Population Pharmacokinetics of Pediatric Lopinavir/Ritonavir Oral Pellets in Children Living with HIV in Africa

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Antiretroviral therapy for children living with HIV (CLHIV) under 3 years of age commonly includes lopinavir/ritonavir (LPV/r). However, the original liquid LPV/r formulation has taste and cold storage difficulties. To address these challenges, LPV/r oral pellets have been developed. These pellets can be mixed with milk or food for administration and do not require refrigeration. We developed the population pharmacokinetic (PK) model and assessed drug exposure of LPV/r oral pellets administered twice daily to CLHIV per World Health Organization (WHO) weight bands. The PK analysis included Kenyan and Ugandan children participating in the LIVING studies (NCT02346487) receiving LPV/r pellets (40/10 mg) and ABC/3TC (60/30 mg) dispersible tablets. Population PK models were developed for lopinavir (LPV) and ritonavir (RTV) to evaluate the impact of RTV on the oral clearance (CL/F) of LPV. The data obtained from the study were analyzed using nonlinear mixed-effects modeling approach. Data from 514 children, comprising a total of 2,998 plasma concentrations of LPV/r were included in the analysis. The LPV and RTV concentrations were accurately represented by a one-compartment model with first-order absorption (incorporating a lag-time) and elimination. Body weight influenced LPV and RTV PK parameters. The impact of RTV concentrations on the CL/F of LPV was characterized using a maximum effect model. Simulation-predicted target LPV exposures were achieved in children with this pellet formulation across the WHO weight bands. The LPV/r pellets dosed in accordance with WHO weight bands provide adequate LPV exposures in Kenyan and Ugandan children weighing 3.0 to 24.9 kg.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ An encapsulated pediatric oral pellet formulation of lopinavir/ritonavir (LPV/r) was developed to facilitate the administration to children. Although the pharmacokinetics (PKs) of LPV/r have been studied previously, little is known about the factors that influence the PKs of this pellet formulation in African children living with HIV.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Information on LPV/r drug exposures and variability in African children using the pediatric oral pellet formulation is limited. This study investigated the PKs of LPV/r in children living with HIV administered the pellet formulation in accordance with World Health Organization (WHO) weight band dosing guidelines.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The LPV/r oral pellets dosed according to WHO weight bands provides adequate LPV exposure in Kenyan and Ugandan children weighing between 3.0 kg and 24.9 kg.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These data support the WHO weight band dosing recommendations for LPV/r pellets in African children.

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Lopinavir/ritonavir (LPV/r) is commonly administered to children living with HIV (CLHIV) as part of combination antiretroviral therapy (ART).[1] Due to the extremely poor palatability of the original LPV/r liquid formulation for young children, novel pediatric solid LPV/r formulations have been sought to replace the liquid. The first solid LPV/r formulation for young children approved by the US Food and Drug Administration was encapsulated oral pellets (or mini "melt" tablets; Cipla Ltd, India), which contain 40 mg lopinavir/10 mg ritonavir (40/10 mg) and offer the advantage of easy administration by mixing with food; unlike the LPV/r liquid, this formulation did not require refrigeration.[2]

Studies found that these oral pellets were as effective as the liquid formulation and acceptable to patients.[3,4] Considerable variability in LPV/r pharmacokinetics (PKs) in children for both the liquid and solid formulations has been observed.[5] Whereas the PKs of the oral pellets has been studied, information on factors influencing its PK parameters and explaining the variability is limited. This information is important to help optimize the dose of this new formulation. Our study aimed to establish a population PK model of LPV/r in African infants using the oral pellets formulation and to assess drug exposures based on World Health Organization (WHO) weight bands dosing recommendations.

