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A Phase II/III Trial of Lopinavir/Ritonavir Dosed According to the Who Pediatric Weight Band Dosing Guidelines

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Abstract

Background—The World Health Organization (WHO) recommends weight band dosing of antiretrovirals for children. Data are limited describing drug exposure/safety of lopinavir/ritonavir (LPV/r) using WHO weight-band dosing.

Methods—IMPAACT P1083 was a phase II/III trial assessing the pharmacokinetics (PK) and short-term safety, tolerance, and efficacy of LPV/r in HIV-infected children 3 to 25 kg dosed according to WHO weight bands, with liquid solution or meltrex extrusion tablets. The main PK target was an area under the curve (AUC_{0–24}) of 80–320 mcg*hr/mL.

Results—Of 97 enrolled participants, median age 2.5 years, 89 (91.8%) completed the protocol. Median LPV dose was 303 mg/m². The geometric mean (90% confidence limits) LPV PK AUC_{0–24} was 196 (177, 217) mcg*hr/mL and C_{min} was 2.47 (1.52, 4.02) mcg/mL. AUC_{0–24} was within the target range for 79% of participants. The median (Q1, Q3) difference between individual observed PK parameters and those expected if FDA dosing guidelines were followed was 30.7 (7.9, 54.3) for AUC_{0–24} and 0.56 (0, 1.27) for C_{min}. Ten (10%) participants had grade 3 or 4 events deemed related to study treatment, mostly asymptomatic laboratory abnormalities. Three participants died of unrelated study treatment causes. At week 24, 57/79 (72%) of

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participants reached viral suppression and the median increase in CD4% (n=83) was 6.0 (p<0.0001).

Conclusions—WHO weight band dosing guidelines in children achieved adequate LPV plasma exposure but was higher than that expected with FDA dosing guidelines. Despite the higher LPV exposure the treatment was well tolerated and the 24-week efficacy data were favorable.

Keywords

lopinavir/ritonavir; pharmacokinetics; children; HIV-1

INTRODUCTION

Despite significant progress in preventing new infant HIV infections and expanding antiretroviral treatment (ART) access to infected children, a large gap persists in many settings between actual and recommended universal antiretroviral treatment (ART) for HIV-infected children. Although the WHO has recommended immediate initiation of ARV therapy for all children regardless of clinical or immunological status, almost half of children living with HIV are still not accessing these life-saving treatments. [1, 2]

Since 2010, the WHO Pediatric ARV Working Group (PAWG) has recommended ARV dosing based on weight bands for use in resource-limited settings (RLS) in order to simplify drug delivery and reduce prescription errors in children [3]. While the WHO ARV weight-band dosing schedule for lopinavir/ritonavir (LPV/r) is now the standard dosing regimen used in most RLS, there are no data describing the plasma concentrations, safety profile or efficacy when LPV is dosed in infants and children following these recommendations. Additionally, genetic variation shown to affect the pharmacokinetics of LPV has not been evaluated in this population.

Data describing both the pharmacokinetics and clinical outcomes of LPV/r are crucial in order to evaluate the current WHO weight band dosing recommendations. The International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) P1083 study aimed to provide these data for LPV/r-naïve children as part of first-line therapy for children under age 3 years and as part of second-line therapy in older children who fail first-line therapy.

METHODS AND MATERIALS

Study Design and Participants

IMPAACT P1083 was a Phase II/III study to establish the pharmacokinetics, safety, tolerance, and virologic effect of LPV/r when dosed according to the WHO ARV weight-band dosing schedule in HIV-infected infants and children. This study was designed to determine the frequency of sub-optimal LPV exposures. The goal was to describe the actual plasma concentrations of LPV achieved with this simplified dosing schedule and to determine whether the WHO ARV weight band dosing guidelines provide LPV exposure that is appropriate, safe, well-tolerated and virologically potent.

Eligibility criteria included LPV/r-treatment naïve HIV-infected infants and children weighing 3 to <25 kg, with no planned concurrent use of non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, entry inhibitors, or protease inhibitors other than LPV/r. All participants' parents or legal guardians provided written informed consent.

