Published in final edited form as:

Clin Pharmacol Ther. 2012 February ; 91(2): 243–249. doi:10.1038/clpt.2011.218.

Assessment of Lopinavir Pharmacokinetics With Respect to Developmental Changes in Infants and the Impact on Weight Band–Based Dosing

Mina Nikanjam¹, Ellen Gould Chadwick², Brian Robbins³, Carmelita Alvero⁴, Paul Palumbo⁵, Ram Yogev², Jorge Pinto⁶, Rohan Hazra⁷, Michael Hughes⁴, Barbara E. Heckman⁸, Edmund V. Capparelli¹, and IMPAACT P1030 Team

¹UC San Diego, La Jolla, CA, US

²Feinberg School of Medicine, Northwestern University, Chicago, IL, US

³Univ of Nebraska Med Center, Omaha, NE, US

⁴Harvard School of Public Health, Boston, MA, US

⁵Dartmouth Medical School, Hanover, NH, US

⁶Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, BR

⁷Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Bethesda MD, US

⁸Frontier Science and Technology Research Foundation, Amherst, NY, US

Abstract

Improved antiretroviral therapies are needed for the treatment of HIV infected infants due to rapid disease progression and drug resistance from perinatal exposure to antiretrovirals. We examined longitudinal pharmacokinetic (PK) data from a clinical trial of lopinavir/ritonavir in HIV-infected infants initiating therapy less than 6 months of age. A population PK analysis was performed using NONMEM to characterize changes in lopinavir (LPV) PK relating to maturational changes in infants, and to assess dosing requirements in this population. We also investigated the relationship between LPV PK and viral dynamic response. Age and ritonavir concentrations were the only significant covariates found. Population PK of LPV was characterized by high apparent clearance in young infants which decreased with age. Although younger infants had lower LPV concentrations, viral dynamics did not correlate with initial LPV exposure. Monte Carlo simulations demonstrated that WHO weight band-based dosing recommendations predicted therapeutic LPV concentrations and provided comparable drug exposure levels comparable to those resulting from US Food and Drug Administration (FDA)-suggested dosing regimens.

Corresponding author: Edmund Capparelli, PharmD 7910 Frost Street, #360 San Diego, CA 92123 ecapparelli@ucsd.edu TEL: (858) 246-0009 FAX: (858) 246-0025.

Conflict of Interest/Disclosure E.V.C. has served as a consultant to GlaxoSmithKline, Bristol-Meyers Squibb, and Johnson & Johnson. E.G.C. has had consultancies with Pfizer and Bristol-Meyers Squibb and has owned stock and/or stock options in Abbott Labs, GlaxoSmithKline, Merck Inc., Bristol-Meyers Squibb, and Schering Plough. M.D.H. received grant support from Roche, and honoraria/consultancy fees from Abbott Labs, Boehringer Ingelheim, Bristol-Meyers Squibb, Chiron, Medicines Development, Roche, Pfizer, Tibotec, and Vironyx. R.Y. has served on speaker's bureaus for Merck Inc. and GlaxoSmithKline. The other authors declared no conflict of interest.

Keywords

population pharmacokinetics; HIV; WHO; AIDS; antiretroviral

INTRODUCTION

While increased antiretroviral access has reduced mother-to-child transmission of HIV, there were still an estimated 370,000 children newly infected with HIV in 2009, with nearly 90% living in sub-Saharan Africa (1). Administration of single-dose nevirapine to mothers and infants is effective in preventing transmission in resource limited settings, however infants who become infected are likely to harbor nevirapine resistant virus and respond poorly to nevirapine containing antiretroviral therapy (2). Recent data from the IMPAACT P1060 trial has shown a decreased incidence of virologic failure in infants and children on lopinavir based therapy compared to nevirapine (3).

HIV progresses much more rapidly in infants and children than adults due to an immature immune system (4) and there are also higher viral loads in infants than in older populations. This high level of viral replication creates the potential for mutations, thus under-dosing in this population could lead to resistance and limit future treatment options. In addition, design of antiretroviral therapies for infants has many unique pharmacokinetic challenges. Young infants have immature renal function and liver enzyme content with decreased CYP3A activity which can lead to slower clearance and a higher risk of drug toxicity (5). Liquid preparations are needed for young infants, which leads to challenges in formulation development. While excipients and alcohols can enhance solubility, the resulting preparation may still have poor or erratic absorption in infants (6).

