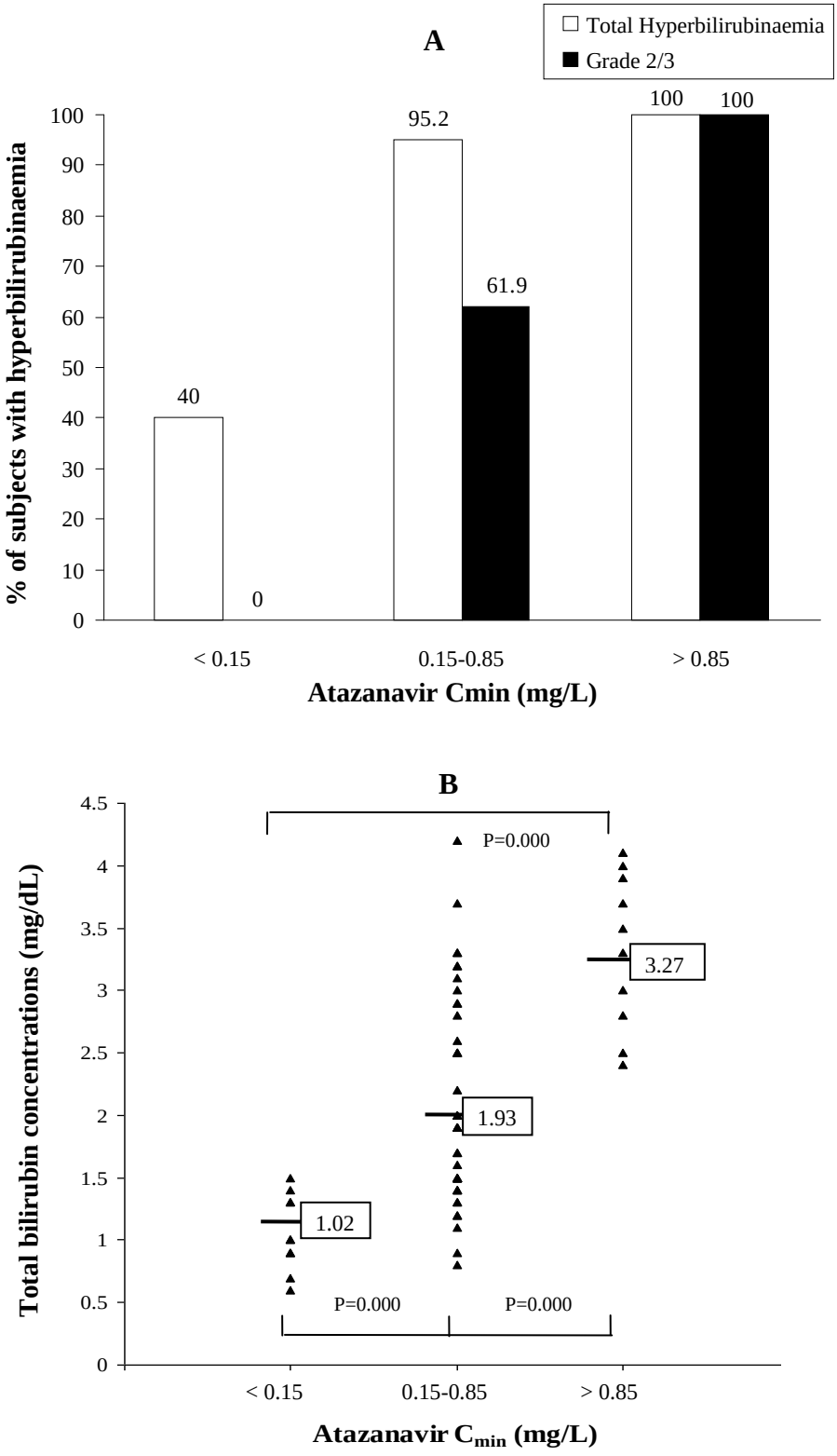


Figure 4. Comparison of (A) hyperbilirubinaemia (B) the geometric mean total bilirubin values classified by therapeutic range.

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