The study protocol was approved by local ethics review committees affiliated with the study sites, by committees affiliated with US collaborating institutions, and by other local and/or national regulatory bodies where applicable and was in accordance with the Helsinki Declaration of 1975, as revised in 2000. The study was registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01172535) (NCT01172535).

Primary Outcome Measures

The main PK exposure parameter of interest was area under curve (AUC) for lopinavir, as determined by a non-compartmental analysis of 12-hour PK sampling for LPV/r after 4 weeks of treatment. Since some participants took different morning and evening doses, estimated AUC₀₋₂₄ was used as the primary PK exposure parameter. The target range for the lopinavir AUC₀₋₂₄ was 80 to 320 mcg*hr/mL. Maximum and minimum concentrations (C_{max} and C_{min}) were also calculated. In addition, the proportion of subjects with an AUC₀₋₂₄ of less than the 10th percentile of the mean expected for adults (AUC₀₋₂₄ <104 mcg*hr/mL) was calculated.

Participants met a safety endpoint if they experienced any Grade 3 or higher toxicity judged by the team to be possibly, probably, or definitely related to study drug.

Participants were considered to have not tolerated medication if they stopped treatment before the 24 week PK visit for any reason other than death/debilitation not related to treatment.

Secondary outcome measures

Adherence was measured by questionnaire and pill count or remaining volume of liquid drug at each visit while on treatment. The outcome measures for adherence were (1) reporting no missed doses, and (2) the amount of medication taken as measured by the site divided by the amount expected with perfect adherence. The outcome measures for treatment efficacy were (1) having HIV RNA viral load <400 copies/mL at the week 24 visit, and (2) having CD4% ≥25 at the week 24 visit.

Analytic Methods

Lopinavir was measured by the Pediatric Pharmacology Laboratory at University of California, San Diego (UCSD) and AMS-PHPT Pharmacology Laboratory at the Faculty of Associated Medical Sciences, Chiang Mai University, Thailand. Both laboratories utilized previously described, validated, reversed-phase multiplex high performance liquid chromatography (HPLC) methods [4] [5]. Both laboratories participated in the DAIDS Clinical Pharmacology QA/QC program which includes proficiency testing for lopinavir in tests samples twice a year. At the UCSD Pediatric Pharmacology Laboratory, the lopinavir lower limit of quantification was 0.091 mcg/mL for with an inter-assay coefficient of

variation (CV) ranged from 6.2 to 11% for the controls and an intra assay CV <4%. At the Chiang Mai Pharmacology Laboratory, the lower limit of quantification was 0.078 mcg/mL with intra- and inter-assay CVs less than 4% for low, middle and high controls.

Clinical and Laboratory Monitoring

Clinical and laboratory events were classified according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004, clarification August 2009 (http://rcc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf). A protocol Clinical Management Committee was established to review clinical and laboratory data reports through by-monthly conference calls and as needed.

Pharmacogenetic analyses

Genetic polymorphisms in genes encoding for SCLO1B1, CYP3A4 and ORM1 were assessed. Specific single nucleotide polymorphisms (SNPs) evaluated were SLCO1B1 (rs4149056), SCLO1B1 (rs4149032), SCLO1B*1B (rs2306283), CYP3A4 (rs2740574), CYP3A4 (rs35599367), ORM1*F2 (rs1126801) and ORM1*S (rs14796186). Single Nucleotide Polymorphisms (SNPs) were detected by real-time PCR following extraction of DNA from dried blood spots (see Supplemental Table 1 for specific primers and probes used to detect each of the SNPs).

Statistical Considerations

The target sample size of 85 participants was chosen to provide 90% confidence intervals where the lower and upper limits would be within 10% of the true AUC for a variety of plausible AUC/CV combinations. It would also provide 80% power to detect the difference between a reference proportion of 25% of participants having $AUC_{0-12} < 52$, as found by Sáez-Llorens [6], and a true proportion of 38%.

