Safety and Pharmacokinetics of Lopinavir/Ritonavir Oral Solution in Preterm and Term Infants Starting Before 3 Months of Age

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Background: Study of liquid lopinavir/ritonavir (LPV/r) in young infants has been limited by concerns for its safety in neonates.

Methods: International Maternal Pediatric Adolescent AIDS Clinical Trials Network P1106 was a phase IV, prospective, trial evaluating the safety and pharmacokinetics of antiretroviral medications administered according to local guidelines to South African preterm and term infants <3 months of age. Safety evaluation through 24-week follow-up included clinical, cardiac and laboratory assessments. Pharmacokinetic data from P1106 were combined with data from International Maternal Pediatric Adolescent AIDS Clinical Trials Network studies P1030 and P1083 in a population pharmacokinetics model used to simulate LPV exposures with a weight-band dosing regimen in infants through age 6 months.

Results: Safety and pharmacokinetics results were similar in 13/28 (46%) infants initiating LPV/r <42 weeks postmenstrual age (PMA) and in those starting ≥42 weeks PMA. LPV/r was started at a median (range) age of 47 (13–121) days. No grade 3 or higher adverse events were considered treatment related. Modeling and simulation predicted that for infants with gestational age ≥27 weeks who receive the weight-band dosing regimen, 82.6% will achieve LPV trough concentration above the target trough concentration of 1.0 μg/mL and 56.6% would exceed the observed adult lower limit of LPV exposure of 55.9 μg·h/mL through age 6 months.

Conclusions: LPV/r oral solution was safely initiated in a relatively small sample size of infants ≥34 weeks PMA and >2 weeks of life. No serious drug-related safety signal was observed; however, adrenal function assessments were not performed. Weight-band dosing regimen in infants with gestational age ≥27 weeks is predicted to result in LPV exposures equivalent to those observed in other pediatric studies.

Key Words: lopinavir/ritonavir, neonates, safety, pharmacokinetics

(*Pediatr Infect Dis J* 2024;43:355–360)

Lopinavir/ritonavir (LPV/r) oral solution is recommended for first-line HIV treatment for age 2 weeks to <4 weeks and for second-line thereafter.[1,2] After life-threatening cardiac, metabolic, renal and central nervous system dysfunctions were reported in neonates given LPV/r oral solution from birth, the United States Food and Drug Administration (FDA) issued an advisory[3] to avoid LPV/r when <2 weeks postnatal age (PNA; time elapsed since birth) and <42 weeks postmenstrual age [PMA, defined as gestational age (GA) plus PNA] unless potential benefit outweighed risk. For earlier administration, the FDA strongly recommends close safety monitoring as the oral solution contains 42.4% alcohol and 15.3% propylene glycol.[3]

Given limited antiretroviral treatment (ART) options for neonates and young infants and potency of LPV/r-based ART compared to nevirapine-based ART,[4] LPV/r is commonly used in neonates <42 weeks PMA in South Africa. The aim of this study was to describe the safety and pharmacokinetics (PK) of LPV/r oral solution in low birth weight (LBW; <2500 g) and normal birth weight (NBW; ≥2500–4000 g) infants initiating LPV/r before 3 months of age. The study focused on LBW and NBW due to limited access of early antenatal ultrasound required for accurate GA determination. ART was prescribed by the treating clinicians as per standard of care. We compared the safety of infants initiating LPV/r oral solution before 42 weeks PMA with those starting at ≥42 weeks PMA. Furthermore, to assess drug exposures, a population PK model was developed to describe LPV exposure in preterm and term infants from birth through 6 months.

METHODS

Study Design and Setting

International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1106 study was a phase IV trial

Accepted for publication December 13, 2023

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The IMPAACT P1106 trial was registered on ClinicalTrials.gov (NCT02383849) on March 9, 2015.

Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with cofunding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC) and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. A.B. received a CIPHER Grant from the International AIDS Society.

