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Suboptimal Lopinavir Exposure in Infants on Rifampicin Treatment Receiving Double-dosed or Semisuperboosted Lopinavir/Ritonavir: Time for a Change

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Background: Although super-boosted lopinavir/ritonavir (LPV/r; ratio 4:4 instead of 4:1) is recommended for infants living with HIV and receiving concomitant rifampicin, in clinical practice, many different LPV/r dosing strategies are applied due to poor availability of pediatric separate ritonavir formulations needed to superboost. We evaluated LPV pharmacokinetics in infants with HIV receiving LPV/r dosed according to local guidelines in various sub-Saharan African countries with or without rifampicin-based tuberculosis (TB) treatment.

Methods: This was a 2-arm pharmacokinetic substudy nested within the EMPIRICAL trial (#NCT03915366). Infants aged 1–12 months recruited into the main study were administered LPV/r according to local guidelines and drug availability either with or without rifampicin-based TB treatment; during rifampicin cotreatment, they received double-dosed (ratio 8:2) or semisuperboosted LPV/r (adding a ritonavir 100 mg crushed tablet to the evening LPV/r dose). Six blood samples were taken over 12 hours after intake of LPV/r.

Results: In total, 14/16 included infants had evaluable pharmacokinetic curves; 9/14 had rifampicin cotreatment (5 received double-dosed and 4 semisuperboosted LPV/r). The median (IQR) age was 6.4 months (5.4–9.8), weight 6.0 kg (5.2–6.8), and 10/14 were male. Of those receiving rifampicin, 6/9 infants (67%) had LPV Ctrough $<$1.0 mg/L compared with 1/5 (20%) in the control arm. LPV apparent oral clearance was 3.3-fold higher for infants receiving rifampicin.

Conclusion: Double-dosed or semisuperboosted LPV/r for infants aged 1–12 months receiving rifampicin resulted in substantial proportions of subtherapeutic LPV levels. There is an urgent need for data on alternative antiretroviral regimens in infants with HIV/TB coinfection, including twice-daily dolutegravir.

Key Words: lopinavir, infants, rifampin, HIV, tuberculosis, CYP3A4, drug–drug interaction

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INTRODUCTION

Tuberculosis (TB) is a major cause of death for children living with HIV (CLHIV).[1] In 2021, of 1.7 million CLHIV, 21,000 died due to TB, accounting for about 20% of total AIDS-related deaths among children.[2] Ritonavir-boosted lopinavir (LPV/r) is regularly used as part of an antiretroviral treatment (ART) regimen for infants living with HIV. However, concomitant use of LPV/r and rifampicin (also known as rifampin), an essential element of first line TB treatment, results in substantially reduced LPV and ritonavir exposure and subsequent treatment failure through induction of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein by rifampicin.[3,4]

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Super boosting of LPV/r by increasing the ritonavir dose to match the LPV dose (ratio 4:4 instead of 4:1) was found to be an appropriate dosing strategy for infants to overcome the interaction with rifampicin[5]; hence, this strategy is recommended in WHO treatment guidelines.[6] In clinical practice, however, other dosing strategies, that is, double-dosed LPV/r (ratio 8:2) or semisuperboosted LPV/r (adding a ritonavir 100 mg crushed adult tablet to the evening LPV/r dose), are used for infants receiving rifampicin due to limited availability and the poor tolerability of separate ritonavir pediatric formulations needed to superboost LPV/r. However, previous research has shown that double dosing of LPV/r in infants and young children receiving rifampicin resulted in subtherapeutic LPV trough plasma concentrations in 60% of children.[7] It must be noted that only 4 infants aged less than 1 year old were included in that study while the activity of LPV and ritonavir metabolism changes greatly during the first year of life due to CYP3A4 maturation.[7]

We evaluated the pharmacokinetics, and exploratory safety and efficacy of LPV/r in infants living with HIV aged ≤12 months receiving LPV/r according to local dosing guidelines cotreated with rifampicin as part of standard TB treatment and compared with infants receiving LPV/r without TB treatment.