The PK analyses only included data from participants for whom all PK parameters were estimable; the remaining analyses included all participants. PK parameters were calculated using non-compartmental pharmacokinetic methods. The Area Under the plasma Concentration-time curve (AUC_{0-12}), was estimated by the trapezoidal method over the dose interval (0–12 hours), maximum observed concentration of drug in plasma (C_{max}) and time of the maximum observed concentration in plasma (T_{max}) taken from observed concentrations. Apparent clearance (CL/F) was calculated as $Dose/AUC_{0-12}$ and normalized to body weight. Due to the relatively flat terminal portion of many of the concentration time profiles, plasma terminal half-life was not estimated. In 8 subjects, the sample scheduled to be collection 12 hours post-dose deviated by more than 0.5 hours (all collected at 11 hours). For these subjects the concentration at 12 hours (C_{12}) was estimated from the final two concentrations: $C_{12} = C_{last} * \exp(-\lambda_z * (12 - t_{last}))$, where t_{last} is the time of the final concentration and λ_z is estimated from the final two measured concentrations as $\ln(C_1/C_2)/(t_2 - t_1)$. AUC_{0-12} was then estimated as $AUC_{0-C_{last}}$ (measured AUC) + $AUC_{C_{last}-C_{12}}$. In addition, profiles were assessed for apparent steady-state conditions. Since at steady-state C_0 is approximately equal to C_{12} , LPV concentration vs. time profiles in which C_0 was within 4

fold of C_{12} ($0.25 \cdot C_{12} < C_0 < 4 \cdot C_{12}$) were deemed to meet the assumption of steady-state. Profiles with C_0 to C_{12} ratios outside the 0.25–4 range were designated “non-steady-state”. In the setting with $C_0 < 0.25 \cdot C_{12}$, $AUC_{0-\infty}$ was estimated and used to determine CL/F using reverse-super positioning.

Since some WHO weight bands have different morning ($Dose_{AM}$) and evening doses ($Dose_{PM}$), the AUC_{0-24} was estimated to provide a metric for daily LPV exposure and it was calculated as AUC_{0-12} (or $AUC_{0-\infty}$) + $AUC \cdot (Dose_{PM}/Dose_{AM})$. In instances where the morning dose and evening dose were the same, the AUC_{0-24} was simply double the AUC_{0-12} . A comparison of the observed exposure, based on WHO weight-band dosing, and the expected exposure in these subjects with the FDA approved dose was performed. The AUC_{0-24} and C_{min} expected if FDA dosing guidelines were followed were estimated by multiplying the observed AUC_{0-24} and C_{min} by $Dose_{FDA}/Dose_{WHO}$. Pharmacokinetic analysis was performed using WinNonlin ver 6.0 (Icon, Dublin).

Geometric means and associated 90% confidence intervals (CI) were calculated for all PK parameters, overall and by weight/formulation strata. The proportion of participants with $AUC_{0-24} < 104$ mcg*hr/mL plus exact 90% binomial confidence limits were calculated overall and by weight/formulation strata. The median difference between the actual AUC_{0-24} and C_{min} versus those expected if FDA dosing guidelines were followed was calculated overall and by weight/formulation strata.

Geometric means and associated 90% confidence limits (CI) of all PK parameters were also calculated for the genetic variants. Student's t-test were used to compare PK parameters between the genetic variants by using the log transformed values. Analyses for PK parameters used 90% confidence intervals; all other analyses (safety, tolerability, etc.) used 95% confidence intervals. Within-participant changes in CD4% and viral load from entry to week 24 were examined using signed rank tests.

Study weeks for reporting of events (going off study or off treatment, adverse events) are calculated from the date of study enrollment. Results for 4 week, 12 week and 24 week visits are reported as of the dates those PK collections occurred.

All analyses except for the calculation of PK parameters were done using SAS 9.4.

RESULTS

Study population

There were 97 participants enrolled from 19 sites in Brazil, Thailand, South Africa and the United States, of whom 57 participants received liquid formulation and 40 received 100/25 mg melt extrusion tablet formulation. The majority of participants (56%) were female. Forty percent were Black, 38% Asian and 32% had Hispanic ethnicity. The median age at entry was 2.5 years, and ranged from 0.1 to 12.8 years. At study entry, the median HIV-1 RNA viral load was 5.2 log₁₀ copies/mL and the median CD4% was 24.2 (Table 1).