Jincheng Yang is currently an employee of AstraZeneca and has stock ownership in the company. However the work was conducted while at University of California, San Diego.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

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ISSN: 0891-3668/24/434-355360
DOI: 10.1097/INF.0000000000004243

evaluating the safety and PK of antiretroviral medications in LBW and NBW infants <3 months of age in South Africa at the Family Centre for Research with Ubuntu in Cape Town and the Perinatal HIV Research Unit in Johannesburg. An experienced neonatologist was part of the study team at each study site. One group enrolled infants receiving LPV/r as part of clinical care. Infants were enrolled during the 7 days before LPV/r initiation and followed for 24 weeks. Between 2015 and 2019, the recommended ART regimen for children <3 years was either LPV/r or nevirapine combined with 2 nucleotide reverse transcriptase inhibitors.[1,5] Consultation with a clinician experienced in pediatric ART was recommended for infants weighing <3 kg.[5] Written informed consent was obtained from the mother or legally authorized representative for every infant. The study was approved by the research ethics committees of Stellenbosch University (M13/08/037) and the University of the Witwatersrand (140303) and registered on ClinicalTrials.gov (NCT02383849).

Infant Safety Monitoring

Laboratory monitoring included hemoglobin, potassium, calcium, creatinine, osmolality and alanine aminotransferase (ALT) with summary statistics generated by visit and compared by PMA at LPV/r initiation (<42 vs. ≥42 weeks) using Wilcoxon rank-sum test with $\alpha = 0.05$. Osmolality was followed as a proxy for propylene glycol toxicity.[6,7] Cardiac monitoring included electrocardiograms (ECGs) and echocardiograms (ECHOs) before and after LPV/r initiation. ECGs were reviewed by the treating clinician and the local cardiologist. QT prolongation was defined as a total QT interval corrected for heart rate (QTc, calculated as $QT/RR^{1/2}$) of >450 ms or change from baseline QTc >60 ms. Adverse events (AEs) were classified as unexpected or expected. Unexpected AEs were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.[8] We also recorded expected AEs based on a prespecified table developed to capture commonly occurring events associated with prematurity or LBW.[9] The proportion of infants with grade 3 or higher AEs were described using point and 90% Clopper-Pearson confidence interval (CI) estimates.

Pharmacokinetic Sample Collection, Assays and Reference Ranges

Plasma samples for LPV and ritonavir (RTV) measurement were collected predose (C_0) at weeks 2, 6, 10, 16 and 24, with additional samples at 1.5 and 4 hours postdose at weeks 2, 10 and 24. LPV and RTV plasma concentrations were determined using a validated liquid chromatography-tandem mass spectrometry assay at the Division of Clinical Pharmacology, University of Cape Town.[10] A LPV trough target of 1.0 μg/mL and LPV exposures[11] between 55.9 and 129.3 μg·h/mL reported in an adult PK study were used as reference ranges.[12]

Pharmacokinetics Analysis

A population PK analysis was performed with nonlinear mixed-effect modeling using NONMEM, Ellicott City, MD (v7.3, ICON). To better characterize LPV PK during early development, the P1106 LPV PK data were merged with infant (≤1 year) PK data from 2 previous IMPAACT PK trials: P1030 (NCT00038480) and P1083 (NCT01172535) (Table, Supplemental Digital Content 1, http://links.lww.com/INF/F387). PK parameters were allometrically scaled by size a priori as weight $(WT)^{0.75}$ applied to clearance (CL/F) and $WT^{1.0}$ applied to volume of distribution (VD/F). LPV concentrations below quantification limits or with concentrations outside of the expected range due to suspected noncompliance [also considering concurrent abacavir (ABC) concentrations when available] were excluded. GA at birth, sex, LBW and PMA were assessed as covariates on LPV CL/F, VD/F and bioavailability (F). A stepwise approach was used for model building and nested models compared using changes in objective function (OFV) (Δ −3.84, $P < 0.05$). A 1000-sample bootstrap and virtual predictive check were performed to validate the model. Finally, we conducted a Monte Carlo simulation using the PK model on a virtual dataset of 98,000 infants[13] receiving weight-band dosing designed to deliver approximately 300/75 mg/m^2 twice daily from birth up to age 24 weeks.