METHODS

Study population and blood collection

Data from children enrolled in the "Lopinavir based ART for HIV-Infected children Globally (LIVING)" study (ClinicalTrials.gov Identifier NCT02346487) were included in the PKs analysis. Briefly, the LIVING studies were conducted in Kenya, Uganda, and Tanzania to evaluate the effectiveness, safety, PKs, and acceptability of LPV/r 40/10 mg oral pellets-based ART in infants and young CLHIV who cannot swallow tablets. The LIVING study was approved by ethical and regulatory bodies in Kenya, Uganda, and Tanzania, following the respective country research guidelines. This PK analysis was approved by the Ethics Committee of Pharmacy, Faculty of Pharmacy, Chiang Mai University (Chiang Mai, Thailand). The inclusion criteria consisted of CLHIV who were treatment-naïve, already receiving first-line liquid LPV/r-based therapy, or experiencing first-line non-nucleoside reverse transcriptase inhibitor (NNRTI) treatment failure. Additionally, eligible participants were required to have a weight between ≥ 3 and < 25 kg at the time of enrollment. Children were excluded if they were using or planning to use specific medications, such as NNRTIs, integrase inhibitors, entry inhibitors, or protease inhibitors (PIs) other than LPV/r. Moreover, those who had treatment failure with PIs with detectable (or strong suspicion of) PI resistance mutations, had a clinical condition that necessitated the use of a forbidden medication in conjunction with LPV/r, or had received experimental drugs for any purpose within 30 days prior to study entry were also ineligible. The administration of LPV/r oral pellets followed the WHO weight bands: children weighing 3–5.9 kg, 6–9.9 kg, 10–13.9 kg, 14–19.9 kg, and 20–24.9 kg received 2, 3, 4, 5, and 6 LPV/r capsules, twice daily, respectively. The capsules of LPV/r pellets were opened and administrated with food or liquid. Drug adherence was assessed at each study visit using self-reporting of missed doses and pill counts. Sparse blood samples were collected during the study follow-up period, starting at 1 month and subsequently every 6 months. At the 1-month visit, 3 blood samples were obtained: immediately before the morning dose, 0–1 hour after taking the drug, and 4–8 hours after taking the drug. Every 6 months, 2 blood samples were obtained: one before the morning dose and another between 2 and 6 hours after drug administration. For this PK analysis, PK samples were obtained from Kenya and Uganda. Drug doses, timing of blood sampling, body weight, post-natal age (PNA), malnutrition status, and the specific antiretroviral (ARV) regimens were documented during each visit.

Measurement of LPV and ritonavir plasma concentrations

The concentrations of both LPV and ritonavir (RTV) were measured utilizing a validated assay using liquid chromatography triple quadrupole mass spectrometry. Blood samples were processed within 1 hour, and plasma stored at −70°C until analysis. All samples were analyzed at the Bio-Analytical Testing Facility at the Faculty of Associated Medical Sciences (AMS-BAT), AMS Clinical Service Center, Faculty of Associated Medical Science, Chiang Mai University. The lower limit of quantification of LPV and RTV was 50 ng/mL. The ranges for intra-day and inter-day variability, expressed as the coefficient of variation, were 0.6% to 3.4% and 1.7% to 3.0%, respectively. This laboratory participates in the US National Institutes of Health (NIH) Clinical Pharmacology Quality Control program.[6]

Population PK analysis

The steady-state PKs of LPV and RTV were analyzed using a nonlinear mixed-effect modeling technique implemented in NONMEM (version 7.3; Icon Development Solutions, Ellicott City, MD) along with Pirana (version 2.9.6). Graphical analysis was conducted using the R package (version 3.1.2, R Development Core team; http://www.r-project.org) and Xpose programs (version 4.5.0). The PK parameters and their variabilities were estimated using the first-order conditional estimation with interaction method.

First, two separate population PK models for LPV and RTV were developed (LPV and RTV intermediate models). Subsequently, these two models were integrated to form a combined model that explored the dynamic interaction between LPV and RTV. The LPV and RTV intermediate models were evaluated using one- and two-compartment models that incorporated first-order absorption and elimination to describe the concentrations of LPV and RTV over time. In addition, absorption delayed models were examined by considering the inclusion of a lag time or incorporating transition compartments. To account for the impact of body weight, allometric scaling was applied to the oral clearance (CL/F) and apparent volume of distribution (V/F) parameters with exponents fixed to 0.75 and 1, respectively, and centered on a median weight of 13.6 kg. The impact of maturation was evaluated though the inclusion of age on CL/F[7,8] using Eq. 1:

$$MF_{PNA} = \frac{PNA^{HILL}}{MAT_{50}{}^{HILL} + PNA^{HILL}} \quad (1)$$

where MF is maturation function, PNA is post-natal age in years, and MAT_{50} is the PNA at which the clearance is 50% of the mature clearance. HILL is a coefficient relating the steepness of the relationship between the maturation function and age.

An exponential model was used to characterize the interindividual variability (IIV) and interoccasion variability (IOV) of LPV and RTV. The residual unexplained variability of LPV and RTV was described using a combined error model and a proportional error model, respectively. The selection of the structural model was based on several factors, including the changes in the objective function value (OFV), the goodness-of-fit (GOF) plots, the precision of parameter estimates, and the successful convergence of the model. Once the structural model was developed, the inclusion of covariates in the model was assessed. The covariates investigated were gender, height, and malnutrition status identified by weight-for-age z-score (WAZ), which is classified as normal (WAZ > −2), moderate (−3 < WAZ < −2), and severe (WAZ < −3). A stepwise approach was used for covariate model building. Continuous covariates were examined using linear, power, and exponential models, whereas categorical covariates were analyzed using additive, fractional, and exponential models. The selection criteria for incorporating covariates into the hierarchical models included

a minimum decrease of 3.84 in the OFV for forward inclusion ($P < 0.05$) and an increase of 6.63 in the OFV for backward deletion ($P < 0.01$).