Eighty-six (89%) participants completed study treatment. Three participants died, two from bacterial pneumonia and one from cardiomyopathy. Four subjects stopped the study drug,

one due to a protocol-defined toxicity, one due to the need to take a disallowed medication, and 2 due to drug intolerance. Four subjects left the study, one for noncompliance with the study regimen, 2 when parents/guardians withdrew consent and one who was lost to follow-up.

Pharmacokinetics of Lopinavir

There were 81 participants for whom all Week 4 PK parameters could be estimated. In 8 subjects the measured pre-dose (C_0) was $<0.25 \times C_{12}$ strongly suggesting a missed prior dose. In half of these subjects the C_0 was below the assay lower limit of quantification (LLOQ) and in the other half C_0 was greater than the LLOQ but less than 0.75 mcg/mL and less than 15% of C_{12} . In these subjects, AUC was calculated as $AUC_{0-\infty}$ of the observed dose, where $AUC_{0-\infty} = AUC_{C_0-\text{last}} + C_{\text{last}}/\lambda_z - C_0/\lambda_z$. There were also eight subjects with $C_0 > 4 \times C_{12}$, suggesting non-steady-state conditions due to ingestion of an additional morning LPV/r dose prior to their intensive PK evaluations. Non-compartmental pharmacokinetic parameters could not be estimated from these profiles. There was also one subject with all LPV concentrations below LLOQ indicating non-adherence so that pharmacokinetic parameters could not be calculated. Participants with and without complete Week 4 PK data had similar characteristics, with the exception that those with missing PK data had lower viral loads at entry than those with complete data (median $\log_{10}$ RNA 4.7 vs. 5.2, Wilcoxon test $p=0.03$).

The geometric mean and associated 90% CI for AUC_{0-24} , $C_{\min}$ and $C_{\max}$, both overall and by weight band/formulation are shown in Table 2. The overall geometric mean AUC_{0-24} (90% CI) was 196 (177, 217). The target range for lopinavir AUC_{0-24} was 80 to 320 mcg*hr/mL. Sixty-four (79%) participants had week 4 AUC_{0-24} in this range; 4 (5%) were below the target range and 13 (16%) were above it. Figure 1 shows dot plots of AUC_{0-24} and $C_{\min}$ by weight band and formulation. The 10–16.9 kg weight band had the highest proportion with AUC_{0-24} above the target range, with more than a quarter exceeding 320 mcg*hr/mL, while 100% of the 5–6.9 kg weight band were in the target range. The overall proportion of participants with AUC_{0-24} below 104 mcg*hr/mL and associated 90% exact confidence limits (CL) was 0.15 (0.09, 0.23).

Solution versus Melt Extrusion Formulation

Of the 81 subjects with full PK assessments, 46 (57%) received LPV/r as solution while 35 (43%) received tablets. The CL/F was higher in subjects receiving the liquid formulation than the tablet (0.179 vs 0.090 L/h/kg). Both AUC (195 vs 265 mcg*h/mL) and $C_{\min}$ (4.2 vs 6.5 mcg/mL) were lower with the liquid formulation despite larger BSA adjusted doses (331 vs 291 mg/m²). However, achievement of target AUC exposure (80–320 mcg*hr/mL) was similar between the formulations - 76% (liquid) vs 83% (tablet). Formulation and weight band were strongly confounded as the younger, lower weight participants all received the liquid formulation, making it impossible to determine if the differences in exposure were related to formulation versus age and weight. All nine subjects that could not have AUC determined due to lack of steady-state conditions were receiving the liquid formulation, suggesting either less adherence or more erratic absorption in these younger subjects.

Comparison of WHO and FDA dosing

The actual AUC_{0-24} and C_{min} of participants were compared with those expected if the FDA dosing guidelines were followed for each participant (Table 3). Lopinavir exposures were higher with the WHO weight band doses. For the entire population combined, the increment with WHO weight band dosing compared to FDA dosing was 15.3% for AUC and 22.7% for C_{min} .