In this study we examined longitudinal pharmacokinetic data from a clinical trial of lopinavir/ritonavir (LPV/r) based combination antiretroviral therapy (cART) in HIV-infected infants initiating therapy less than 6 months of age. Previously published results from this trial demonstrated favorable virologic suppression and clinical efficacy (7-9), but lower LPV exposure in the youngest infants (7). We performed a population pharmacokinetic (PK) analysis to characterize maturational changes in LPV pharmacokinetics and assess LPV dosing requirements in infants. We also explored the potential relationship between the PK of LPV and viral dynamic response.

RESULTS

Pharmacokinetic analysis

Thirty one infants were enrolled in the study; one infant discontinued the study before 2 weeks, thus intensive and sparse pharmacokinetic data were available from 30 infants (607 samples total). Table 1 summarizes patient characteristics at study entry. Patients were separated into two cohorts with Cohort 1 initiating therapy between 2 and 6 weeks of age and Cohort 2 initiating therapy between 6 weeks and 6 months of age. LPV sparse (C12 trough) concentrations were available through 60 months of age. Of the 30 original subjects, data were available for 27, 22 and 9 subjects after 1, 2 and 3 years (yrs) of age, respectively. Lopinavir pre-dose concentrations increased during the first year of life and median LPV levels were higher at the one year intensive PK visit than at week 2.

After allometric scaling for size, an age effect was still present in the population PK model. Incorporating postnatal age in a non-linear manner on bioavailability (F) yielded the greatest improvement of the model (Table 2, equations). The model was not significantly improved by the incorporation of food information as a covariate of bioavailability (formula vs. solid

food and volume of formula). Within-subject differences in concentration levels between visits were found to be due to changes in bioavailability. Most patients (26/30) had at least two intensive PK visits (2 wk and 1 yr). Non-adherent patients (pre-dose below quantifiable limit) and those requiring dose adjustments (1 patient required a dose increase due to low levels) had repeat intensive evaluations, thus 6 subjects had 3 intensive PK visits and one had 4 intensive PK visits. LPV concentrations measured following observed administration in clinic were noted to have a lower residual error than non-observed doses, thus separate error terms were incorporated into the model.

Ritonavir (RTV) concentration correlated well with lopinavir concentration (data not shown) and was a highly significant covariant in the model. Adding RTV concentration as a covariate on clearance (CL), volume of distribution (V_d), or F as a function of RTV concentration improved the model. Despite the magnitude of the RTV association with LPV pharmacokinetics, a final model without RTV was developed to assess infant dosing recommendations, since RTV concentration information is not available a priori to predict LPV disposition and guide therapy.

Postnatal age was the only significant covariate used in the final model. As there was only one covariate in the univariate screening process, the forward selection approach was not necessary. The goodness of fit plots for the final model are shown in Figures 1A and 1B. The final model parameters are shown in Table 2. The residual error following observed drug administration is much less than the error with unobserved dosing. Post-hoc estimates show bioavailability increasing in a logarithmic manner (data not shown), while apparent clearance (CL/F) declines exponentially (Figure 2).

Monte Carlo simulations were performed using the study dose (300 mg/m²), FDA dosing (300 mg/m², <6 months of age; 230 mg/m², >6 months of age), and WHO weight band dosing recommendations (10). Median LPV trough concentrations (C₁₂) for each of the 3 age groups (0.5-2m, 3-6m, >6m) were similar with all dosing methods (Figure 3A). Older infants (>3m) had higher LPV trough concentrations than younger infants (<3m). The previously reported median adult trough level of 4.2 µg/ml (11) was approached in older infants (>3m). The frequency of low concentrations (<1 µg/mL) with the study and FDA doses was 8.1% in infants <3 months of age, but rare (<1%) in older infants (Figure 3B). The WHO weight band dosing recommendations predicted a lower frequency (4.2%) of troughs <1 µg/mL in the youngest infants. The median LPV AUC was similar with all dosing recommendations. Younger infants (<3m) had lower AUC than older infants (>3m), and older infants approximated adult exposure levels (11) (Figure 3C).

Viral Dynamics and Pharmacodynamic analysis

Viral RNA data were available for 29 infants and have previously been presented (7, 8). Sixty two percent of infants achieved viral suppression (HIV RNA <400 copies/mL on consecutive visits) by week 24. Of the 11 infants not achieving suppression by week 24, 10 achieved suppression at a later time. Samples prior to viral suppression were used for viral RNA curve fitting for each subject (276 samples). The median early phase viral RNA decay (α) was 0.31 days⁻¹ (range: 0.29-0.32 days⁻¹) and the median late phase decay (β) was 0.048 days⁻¹ (range: 0.004-0.122 days⁻¹).