METHODS

Study Design and Participants

This is a 2-arm pharmacokinetic substudy nested within the EMPIRICAL multicenter, open-label randomized controlled clinical trial (#NCT03915366) to evaluate whether empirical treatment against cytomegalovirus and tuberculosis improves survival of infants living with HIV admitted with severe pneumonia.[8] Inclusion criteria for the main trial were as follows: aged 28–365 days with confirmed HIV infection with pneumonia and criteria for admission and parenteral antibiotics following WHO guidelines.[8] Eligible infants were randomized to 1 of 4 arms: (1) standard of care (SOC antibiotics, therapeutic cotrimoxazole, and prednisolone), (2) SOC plus 6 month rifampicin-based TB treatment, (3) SOC plus 15 days of valganciclovir, and (4) SOC plus TB treatment plus valganciclovir. If TB was diagnosed after enrolment, infants not randomized to TB treatment were also treated with rifampicin-based TB treatment.[8]

For this PK substudy, enrolled infants weighing more than 3 kg at the time of PK sampling and receiving LPV/r with (rifampicin arm) or without (control arm) rifampicin-based TB treatment were recruited from hospitals in Mozambique, Zambia, and Zimbabwe. The use of concomitant medications, other than rifampicin, known to have drug–drug interactions with lopinavir, having grade 4 anemia or being likely to progress to Grade 4 anemia at the time of sampling (see Table S1, Supplemental Digital Content, http://links.lww.com/QAI/C24 for more details), and vomiting within 4 hours of drug administration were exclusion criteria for this substudy. The EMPIRICAL trial protocol, including pharmacokinetic substudies, was approved by local ethics committees and national authorities.

Procedures

Lopinavir/r oral solution or granules used in the trial were not trial investigational drugs and were dispensed according local guidelines. Infants enrolled in Mozambique and Zambia received LPV/r dosages following WHO weight-band dosing,[6] whereas in Zimbabwe, the national guidelines deviate from WHO guidelines and include 1 dose for infants weighing 3–10 kg (LPV/r morning dose: 160/40 mg and evening dose: 80/20 mg). In Mozambique, infants on concomitant rifampicin were switched to a triple nonnucleoside reverse transcriptase inhibitor (NRTI) ART regimen with zidovudine, lamivudine, and abacavir and were not eligible for this PK substudy as they did not receive LPV/r. Infants from Zambia received double-dosed LPV/r during rifampicin cotreatment. In Zimbabwe, semisuperboosted LPV/r was administered to infants, following local guidelines. In all participating countries, rifampicin dispersible tablets were dosed in accordance with WHO pediatric dosing guidance (2014 edition); infants weighing 4–7 kgs received 75 mg and those weighing 8–10 kgs received 150 mg rifampicin.[9] Weight-band dosages of LPV/r for the various countries are included in Table S2, Supplemental Digital Content, http://links.lww.com/QAI/C24. Pharmacokinetic sampling was performed after a morning dose of LPV/r and rifampicin. All infants received breast milk, fresh milk, or formula within 30 minutes before, or after the administration of LPV/r, thus, were considered fed. Treatment adherence during the 3 days before PK sampling was recorded by the caretaker and confirmed for all infants.

Six blood samples were taken over 12 hours (predose and 2, 4, 6, 8, and 12 hours after drug administration) within 30–60 days after enrolment in the main trial and at least 14 days after initiation of LPV/r and rifampicin for the rifampicin arm. The total blood volumes drawn did not exceed the maximum allowable limits (2.5% of the total blood volume for sick children).[10] Concentrations of LPV and ritonavir in plasma were measured using ultra performance liquid chromatography with ultraviolet detection[11] at the Department of Pharmacy, Radboud University Medical Centre, Nijmegen, the Netherlands. This laboratory participates in an international interlaboratory quality control program for therapeutic drug monitoring of antiretroviral drugs, including LPV/r.[12] The lower limits of quantification of the assay are 0.105 mg/L (LPV) and 0.045 mg/L (RTV). Within-run and between-run precision, reported as coefficient of variation, ranged from 0.6% to 4.2% and 0.3%–1.8%, respectively. The assay accuracy range was 98.2%–105.6%.

Statistical Analysis

LPV and ritonavir pharmacokinetic parameters were determined with noncompartmental PK analysis using WinNonlin (Phoenix 64 version 8.3, Certara) and were described as median and associated interquartile range. The first concentration below the lower limit of quantification (LLOQ) at the end of the curve was set to 1/2 LLOQ corrected for an increased apparent LLOQ in case samples needed to be diluted because of small volumes of plasma. The subsequent values below LLOQ were set at undetectable. The maximum concentration (C_{max}) was derived from the plasma concentration–time curve. The linear up-log down trapezoidal method was used to calculate the area-under-the-curve

between 0 and 12 hours after dosing ($AUC_{0–12h}$) and oral clearance (CL/F). The number of children with a trough plasma concentration (C_{trough}) lower than the minimum effective concentration of LPV (1.0 mg/L)[13] was summarized for both treatment arms. Treatment adherence was considered unlikely when a predose LPV concentration was >15 times lower than the C_{trough} after observed medication intake on the PK day; hence, theses pharmacokinetic profiles were regarded as nonevaluable.