Safety and tolerance

Thirty-two (33%) participants had grade 3 or 4 events with a high proportion (14%) experiencing grade 3 or 4 serum amylase events. Ten (10%) participants had grade 3 or 4 events assessed by the team as possibly, probably, or definitely related to study treatment. Except for one episode of herpes zoster, all other events were asymptomatic laboratory abnormalities: five (5%) hyperamylasemia, two (2%) neutropenia, one (1%) elevated triglycerides, and one (1%) elevated SGPT/SGOT. The LPV AUC_{0-24} did not differ significantly between those subjects with and without grade 3 or 4 events, median (IQR) respectively 196.6 (117.0, 330.7) vs 227.9 (134.8, 286.1) mcg*h/mL.

Three participants died while on study. Two deaths were from bacterial pneumonia and one from cardiomyopathy, at study weeks 20, 26 and 4, respectively. All were assessed by the team as not related to study treatment.

Participants were considered to have not tolerated medication if they stopped treatment for any reason other than completing treatment or death/debilitation not related to treatment. Ninety (93%) participants tolerated treatment up to 24 weeks.

Adherence

Adherence questionnaires were administered at each PK visit. In the vast majority of cases at each time point, the primary caregiver was responsible for administering meds, either alone or shared with someone else. At the week 4 intensive PK visit, 89% reported no missed medication doses. By week 24, this had fallen to 77%. Across all three PK visits, there were 60 responses reporting problems giving LPV/r. The most frequent problems cited were "Tastes bad" (n=19), "Refused to take" (n=17), "Forgot" (n=15), "Change in routine" (N=9), and "Child was ill" (N=5). Five wrote that the child had trouble swallowing the tablet, felt nauseous, or spit it out. Adherence was also assessed by measuring the amount of medication used up (number of tablets or weight/volume of liquid) and comparing it to the expected amount. Between 66% to 70% of participants brought their medications to the visit. Of those who did, the median (25th percentile, 75th percentile) proportion of doses used was 1.00 (0.97, 1.10) at week 4, 0.99 (0.88, 1.01) at week 12, and 1.00 (0.91, 1.01) at week 24.

Treatment efficacy

Table 4 shows CD4% and HIV-1 RNA viral load for participants with data for both study entry (week 0) and week 24 visits. Median viral load at entry was 5.2 log₁₀ copies/mL and this significantly decreased (p<0.001) to 1.9 log₁₀ copies/mL at week 24. At entry, all participants had viral loads >400 copies/mL, while 72% of subjects reached viral

suppression (<400 copies/mL) at Week 24. The median CD4% at entry was 24.1; at week 24 it was 29.5. CD4 percentages were significantly better at week 24, with the median change in CD4% 6.0, $p < 0.0001$. At entry, 46% of participants had CD4% ≥ 25 ; this rose to 71% at the week 24 visit.

Pharmacogenetics

Of the genetic variants evaluated, only the SLCO1B1 rs4149032 polymorphism was found to significantly affect lopinavir concentrations. As shown in Table 5, subjects with a C allele (C/C + T/C) had a higher geometric mean AUC_{0-24} compared to subjects homozygous for T/T (222.2 versus 160.9; $p = 0.02$, Figure 2). Consistent with the elevated AUC_{0-24} , the geometric means of C_{min} and C_{max} were 72.6% and 26.4% higher in those carrying the C allele ($p = 0.15$ and $p = 0.04$, respectively). Similarly, as would be expected, the geometric mean CL/F was 27.8% lower in those children with the C allele compared to the T/T group ($p = 0.03$). Prevalence of C/C+T/C genetic variants was not affected by country of origin or ethnicity.

