

Plasma pharmacokinetics of once-daily abacavir- and lamivudine-containing regimens and week 96 efficacy in HIV-infected Thai children

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Abstract

Background: Abacavir and lamivudine are approved for once-daily use in HIV-infected adults. Limited pharmacokinetic (PK) data for abacavir and lamivudine in children are available.

Methods: A crossover study to compare PK of once- versus twice-daily abacavir and lamivudine was conducted in virologically suppressed HIV-infected Thai children aged <18 years, with bodyweight of at least 14 kg, HIV RNA <50 copies/mL and HLA-B*5701 negative. Abacavir and lamivudine daily doses by bodyweight were 300 and 150 mg for 14–<20 kg, 450 and 300 mg for 20–<25 kg, and 600 and 300 mg for ≥25 kg, respectively. Originator abacavir and lamivudine scored tablets were administered. Intensive PK sampling was performed after 14 days of each dose. PK parameters were determined using non-compartmental analysis.

Results: Thirty children (57% male) were enrolled, 10 per weight band. Median (IQR) age was 8.8 (6.6–11.3) years and bodyweight was 21.9 (19.2–30.6) kg. The geometric means (GM) AUC_{0–24} of once- and twice-daily abacavir were 14.43 and 10.65 mg.h/L, respectively. The geometric mean ratio (GMR) of AUC_{0–24} for once- versus twice-daily abacavir dosing was 1.36 [90% confidence interval (CI) 1.11–1.66]. The GM AUC_{0–24} of once- and twice-daily lamivudine were 17.70 and 18.11 mg.h/L, respectively. The GMR of AUC_{0–24} for once- versus twice-daily lamivudine dosing was 0.98 (90% CI 0.84–1.14). At 96 weeks, 90% had HIV RNA <50 copies/mL and there were no serious adverse events.

Conclusion: Abacavir exposure was greater with once-daily dosing, while lamivudine once- and twice-daily exposures were bioequivalent. Once-daily abacavir and lamivudine using weight-band dosing is a treatment option for children.

Keywords: abacavir, lamivudine, pharmacokinetics, once-daily, HIV-infected children

Introduction

According to UNAIDS there are 647,000 children aged under 15 years who receive antiretroviral treatment (ART) [1]. ART suppresses viral replication allowing restoration and/or preservation of the immune system. Long-term viral suppression requires continuous drug adherence but this can be challenging for children and adolescents. Currently, there are a limited number of regimens and formulations for children. Pill burden and dosing schedules are also critical for long-term drug adherence. Once-daily dosing has been shown to significantly improve drug adherence [2] with high levels of acceptability in children [3,4].

Abacavir and lamivudine are nucleoside reverse transcriptase inhibitors (NRTIs) recommended in the current World Health Organization (WHO) paediatric ART guidelines [5]. Both drugs are well tolerated and have no food restrictions or major drug–drug interactions. Abacavir also has a good long-term safety profile with fewer lipid abnormalities compared to stavudine [6]. Pharmacokinetic (PK) studies of abacavir and lamivudine comparing once- versus twice-daily dosing in African and European children have been performed [4,7,8] and have demonstrated bioequivalence in HIV-infected Ugandan children aged 3–12 years [4] and European children aged 3 months–3 years [8]. However, there are no published

pharmacokinetic studies of abacavir in Asian children.

There are few PK studies of lamivudine in Thai children [9,10]. Vanprapar *et al.* [10] reported that the area under the concentration–time curve (AUC) of lamivudine in HIV-infected Thai children age ≥6 months–13 years using the lamivudine liquid formulation was similar to that reported in the PENTA 13 and PENTA 15 European studies [7,8]; however, increased lamivudine exposure was observed with the tablet formulation. Higher drug concentrations have been reported with other ARTs at standard doses in Thais [11,12]. Our objectives were to compare the PK parameters of abacavir and lamivudine administered once- versus twice-daily in HIV-infected Thai children following the current WHO weight-band dosing recommendation, and to compare our data with those of the ARROW study in African children where similar dosages were used [4].

Material and methods

This was a single-arm, open-label, crossover PK study of once-daily versus twice-daily abacavir and lamivudine (clinicaltrials.gov number NCT01656122). The study was conducted at the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), Thai Red Cross AIDS Research Centre, Bangkok, Thailand. HIV-infected children younger than 18 years old, bodyweight at least 14 kg, on stable ART with an HIV RNA <50 copies/mL were enrolled. Exclusion criteria were: a positive HLA-B*5701 test; having conditions that may interfere with PK assessments such as vomiting or diarrhoea ≥ grade 3; abnormal

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alanine transaminase; haemoglobin or creatinine \geq grade II according to the 2004 Division of AIDS (DAIDS) toxicity grading table [13]; history of poor adherence to ART; and concomitant treatment with drugs known to influence the PK of abacavir (e.g. ethanol and methadone). This study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University. All caregivers provided written informed consent and children aged 7 years and above who knew their HIV status were also asked to provide assent.