Population PK post-hoc AUC estimates (from intensive PK evaluations at week 2) were compared to viral decay parameters (α , β) using Spearman correlation coefficients ($r=0.0006$, α ; $r=0.12$, β). No significant correlations were found ($p=1.00$, α ; $p=0.52$, β). Infants were stratified by high vs. low lopinavir exposure, with high exposure being defined as an AUC>50 µg*hr/mL (intensive PK, at week 2). A comparison between high vs. low exposure for α and β revealed no significant differences (Wilcoxon rank sum test: $p=0.50$,

α ; $p=0.74$, β). Viral decay parameters α and β were compared between cohorts 1 and 2 using a Wilcoxon rank-sum test with no significant differences observed ($p=0.45$, α ; $p=0.11$, β).

DISCUSSION

Design of oral therapies for infants poses unique pharmacokinetic challenges. Drug metabolism and excretion, which may be immature in an infant at birth, can increase rapidly as the infant matures, necessitating dose modifications in the first few months of life. Suitable oral formulations for infants must address issues of drug solubility and stability while limiting use of excipients that may increase toxicity in the neonatal population. In addition, the immaturity of the infant gastrointestinal (GI) system also may affect the rate and extent of oral drug absorption (12), resulting in a lower bioavailability and higher apparent clearance in neonates as compared to older children and adults (6).

LPV undergoes rapid first-pass metabolism in the liver by CYP3A4 and CYP3A5. RTV inhibits the CYP3A4 isoenzyme and results in reduced LPV first pass metabolism and LPV clearance by the liver when administered as LPV/r combination therapy. LPV/r is primarily eliminated by the fecal route as inactive metabolites with urinary excretion accounting for <2% of the eliminated drug. At steady state, LPV is 98%–99% bound to plasma proteins, binding to both α -1-acid glycoprotein and albumin. The standard adult dose of 400 mg/100 mg twice daily produces a mean trough concentration of 5.2 $\mu\text{g/mL}$ (13). By contrast, the mean reported trough concentration in children 6 months–12 yrs of age dosed at 230 mg/57.5 mg twice daily was 4.7 $\mu\text{g/mL}$, whereas a 300 mg/75 mg dose yielded 7.9 $\mu\text{g/mL}$ (14). A target trough concentration of greater than 1 $\mu\text{g/mL}$ is recommended for treating wild-type virus, as this level is 15 fold higher than the human serum-adjusted EC_{50} for wild-type virus and would likely be sufficient to halt viral replication (Kaletra label, adult guidelines, AIDSInfo.com).

An initial non-compartmental analysis of data collected in this study indicated a large difference between groups starting therapy at different ages but did not indicate if these large differences were due to age, duration of HIV infection (younger infants with shorter time infected), or other population effects. By employing a population PK approach, we were able to demonstrate that the difference was due to age while providing a continuous picture of developmental changes in lopinavir apparent clearance. The analysis also characterized within-subject variability in addition to between-subject variability for measurements made at the intensive PK visits. For purposes of analysis, the age range was extended to 4 years.

Both age and RTV concentration were highly significant and important covariates in the model, accounting for much of the variability in the data and greatly impacting the objective function. RTV acts as a competitive inhibitor of CYP3A metabolism and to a lesser extent of MDR1. Lopinavir is a substrate for both pathways, thus high RTV concentration may result in inhibition of LPV metabolism, extrusion by enterocytes into the GI lumen, and retention of LPV in the GI tract. Additionally, RTV is predominantly metabolized by the same CYP3A pathway as LPV and as such RTV concentrations may serve as a marker of inherent differences in metabolism and absorption between individuals. High apparent clearance has been seen in infants taking RTV, and its influence may contribute to the observed age differences in LPV pharmacokinetics (15). In contrast to prior studies (16, 17), this is the first study of LPV/r in children where RTV was used as a covariate in the model. Among the published population PK studies of LPV/r in adults (18–23), two considered RTV as a fixed effect on clearance (18, 23). These studies demonstrated seven-fold (18) and 8–11 fold (23) differences in apparent clearance over the range of observed RTV AUCs and

concentrations, respectively. The RTV model in the current study predicted a nine-fold difference in apparent clearance over the range of observed RTV pre-dose concentrations. Despite the strength of RTV as a covariate on LPV pharmacokinetics, it is limited in that it cannot be used a priori to predict LPV pharmacokinetics and optimize dosing at the individual or population level. Given that one of our primary objectives was to improve infant dosing of LPV, we constructed a “final” model without RTV as it could not be easily employed in our simulations of dosing recommendations.