For the CYP3A4 rs2740574 polymorphism, subjects with the G allele compared to A/A homozygotes showed an increased mean CL/F of 30.7%, but geometric mean AUC_{0-24} was only 7.7% lower and these findings were not statistically significant ($p = 0.07$ and $p = 0.33$, respectively). Similarly, subjects with a G allele had a mean C_{min} 39% lower and a mean C_c 12.5% lower when compared to A/A homozygotes ($p = 0.15$ and $p = 0.24$, respectively).

DISCUSSION

The WHO currently recommends a LPV/r-based regimen as the first line treatment for HIV-infected children less than 3 years of age, and as the second-line for children older than 3 years failing an efavirenz- or nevirapine-based initial regimen [1]. Given the limited therapeutic options for infants and young children, it is critical to generate data informing exposure, safety and efficacy of LPV/r dosed according to WHO simplified weight-band tables. This study demonstrates that children weighting 3 to 25 kilograms receiving LPV/r dosed according to the WHO weight band dosing recommendation achieve adequate plasma exposure. Seventy nine percent of children with full week 4 PK data met the target AUC_{0-24} range (80 to 320 mcg*hr/mL), with only four (5%) below the target range and 13 (16%) above it. The overall geometric mean AUC_{0-24} was 196 mcg*hr/mL. Clinical outcomes were good, with 72% of participants achieving HIV-1 viral load <400 copies/mL and 71% achieving CD4% ≥ 25 at the week 24 visit.

By comparison, Sáez-Llorens *et al.* [6], using the liquid LPV/r formulation achieved a mean AUC_{0-12} of 72.6 using the FDA approved LPV dose of 230mg/m², which is equivalent to an AUC_{0-24} of 145.2, indicating that the WHO dosing recommendations are not leading to under-dosing. Four (9%) participants on liquid formulation had AUC_{0-24} below the target range. However, the AUC was similar for liquid and tablet in the overlap weight band 10–16.9 kg, suggesting that age rather than formulation was the cause for the lower AUCs. The increase in LPV apparent clearance (CL/F) observed at lower weight bands is consistent with what has been reported elsewhere [7, 8].

In the CHAPAS-2 trial, conducted in Ugandan children aged 3 months to 13 years, a novel generic minitab pellet formulation stored in capsules (40/10 mg LPV/r) was not bioequivalent to innovator solution (80/20 mg LPV/r) or generic tablet (100/25 mg LPV/r), with exposure with minitabs higher than with that solution and lower than that with tablets. Despite the high variability in pharmacokinetic parameters, subtherapeutic trough concentrations were rare and the minitabs were more acceptable than solution for children less than 4 years, mostly due to ease of transportation and storage, although taste remained a concern [9]. We also saw a difference in LPV/r PK in participants based on formulation. The liquid solution formulation overall achieved lower LPV concentrations than the tablet. Since the tablet formulation was only given to larger, older children weighing at least 10 kg, age and formulation findings are confounded. However, the one weight band that received both solution and tablet formulations, 10–16.9 kg, had similar PK results.

LPV/r treatment was generally safe and very well tolerated. Ten (10%) participants had grade 3 or 4 events assessed by the team as possibly, probably, or definitely related to study treatment. Three participants died; all deaths were assessed by the team as not related to study treatment. Ninety (93%) participants tolerated treatment. Adherence was also good in our study population. At the week 4 intensive PK visit, 89% reported no missed medication doses. By week 24, this had fallen to 77%.

The potential impact of pharmacogenomics on lopinavir pharmacokinetics was also explored. Genetic variants within the OATP/SLCO family of polypeptide organic anion transporters have been associated with lopinavir pharmacokinetics. Lopinavir and other HIV protease inhibitors are substrates for transporters SLCO1B1 and SLCO1A2, and the SLCO1B1 521-T/C genetic variant is associated with higher plasma levels of lopinavir in adults [10–13]. We also saw a modest impact of this variant on lopinavir pharmacokinetics in children. While other polymorphisms in genes encoding for CYP3A4 and ORM1 have been implicated in altering the pharmacokinetics of protease inhibitors including lopinavir [14, 15], we did not find a significant influence in the current study.