Drug formulation and dosing

Abacavir (Ziagen) 300-mg scored tablets and lamivudine (Epivir) 150-mg tablets were used. The choice of other ART within the regimen was up to the attending physician according to the standard of care in Thailand. Participants were divided in to the following three bodyweight bands; 14–<20, 20–<25 and \geq 25 kg. Abacavir and lamivudine twice-daily dosing was given following the 2010 WHO weight bands, except a greater lamivudine dose was given for children weighing 20–<25kg for convenience and consistency with local practices [14]. Abacavir and lamivudine daily doses by bodyweight were 300 and 150 mg for 14–<20 kg, 450 and 300 mg for 20–<25 kg, and 600 and 300 mg for \geq 25 kg, respectively. At the entry visit, children who were not receiving abacavir and lamivudine changed their two NRTIs to abacavir and lamivudine twice daily, and dosed according to the weight bands described in Appendix 1. Adherence to abacavir and lamivudine was measured by pill count.

Pharmacokinetic sampling

Two PK profiles were obtained for each child, at least 2 weeks apart. The first PK sampling was performed 14 days after enrolment in the study while using abacavir and lamivudine twice daily. Blood samples were drawn pre-dose (time point 0) and then at 1, 2, 3, 4, 6, 8 and 12 hours post-drug ingestion. Following completion of the PK sampling, the abacavir and lamivudine doses were immediately changed to once-daily dosing (same total daily dose and taken in the morning). The second PK visit was scheduled for 2 weeks later. The PK sampling was identical to the first PK visit but an additional sample was drawn at 24 hours post-dose. Breakfast (non-standardised, but mostly porridge) was consumed following the pre-dose sample. All blood samples were centrifuged, aliquoted and stored at -70 C. Abacavir and lamivudine plasma concentrations were measured at the Program for HIV Prevention and Treatment Laboratory at the Faculty of Associated Medical Sciences, Chiang Mai University. Plasma abacavir and lamivudine concentrations were measured using a validated high-performance liquid chromatography (HPLC) assay. The average accuracy was 94–110% and precision (inter- and intra-assay) was <11% of the coefficient of variation (CV). The lower limit of quantification for abacavir and lamivudine plasma concentrations was 0.025 mg/L. External quality controls were provided by the AIDS Clinical Trial Group, USA, Pharmacology Quality Control Program [15].

CD4% and CD4 cell count were tested at the baseline visit. Plasma HIV RNA was performed at baseline and at both PK visits and every 24 weeks until week 96. Complete blood count, alanine transaminase and serum creatinine were also performed on the PK days and every 24 weeks until week 96.

Statistical considerations

Sample size

No formal sample-size calculation was required as this is a descriptive PK study. In general, at least eight patients per weight

band is an appropriate number to describe the PK properties of a drug and the interpatient variability in sufficient detail. Here we included 10 children per weight band to allow for losing up to two children per weight band to follow-up.

Statistical analysis

Baseline characteristics were described using medians and interquartile ranges (IQR) and percentage. The area under the plasma concentration–time curve (AUC) for the time points 0–12 h (AUC_{0-12}), 0–24 h (AUC_{0-24}), maximum concentration (C_{max}), minimum concentration (C_{min}), and the apparent oral clearance normalised to bodyweight (CL/F/kg) were calculated using WinNonlin (version 5.2; Pharsight, Mountain View, CA, USA). The AUC_{0-24} of lamivudine and abacavir following twice-daily dosing when using similar doses in the morning and evening was calculated by multiplying the AUC_{0-12} by 2. However, the AUC_{0-12} of twice-daily dosing abacavir of children in the 20–<25 kg weight band was multiplied by 3 due to unequal morning and evening dosing for abacavir.

The geometric mean ratios (GMR) for the AUC_{0-24} for once-daily and twice-daily dosing were considered bioequivalent in accordance with US Food and Drug Administration (FDA) criteria if the 90% confidence interval (CI) fell between 0.80 and 1.25 [16]. Each PK parameter was compared for each weight band using paired Student's *t*-tests. The analyses were performed in STATA version 12 (StataCorp, College Station, TX, USA). The PK data from our study were compared with data from 30 Ugandan HIV-infected children with similar weight bands and formulations of abacavir (scored tablets) and lamivudine in the ARROW study [4]. In addition, Thai children in the 20–<25 kg weight band were exposed to an increased dose of lamivudine compared to Ugandan children; therefore, we performed a subgroup analysis whereby these children were excluded, and then data from the other Thai children were compared with that from the Ugandan children.

Wilcoxon signed-rank test and McNemar's test were used to compare medians of continuous variables and percentage of category variables between baseline and week of follow-up, respectively. Abnormal lipids were defined as total cholesterol (TC) \geq 200 mg/dL, triglyceride (TG) \geq 150 mg/dL and high density lipoprotein (HDL) <40 mg/dL [17].