RESULTS

Infant Characteristics

Between August 2015 and September 2019, 28 infants were enrolled, 27 for HIV treatment and 1 for HIV prophylaxis (Table 1). All infants received LPV/r and lamivudine (3TC), 27 received ABC, and 1 received zidovudine. LPV/r was started before 42 weeks PMA in 13/28 (46%) of infants and the median (range) at first LPV/r dose was 47 (13–121) days.

Clinical and Laboratory Findings

Twenty-eight infants on LPV/r were included in the safety analysis; however, safety blood tests (potassium, calcium, creatinine, osmolality, ALT and hemoglobin) could not be collected for 3 infants. One death occurred before the scheduled 2-week post-LPV/r initiation safety blood sampling could be performed. This term infant, 8 weeks of age, had a 7-day history of gastroenteritis complicated by hypernatremia and acute kidney injury, which were corrected on hospitalization. LPV/r was then initiated and the infant was discharged after 2 days. Unfortunately, the infant died at home a day later. The study and protocol team assessed the death as unrelated to treatment due to the 7-day history of gastroenteritis preceding LPV/r and the infant's relatively older age at time of LPV/r initiation. Safety monitoring laboratory tests were not performed for 2 additional infants. LPV/r was discontinued after 7 days in 1 infant who began LPV/r following an indeterminate HIV PCR result until a second PCR was negative. A third infant on LPV/r had a negative birth HIV PCR and was recruited into the prevention arm. Unfortunately, HIV infection was confirmed at week 16. At age >12 weeks, the infant was too old for enrollment in the treatment arm, and initial specific safety bloods were not performed. The infant appropriately began LPV/r-based ART and exited the study at week

TABLE 1. Infant Characteristics by Postmenstrual Age at Time of Study Entry (n = 28)

	Total	PMA <42 Weeks	PMA ≥42 Weeks
Baseline	N = 28	N = 13	N = 15
Sex (Male)	13 (46)	5 (38%)	8 (53%)
Birth weight (kg)	2288 (1360–3320)	2130 (1360–2470)	2460 (1730–3320)
Low birth weight (<2500 g)	21 (75)	13 (100%)	8 (53%)
Gestational age at birth (wk)	36 (27–39)	35 (27–38)	36 (31–39)
Enrollment age (d)	43 (9–78)	41 (11–64)	49 (9–78)

Values are number (%) or median (range). Study entry took place within 7 days before LPV/r initiation.

24. Safety monitoring tests were available for the remaining 25/28 (89%) infants, all of whom completed 24 weeks of LPV/r (Table, Supplemental Digital Content 2, http://links.lww.com/INF/F387).

Chemistry and hematologic values aligned with typically expected results in young infants. No clinically significant differences were observed between infants starting LPV/r oral solution at PMA <42 weeks versus ≥42 weeks. Eight of 71 (11%) potassium concentrations (Figure, Supplemental Digital Content 3, http://links.lww.com/INF/F387) were elevated (>6.6 to ≤7.1 mmol/L). These elevated potassium levels were observed in 7 asymptomatic infants, deemed due to difficult phlebotomy and considered unrelated to treatment by clinical and study teams. No coinciding low sodium levels were reported, and no symptoms or signs of clinical shock were observed. One potassium level of 7.1 mmol/L was associated with a borderline elevated creatinine of 38 µmol/L (upper normal limit: 35 µmol/L) that resolved spontaneously in the absence of other signs of renal dysfunction. All other creatinine levels were within normal range, and no hypokalemia or calcium abnormalities were documented. A slightly increased osmolality of 307 mOsm/kg (upper normal limit: 305 mOsm/kg) occurred in 1 infant but resolved on follow-up. Two infants developed ALT values above the upper limit of normal (40 IU/L). One had a grade 1 ALT of 70 IU/L and one had a grade 2 ALT of 155 IU/L following ingestion of a hepatotoxic traditional medicine. LPV/r, ABC and 3TC were stopped for 8 days and the AE resolved to a grade 1 (86 IU/L). The same ART was then restarted without further complications. Two infants developed jaundice that resolved following phototherapy.