Age was the only other significant covariate in the model. Apparent clearance (CL/F) was found to decrease during the first year of life. Aside from the developmental switch from CYP3A7 to CYP3A4 isoform in the first few weeks of life, there are no data to suggest that intrinsic drug metabolism rapidly declines early in life. We therefore postulate that the age effect is primarily due to an increase in bioavailability. LPV bioavailability is highly dependent on food intake, particularly fat. In adults receiving LPV/r, a marked food effect has been observed with a mean increase of 80% and 54% in AUC and peak plasma concentration (C_{max}), respectively, with a moderate fat meal as compared to fasting (Kaletra label). High fat meals showed even greater increases in AUC and C_{max} as compared to fasting (130% and 56%, respectively). Given that an infant’s diet changes dramatically during the first year of life from an exclusively liquid liquid diet to one that includes an increasing amount of solid foods, changes in bioavailability are the most likely source of the observed differences in the PK of drugs. We attempted to utilize food intake as a covariate in the model, but it did not improve the model. This is likely due to the intrinsic difficulty in controlling and capturing informative concomitant food intake data in infants. Thus, it is likely that developmental and dietary changes in infants lead to enhanced LPV/r bioavailability in older infants.

The overall weight adjusted apparent clearance in this study is greater than previously seen in older pediatric populations (14). It is consistent with the reported low lopinavir concentrations seen in infants less than 2 years of age (24). The current study also expands on the prior pediatric population pharmacokinetic study conducted by Jullien et al (16). Their study utilized data generated from clinical monitoring which included 157 pediatric patients ages 3 days to 18 years. While the overall number of subjects was larger in Jullien’s study, it contained fewer infants and used only sparse sampling, thus making it less focused on the developmental changes observed in infants than the current study. As compared with their results, our model predicts a larger overall age-related effect, with higher LPV CL/F values during the first few months of life; however, for infants 5 months of age, the findings were similar in the two studies (0.19–0.20 l/h/kg).

The World Health Organization (WHO) has developed weight band dosing to simplify delivery of antiretroviral therapy in resource limited settings (10). The current WHO weight band dosing recommends a higher dose range for LPV/r than the FDA labeled dose in young infants. Monte Carlo simulations showed that with both dosing recommendations AUC and trough concentration distributions are lower in infants than older pediatric populations. While all three dosing strategies project low troughs (<1 µg/mL) in less than 1% of infants >3 months of age, the higher dose in the WHO weight-band dosing paradigm reduces the frequency of troughs <1 µg/mL from 8% (FDA dosing) to 4% in infants <3 months of age. Due to the high frequency of low trough concentrations, infants in this age group might benefit from more frequent monitoring to assess efficacy of therapy as compared to older children. However because the development of resistance to LPV requires several deleterious mutations in the protease gene, it is unlikely that the short period of low LPV exposure before 3 months of age will have a long term impact (25). Despite all three dosing methods performing comparably in older infants, the WHO weight-band dosing allows for a comparison of weight to a compact table of doses while the BSA based methods (study and

FDA dosing) require obtaining an accurate height and completing a calculation with rounding to ascertain the required dose. Thus the WHO dosing may also be preferable in most settings to limit errors in dosing caused by calculation and inaccurate height measurements.

Of interest, the pharmacodynamic analysis showed little relation between viral RNA levels and LPV pharmacokinetic parameters. Almost every infant in the study showed viral suppression regardless of cohort or initial drug exposure. This seemingly paradoxical response may be explained by the rapid increases seen in LPV exposure in the younger cohort (Cohort 1) during the course of the study. Additionally, persistent low LPV concentrations ($<1 \mu\text{g/mL}$) were rare in the study. The patients maintained trough levels substantially above the human serum-adjusted half maximal effective concentration for the wild-type virus ($0.04\text{--}0.18 \mu\text{g/mL}$) (Kaletra label), and this probably contributed to the difficulty in observing a viral dynamic effect. Another possibility is that the observed initial viral load reduction was the result of other antiretroviral medications used in the study (e.g., azidothymidine and lamivudine). Previous studies have shown that the initial effect of dual nucleoside reverse-transcriptase inhibitor therapy on viral load reduction is substantial (26, 27). The viral dynamics may have also been confounded by the early initiation of therapy which may have impacted the virologic set point.

In conclusion, the population PK of lopinavir is characterized by a high apparent clearance in young infants which decreases with age and can be modeled as an improvement of drug absorption (bioavailability). Dietary changes likely play a large role in infant lopinavir absorption. While younger infants had lower lopinavir (and ritonavir) concentrations, viral dynamics did not relate to early lopinavir exposure of drug. Our model indicates WHO proposed weight band dosing achieves therapeutic lopinavir concentrations for infants.