After the separate LPV and RTV models had been developed, a combined model describing the interaction between LPV and RTV was investigated. A sequential approach was used to develop an interaction model. Initially, the individual posterior RTV concentrations ($C_{RTV,IPRED}$) were estimated based on the RTV model. Subsequently, these $C_{RTV,IPRED}$ values were utilized as inputs to describe the inhibition of LPV clearance. Linear, exponential, and maximum-effect models (with a maximum inhibition (I_{max})), were tested to describe the inhibitory effect of RTV concentration on oral clearance of LPV.[9]

Model evaluation

Prediction- and variability-corrected visual predictive checks (pvcVPC) and bootstrapping was performed to determine the predictability and reliability of the final model.[10,11] The pvcVPC analysis consisted of generating 1,000 simulated datasets. The 95% confidence intervals (CIs) for the medians, as well as the 5th and 95th percentiles of the simulated concentrations, were plotted against the corresponding percentiles of the observed data. The purpose was to compare the simulated and observed data and evaluate the model's predictive performance. The bootstrap analysis involved generating 1,000 replicates by randomly sampling with replacement from the original data. The medians and 95% CIs (obtained from the 2.5th and 97.5th percentiles) derived from the bootstrap analysis were then compared with the corresponding values obtained from the final model. This comparison aimed to assess the consistency and agreement between the results of the final model and those obtained from the bootstrap analysis.

Simulations

Monte Carlo simulations were performed to predict LPV exposure (LPV AUC_{0-12}) across WHO weight bands using a standardized *in silico* pediatric population with demographics representative of African CLHIV.[12] Initially, individual RTV concentrations (RTV C_{trough}) were simulated by incorporating the fixed and random effects from the RTV intermediate model. For each group of significant covariates, 200 replicates of RTV C_{trough} were generated. These simulated RTV C_{trough} values were then used as inputs in the interaction model to generate steady-state LPV exposures. A total of 500,000 children weighing 3–24.9 kg (100,000 children for each weight bands) were simulated. The target LPV exposure was defined as an AUC_{0-12} between 40 and 160 mg·h/mL, as reported in older children, and an LPV concentration at 12 hours after dosing (C_{12}) above 1.0 mg/L.[13]

RESULTS

Demographic characteristic

A total of 2,998 plasma concentrations of LPV/r were collected from 514 children who participated in the LIVING study. The baseline demographic characteristics of all the participants and participants by weight band are presented in **Table 1** and **Table S1**. According to the observed data, the percentages of children with LPV C_{12} above 1.0 mg/L were 92%, 91%, 91%, and 93% at the 1-month, 6-month, 12-month, and 18-month visits, respectively (**Figure S1**). Furthermore, the percentages of children whose predicted AUC_{0-12} (calculated by dividing the dose by the estimated individual CL/F) within the target range were 75.8%, 76.7%, 81%, and 82% at the 1-month, 6-month, 12-month, and 18-month visits, respectively (**Figure S2**).

Population pharmacokinetic analysis

A one-compartment model with first-order absorption and elimination best described the PK properties of LPV and RTV. The addition of lag time in the LPV and RTV models improved the model fits (ΔOFV = −55.642 and −106.129, respectively). The IIV for absorption rate constant (K_a) of RTV could not be accurately estimated. The inclusion of IOV on bioavailability (F) of LPV and RTV significantly improved the fit (ΔOFV of −360.118 and −434.992, respectively). The IOV of F for LPV and RTV were estimated to be 33.60% and 45.8%, respectively.

Table 1 Summary of demographic and clinical characteristics of participants

Characteristics	Values
Number of subjects, *n*	514
Number of samples, *n*	2,998
Sex, *n* (%)	Male: 248 (48.25) Female: 266 (51.75)
Age, years, mean ± SD (range)	3.28 ± 2.01 (0.3–12.4)
Body weight, kg, mean ± SD (range)	12.56 ± 3.97 (4.6–25)
Malnutrition status –WAZ	
Normal or mild malnutrition (WAZ > −2), *n* (%)	374 (72.76)
Moderate acute malnutrition (WAZ < −2 to −3), *n* (%)	88 (17.12)
Severe acute malnutrition (WAZ < −3), *n* (%)	45 (8.75)
Missing data, *n* (%)	6 (1.17)

WAZ, weight for age z score.

The incorporation of allometric scaling on LPV and RTV significantly reduced the OFV (ΔOFV = −181.519 and −8.826, respectively). Thus, the effect of body weight was added on the CL/F and V/F of LPV and RTV. Sex was tested as a covariate on PK parameters but was not significant. Including maturational changes as a function of age did not improve the model fit for either LPV or RTV. The malnutrition status was identified as a significant covariate on the CL/F of both LPV and RTV during forward inclusion step. However, it did not retain significance during the backward deletion step. The final parameter estimates for the LPV and RTV intermediate models are shown in **Table 2**.