Electrocardiogram and Echocardiogram Findings

Twenty-four infants had 121 ECGs and 77 ECHOs performed. QTc prolongation was documented once in an asymptomatic infant ≥42 weeks PMA at LPV/r initiation. The QTc prolongation of 466 ms was assessed by the cardiologist as borderline abnormal, occurred in the presence of a normal potassium and calcium and resolved spontaneously while continuing LPV/r treatment. Another 5 asymptomatic infants had QTc increases of >60 ms from baseline with no interruptions or changes to LPV/r administration (Table, Supplemental Digital Content 4, http://links.lww.com/INF/F387). Two infants had mild ECHO abnormalities detected while receiving LPV/r, a slightly thickened interventricular septum (5–6 mm) in one and mild pulmonary valve stenosis in another.

Unexpected and Expected Adverse Events

Fifteen of 28 infants (53.6%; 90% CI: 36.6%–69.9%) met safety endpoints of a grade 3 or higher AE, including one 8-week-old infant with gastroenteritis who died at home 1 day after hospital discharge. None of the grade 3 or higher AEs were considered related to LPV/r and were thought to be associated with prematurity and HIV disease. No AE led to permanent LPV/r discontinuation. Twelve infants (42.9%; 90% CI: 26.9%-60%) had grade 3 or 4 unexpected AEs (Table, Supplemental Digital Content 5, http://links.lww.com/INF/F387) with resolution to grade 2, apart from 1 infant with tracheobronchitis and upper respiratory tract infection whose mother withdrew consent after onset of symptoms, another with malnutrition and one underweight for age infant. Five infants (17.9%; 90% CI: 7.3%–33.9%) had grade 3 or 4 expected AEs (Table, Supplemental Digital Content 6, http://links.lww.com/INF/F387).

IMPAACT P1106 Study LPV/r Pharmacokinetic Results

Among the 28 infants enrolled, 3 infants had no PK samples: 1 due to death, 1 discontinued LPV/r after a negative HIV result and 1 participant was first diagnosed with HIV at study exit. Twenty-five infants were included in the PK analysis (Table 2). The median LPV dose was 418.2 mg/m^2 (23.6 mg/kg) across all visits. Figure 1 illustrates the median normalized LPV concentrations by PMA category. Of the 267 available LPV concentrations, 118 (44.2%) were sampled at trough (C_0), 75 (28.1%) at 1.5 hours postdose and 74 (27.7%) at 4 hours postdose. Forty-seven of 267 (17.6%) PK specimens were excluded (22 below the quantifiable limit and 25 that met nonadherence criteria in participants who had been discharged). The median [interquartile range (IQR)] LPV C_0 across all visits was 5.14 (2.95–8.51) µg/mL. No differences in LPV trough concentrations were observed at study week 2 between infants initiating LPV/r <42 weeks versus starting at ≥42 weeks PMA (7.20 vs. 6.66 µg/mL; P = 0.437). LPV C_0 measurements were above the trough target concentration of 1.0 µg/mL in 80/86 (93%) observations and 16/86 (19%) had a trough target above 10 µg/mL. The median (IQR) RTV C_0 across all visits was 0.11 (0.05–0.18) µg/mL.

LPV Modeling and Simulation Results for P1106, P1030 and P1083 Studies

A one-compartment structural model described the LPV concentration data of infants ≤1 year of age (Table, Supplemental Digital Content 7, http://links.lww.com/INF/F387). Untransformed age using a power model led to the most significant drop in OFV on bioavailability (F) and was retained in the final model (ΔOFV: −36.849). The final population PK parameter estimates were CL/F as $0.38 \cdot WT^{0.75}$, VD/F as $2.47 \cdot WT$ and F as $1 \cdot (PMA/54.5)^{1.19}$. Using the final model, we simulated 98,000 infants up to a PNA of 24 weeks with GA ranging from 27 to 40 weeks using a predefined weight-based LPV/r dosing scheme (Table 3). Simulation revealed an increasing trend of LPV C_0 and area under the concentration-time curves (AUCs) both by GA at birth and weeks postpartum. LPV trough concentrations increased over time across all 3 GA groups (Fig. 2). Over the 24-week period, 79.0%, 82.5% and 86.3% of infants with GAs ≥27 to <30 weeks, 30 to <36 weeks and >36 weeks had C_0 above 1.0 µg/mL, respectively. Similarly, 49.4%, 55.8% and 64.6% of the infants in the GA of ≥27 to <30 weeks, ≥30 to <36 weeks and >36 weeks groups had AUCs above 55.9 µg·h/mL across the 24-week period (Figure, Supplemental Digital