METHODS

Study Design

International Maternal-Pediatric-Adolescent AIDS Clinical Trials (IMPAACT)/ Pediatric AIDS Clinical Trials Group (PACTG) protocol P1030 is a recently completed multicenter, Phase I/II open label trial performed in the United States and Brazil (7, 8). The study treatment consisted of the liquid formulation of LPV/r dosed at lopinavir 300 mg/m^2 /ritonavir 75 mg/m^2 in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) for HIV-infected infants enrolled between the ages of 2 weeks and 6 months weighing $\geq 2.5 \text{ kg}$ and born at ≥ 32 weeks gestation.

Twelve hour intensive pharmacokinetic studies were performed at study week 2 and when subjects reached one year of age. For the week 2 study, if the trough LPV concentration (C_{trough}) was $<1 \mu\text{g/mL}$ in a subject whose adherence was assessed to be adequate, the LPV/r dose was increased to $450/112.5 \text{ mg/m}^2$ twice daily. For subjects in whom the area under the LPV concentration–time curve in the first 12 hours (AUC_{0–12}) was $>170 \mu\text{g} \cdot \text{h/mL}$, the LPV/r dose was reduced to $230/57.5 \text{ mg/m}^2$ twice daily. In subjects requiring dose adjustments, a repeat PK study was performed 2 weeks following the dose change.

The study was approved by the Institutional Review Board for each participating site and written informed consent was obtained from each child's legal guardian before performance of any study-specific procedure. Guidelines of the Department of Health and Human Services governing experimentation in human subjects were followed.

Pharmacokinetic methods

Intensive pharmacokinetic studies were carried out at week 2 of LPV/r therapy and again when the subjects reached the age of 1 year. For this purpose, blood samples were obtained prior to the morning dose (administered under supervision) and at 2, 4, 8 and 12 hours following an observed dose. In subjects requiring dose adjustment, a repeat PK study was done 2 weeks after the dosage change with blood samples obtained pre-dose and at 4 and 12 hours post dose. Pre-dose concentration samples were also collected every 4-12 weeks throughout the study and stored at -70°C prior to analysis. A multi-analyte HPLC assay using reverse phase HPLC separation was used to quantitate lopinavir and ritonavir and performed at St Jude Children's Research Hospital pharmacology laboratory as previously described (7).

Pharmacokinetic analysis

Pharmacokinetic data were analyzed using the computer program NONMEM (version VI) with a GNU Fortran G77 Compiler. An open one-compartment model (ADVAN2, TRANS2 subroutine) and first-order conditional estimation method (FOCE with interaction) were used to describe the data. An exponential-normal distribution error model was used to describe intersubject variability, and a combination residual error model was used to describe the residual error that could not be explained by the model and could not be attributed to intersubject variability. The drug concentration levels in the subjects were assumed to be at steady state. Where nonadherence was suspected (predose levels below quantifiable limit at any visit), the dose administered during that visit was recorded as a non-steady-state, single dose of the drug.

Pharmacokinetic parameters were scaled by subject size, with clearance (CL) scaled by allometric weight ($\text{WT}^{0.75}$) and volume of distribution (Vd) scaled by weight ($\text{WT}^{1.0}$), before evaluation of other potential covariates (28). Potential covariates were added to the model on CL, Vd, or bioavailability (F) one at a time as either a linear or non-linear function, with covariates that improved the model fitting by a change in the objective function of at least 4 ($P < 0.05$) being retained in the initial covariate screen. All covariates found in this phase were evaluated using a forward selection approach with a change in objective function of at least 6.6 for retention in the final model.

RTV concentration was assessed as a linear covariate on CL, Vd, or F. RTV AUC (from non-compartmental analysis) was also assessed as a linear covariate on CL, Vd, or F and was scaled by median RTV AUC. Information about food was collected on some visits. This information included whether the infant ate any solid food and the volume of formula consumed with the drug dose. Food was considered as a covariate for bioavailability in the model. Separate bioavailability terms were used for the consumption of formula alone as compared to formula with solid food. Estimated food volume consumed was also assessed as a potential covariate for bioavailability.

To account for intra-subject variability between intensive PK visits, inter-occasion variability was tested on clearance (CL), volume of distribution (Vd), and F separately. The residual variability in LPV concentrations following doses with observed administration in the clinic for intensive PK evaluations was found to be lower than following unobserved administration. Separate error terms were used for concentrations following observed and unobserved doses. Empiric Bayesian estimates of individual infant pharmacokinetic parameters were generated from the final model using the POSTHOC subroutine. The final model was cross-validated using a one-by-one removal approach to assess pharmacokinetic model performance.

Monte Carlo simulations were performed using the final model to generate concentration profiles for 10,000 virtual infants from 2 weeks to one year of age. The WHO dosing recommendations go down to 6 weeks of age and were extrapolated for infants between 2-6 weeks based on weight bands (10). The resulting lopinavir concentration profiles for the study dose (lopinavir 300 mg/m²), FDA dose (lopinavir 300 mg/m², <6 months of age; 230 mg/m², >6 months of age) and the WHO weight-band dose were compared to standard adult lopinavir exposure of 400 mg twice a day of lopinavir.