The impact of RTV on LPV CL/F was most accurately represented by an I_{max} model (ΔOFV = −1013.488). This interaction model was incorporated into the final combined model,[9] as depicted in Eq. 2:

$$CL/F_{LPV} = \theta_1 \times 1 - \left(\frac{I_{max} \times C_{RTV}}{IC_{50} + C_{RTV}}\right) \quad (2)$$

where CL/F_{LPV} represents the oral clearance of LPV, θ_1 denotes the typical value of CL/F in the absence of RTV, I_{max} corresponds to the maximum inhibitory effect of RTV on LPV CL/F, IC_{50} represents the concentration of RTV required to achieve 50% of the I_{max}, and C_{RTV} represents the concentration of RTV.

The I_{max} could not be accurately estimated with our data and was fixed to 0.9 based on a previous study in children using LPV/r.[14] With the fixed I_{max} the IC_{50} was estimated to be 0.049 mg/L.

Table 2 Parameter estimates from NONMEM and bootstrapping analyses of intermediate LPV and RTV models

	LPV		RTV	
Parameter	Estimated value	%RSE	Estimated value	%RSE
CL/F (L/h/13.6 kg)	1.56	2.00	11.40	3.00
V/F (L/13.6 kg)	24.10	8.00	38.80	12.30
K_a (/h)	0.46	14.10	0.16	9.80
T_{LAG} (h)	0.46	8.20	0.29	5.80
IIVCL, %CV	24.50	7.80	32.60	10.00
IIVV, %CV	32.10	25.30	74.20	18.30
IIVKA, %CV	81.10	16.40	–	–
IOV F, %CV	33.60	4.70	45.80	6.40
RUV				
Proportional (%)	15.80	35.70	51.60	4.00
Additive (mg/L)	6.54	11.00	–	–

Parameter estimates are scaled to typical patient at 13.6 kg.
%CV, percent coefficient variation; %RSE, relative standard error; CL/F, apparent oral clearance; F, bioavailability; IIV, interindividual variability; IOV, interoccasion variability; K_a, absorption rate constant; LPV, lopinavir; NONMEM, nonlinear mixed effects modeling; RSE defined as: (SEestimate/estimate)×100, where SE is standard error; RTV, ritonavir; RUV, residual variability; T_{LAG}, absorption lag time; V/F, apparent volume of distribution.

The NONMEM code for the final model was provided in the Supplementary material. The population PK parameters obtained from the final combined model are presented in **Table 3**. The GOF plots displayed in **Figure 1** demonstrate that the model does not exhibit any evident bias or misspecification.

Model evaluation

The pvcVPC indicated that the median, 5th, and 95th percentiles of the observed data were well within the 95% CIs of the corresponding percentiles of the simulated data (**Figure 2**). Out of 1,000 bootstrap analysis runs, 946 runs achieved successful convergence and minimized with appropriate covariance. The results obtained from the bootstrap analysis are presented in **Table 3**. The median and 95% CI obtained from the bootstrap analysis closely matched the values estimated from the final model.

Simulation for dose optimization

The simulated LPV C_{12} per the WHO weight bands dosing recommendation is shown in **Figure 3**. The percentages of children having LPV C_{12} above 1.0 mg/L were 99.8%, 99.9%, 99.9%,

Table 3 Parameter estimates from NONMEM and bootstrapping analyses of final combined model

	NONMEM results				Bootstrap results		
Parameter	Estimated value	%RSE	2.5th[a]	97.5th[a]	Median	2.5th	97.5th
Lopinavir							
CL/F (L/h/13.6 kg)	5.70	2.90	5.38	6.02	5.70	5.38	6.02
V/F (L/13.6 kg)	29.90	4.60	27.23	32.57	30.10	26.86	32.85
K_a (/h)	0.50	10.50	0.40	0.60	0.53	0.36	0.65
T_{LAG} (h)	0.46	8.10	0.39	0.53	0.50	0.28	0.64
IIVCL, %CV	14.60	11.40	10.86	17.61	14.70	10.96	17.52
IIVV, %CV	31.90	10.90	24.14	38.17	32.22	23.87	38.23
IIVKA, %CV	88.40	10.90	66.85	105.70	87.93	64.32	107.17
IOV F, %CV	19.90	10.30	15.31	23.57	19.92	15.29	23.61
RUV							
Proportional (%)	26.20	18.30	26.18	26.22	25.90	21.11	30.54
Additive (mg/L)	3.18	16.40	2.16	4.20	3.26	2.17	4.19
Lopinavir–ritonavir interaction							
I_{max}	0.9 Fix	–	–	–	–	–	–
IC_{50} (mg/L)	0.049	5.10	0.040	0.050	0.049	0.044	0.054