TABLE 2. LPV/r Dosing, Infant Characteristics and Trough Concentrations at Time of Pharmacokinetic Sampling (n = 25)

	Study Week 2	Study Week 6	Study Week 10	Study Week 16	Study Week 24
LPV dose (mg/kg)	26.6 (19.6–35.0)	23.6 (17.6–31.9)	23.0 (18.1–29.0)	23.0 (18.5–27.2)	21.9 (16.8–28.4)
LPV dose (mg/m^2)	426.3 (317.1–504.7)	401.8 (336.4–533.6)	395.5 (337.9–523.8)	441.4 (354.7–503.4)	426.6 (370.7–522.9)
Weight (kg)	3.7 (2.00–5.39)	4.61 (2.96–5.68)	4.99 (3.79–6.79)	5.88 (3.86–7.68)	6.85 (5.29–8.93)
Postnatal age (wk)	8 (4–13)	12 (8–17)	16 (10–21)	22 (17–27)	30 (26–35)
Postmenstrual age (wk)	43.57 (36.14–49.57)	48.14 (40.14–54.42)	51.78 (44.14–58.00)	57.86 (51.57–62.86)	66.21 (58.57–70.71)
LPV trough concentration (µg/mL)	4.4 (1.0–14.4)	4.7 (0.6–13.5)	6.4 (1.1–11.3)	5.2 (0.9–17.6)	5.2 (0.8–14.9)
RTV trough concentration (µg/mL)	0.06 (0.02–0.42)	0.10 (0.01–0.86)	0.11 (0.01–0.34)	0.12 (0.03–0.94)	0.16 (0.04–0.79)

Values are number (%) or median (range). Forty-seven PK samples were removed due to below quantification limits or nonadherence.

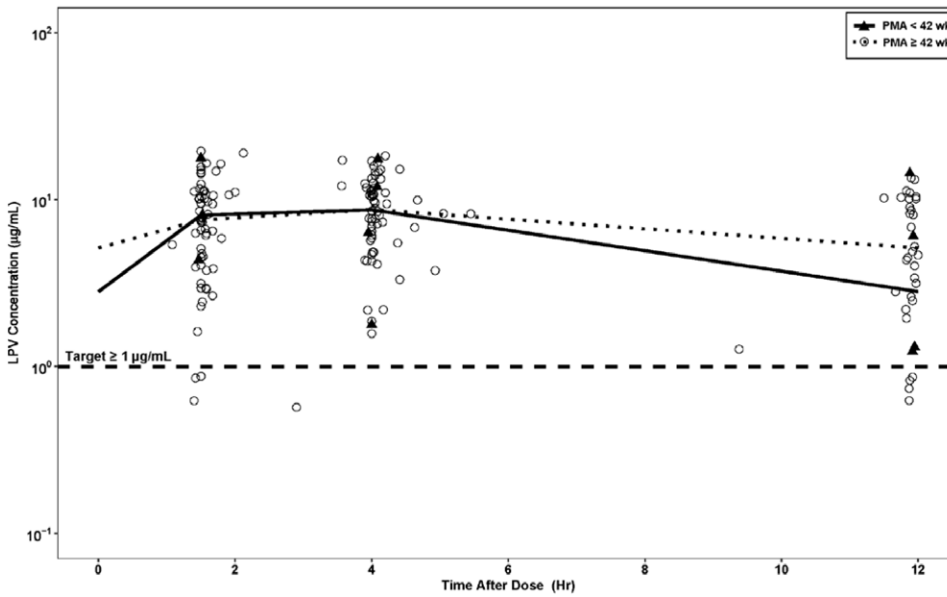

FIGURE 1. Measured nondose normalized LPV concentrations for infants in IMPAACT P1106. Solid line represents median concentration in infants with PMA <42 weeks and dotted line represents the median concentration in infants with PMA ≥42 weeks. Infant time 0-hour collected LPV concentration was assumed to be representative of trough level at 12 hours. Majority of infants LPV trough concentrations are above 1 µg/mL. LPV target indicates LPV trough concentration of ≥1 µg/mL.