Results

Between July and October 2012, 30 HIV-infected children, 17 (57%) male, were enrolled in the study. The median age (IQR) was 8.8 (6.6–11.3) years and bodyweight (IQR) was 21.9 (19.2–30.6) kg. Ten children were enrolled in each weight band. Fourteen children (47%) had history of CDC clinical classification C. Median (IQR) CD4 percentage and count were 29.5 (27.0–35.0)% and 841 (580–1073) cells/mm³, respectively. All children received lamivudine prior to enrolment. Four children (13%) were taking abacavir prior to enrolment with a median duration of 37 weeks. The antiretroviral regimens included abacavir/lamivudine plus efavirenz (60%, $n=18$), abacavir/lamivudine plus lopinavir/ritonavir (37%, $n=11$) and abacavir/lamivudine plus nevirapine (3%, $n=1$). Seven, 2 and 2 children were receiving lopinavir/ritonavir in the 14–<20, 20–<25 and $>$ 25 kg weight bands, respectively ($P<0.01$). Antiretroviral regimens were the same during the two PK visits. The mean (SD) adherence by pill counts at day of screening visit was 100 (5.5)%. The mean (SD) adherence by pill counts recorded at the first and second PK sampling visits was 98.1 (2.9)% and 98.5 (2.9)%, respectively. All children had HIV RNA <50 copies/mL at enrolment and after completing both PK visits. Two children were receiving rifampin

as part of anti-tuberculosis therapy together with abacavir/lamivudine plus efavirenz during the study. One child was taking co-trimoxazole for *Pneumocystis (carinii) jirovecii* pneumonia prophylaxis throughout the study. Other concomitant medications were digoxin, bosentan and spironolactone in a child with pulmonary hypertension, cetirizine (1), ferrous fumarate plus multivitamin (1) and propylthiouracil (1).

Abacavir pharmacokinetics

The GM AUC_{0-24} of once- and twice-daily abacavir were 14.43 and 10.65 mg.h/L, respectively (Table 1). The GMR of AUC_{0-24} for once- versus twice-daily abacavir dosing was 1.36 (90% CI 1.11–1.66). Once-daily abacavir had a greater AUC_{0-24} and C_{max} ($P < 0.001$ and $P = 0.001$, respectively) but lower C_{min} and apparent oral clearance (both $P < 0.001$) compared to twice-daily abacavir. The concentrations versus time profiles of abacavir are shown in Figure 1a. Abacavir pharmacokinetic parameters in each weight band are shown in Table 2. Within each weight band, once-daily abacavir had a greater AUC_{0-24} and C_{max} (all $P < 0.05$ except $P = 0.07$ for AUC_{0-24} of weight band 20–<25 kg) but lower C_{min} and apparent clearance (all $P < 0.05$) compared to twice-daily abacavir. When comparing AUC_{0-24} between each weight band, children in the 14–<20 kg weight band had lower AUC_{0-24} of abacavir compared to other weight bands for both twice-daily and once-daily regimens (both $P = 0.01$)

Lamivudine pharmacokinetics

The PK parameters of lamivudine for the 30 children are shown in Table 1. The GM of once- and twice-daily lamivudine AUC_{0-24} were 17.70 and 18.11 mg.h/L, respectively (Table 1). The GMR of AUC_{0-24} for once-daily versus twice-daily dosing was 0.98 (90% CI 0.84–1.14).

Once-daily lamivudine had a greater C_{max} ($P < 0.001$) but lower C_{min} ($P < 0.001$) compared to twice-daily lamivudine. There were no differences in AUC_{0-24} and apparent clearance between once-