%CV, percent coefficient variation; %RSE, relative standard error; CL/F, apparent oral clearance; F, bioavailability; IC_{50} is the RTV concentration to reach 50% of the I_{max}; IIV, interindividual variability; I_{max} is the maximum inhibitory effect of RTV on LPV CL/F; IOV, inter-occasion variability; K_a, absorption rate constant; LPV, lopinavir; NONMEM, nonlinear mixed effects modeling; RSE defined as: (SEestimate/estimate)×100, where SE is standard error; RTV, ritonavir; RUV, residual variability; T_{LAG}, absorption lag time; V/F, apparent volume of distribution.
[a]Calculated as the final parameter estimate ±1.96 · SE. Parameter estimates are scaled to typical patient at 13.6 kg.

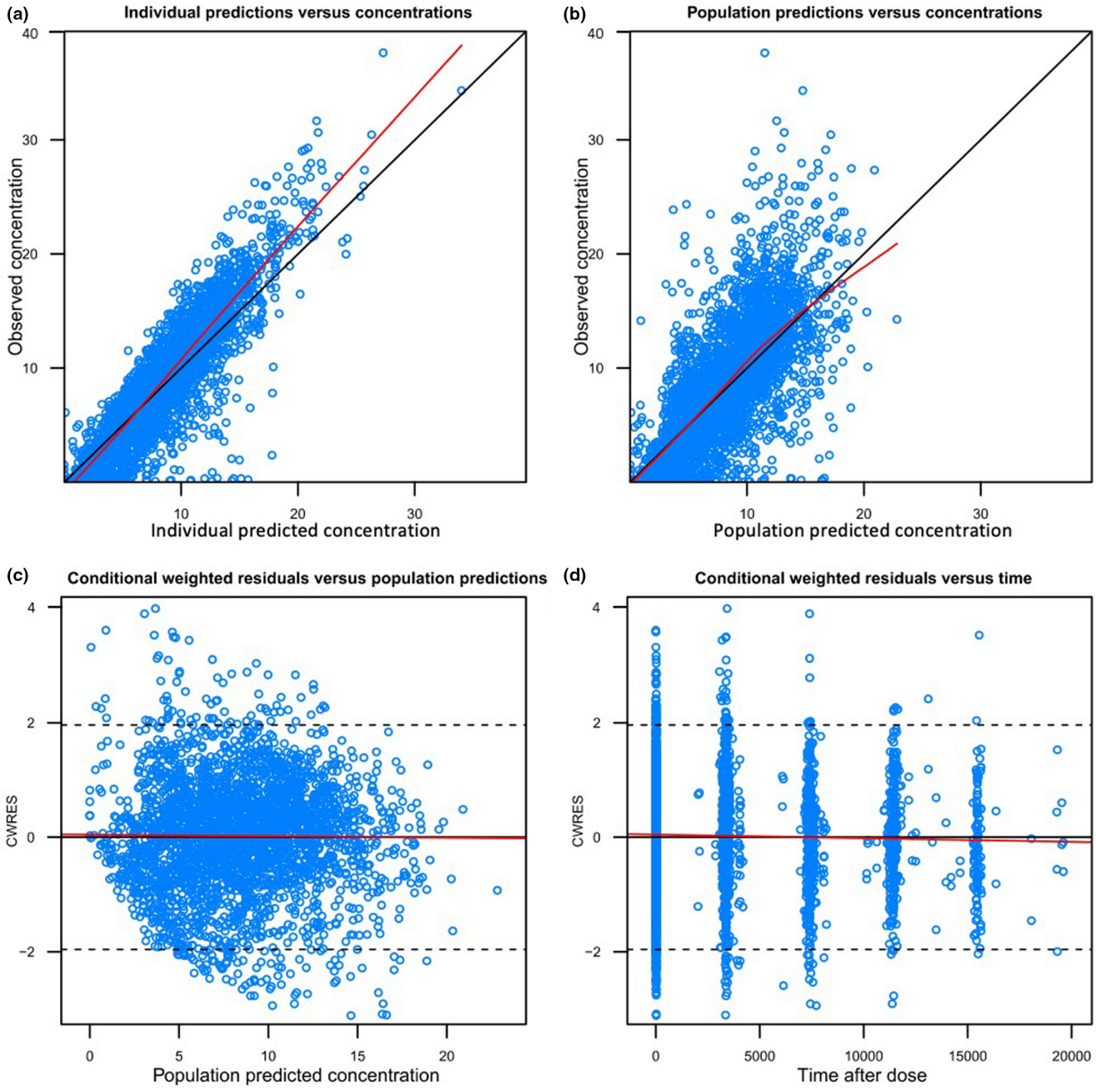

Figure 1 Goodness-of-fit plots of the final model of LPV/r: (**a**) observed lopinavir concentrations vs. individual predicted concentrations (IPRED); (**b**) observed lopinavir concentrations vs. population predicted concentrations (PRED); (**c**) conditional weighted residuals (CWRES) vs. PRED; (D) CWRES vs. time after dose. Red lines in (**a**) and (**b**) show regression, and in (**c, d**) show zero.