TABLE 3. LPV/r Weight-band Dosing Used for Simulations

Weight Band	LPV/r Volume Twice Daily
≥1.00 to <1.50 kg	0.5 mL
≥1.50 to <2.00 kg	0.6 mL
≥2.00 to <2.50 kg	0.75 mL
≥2.50 to <3.00 kg	0.8 mL
≥3.00 to <3.50 kg	0.9 mL
≥3.50 to <4.00 kg	1 mL
≥4.00 to <4.50 kg	1.1 mL
≥4.50 to <5.00 kg	1.2 mL
≥5 to <6 kg	1.5 mL

LPV/r oral solution: 80 mg lopinavir and 20 mg ritonavir per milliliter.

Content 8, http://links.lww.com/INF/F387; Table, Supplemental Digital Content 9, http://links.lww.com/INF/F387), corresponding to the observed lower limit of adult LPV exposure in a PK study of 19 adults living with HIV who received multiple dosing of 400/100 mg LPV/r twice daily over 3 weeks.[14]

DISCUSSION

The LPV/r oral solution was safe in our study population of predominantly LBW and preterm infants who began LPV/r-based ART after age 2 weeks and before age 3 months. Importantly, almost half of all infants initiated LPV/r before 42 weeks PMA, with no safety or PK differences compared with results in those starting LPV/r at ≥42 weeks PMA. LPV PK parameters were similar to those previously observed in term infants who began treatment below age 6 weeks receiving the same oral LPV/r solution.[15] While AEs were common, as expected for this study population, no grade 3 or higher AEs were considered treatment related.

An FDA Drug Safety Communication in 2011 noted potential toxicity with use of LPV/r oral solution in preterm neonates in the immediate postnatal period and in term neonates <14 days of age. This followed 10 postmarketing cases of life-threatening reports occurring predominantly in preterm neonates (28–34 weeks GA) receiving LPV/r, with onset of toxicity observed within 6 days in 8 infants. The toxicities reported were consistent with possible LPV/r, ethanol and/or propylene glycol toxicity. The FDA Adverse Events Reporting System (AERS) database (2000–2010) reported 7 infants with cardiac dysfunction, including cardiogenic shock in one infant who died from an LPV/r overdose.[3] A complete heart block and dilated cardiomyopathy developed in a set of twins at 28 weeks' gestation[16] and in another set of twins of 32 weeks' gestation, one developed complete heart block with dilated cardiomyopathy and the other a mild bradycardia.[17] All of these symptoms resolved after stopping LPV/r. LPV concentrations were determined for 5 infants with the highest LPV concentrations ranging from 16.2 to 29.2 µg/mL.[3] It is unclear if the relatively high LPV exposure contributed to this infant's cardiac toxicity. LPV causes PR and QT interval prolongation and atrioventricular block in adults with very high LPV concentrations.[12] In our study, no infant developed clinical symptoms or signs of cardiac dysfunction; however, it is important to note that LPV/r was only started after 13 days PNA and at ≥ 34 weeks PMA. Acute renal failure was also documented in the AERS review in 5 infants; 4 with hyperkalemia and 1 with an increased serum creatinine.[3] We had no infants with acute renal failure. Seven asymptomatic study infants had elevated serum potassium levels, likely due to hemolysis associated with infant blood drawing rather than true hyperkalemia; all were assessed as unrelated to treatment. In contrast to the AERS review, we had no infants with neuromuscular toxicity, respiratory complications or gastrointestinal AEs considered related to LPV/r.