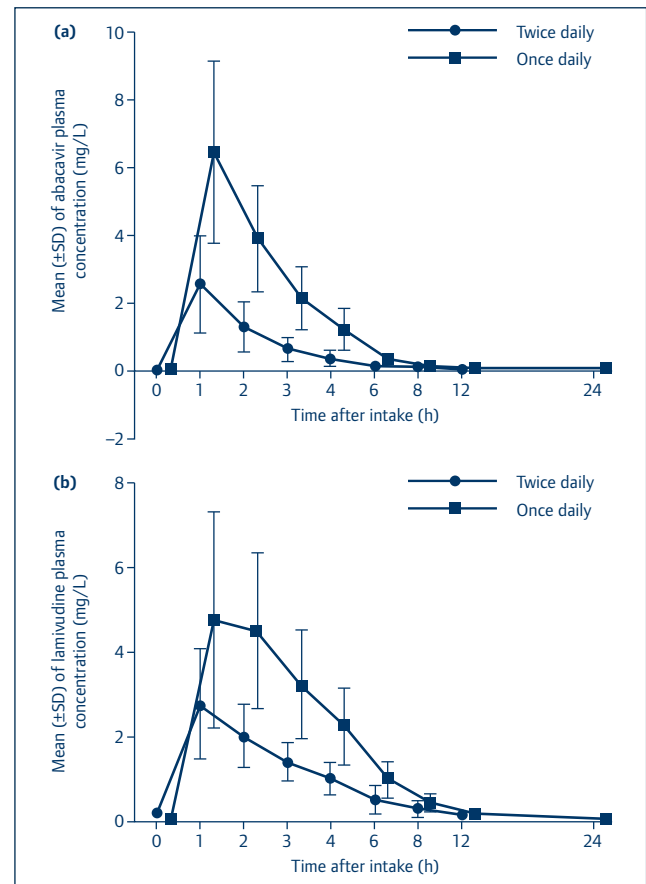


Figure 1. Mean plasma concentration of (a) abacavir and (b) lamivudine

and twice-daily lamivudine (both $P > 0.5$). Table 2 shows lamivudine pharmacokinetic parameters in each weight band. There was no statistically significant difference in AUC_{0-24} between once- and twice-daily dosing of lamivudine within each

Table 1. Pharmacokinetic parameters of abacavir and lamivudine for twice- and once-daily dosing

Our study (n=30)	ARROW (n=36)								
	Twice-daily GM (95% CI)	Once-daily GM (95% CI)	GMR (90% CI)	P value	Twice-daily GM (95% CI)	P value*	Once-daily GM (95% CI)	P value**	GMR (90% CI)
Abacavir									
AUC_{0-24} , mg.h/L	10.65 (8.63–13.14)	14.43 (12.62–16.51)	1.36 (1.19–1.55)	<0.001	15.60 (13.71–17.75)	<0.001	15.28 (13.33–17.51)	0.45	0.98 (0.89–1.08)
C_{max} , mg/L	2.11 (1.59–2.80)	5.98 (5.07–7.06)	2.84 (2.28–3.53)	0.001	4.18 (3.69–4.73)	<0.001	6.84 (5.92–7.90)	0.14	1.64 (1.43–1.88)
C_{min} , mg/L	0.019 (<0.025–0.07)	<0.025 (<0.025–0.041)	NA	<0.001	0.021 (<0.025–0.115)	NA	0.006 (<0.025–0.037)	NA	NA
CL/F/kg, L/h/kg	1.96 (1.56–2.47)	1.26 (1.12–1.43)	0.65 (0.55–0.75)	<0.001	1.23 (1.09–1.39)	0.02	1.24 (1.09–1.40)	0.94	1.00 (0.91–1.11)
Lamivudine									
AUC_{0-24} , mg.h/L	18.11 (16.07–20.41)	17.70 (14.14–22.15)	0.98 (0.84–1.14)	0.81	11.97 (10.70–13.38)	<0.001	12.99 (11.35–14.86)	<0.001	1.09 (0.98–1.20)
C_{max} , mg/L	2.84 (2.25–3.06)	5.24 (3.32–5.91)	1.69 (1.35–2.09)	<0.001	1.80 (1.59–2.04)	0.004	3.17 (2.76–3.64)	0.004	1.76 (1.58–1.96)
C_{min} , mg/L	0.100 (0.057–0.284)	0.057 (<0.0025–0.163)	NA	<0.001	0.081 (0.036–0.343)	NA	0.050 (0.018–0.125)	NA	NA
CL/F/kg, L/h/kg	0.56 (0.51–0.60)	0.58 (0.47–0.71)	1.05 (0.87–1.25)	0.64	0.79 (0.71–0.88)	0.28	0.72 (0.64–0.81)	0.63	0.90 (0.82–1.00)

* When compared with twice-daily PK data between our study and the ARROW study [4]

** When compared with once-daily PK data between our study and the ARROW study [4]

Data are presented as geometric means (GM; 95%CI) except for C_{min} (median; range)

GM: geometric mean; GMR: geometric mean ratio for the AUC_{0-24} once-daily/twice-daily; CI: confidence interval; AUC_{0-24} : daily area under the curve; C_{max} : maximum concentration; C_{min} : minimum concentration; CL/F/kg: apparent oral clearance normalised to bodyweight; NA: not applicable

Table 2. Abacavir and lamivudine pharmacokinetic parameters between weight brands

