PHARMACOKINETICS AND SAFETY OF LOPINAVIR/RITONAVIR SOLUTION IN HIV-INFECTED NEWBORNS

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Introduction

- Life-threatening cardiac, metabolic, renal and central nervous system dysfunction in newborns receiving LPV/r in the first weeks of life led to revised labeling from the United States Food and Drug Administration (FDA) in 2011 to recommend use only when > 2 weeks postnatal age (PNA; time elapsed since birth) and > 42 weeks postconceptional age (PCA; gestational age plus PNA), unless the benefit outweighs the potential risks (1).
- Lopinavir/ritonavir (LPV/r) solution contains 42.4% alcohol and 15.3% propylene glycol.
- Early initiation of combination antiretroviral therapy (cART) is now feasible by HIV PCR testing at birth and recommended by the World Health Organization (2). First-line cART for South African children < 3 years of age consists of either LPV/r (a protease inhibitor; PI) or nevirapine (a non-nucleoside reverse transcriptase inhibitors; NNRTI) with 2 nucleoside reverse transcriptase inhibitors (NRTIs).
- Since the FDA advisory for LPV/r, only nevirapine (with lamivudine and zidovudine) is available for newborns < 42 weeks PCA.
- LPV/r has better infant outcomes than NNRTI-based cART, regardless of prior nevirapine exposure (3,4). The high threshold of LPV/r for resistance compared to NNRTIs (5) supports its use. In a recent multi-country analysis, NNRTI resistance was prevalent in 53% of newly diagnosed African HIV-infected infants and young children, especially when exposed to antiretrovirals through PMTCT (6).
- While LPV/r has clear advantages for cART in newborns and is commonly used in clinical practice in HIV infected low and normal birth weight newborns in South Africa, limited data are available on its pharmacokinetics (PK) and safety in this medically fragile population.

Objective

- To describe the PK and safety of LPV/r solution in HIV-infected low birth weight - (LBW; < 2500 grams) and normal birth weight (NBW; ≥ 2500-4000 grams) newborns receiving LPV/r in clinical care.

Methods

- IMPAACT P1106 is an opportunistic multi-arm Phase IV prospective study of the PK and safety in newborns receiving antiretroviral and antituberculosis medicines in clinical care.
- Sites: Family Clinical Research Unit (FAM-CRU) in Cape Town and the Perinatal HIV Research Unit (PHRU) in Johannesburg, South Africa
- In this 6 arm study, arm 5 focused on LPV/r treatment in LBW and NBW HIV-infected newborns < 3 months of age. Participants were enrolled within 7 days prior to LPV/r initiation through 12 weeks of life. HIV-infected newborns on nevirapine, lamuvidine and zidovudine were transitioned to LPV/r, lamuvudine and zidovudine at clinician discretion.
- LPV/r dosage was 300/75 mg/m^2 twice daily. All newborns were followed to 6 months post-LPV/r initiation.
- Newborn characteristics and safety data were collected at study entry (within 7 days prior to LPV/r initiation) and again at days 3-5, days 7-9 and week 2, 6, 10, 16 and 24 post LPV/r initiation.
- Plasma for LPV/r assay was collected pre-dose (C0) at week 2, 6, 10, 16 and 24 and at 1.5 and 4 hours post-dose at week 2, 10 and 24 post LPV/r initiation. LPV was measured by LC/MS/MS (lower limit of quantitation of 0.02 µg/mL). The LPV trough target (C0) was >1 µg/mL.
- Laboratory safety monitoring included the collection of alanine aminotransferase (ALT), creatinine, potassium, calcium, haematocrit and osmolality at specified intervals.

Methods (continued)

- Cardiac safety monitoring comprised 5 electrocardiograms (ECGs) and 3 echocardiograms (ECHOs) for each newborn:
  - 1 ECG before LPV/r initiation and again at days 3-5, days 7-9 days, week 2 and week 6 post LPV/r initiation.
  - QTc (QT interval corrected for heart rate) prolongation was defined as total QTc > 450 msec or a change from QTc baseline of > 60 msec calculated through Bazett's formula.
  - 1 cardiac ECHO was performed before LPV/r initiation, at day 7-9 and week 6 post LPV/r initiation.
- Adverse events (AEs), potentially harmful to a newborn, were classified as follows: Expected: events pre-identified as commonly associated with prematurity or LBW. Unexpected: unanticipated events not commonly associated with prematurity. The primary composite safety endpoint included death and Grade 3/4 AEs.

Results

- Arm 5 accrued 25 newborns with confirmed HIV-infection between November 2015 and July 2017.