Transient adrenal dysfunction has also been reported in neonates on LPV/r for prevention of HIV. Significant increases in 17-hydroxyprogesterone (17OHP) concentrations were observed in neonates started on LPV/r, compared with those receiving a regimen without a protease inhibitor. Moreover, 3 of 7 neonates (all

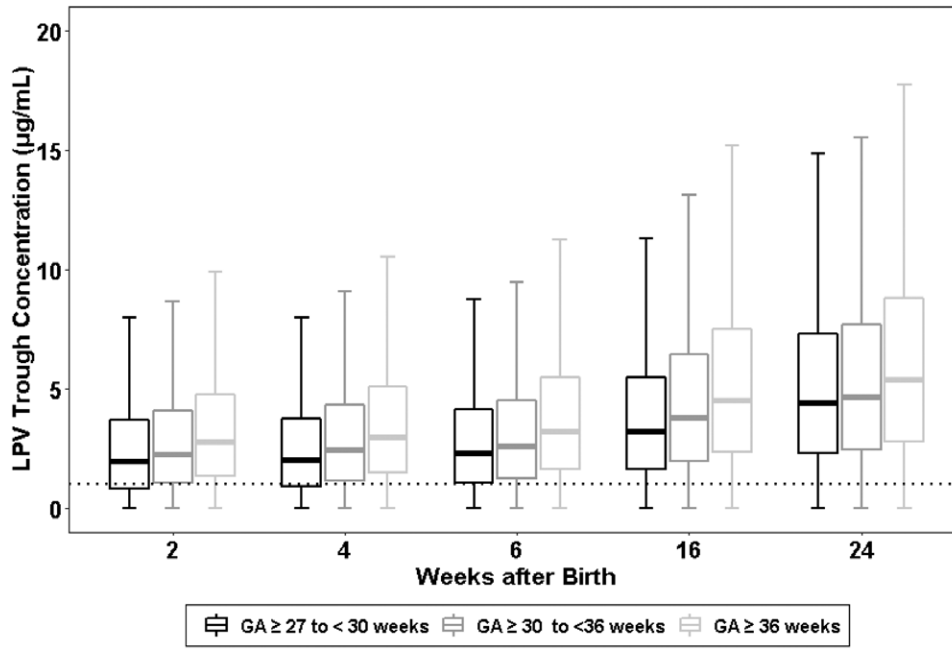

FIGURE 2. Model-simulated LPV trough concentrations of 98,000 virtual infants using a predetermined dosing regimen (Table, Supplemental Digital Content 6, http://links.lww.com/INF/F387) across 4, 6, 16 and 24 weeks after birth stratified by gestational age ≥27 to <30 weeks, 30 to <36 weeks and ≥36 weeks. The dashed line represents the LPV effective trough concentration of 1 µg/mL.

preterm) with very high 17OHP levels experienced life-threatening events compatible with an adrenal crisis: that is, hyponatremia, hyperkalemia and one case of cardiogenic shock. All symptoms resolved after LPV/r discontinuation.[18] Following these important findings, a study by the same authors evaluated the adrenal-hormone profiles of infants receiving LPV/r or 3TC for HIV prevention during breastfeeding at week 6 and 26 of life. At week 6, high dehydroepiandrosterone (DHEA) levels were observed in the LPV/r group. These DHEA levels decreased over time but remained higher at week 26 in the LPV/r group than the 3TC group. No clinical toxicity suggestive of adrenal dysfunction was observed throughout age 1 year.[19] The clinical impact of these abnormal laboratory changes in immature neonates on LPV/r must be further explored. Fortunately, we had no study infants hospitalized for adrenal insufficiency but cannot comment on any 17OHP or DHEAS levels as these were not assessed.

The LPV/r oral solution, which contains high volumes of ethanol and propylene glycol, was the only pediatric oral LPV/r formulation available at the time for young infants. Adding these excipients/solvents increases LPV/r solubility but may have also increased the risk of toxicity. This may be due to both ethanol (95%) and propylene glycol (55%) being metabolized by alcohol dehydrogenase, which has low activity at birth that rapidly increases early in life.[20,21] Ethanol also competitively inhibits propylene glycol metabolism, which further delays propylene glycol elimination, leading to accumulation.[3] Alone, propylene glycol has a prolonged half-life in preterm infants (10.8–30.5 hours)[22,23] but with a rapid increase in clearance after birth. A recent pharmacokinetic model predicted a 10-fold difference in propylene glycol clearance in preterm and term neonates at age 1 month with the largest increase in the first 2 weeks of life,[21] reinforcing caution when using these formulations early in life.