Parameters	Weight bands	Twice-daily GM	Once-daily GM	90% CI	P value
<i>Abacavir</i>					
Dose (mg/kg)	14–<20 kg	17.26 (15.83–18.83)	17.03 (15.65–18.53)	NA	NA
	20–<25 kg	19.87 (19.12–20.64)	20.09 (19.18–21.05)	NA	NA
	≥25 kg	17.78 (16.02–19.72)	17.84 (16.27–19.56)	NA	NA
AUC _{0–24} (mg.h/L)	14–<20 kg	7.67 (6.28–9.37)	10.49 (9.04–12.18)	1.36 (1.21–1.55)	0.001
	20–<25 kg	10.14 (5.96–17.25)	15.83 (13.47–18.59)	1.56 (1.04–2.34)	0.07
	≥25 kg	15.53 (12.26–19.66)	18.11 (13.81–23.74)	1.17 (1.04–1.24)	0.002
C _{max} (mg/L)	14–<20 kg	2.05 (1.63–2.57)	4.99 (3.95–6.3)	2.44 (1.93–3.07)	<0.001
	20–<25 kg (0.78–2.41)	1.37 (4.8–7.88)	6.15 (2.51–8)	4.48	0.001
	≥25 kg	3.34 (2.4–4.65)	6.97 (5.28–9.2)	2.09 (1.82–2.4)	<0.001
C _{min} (mg/L)	14–<20 kg	0.013 (0.013–0.038)	<0.0025 (0.0125–0.0043)	NA	0.01
	20–<25 kg	0.01875 (0.0125–0.35)	<0.0025 (<0.0025–<0.0025)	NA	
	≥25 kg	0.037 (<0.0025–0.064)	<0.0025 (<0.0025–<0.0025)	NA	0.005 0.01
CL/F/kg (L/h/kg)	14–<20 kg	2.25 (1.79–2.81)	1.64 (1.37–1.97)	0.73 (0.63–0.85)	0.001
	20–<25 kg	2.92 (1.73–4.92)	1.26 (1.08–1.46)	0.43 (0.26–0.7)	0.003
	≥25 kg	1.14 (0.94–1.39)	0.98 (0.78–1.23)	0.86 (0.79–0.93)	0.002
<i>Lamivudine</i>					
Dose (mg/kg)	14–<20 kg	8.63 (7.91–9.41)	8.52 (7.83–9.27)	NA	NA
	20–<25 kg	13.24 (12.75–13.76)	13.39 (12.79–14.03)	NA	NA
	≥25 kg	8.89 (8.01–9.86)	8.92 (8.13–9.78)	NA	NA
AUC _{0–24} (mg.h/L)	14–<20 kg	13.75 (11.58–16.33)	10.66 (6.15–18.47)	0.77 (0.44–1.37)	0.34
	20–<25 kg	23.78 (21.21–26.67)	25.29 (21.5–29.76)	1.06 (0.92–1.23)	0.36
	≥25 kg	18.16 (14.84–22.22)	20.57 (17.08–24.78)	1.13 (0.95–1.35)	0.13
C _{max} (mg/L)	14–<20 kg	2.1 (1.72–2.57)	2.61 (1.19–5.71)	1.24 (0.59–2.64)	0.53
	20–<25 kg	3.39 (2.63–4.36)	6.59 (5.44–7.98)	1.94 (1.37–2.76)	0.002
	≥25 kg	2.55 (1.83–3.54)	5.06 (3.86–6.64)	1.99 (1.62–2.44)	<0.001
C _{min} (mg/L)	14–<20 kg	0.083 (0.07–0.096)	0.05 (0.04–0.06)	NA	0.01
	20–<25 kg	0.11 (0.09–0.13)	0.068 (0.05–0.07)	NA	0.005
	≥25 kg	0.13 (0.09–0.13)	0.06 (0.04–0.06)	NA	0.005
CL/F/kg (L/h/kg)	14–<20 kg	0.56 (0.5–0.62)	0.87 (0.5–1.5)	1.38 (0.77–2.48)	0.24
	20–<25 kg	0.56 (0.5–0.62)	0.52 (0.45–0.61)	0.94 (0.81–1.09)	0.36
	≥25 kg	0.49 (0.43–0.56)	0.43 (0.37–0.5)	0.88 (0.74–1.05)	0.14

NA: not available; GM: geometric mean; GMR: geometric mean ratio for the AUC_{0–24} once-daily/twice-daily

weight band (all P values >0.05). Data for children taking once-daily lamivudine in weight bands $20 < 25$ kg and ≥ 25 kg showed a greater C_{max} ($P=0.002$ and $P<0.001$, respectively) compared to twice-daily lamivudine. The lamivudine C_{min} was lower within each weight band following once-daily compared to twice-daily dosing (all $P<0.05$). There were no differences in AUC_{0-24} and apparent oral clearance between once- and twice-daily lamivudine for all weight bands (all $P>0.5$). Figure 1b shows plasma concentration versus time profiles.

When comparing AUC_{0-24} between each weight band, children in the $14 < 20$ kg weight band had lower AUC_{0-24} for lamivudine compared to other weight bands for both once-daily and twice-daily regimens (both $P=0.01$). Because children in the $20 < 25$ kg weight band were given higher than WHO-recommended doses, we performed a subgroup analysis by excluding the 10 children in this weight band. The GMR of AUC_{0-24} for once-daily versus twice-daily dosing was 0.94 (90% CI 0.74–1.18), which was no different to results for the whole group.

Comparison of PK parameters of Thai children in this study with Ugandan children in the ARROW study

Children in our study had significantly lower GM AUC_{0-24} with twice-daily abacavir ($P<0.001$) but a similar GM AUC_{0-24} for once-daily abacavir ($P=0.45$) when compared with the data from the ARROW study [4] (Table 1). In addition, no differences in C_{max} and apparent clearance of once-daily abacavir between Thai and African children were found (all $P>0.5$).