Table 1. Characteristics of HIV-infected newborns on LPV/r at study entry (n=25)

Characteristic	N (%)[1]
Male gender	13 (52)
Ethnicity (Black African) [2]	22 (88)
Birth weight (kg)	2.130 (1.775, 2.630)
Gestational age at birth (weeks)[3]	35.4 (32.0, 37.0)
Low birth weight	18 (72)
Enrollment age (days)	45 (35, 61)
Post conceptional age at entry (weeks)	41 (40.6, 42.6)

[1] Values are median and (IQR) unless specified otherwise
[2] Mixed race in 3 newborns
[3] Gestational age not available for 3 newborns

- As of 26 January 2018, 206 LPV concentrations are available from 23 newborns. The median (IQR) PCA age for the 23 newborns at initiation of LPV/r therapy was 41.9 (40.6, 42.6) weeks. Thirteen of 23 (57%) initiated LPV/r therapy < 42 weeks PCA age. Of these, the PCA range was 33.9 to 41.9 weeks. Participant characteristics and LPV concentrations at PK sampling are in Table 2.

Table 2. Characteristics of HIV-infected newborns on LPV/r at time of PK sampling (n=23)[1]

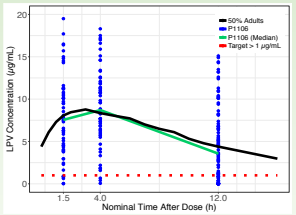
Characteristic	Week 2	Week 6	Week 10	Week 16	Week 24
Current WT (kg)	3.6 (3.4, 4.1)	4.5 (4.1, 4.9)	5.0 (4.5, 5.6)	5.6 (5.4, 6.6)	6.8 (5.8, 8.1)
Dose (mg/kg)	27.1 (24.7, 28.9)	23.7 (21.9,27.2)	22.6 (20.3, 25.7)	22.7 (19.9, 26.1)	20.8 (17.5, 26.0)
PNA (weeks)	8.9 (7.8, 10.8)	12.9 (11.8, 14.9)	17.0 (16.1,19.0)	23.0 (21.8, 24.5)	31.2 (29.8, 32.6)
PCA (weeks)	43.5 (42.7, 44.9)	47.5 (46.7,48.8)	51.8 (50.6,52.9)	57.2 (56.2, 58.8)	65.8 (64.6, 66.6)
C_0 (µg/mL)[2]	1.8 (0.7, 7.7)	4.6 (1.0, 6.8)	4.5 (1.7, 7.6)	3.1 (0.1, 6.8)	4.0 (0.3, 12.4)
$C_{1.5}$ (µg/mL)[3]	6.1 (3.9, 9.5)	15	9.6 (6.5, 10.8)	–	4.7 (3.0, 11.3)
C_4 (µg/mL)[3]	7.2 (5.5, 11.2)	13.4	9.2 (7.0, 11.2)	–	11.3 (6.9, 14.9)

[1] Values are median and (IQR)
[2] Only one 1.5 and 4 hour post LPV dose measurement was taken on week 6 and none were taken on week 16
[3] C_0 = LPV concentration at predose; $C_{1.5}$ = LPV concentration at 1.5 hours postdose; C_4 = LPV concentration at 4 hours post dose

Results (continued)

- Of the 206 LPV measurements, 93 were sampled at trough (C0), 57 at 1.5 hours postdose, and 56 at 4 hour postdose. Fifteen PK specimens were below the lower limit of quantification (LLOQ) of 0.02 µg/mL. For statistical analysis, specimens <LLOQ were assigned values of 0.01 µg/mL (half of the LLOQ). The median (IQR) C0 was 3.6 (0.6, 7.4) µg/mL, with 1.5 and 4 hour levels approximately 2-2.5 times higher. Figure 1 depicts observed LPV concentrations versus the nominal time after dose and visually compares median observed LPV concentrations for participants in this study to 50th percentile predicted adult concentrations. 65 of 93 (69.9%) LPV C0 measurements were above the trough target concentration of 1 µg/mL.

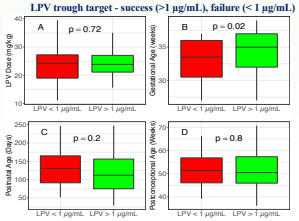
Figure 1. Observed lopinavir concentrations plotted by nominal time after dose



The dosing interval for LPV is 12 hours. The nominal time after dose of 12 hours = C_0.

- Figure 2 illustrates participant characteristics in relation to the LPV trough target of 1 µg/mL. The mean gestational age of participants with LPV concentrations above the target trough (34.6 weeks) was greater than those who fell below (32.8 weeks, p = 0.02), while no differences were observed between dose, postnatal age, or postconceptional age and trough target success.