99.9%, and 100% for children 3–5.9 kg, 6–9.9 kg, 10–13.9 kg, 14–19.9 kg, and 20–24.9 kg, respectively. The simulated LPV AUC_{0-12} per the WHO weight bands dosing recommendation is shown in **Figure 4**. The percentages of children with an AUC_{0-12} within the target range were 84.9%, 80.8%, 79.8%, 84.0%, and 85.2% for children 3–5.9 kg, 6–9.9 kg, 10–13.9 kg, 14–19.9 kg, and 20–24.9 kg, respectively.

DISCUSSION

In this study, a population PK model describing the PKs of LPV and RTV in Kenyan and Ugandan CLHIV using LPV/r oral pellets was developed. The PKs of both LPV and RTV were best described by a one-compartment model with first-order absorption and elimination, including a lag time. Although a previous study by Zhang *et al.*[15] showed that a two-compartment model best describes the PKs of RTV, our data did not support the two-compartment model. It is likely that different blood sampling schedules account for the different structural models identified in the two studies. RTV absorption has also been characterized by a transit compartment[14,15]; but this absorption model could not be described with our data. The GOF plots of the LPV final model revealed a slight underprediction at high LPV concentrations

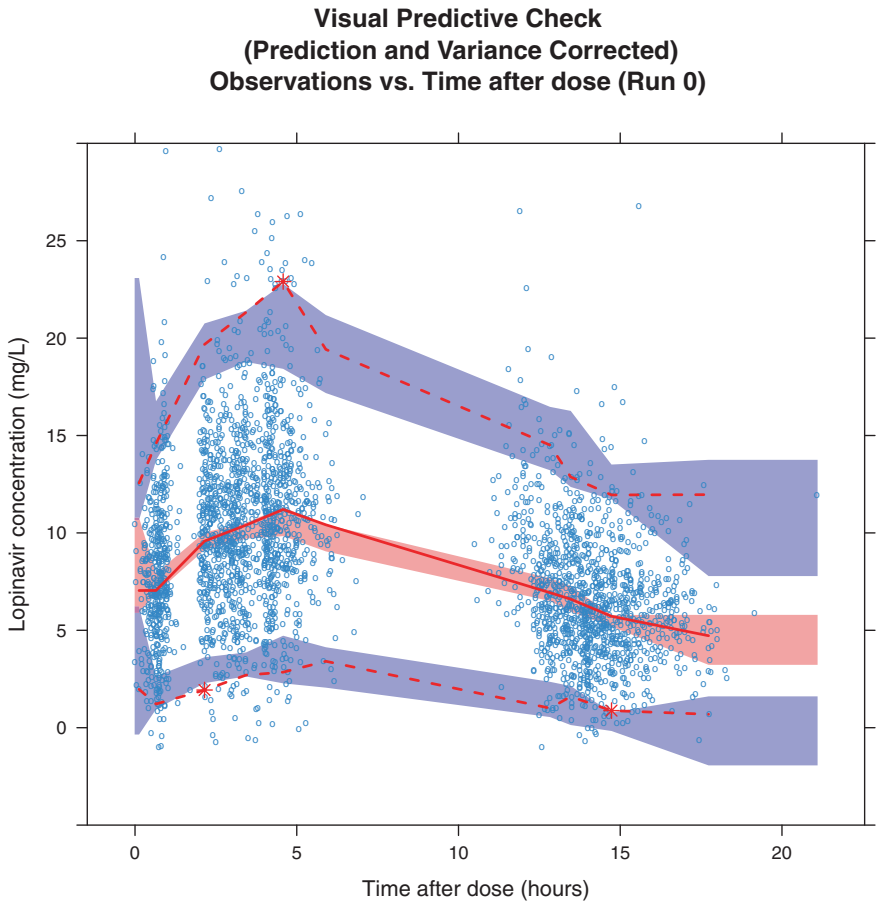

Figure 2 Plot of pvcVPC of LPV with the final interaction model. The red line is the 50th percentile, and red dotted lines are the 5th and 95th percentiles, of the observed concentrations. Shaded areas are the 95% CIs of the corresponding model-predicted percentiles. CI, confidence interval; LPV, lopinavir; pvcVPC, prediction-corrected visual predictive check.