Virology methods

Samples for HIV RNA were collected at study entry, at 2 and 4 weeks, then every 4 weeks through week 24 and every 12 weeks for the remainder of the study. The Amplicor HIV-1 Monitor test, version 1.5 (Roche Molecular Systems, Pleasanton, CA) was used to determine quantitative plasma HIV-1 RNA levels (lower limit of quantitation (LLOQ) = 400 RNA copies/mL). All assays were performed at the UMDNJ Core Virology Laboratory, which is DAIDS-certified, with incorporated quantitative standards supplied by the DAIDS Virology Quality Assurance Program (29).

Pharmacodynamic analysis

Plasma viral RNA data for each subject from initiation of therapy to time of suppression were fit to a biexponential decay model: $V(t) = V_0(Ae^{-\alpha t} + Be^{-\beta t})$, e is the base of the natural logarithm, α is the rate constant for early phase cell death and β is the rate constant for late phase cell death, t represents time, V_0 is baseline viral RNA level. $V(t)$ is viral RNA at a given time. A is the percentage of cells that undergo early phase cell death and B is the percentage of cells that undergo late phase cell death. Time of viral suppression was defined as the first time RNA levels less than 400 copies/mL were recorded on consecutive visits. The values of α (early phase cell death) and β (late phase cell death) were determined in NONMEM using a two compartment exponential decay model starting with steady state virus generation followed by abrupt cessation of virus generation at the initiation of therapy ($n=28$). Alternatively a monoexponential decay model with a single parameter (β) was modeled in patients who did exhibit early phase cell death ($n=1$). Potential relationships between viral dynamic and pharmacokinetic parameters were assessed with Spearman correlation coefficients and general linear model analysis. Statistical analyses were performed using SAS (version 9.1) and p-values less than 0.05 were considered significant.

Acknowledgments

The study team wishes to thank John Rodman PharmD for his contributions to the design and performance of the study, Donald Barkauskas PhD for his assistance with the model cross-validation, Abbott Laboratories for donation of the study drug, and the patients and families who participated in this study.

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) [U01 AI068632], the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Institute of Mental Health (NIMH) [AI068632]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. This work was supported by the Statistical and Data Analysis Center at Harvard School of Public Health, under the National Institute of Allergy and Infectious Diseases cooperative agreement #5 U01 AI41110 with the Pediatric AIDS Clinical Trials Group (PACTG) and #1 U01 AI068616 with the IMPAACT Group. Support of the sites was provided by the National Institute of Allergy and Infectious Diseases (NIAID) and the NICHD International and Domestic Pediatric and Maternal HIV Clinical Trials Network funded by NICHD (contract number N01-DK-9-001/HHSN267200800001C).