Thai children had a significantly greater GM AUC_{0-24} and C_{max} for both once- and twice-daily lamivudine than Ugandan children [4] (all $P<0.05$) (Table 1). No apparent difference in clearance between Thai and African children for both once- and twice-daily lamivudine was found.

By subgroup analysis, excluding the 10 children in the $20 < 25$ kg weight band who were given higher-dose lamivudine, the GM (SD) of AUC_{0-24} for lamivudine in Thai versus Ugandan children for once-daily dosing were 15.81 (1.34) versus 11.97

(3.89) mg.h/L ($P=0.001$) and AUC_{0-24} with twice-daily lamivudine were 14.81 (1.92) versus 12.99 (5.02) mg.h/L ($P=0.12$), respectively.

Efficacy and safety over 96 weeks

During 96 weeks of follow-up, no child in the study had HIV disease progression, had serious adverse events or discontinued the study medication. All children took their abacavir and lamivudine once-daily regimen until 96 weeks.

During the study, one girl aged 11 had HIV RNA 47,304 copies/mL at week 48 while using abacavir/lamivudine/efavirenz. The patient had poor adherence to ART. A genotype test found D67N, V75L and G190Q. The regimen was changed to abacavir/lamivudine/lopinavir/ritonavir and her HIV RNA at week 96 was <50 copies/mL.

At week 96, 17 children were taking abacavir/lamivudine/efavirenz and 13 were taking abacavir/lamivudine/lopinavir/ritonavir. There were no significant differences in CD4% and CD4 cell count at week 96 compared to baseline (Table 3). Of the children, 27 (90%) had HIV RNA <50 copies/mL at week 96 after enrolment (Table 3). Three children, one from each weight band, had HIV RNA >50 copies/mL. Among these, two had poor adherence by pill count ($<95\%$). Over 96 weeks, none had grade II or higher laboratory abnormalities.

Discussion

Our study found that the GMR AUC_{0-24} of once-daily versus twice-daily abacavir was greater than the pre-defined FDA criteria for bioequivalence. However, there was no significant difference for the GM AUC_{0-24} of once-daily abacavir compared with previous data in HIV-infected Ugandan children [4]. The GMR AUC_{0-24} of once-daily versus twice-daily lamivudine was bioequivalent as per the pre-defined FDA criteria. At 96 weeks, the majority of children had suppressed HIV RNA and none had experienced serious adverse events.

The AUC_{0-24} of once-daily abacavir was greater than that of

Table 3. Treatment outcomes over 96 weeks

	Week 0	Week 48	Week 96
Haemoglobin (g/dL)	12.5 (11.6–12.9)	13 (12.5–13.6)*	12.8 (12.1–13.4)
CD4%	30 (27–35)	31 (26–34)	30 (26–34)
CD4 count (cells/mm ³)	841 (580–1073)	89.5 (738–1219)*	860 (673–1072)
Number (%) of children with HIV RNA <50 copies/mL	30 (100)	29 (97)	27 (90)
Alanine transaminase (U/L)	23 (20–27)	16 (12–19)*	14 (11–19)*
Creatinine (mg/dL)	0.4 (0.3–0.5)	0.6 (0.5–0.7)*	0.6 (0.5–0.6)*
Creatinine clearance (mL/min/1.73m ²)	125.7 (101.8–150.3)	90.7 (82.5–96.6)*	97.7 (88.9–101.4)*
Number (%) of children with creatinine clearance <90 mL/min/1.73m ²	1 (3.3)	14 (46.7)*	8 (26.7)*
Adherence by pill count (%)	99 (98–100)	100 (93–100)	100 (99–100)
<i>Fasting blood</i>			
Total cholesterol (mg/dL)	169 (158–194)	183 (172–203)*	179 (159–199)*
Number (%) of children with cholesterol >200 (mg/dL)	4 (13)	8 (27)	7 (23)
Triglyceride (mg/dL)	99 (66–124)	103.5 (84–169)*	102 (76–138)
Number (%) of children with triglyceride >150 mg/dL	0	3/24 (13)	3/28 (11)
HDL (mg/dL)	54.5 (45–70)	54 (48–61)	47 (43–62)
Number (%) of children with HDL ≤ 40 mg/dL	6 (20)	3 (10)	5 (17)
Glucose (mg/dL)	80.5 (77–85)	82.5 (79–89)*	86 (79–92)*

Data are presented as median (IQR) unless otherwise described

*Comparison median difference from baseline (P value <0.05)

twice-daily abacavir despite the equal daily dose. When compared to published data from the ARROW [4] and PENTA 15 trials [8], our PK profiles for once-daily abacavir showed similar results. Plasma abacavir pharmacokinetics are linear and dose-proportional [18] but even though the morning dose with once-daily dosing was exactly twice that of the twice-daily dose, we observed a greater than dose-proportional increase of abacavir C_{max} (2.11 versus 5.98 mg/L). This finding is similar to that observed in the PENTA 13 study performed in children age 2–16 years (C_{max} 2.14 versus 4.80 mg/L) [7]. The once-daily GM AUC_{0-24} of our study was approximately 30% higher than the twice-daily AUC_{0-24} , which is similar to the findings of PENTA 13. The PENTA authors suggested that the most likely explanation was saturation of the first-pass metabolism, which is the intestinal and hepatic degradation or alteration of the drug, before it enters the circulation [7], as the AUC and the C_{max} were increased but the C_{min} was not. This is also a possible explanation in our study.