and a high IIV of K_a for LPV (81%) was observed. Whereas caregivers were guided on the administration of the LPV/RTV pellets, the type of food was not standardized and varied between the communities and cultures of the African countries. There is evidence that food intake influences the PK of LPV,[16] potentially resulting in increased variability of the K_a. For children weighing 13.6 kg, the population estimates of LPV CL/F and V/F in our study were 5.70 L/h and 29.90 L, respectively, and for RTV CL/F and V/F were 11.40 L/h and 38.8 L, respectively. Our estimate of the CL/F of LPV was slightly higher compared with previous reports on children using liquid and tablet formulations,[17–20] except for the study by Zhang *et al*., which reported similar CL/F values for LPV and RTV in children without rifampicin. The direct inhibition of LPV CL/F by RTV was best described using an I_{max} model. Our analysis revealed that an RTV concentration of 0.049 mg/L corresponded to a 50% reduction in LPV CL/F, consistent with a previous study that reported a similar threshold of 0.05 mg/L.[14]

In our model, the influence of weight was incorporated allometrically to account for developmental growth; However, the inclusion of maturational changes based on age did not result in an improved fit of the model. This lack of association could be due to limited data on children younger than 1 year old (11.9%). Both LPV and RTV are primarily metabolized by cytochrome P450 3A4 (CYP3A4) enzymes.[21] The activity of CYP3A4 undergoes a rapid increase after birth,[22] and there is evidence indicating that CYP3A4 mRNA levels in liver samples obtained at birth reach maturity comparable to adult levels within 1 week. Additionally, its activity reaches ~30–40% of adult levels by around 1 month of age[23] and becomes fully developed within the first year of life.[24]

Malnourished children may undergo physiological changes that affect a drug's PKs.[25] It is unclear how nutritional status affects the PKs of LPV and RTV. A previous study showed that LPV exposures were reduced by 48% in Ugandan children with malnutrition compared with children from high-income countries.[25] Additionally, CLHIV with severe malnutrition were found to have significant PK variability, reduced LPV bioavailability, and increased CL/F,[17] compared with the estimated CL/F in non-malnourished children.[15,25,26] According to the results of our study, the PKs of LPV and RTV are not impacted by either moderate or severe malnutrition. This could be due to the low proportion of children with moderate and severe malnutrition (17.12% and 8.75%, respectively) in our study population. Therefore, it is necessary to evaluate the influence of malnutrition on the PKs of LPV and RTV in a larger sample of malnourished children.

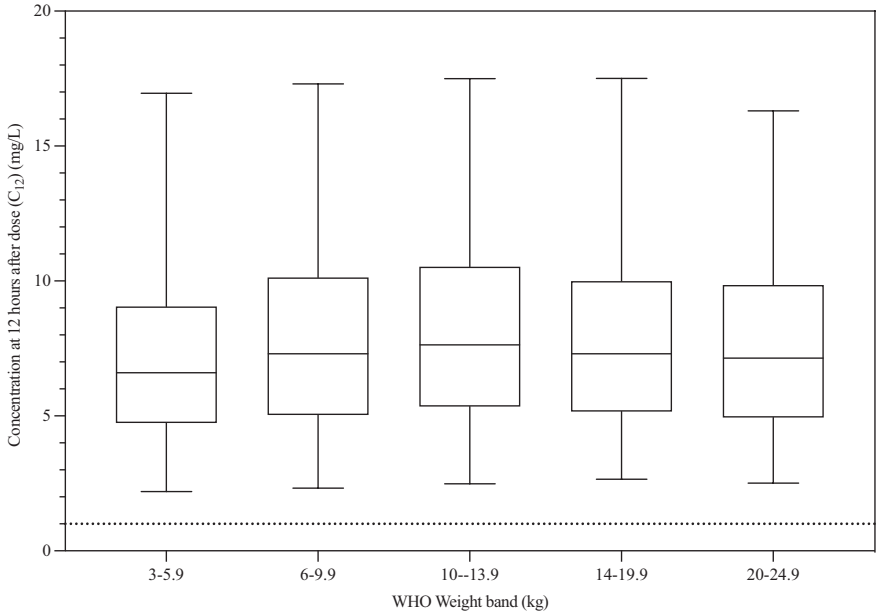

Figure 3 Simulated steady-state LPV C_{12} according to WHO weight bands. The box-and-whisker plots (the lower and upper limits of individual boxes denote the 25th and 75th percentiles, and the whiskers represent 2.5–97.5th percentiles) show simulated C_{12} of LPV, according to WHO weight bands dosing recommendations. The black dotted line is the target C_{12} of 1 mg/L. C_{12}, concentrations at 12 hours after dose; LPV, lopinavir; WHO, World Health Organization.