While the simplified WHO weight-band dosing did result in higher exposures than would be expected with FDA dosing, the modest magnitude of difference and the lack of toxicity indicates the potential utility of this dosing strategy. A formulation specific dosing approach could be designed to achieve a higher percentage in the target range. However, the complexity of different doses based on formulation and the lack of toxicity seen with modestly higher AUCs supports the current unified dosing approach across formulations. In October 2014, UNAIDS launched the “90:90:90” targets to help end the AIDS epidemic: by 2020, 90% of people living with HIV will be diagnosed, 90% of those diagnosed will be on sustained antiretroviral therapy (ART) with 90% viral suppression in those on ART [16]. The greatest challenge in achieving these targets will be ensuring that their reach is extended to all populations. For the pediatric population, this will require providing treatment to 2.4 million HIV-infected infants, children and adolescents by 2020 [17]. In order to achieve these ambitious targets and to reduce the high, early mortality of pediatric HIV, the development of easy to administer, solid, heat stable and affordable ARV formulations that are conformable to age and weight band dosing requirements is essential. Our findings

demonstrate that LPV/r can be administered using weight band dosing to achieve safe and effective drug levels in HIV-infected children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Lopinavir C_{min} and AUC₀₋₂₄ by weight band and formulation

Figure 2.
SLCO1B1 (rs21317791) – AUC by Genotype

Table 1

Characteristics of Study Participants at Entry

Characteristic		Total (N=97)
Sex	Male	43 (44%)
	Female	54 (56%)
Race	Asian	37 (38%)
	Black or African American	39 (40%)
	White	7 (7%)
	Other	6 (6%)
	Unknown	8 (8%)
Ethnicity	Hispanic or Latino	31 (32%)
	Not Hispanic or Latino	42 (43%)
	Unknown	24 (25%)
Country	Brazil	32 (33%)
	South Africa	23 (24%)
	Thailand	37 (38%)
	USA	5 (5%)
Age at entry (years)	Median (Q1, Q3)	2.5 (0.5, 6.2)
	Min, Max	0.1, 12.8
Entry RNA log ₁₀ (copies/mL)	Median (Q1, Q3)	5.2 (4.6, 5.7)
	<3	2 (2%)
	3 – <4	10 (10%)
	4 – <5	27 (28%)
	5+	57 (59%)
	Missing	1 (1%)
Entry CD4%	Median (Q1, Q3)	24.2 (15.8, 29.0)
	CD4% < 15	22 (23%)
	15 ≤ CD4% < 25	29 (30%)
	CD4% ≥ 25	46 (47%)

Table 2
Lopinavir Geometric Means for AUC₀₋₂₄, C_{min} and C_{max}, Overall and by Weight Band/Formulation

Weight Band	Formulation	N	AUC ₀₋₂₄ with 90% Confidence Limits [#]			C _{min} with 90% Confidence Limits			C _{max} with 90% Confidence Limits		
			Geometric Mean	(LCL, UCL)	Min.	Max.	* Geometric Mean	(LCL, UCL)	Min.	Max.	Max.
Overall	–	81	196	(177, 217)	45	564	2.47	(1.52, 4.02)	0.00	17.45	29.17
3 – 4.9 kg	Liquid	11	161	(109, 237)	45	340	2.92	(1.59, 5.39)	0.19	7.52	17.44
5 – 6.9 kg	Liquid	9	124	(102, 149)	86	236	0.51	(0.04, 6.60)	0.00	6.26	13.04
7 – 9.9 kg	Liquid	15	168	(130, 218)	72	522	1.18	(0.24, 5.71)	0.00	13.83	29.17
10 – 16.9 kg	Liquid	11	236	(164, 340)	59	564	5.86	(3.68, 9.33)	1.22	17.45	28.78
10 – 16.9 kg	Tablet	18	253	(216, 298)	92	439	4.87	(3.40, 6.96)	0.62	14.33	21.64
17 – 19.9 kg	Tablet	6	166	(110, 251)	93	393	3.78	(2.61, 5.48)	2.27	6.94	22.97
20 – 24.9 kg	Tablet	11	253	(216, 295)	122	341	2.31	(0.25, 21.71)	0.00	13.04	21.24

* Values of C_{min} less than the lower limit of detection have been set to that limit (0.01 mcg/mL) for the purpose of calculating the geometric mean.