Children in the 14–<20-kg weight band had lower abacavir AUC_{0-24} compared to the other two weight bands. This might be explained by the effect of a drug interaction between lopinavir/ritonavir because 70% of children in this weight band received lopinavir/ritonavir compared to only 20% in the other weight bands. A study by Waters *et al.* showed that concomitant administration of lopinavir/ritonavir decreased abacavir exposure by 32% [19].

The GMR AUC_{0-24} of once-daily versus twice-daily lamivudine was acceptable for the pre-defined FDA criteria for bioequivalence. In our study, the GM AUC_{0-24} of lamivudine was greater than that from the data for the Ugandan children, aged 3–12 years, who used lamivudine tablets with a mean daily dose of 9.6 mg/kg [4]. This difference might be explained by an effect of ethnicity on ART exposure [11]. Our lamivudine GM AUC_{0-24} were higher than other Thai studies using twice-daily fixed-dose combination tablets containing lamivudine, most probably because the median daily dose of lamivudine was lower in those studies (8.2 mg/kg, GM AUC_{0-24} was 12.7 and 15.6 mg.h/L, respectively) [9,10]. Also, in our study, the lamivudine daily dose in the 20–<25-kg weight band was significantly higher and the corresponding lamivudine AUC_{0-24} for both once- and twice-daily dosing were greater. Frequency of adverse events was similar with both dosages, and no adverse events were observed in children with high abacavir concentrations. Moreover, children remained virally suppressed throughout both PK visits.

Our study has several limitations. First, the PK tests were performed in the outpatient setting, and therefore we did not directly observe the children taking their antiretroviral drugs in the days prior to the PK visit. However, we performed pill counts to ensure adherence to the regimen and that patients had reached a steady state prior to conducting PK sampling. Secondly, we did not measure the active intracellular triphosphate anabolite of abacavir and lamivudine due to the requirement for a large blood volume for testing, and the complexity in sample collection and processing. Abacavir's intracellular anabolite, carbovir-triphosphate (CBV-TP), has an elimination half-life of more than 20 hours, supporting once-daily dosing [18]. Moyle *et al.* reported that a once- and twice-daily regimen of abacavir had similar levels of intracellular CBV-TP in HIV-infected adults [20]. Lastly, it is notable that abacavir C_{min} was significantly lower, to the limit of detectability, in some children, but efficacy data are not available. Technau *et al.* reported significantly lower rates of virological suppression in African children using abacavir and lamivudine compared to stavudine and lamivudine-based regimens [21]. A strength of our study is

that it reports the first pharmacokinetic data of abacavir in Asian HIV-infected children, using the recommended weight-band dosing, which is simple and can be adopted in resource-limited settings.

In conclusion, this PK study of HIV-infected Thai children using the adult scored tablets demonstrated that the GMR of abacavir once/twice-daily was higher than US FDA bioequivalency criteria but the GM of once-daily abacavir was comparable with previous data in HIV-infected African children, a population with well-established efficacy and safety data [4]. Lamivudine once and twice daily were bioequivalent. Once-daily abacavir- and lamivudine-containing regimens had favourable safety profiles and the majority of children remained virally suppressed at 96 weeks.

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Conflict of interest statement

JA has received speakers' fees or honoraria from Roche, Gilead, ViiV and Abbott. The other authors declare no conflict of interest and that members of their immediate families do not have a financial interest in, or arrangement with, any commercial organisation that may have a direct interest in the subject matter of this article.

References

- UNAIDS. Report on the Global AIDS Epidemic 2013. Available at: http://www.unaids.org/sites/default/files/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf (accessed May 2015).
- Maitland D, Jackson A, Osorio J *et al.* Switching from twice-daily abacavir and lamivudine to the once-daily fixed-dose combination tablet of abacavir and lamivudine improves patient adherence and satisfaction with therapy. *HIV Med* 2008; **9**: 667–672.
- LePrevost M, Green H, Flynn J *et al.* Adherence and acceptability of once daily Lamivudine and abacavir in human immunodeficiency virus type-1 infected children. *Pediatr Infect Dis J* 2006; **25**: 533–537.
- Musiime V, Kendall L, Bakeera-Kitaka S *et al.* Pharmacokinetics and acceptability of once- versus twice-daily lamivudine and abacavir in HIV type-1-infected Ugandan children in the ARROW Trial. *Antivir Ther* 2010; **15**: 1115–1124.
- WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2013. Available at: <http://www.who.int/hiv/pub/guidelines/arv2013/en/> (accessed May 2015).
- Podzamczar D, Ferrer E, Sanchez P *et al.* Less lipatrophy and better lipid profile with abacavir as compared to stavudine: 96-week results of a randomized study. *J Acquir Immune Defic Syndr* 2007; **44**: 139–147.
- Bergshoeff A, Burger D, Verweij C *et al.* Plasma pharmacokinetics of once- versus twice-daily lamivudine and abacavir: simplification of combination treatment in