REFERENCES

- (1). Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO). AIDS epidemic update: December 2010. Available at: http://data.unaids.org/pub/EPISlides/2010/20101123_GlobalReport_em.pdf
- (2). Nolan M, Fowler MG, Mofenson LM. Antiretroviral prophylaxis of perinatal HIV-1 transmission and the potential impact of antiretroviral resistance. *J. Acquir. Immune Defic. Syndr.* 2002; 30:216–229. [PubMed: 12045685]
- (3). Palumbo P, et al. Antiretroviral treatment for children with peripartum nevirapine exposure. *N. Engl. J. Med.* 363:1510–1520. [PubMed: 20942667]
- (4). Jaspán HB, Lawn SD, Safrit JT, Bekker LG. The maturing immune system: implications for development and testing HIV-1 vaccines for children and adolescents. *Aids.* 2006; 20:483–494. [PubMed: 16470112]
- (5). Milsap RL, Jusko WJ. Pharmacokinetics in the infant. *Environ. Health Perspect.* 1994; 102(Suppl 11):107–110. [PubMed: 7737034]
- (6). Winstanley PA, Orme ML. The effects of food on drug bioavailability. *Br. J. Clin. Pharmacol.* 1989; 28:621–628. [PubMed: 2692684]
- (7). Chadwick EG, et al. Pharmacokinetics, safety and efficacy of lopinavir/ritonavir in infants less than 6 months of age: 24 week results. *AIDS.* 2008; 22:249–255. [PubMed: 18097227]
- (8). Chadwick EG, et al. Early initiation of lopinavir/ritonavir in infants less than 6 weeks of age: pharmacokinetics and 24-week safety and efficacy. *Pediatr. Infect. Dis. J.* 2009; 28:215–219. [PubMed: 19209098]
- (9). Chadwick EG, et al. Long-term outcomes for HIV-infected infants less than 6 months of age at initiation of lopinavir/ritonavir combination antiretroviral therapy. *Aids.* 25:643–649. [PubMed: 21297419]
- (10). Summary of WHO pediatric antiretroviral therapy dosing: Annex E. Available at: http://www.who.int/hiv/paediatric/Sum_WHO_ARV_Ped_ARV_dosing.pdf
- (11). Murphy RL, et al. ABT-378/ritonavir plus stavudine and lamivudine for the treatment of antiretroviral-naïve adults with HIV-1 infection: 48-week results. *Aids.* 2001; 15:F1–9. [PubMed: 11192874]
- (12). Rowland, M.; Tozer, TN. Clinical pharmacokinetics: concepts and applications. Third edn. Lippincott, Williams, and Wilkins; Philadelphia: 1995.
- (13). Chandwani A, Shuter J. Lopinavir/ritonavir in the treatment of HIV-1 infection: a review. *Ther. Clin. Risk. Manag.* 2008; 4:1023–1033. [PubMed: 19209283]
- (14). Saez-Llorens X, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. *Pediatr. Infect. Dis. J.* 2003; 22:216–224. [PubMed: 12634581]
- (15). Chadwick EG, et al. Ritonavir-based highly active antiretroviral therapy in human immunodeficiency virus type 1-infected infants younger than 24 months of age. *Pediatr. Infect. Dis. J.* 2005; 24:793–800. [PubMed: 16148846]
- (16). Jullien V, et al. Population analysis of weight-, age-, and sex-related differences in the pharmacokinetics of lopinavir in children from birth to 18 years. *Antimicrob. Agents Chemother.* 2006; 50:3548–3555. [PubMed: 16940058]
- (17). Rakhmanina N, van den Anker J, Baghdassarian A, Soldin S, Williams K, Neely MN. Population pharmacokinetics of lopinavir predict suboptimal therapeutic concentrations in treatment-experienced human immunodeficiency virus-infected children. *Antimicrob. Agents Chemother.* 2009; 53:2532–2538. [PubMed: 19258274]
- (18). Crommentuyn KM, et al. Population pharmacokinetics of lopinavir in combination with ritonavir in HIV-1-infected patients. *Br. J. Clin. Pharmacol.* 2005; 60:378–389. [PubMed: 16187970]
- (19). Dailly E, Allavena C, Raffi F, Joliet P. Pharmacokinetic evidence for the induction of lopinavir metabolism by efavirenz. *Br. J. Clin. Pharmacol.* 2005; 60:32–34. [PubMed: 15963091]
- (20). Dailly E, Gagnieu MC, Allavena C, Raffi F, Joliet P. No significant influence of saquinavir hard-gel capsule administration on pharmacokinetics of lopinavir in combination with ritonavir: a population approach. *Ther. Drug Monit.* 2005; 27:782–784. [PubMed: 16306855]

- (21). Dailly E, Reliquet V, Raffi F, Joliet P. A population approach to study the influence of nevirapine administration on lopinavir pharmacokinetics in HIV-1 infected patients. *Eur. J. Clin. Pharmacol.* 2005; 61:153–156. [PubMed: 15761750]
- (22). Bouillon-Pichault M, et al. Population analysis of the pregnancy-related modifications in lopinavir pharmacokinetics and their possible consequences for dose adjustment. *J. Antimicrob. Chemother.* 2009; 63:1223–1232. [PubMed: 19389715]
- (23). Molto J, et al. Simultaneous population pharmacokinetic model for lopinavir and ritonavir in HIV-infected adults. *Clin. Pharmacokinet.* 2008; 47:681–692. [PubMed: 18783298]
- (24). Verweel G, et al. Plasma concentrations of the HIV-protease inhibitor lopinavir are suboptimal in children aged 2 years and below. *Antivir. Ther.* 2007; 12:453–458. [PubMed: 17668553]
- (25). Walmsley S, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N. Engl. J. Med.* 2002; 346:2039–2046. [PubMed: 12087139]
- (26). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet.* 2002; 359:733–740. [PubMed: 11888583]
- (27). Moolasart P, Likanonsakul S. The efficacy of combined zidovudine and lamivudine compared with that of combined zidovudine, lamivudine and nelfinavir in asymptomatic and early symptomatic HIV-infected children. *Southeast Asian J. Trop. Med. Public Health.* 2002; 33:280–287. [PubMed: 12236426]
- (28). Anderson BJ, Allegaert K, Holford NH. Population clinical pharmacology of children: general principles. *Eur. J. Pediatr.* 2006; 165:741–746. [PubMed: 16807730]
- (29). Yen-Lieberman B, et al. Evaluation of a quality assurance program for quantitation of human immunodeficiency virus type 1 RNA in plasma by the AIDS Clinical Trials Group virology laboratories. *J. Clin. Microbiol.* 1996; 34:2695–2701. [PubMed: 8897167]

Figure 1. Goodness of fit plots. LPV concentrations (intensive and sparse PK data) from the study were compared with: A. Individual predictions for LPV levels and B. Population PK predicted LPV levels.