[#] The target range for LPV AUC₀₋₂₄ was 80 to 320 mcg*hr/mL based on studies establishing safety and efficacy of LPV/r.

Table 3

Differences Between AUC_{0-24} and C_{min} following WHO versus FDA Dosing Recommendations. The WHO AUC_{0-24} and C_{min} represent the values observed in the current study with WHO weight band dosing. The FDA AUC_{0-24} and C_{min} values represent the expected values if these same subjects had received LPV/r using FDA recommended dosing. In subjects in whom the WHO and FDA recommend the same dose, the AUC and C_{min} are identical and the differences is equals 0.

	N	WHO - FDA AUC_{0-24} Difference (mcg*hr/mL)			WHO - FDA C_{min} Difference (mcg/mL)		
		Q1	Median	Q3	Q1	Median	Q3
Weight Band and Formulation							
3 – 4.9 kg/Liquid	11	39.3	57.5	93.6	0.99	1.23	1.81
5 – 6.9 kg/Liquid	9	30.7	40.2	52.6	0.39	0.84	0.96
7 – 9.9 kg/Liquid	15	15.8	31.4	44.4	0.15	0.39	1.26
10 – 16.9 kg/Liquid	11	13.8	29.2	58.9	0.31	0.78	1.64
10 – 16.9 kg/Tablet	18	0.0	0.0	16.1	0.00	0.00	0.32
17 – 19.9 kg/Tablet	6	0.0	0.0	0.0	0.00	0.00	0.00
20 – 24.9 kg/Tablet	11	25.9	54.3	57.2	0.63	1.37	1.86
Overall	81	7.9	30.7	54.3	0.00	0.56	1.27

Table 4

CD4% and Viral Load for Participants with Week 24 Data

		Week	
		0	24
Viral load (copies/mL)	N	79	79
	Median (Q1, Q3)	163,000 (44,910, 562,996)	88 (50, 550)
	<400 copies/mL	0 (0%)	57 (72%)
	400 – 10,000 copies/mL	10 (13%)	12 (15%)
	>10,000 copies/mL	69 (87%)	10 (13%)
CD4%	N	83	83
	Median (Q1, Q3)	24 (16, 30)	30 (24, 35)
	CD4% < 15	18 (22%)	5 (6%)
	15 CD4% < 25	27 (33%)	19 (23%)
	CD4% 25	38 (46%)	59 (71%)

Table 5

Lopinavir Geometric Means and Coefficient of Variance for CL/F, C_{min}, C_{max} and AUC₀₋₂₄ by SLCO1B1 rs4149032 polymorphism

PK Parameter	SLCO1B1 Position with Gene (rs#)	Genotype	Count	Geometric Mean with 90% Confidence Limits			Coefficient of Variance with 90% Confidence Limits			P-value
				Geometric Mean	(Lower CL,	Upper CL)	Coefficient of Variance	(Lower CL,	Upper CL)	
CL/F	21317791	C/C+T/C	49	0.13	(0.11,	0.15)	0.61	(0.51,	0.77)	0.029
	rs4149032	T/T	32	0.18	(0.15,	0.23)	0.92	(0.73,	1.30)	
C _{min}	21317791	C/C+T/C	49	3.88	(2.84,	5.30)	2.11	(1.57,	3.26)	0.147
	rs4149032	T/T	32	2.37	(1.41,	3.98)	4.41	(2.65,	11.27)	
C _{max}	21317791	C/C+T/C	49	12.34	(11.07,	13.76)	0.48	(0.41,	0.59)	0.041
	rs4149032	T/T	32	9.76	(8.26,	11.52)	0.60	(0.49,	0.80)	
AUC	21317791	C/C+T/C	49	222.24	(199.05,	248.13)	0.49	(0.41,	0.60)	0.016
	rs4149032	T/T	32	160.87	(132.98,	194.62)	0.71	(0.57,	0.96)	