- HIV-1-infected children (PENTA-13). *Antivir Ther* 2005; **10**: 239–246.
8. Paediatric European Network for Treatment of AIDS (PENTA). Pharmacokinetic study of once-daily versus twice-daily abacavir and lamivudine in HIV type-1-infected children aged 3–<36 months. *Antivir Ther* 2010; **15**: 297–305.
 9. Chokephaibulkit K, Cressey TR, Capparelli E *et al*. Pharmacokinetics and safety of a new paediatric fixed-dose combination of zidovudine/lamivudine/nevirapine in HIV-infected children. *Antivir Ther* 2011; **16**: 1287–1295.
 10. Vanprapar N, Cressey TR, Chokephaibulkit K *et al*. A chewable pediatric fixed-dose combination tablet of stavudine, lamivudine, and nevirapine: pharmacokinetics and safety compared with the individual liquid formulations in human immunodeficiency virus-infected children in Thailand. *Pediatr Infect Dis J* 2010; **29**: 940–944.
 11. van der Lugt J, Avihingsanon A. Clinical pharmacology and pharmacokinetics of antiretrovirals in Asia. *Asian Biomed* 2009; **3**: 53–62.
 12. Avihingsanon A, van der Lugt J, Kerr SJ *et al*. A low dose of ritonavir-boosted atazanavir provides adequate pharmacokinetic parameters in HIV-1-infected Thai adults. *Clin Pharmacol Ther* 2009; **85**: 402–408.
 13. National Institute of Allergy and Infectious Disease. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events version 1.0, December 2004; clarification August 2009. Available at: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf (accessed May 2015).
 14. WHO. Antiretroviral therapy for HIV infection in infants and children: towards universal access: recommendations for a public health approach 2010 revision. 2010. Available at: <http://www.who.int/hiv/pub/paediatric/infants2010/en/> (accessed June 2015)
 15. Holland DT, DiFrancesco R, Connor JD, Morse GD. Quality assurance program for pharmacokinetic assay of antiretrovirals: ACTG proficiency testing for pediatric and adult pharmacology support laboratories, 2003 to 2004: a requirement for therapeutic drug monitoring. *Ther Drug Monit* 2006; **28**: 367–374.
 16. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Bioavailability and Bioequivalence Studies for Orally Administered Drug Products: General Considerations March 2003 BP Revision 1. Updated March 2003. Available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070124.pdf (accessed July 2012).
 17. Grundy SM, Cleeman JI, Daniels SR *et al*. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; **112**: 2735–2752.
 18. Yuen GJ, Weller S, Pakes GE. A review of the pharmacokinetics of abacavir. *Clin Pharmacokinet* 2008; **47**: 351–371.
 19. Waters LJ, Moyle G, Bonora S *et al*. Abacavir plasma pharmacokinetics in the absence and presence of atazanavir/ritonavir or lopinavir/ritonavir and vice versa in HIV-infected patients. *Antivir Ther* 2007; **12**: 825–830.
 20. Moyle G, Boffito M, Fletcher C *et al*. Steady-state pharmacokinetics of abacavir in plasma and intracellular carbovir triphosphate following administration of abacavir at 600 milligrams once daily and 300 milligrams twice daily in human immunodeficiency virus-infected subjects. *Antimicrob Agents Chemother* 2009; **53**: 1532–1538.
 21. Technau KG, Schomaker M, Kuhn L *et al*. Virologic response in children treated with abacavir-compared with stavudine-based antiretroviral treatment: a South African multi-cohort analysis. *Pediatr Infect Dis J* 2014; **33**: 617–622.

Appendix 1. Abacavir and lamivudine dosing used in this study

Weight (kg)	Twice-daily dosing	Once-daily dosing
<i>Abacavir</i>		
14–<20 kg	150 mg (0.5 tablet) every 12 hours	300 mg (1 tablet) every 24 hours
20–<25 kg	150 mg (0.5 tablet) morning 300 mg (1 tablet) evening, 12 hours later	450 mg (1.5 tablets) every 24 hours
≥25 kg	300 mg (1 tablet) every 12 hours	600 mg (2 tablets) every 24 hours
<i>Lamivudine</i>		
14–<20 kg	75 mg (1/2 tablet) every 12 hours	150 mg (1 tablet) every 24 hours
>20 kg	150 mg (1 tablet) every 12 hours	300 mg (2 × 150 mg tablets) every 24 hours

All dosing was consistent with the 2010 World Health Organization (WHO) guideline [14] except for lamivudine dosing for 20–25 kg bodyweight in which 300 mg total daily dosing was used instead of 22 mg as recommended in the guideline