The WHO has developed recommendations for weight bands dosing to make it easier to administer ARV medication across resource-limited settings. The simulations of the final model showed that LPV exposure in African children with HIV was within the target exposure range reported in older children, according to WHO weight bands dosing. The percentage of children who achieve the target trough concentration is slightly greater in the simulations when compared with observed concentrations. This slight bias in the model could be attributed to noncompliance and/or malnutrition. The LIVING study was a pragmatic study that was close to "real-life" and under-reporting of compliance may have occurred, especially with predose samples where the prior dose was not observed. Previous studies have also indicated that children with malnutrition exhibit reduced exposure to LPV

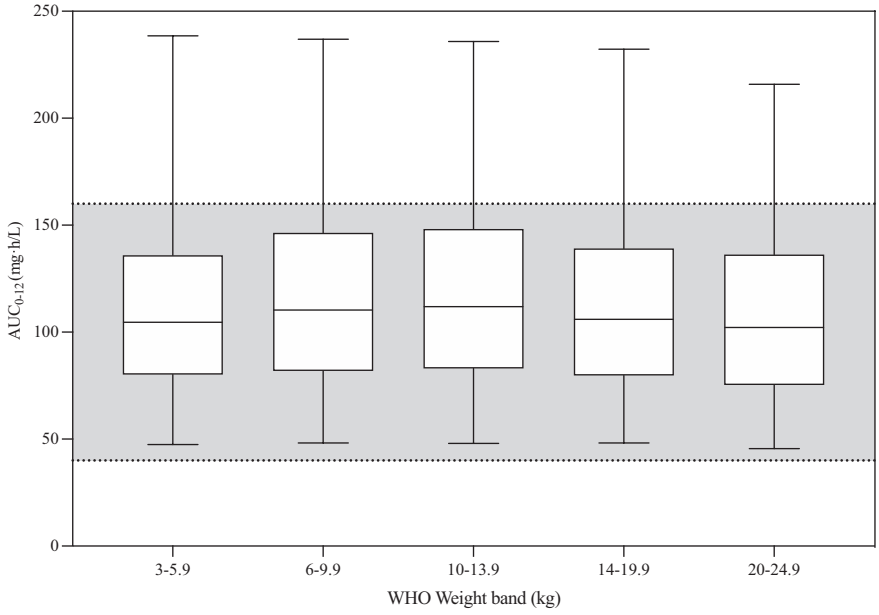

Figure 4 Simulated steady-state LPV AUC_{0-12} vs. body weight. The box-and-whisker plots (the lower and upper limits of individual boxes denote the 25th and 75th percentiles, and the whiskers represent 2.5–97.5th percentiles) show the simulated AUC_{0-12} of LPV, according to WHO weight bands dosing recommendations (white). Target AUC_{0-12} (40 to 160 mg.h/L) is shown by the shaded area. AUC_{0-12}, area under the curve from 0 to 12 hours; LPV, lopinavir; WHO, World Health Organization.

concentrations.[17,25] Despite the fact that around 25% of the children living with HIV in our study exhibited moderate to severe malnutrition, our study did not observe a significant impact of malnutrition on LPV PK parameters.

Our study has several limitations to consider. First, this study evaluated a limited number of patient characteristics. Other important covariates, including co-medications, were not investigated. Second, the lack of information on children under the age of 3 months limited our ability to explore the maturation effect. The LIVING studies were conducted under real-world conditions which may have contributed to variability in drug intake and sample collection timepoints. Although the impact of these variations on these data cannot be excluded, the risk was deemed low given the large size of the study population. Due to the limited number of severely malnourished children in our study, it is difficult to observe the effect of malnutrition on the PKs of LPV, and further research is required.

To our knowledge, this is the first population PK study in a large sample of African CLHIV, which integrates covariates affecting PK parameters of LPV/r pellets in young children in Africa. Our findings indicate that the LPV exposure observed in African children who received LPV/r pellets according to WHO weight bands falls within the reference range reported for liquid and tablet formulations.

CONCLUSION

A population PK model for LPV that integrates the interaction with RTV was developed. Results of the simulation indicate that the WHO weight bands dosing recommendation is appropriate for LPV/r pellets in Kenyan and Ugandan CLHIV.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

E.A.B. has served as advisory board and or consulted for MERCK, ViiV and Gilead. J.K.M. has served as *ad hoc* advisory boards for ViiV, GSK, and Pfizer. V.M. has served on an advisory board membership or is receiving support for conference attendance, with ViiV Healthcare and Viatris. All other authors declared no competing interests for this work.

AUTHORS CONTRIBUTIONS

All authors wrote the manuscript. T.R.C. and B.P. designed the research. All authors performed the research. S.C., T.R.C., and B.P. analyzed the data.

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