Lopinavir is highly protein bound with poor bioavailability, and coformulation with RTV increases LPV plasma concentrations. An adult PK study in which LPV/r at 400/100 mg was administered twice daily resulted in a mean steady state LPV trough concentration of 5.5 ± 2.7 µg/mL,[12] similar to our study observations. The median (IQR) LPV C_0 across all visits in our study for infants receiving average LPV doses of 418.22 mg/m^2 twice daily was 5.14 (2.95–8.51) µg/mL. Most infants in P1106 had LPV trough concentrations above the minimal effective target concentration of 1.0 µg/mL, corresponding to a 15-fold margin above the estimated IC_{50} for LPV.[11] In a study of adults, LPV AUC over a 12-hour dosing interval was 92.6 ± 36.7 µg·h/mL.[12] These LPV AUC exposures in adults were much higher than those observed in pediatric studies in which infants (14 days to 6 weeks) receiving LPV/r at 300/75 mg/m^2 twice daily had a median LPV exposure of 36.6 (range: 27.9–62.6) µg·h/mL. Despite this lower AUC, 8 of these 10 infants achieved virologic control by 24 weeks.[15] Moreover, findings in 100 children (6 months to 12 years) receiving LPV/r at 300/75 mg/m^2 with similar low AUC LPV/r exposures reported excellent antiviral activity, with 79% of participants having a plasma viral load <400 copies/mL at week 48.[24] There are many potential reasons for low LPV AUC exposures early in life, including low RTV concentrations, altered protein binding and poor absorption with LPV bioavailability increasing with age. A simulation of virtual infants using our model indicates that a dose higher than 300/75 mg/m^2 twice daily may be needed to ensure increased LPV exposures in most infants. The decision to use a higher dose should, however, be carefully considered against the potential increased risk of toxicity using this oral solution formulation from birth, cautioning against this approach.

A limitation of the P1106 study was that HIV viral load reporting was not required. We could, therefore, only assess potential efficacy and adherence from measuring plasma ARV concentrations. A strength of our study was very robust study safety monitoring. The P1106 protocol team and study site representatives jointly reviewed the

toxicity reports monthly and an independent safety monitoring committee convened every 6 months to review all safety data. LPV and RTV concentrations were reported in real time to clinical caregivers to support dosing modifications and a protocol pharmacologist was available for consultation and interpretation of results.

With few neonatal ARV formulations available, LPV/r-based ART remains an important neonatal therapeutic option. Our study suggests that the oral LPV/r solution is safe and effective in preterm infants after a PMA of 34 weeks and 2 weeks PNA, which is below the recommended FDA threshold. Our modeling and simulations suggest LPV plasma concentrations will be appropriate when using the proposed weight-band dosing regimen in infants with GA of at least 27 weeks when started after age 2 weeks. One reason why we saw no LPV/r-related toxicity could be rapid maturation of enzyme pathways in the first 2 weeks of life, independent of PMA. New solid LPV/r pediatric formulations are now being manufactured by Viatris, Hyderabad, Telangana, India, which may have a role from birth. The PETITE study underway in South Africa recently assessed the PK and safety of 2 sachets of 40/10 mg LPV/r granules twice daily with a quarter of the 120/60 mg ABC/3TC dispersible tablet once daily (Viatris) in term neonates. The solid ARV formulations were safe, well-tolerated and achieved therapeutic drug exposures through 4 weeks of life,[25] raising the question of the extent to which excipients in the LPV/r oral solution were responsible for the initial toxicities observed shortly after birth. Nevertheless, LPV/r has an important role to play when initiating early ART in neonates to reduce HIV disease progression and mortality[26] while we await PK and safety data on dolutegravir in neonates or should dolutegravir resistance be present or suspected.

ACKNOWLEDGMENTS

The authors thank the infants, their families and the staff of the participating research sites. The authors also acknowledge cardiology support from A. Cilliers and J. Lawrenson.

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