Figure 2. Participant characteristics stratified by LPV trough target - success (>1 µg/mL), failure (< 1 µg/mL)

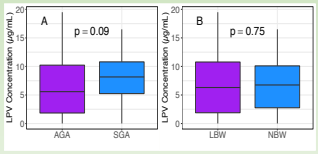


Significance calculated using the student's t test for unpaired samples.

Results (continued)

- No difference was observed in LPV concentrations when stratified by fetal growth or birth weight (Figure 3).

Figure 3. LPV concentrations stratified by fetal growth



AGA = appropriate for gestational age; SGA = small for gestational age; LBW = low birth weight; NBW = normal birth weight. Significance was calculated using the student's t test for unpaired samples.

Adverse events

- As of 26 January 2018, 24 of 25 newborns are off-study (22 completed follow-up, 1 died and 1 withdrew consent) and 1 is still on study.
- All 24 Arm 5 safety evaluable newborns also received lamuvidine. Other medications included abacavir n=22 (92%), nevirapine n=21 (88%), zidovudine n=20 (83%) and trimethoprim-sulfamethoxazole n=20 (83%). One newborn was on isoniazid preventive therapy.
- Of the 24 newborns included in the safety analysis, 14 (58 %) met the primary composite safety endpoint: 1 had a Grade 3/4 Expected AE, 9 had Grade 3/4 Unexpected AEs and 4 had both Grade 3/4 Unexpected and Expected AEs. One newborn (day 4 LPV/r) died a day after hospitalization for acute gastroenteritis at 8 weeks of life.

Table 4. Expected Adverse Events

Episodes	Grade	Newborns
Gastro-intestinal dysfunction (n=1) Respiratory insufficiency (n=1) Sepsis (n=2) Thrombocytopenia (n=1)	3	3
Sepsis (n=1) Hypotension (n=1) Electrolyte disorder (n=1)	4	2

Table 5. Unexpected Adverse Events

Episodes	Grade	Newborns
Gastrointestinal dysfunction (n=10) Respiratory tract infections (n=7) Bacterial sepsis (n=1) Meningitis pneumococcal (n=1) Abnormal potassium (n=4)	3	10
Gastroenteritis (n=1) Abnormal potassium (n=1)	4	2

- All Grade 3 and 4 AEs were considered unrelated to LPV/r. All Grade 4 Expected and Unexpected AEs resolved. All Grade 3 Expected AEs resolved at later visits, except one newborn with sepsis at the last study visit who was taken off- study on the same day. All Grade 3 Unexpected AEs resolved or were down-graded to Grade 1/2, except for 3 newborns with malnutrition, underweight and an upper respiratory tract infection, respectively.

Results (continued)

- Additional laboratory safety bloods included monitoring of alanine transferase (ALT), osmolality, calcium and creatinine. The median and (interquartile range) are described below:

Alanine transferase (IU/L)	16 (13 – 21)
Osmolality (mOsm/kg)	290 (288 – 294)
Calcium (mmol/L)	2.61 (2.53 – 2.66)
Creatinine (µmol/L)	24 (20 – 27)

- Two newborns developed ALT values above the upper limit of normal (40 IU/L); 70 IU/l (Grade 1) and 155 IU/L (Grade 2), respectively. The Grade 2 ALT event was associated with a history of hepatotoxic traditional medicine and resolved on follow-up. One newborn had a slightly raised osmolality value of 307 mOsm/kg (305 mOsm/kg the upper limit of normal). No calcium or creatinine abnormalities were noted for any newborn on LPV/r.

Electrocardiogram (ECG) and Echocardiogram (ECHO) findings

- Despite newborns undergoing physiological QTc prolongation that commonly resolves by six months of age, none had a documented QTc prolongation of > 450 msec.The median and (IQR) QTc interval was 395 (364 – 412) msec at baseline versus 420 (400 – 430) msec, respectively post LPV/r initiation. Four newborns had QTc changes from baseline of > 60 msec; but all were asymptomatic throughout and clinically well at their 24 week study visit. All newborn ECHOs were normal except for two with mild abnormalities; a slightly thickened interventricular septum (5-6 mm) and mild pulmonary valve stenosis. No cardiac complications were observed throughout the study period.

Conclusions

In our population of HIV-infected low and normal birth weight neonates and young infants receiving LPV/r at doses of 300/75 mg/m^2 twice daily:

- We observed no treatment related adverse events
- LPV concentrations were similar to those seen in adults, with most C0 >1 µg/mL.
- LPV/r was well tolerated and achieved effective plasma exposures in our study participants, including those who started therapy prior to 42 weeks postconceptional age.
- Our data suggests that LPV/r can be safely and effectively used in neonates below the postnatal and postconceptional age thresholds in the FDA recommendations.

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