Figure 2.

Population PK model results. Estimated lopinavir apparent clearance (CL/F) versus age. The post-hoc empiric Bayesian estimated CL/F was derived from the final pharmacokinetic model for intensive and sparse PK visits. The solid line represents the population based apparent clearance profile which was derived using the allometrically scaled median weight for each age group (WHO 50th percentile weight). Cross-validation of the final model demonstrated a median absolute error similar to the residual error of the model, (50%, 25% to 112%, 25th–75th percentile). There was positive bias in the model with a median error of 18% (–29% to 112%, 25th–75th percentile) likely due to some non-adherence before sparse sample collections.

Figure 3.

Monte Carlo simulations using the FDA dose (300 mg/m², <6 months of age; 230 mg/m² >6 months of age), study dose (300 mg/m²), and WHO weight band dosing recommendations. Median and interquartile range (IQR) of WHO weight band dosing (mg/m²): 0.5-2 months: 377.3 (337.4 – 421.8), 3-6 months: 309.4 (285.9 – 366.7), >6 months: 286.6 (262.7 – 306.7). A. Median LPV trough concentrations (C12). Data represent the median and inter-quartile range of LPV trough concentrations. Median adult trough level is presented by dashed line (4.2 µg/mL). B. Predicted frequency of very low LPV troughs (<1 µg/mL). C. Median drug exposure (area under the curve). Data represent the median and interquartile range of LPV AUC (µg*hr/mL). Mean adult AUC level is presented by dashed line (82.8 µg*hr/mL).

Table 1

Subject characteristics at study entry.

	Cohort 1			* (N=10)			Cohort 2			Δ (N=20)		
	Median	IQR	□	Range	Median	IQR	Range	Median	IQR	Range	Median	IQR
Age (months)	1.3	1.2 – 1.3		0.8 – 1.4	3.5	2.4 – 5.2	1.6 – 5.9	3.5	2.4 – 5.2	1.6 – 5.9		
Weight (kg)	4	3.3 – 4.3		2.9 – 5.3	5.2	4.7 – 6.4	4.1 – 9.9	5.2	4.7 – 6.4	4.1 – 9.9		
BSA (m2)	0.24	0.22 – 0.25		0.20 – 0.29	0.29	0.27 – 0.33	0.24 – 0.43	0.29	0.27 – 0.33	0.24 – 0.43		
Dose (mg)	64	64 – 80		64 – 87	80	80 – 104	64 – 128	80	80 – 104	64 – 128		
Baseline RNA (log10 copies/mL)	6	5.4 – 6.2		4.7 – 7.2	5.7	5.2 – 6.2	3.7 – 6.9	5.7	5.2 – 6.2	3.7 – 6.9		
Baseline CD4 T-cell (%)	41	32 – 49		16 – 59	32	21 – 39	11 – 48	32	21 – 39	11 – 48		
Gender	70% male, 30% female			35% male, 65% female								

* Initiating LPV/r between 2 to 6 weeks of age

Δ Initiating LPV/r between 6 weeks to 6 months of age

□ IQR = interquartile range (25th to 75th percentile)

Table 2

Population PK parameters

	Final Parameter	Standard Error
θ_1	0.507	0.217
θ_2	3.21	1.38
θ_3	0.533	0.157
θ_4	0.147	0.105
θ_5	1.94	1.12
Variability		
Inter-subject (CL)	26.90%	5.30%
Inter-subject (V)	40.30%	10.40%
Inter-subject interaction (CL-V)	27.90%	7.74%
Inter-occasion (F)	74.00%	12.51%
Error		
Proportional (Observed Dose)	28.50%	3.19%
Proportional (Non-observed Dose)	70.10%	3.71%
Additive ($\mu\text{g/mL}$)	0.22	0.069
$\text{CL} = \theta_1 \times \text{WT}^{0.75}$	$\text{V} = \theta_2 \times \text{WT}$	
$\text{F} = (1 + \theta_5 (1 - e^{-(\text{Age} \cdot 1.35) \theta_4}))$	$\text{KA} = \theta_3$	

Population PK final parameter and standard error estimates. Equations for clearance (CL), volume of distribution (V), bioavailability (F), and the absorption rate constant (KA) used in the model.