The Spearman rank test was used to assess correlation between LPV $AUC_{0–12h}$ and age, weight for age, weight for height, ritonavir $AUC_{0–12h}$, and LPV dose/kg, adjusting for concomitant TB treatment. IBM SPSS Statistics software (version 25) was used to perform the statistical tests.

Efficacy of HIV treatment was assessed based on a cross-sectional HIV RNA viral load measurement at day 180 visit of the main trial and compared between those receiving rifampicin and those who did not. Infants having a VL >1000 copies/mL were considered failing on ART.

RESULTS

Demographics

A total of 16 infants were included in the PK substudy. Two infants were considered nonadherent (1 in control arm and 1 in rifampicin arm); therefore, 14 infants (all ART-naïve) had evaluable pharmacokinetic curves. Of these 14 infants, 9 were on rifampicin cotreatment (5 received double-dosed and 4 semisuperboosted LPV/r) and 5 received LPV/r without rifampicin. The median (IQR) age was 6.4 months (5.4–9.8), weight 6.0 kg (5.2–6.8). The participants' demographics per study arm are included in Table 1.

Pharmacokinetic Analyses

Of those on rifampicin with evaluable pharmacokinetic curves, 6/9 (67%) infants had LPV C_{trough} <1.0 mg/L (3/5 using double-dosed LPV/r and 3/4 semisuperboosted LPV/r), whereas 1/5 (20%) infants had subtherapeutic LPV levels; see Figure 1 for individual PK parameters. Combined LPV PK parameters are shown in Table 1, and RTV PK parameters are included in Table S3, Supplemental Digital Content, http://links.lww.com/QAI/C24. The median LPV apparent oral clearance was approximately 3.3-fold higher for individuals receiving rifampicin.

LPV $AUC_{0–12h}$ correlated strongly with ritonavir $AUC_{0–12h}$.(details included in Figure S1 and Table S4, Supplemental Digital Content, http://links.lww.com/QAI/C24. No correlation was found between LPV $AUC_{0–12h}$ and age, weight for age, weight for height, and LPV dose/kg.

Efficacy and Safety

There were 79 reportable adverse events (53 reported in 10/10 infants in the rifampicin arm; 26 in 6/6 infants in the control arm), including 24 serious adverse events (SAE; 19 reported in 7/10 infants in the rifampicin arm; 5 in 5/6 infants in the control arm). Four liver function alterations and 2 skin rashes were potentially related to TB treatment; none of which were considered SAE or resulted in treatment discontinuation. Viral load data at 180 days after enrolment in the main trial were available for 14/16 infants; 63% (5/8) in the rifampicin arm and 50% (3/6) in the control arm had a VL >1000 copies/mL. The proportion of infants with a VL >1000 copies/mL for those having C_{trough} <1.0 mg/L was 67% (4/6) and for those with C_{trough} >1.0 mg/L was 50% (4/8).

DISCUSSION

In this study, we found that LPV/r dosing strategies that are used in clinical practice during concomitant rifampicin use (double-dosing and semisuperboosting) resulted in substantial proportions of subtherapeutic LPV levels in infants. These low C_{trough} could result in treatment failure and ART resistance development.

These findings are in concordance with data from a previous study that reported 60% of children receiving double-dosed LPV/r with rifampicin to have subtherapeutic LPV C_{trough}.[7] Our data confirm low C_{trough} in infants 1–12 months old. In addition, this is the first study to include pharmacokinetic data of LPV semisuperboosting in combination with rifampicin. The semisuperboosting approach included crushing of 100 mg film-coated RTV tablets while RTV bioavailability sharply decreases for these tablets when crushed.[14] This could have contributed to the high proportion of subtherapeutic LPV C_{trough} in this group.

TABLE 1. Participant Demographics and Lopinavir Pharmacokinetic Parameters

	Control Arm (n = 5)	Rifampicin Arm (n=9)
Demographics		
Male/female	5/0	5/4
Weight (kg)	6.4 (5.2–7.1)	6.3 (5.2–6.9)
Age (mo)	5.8 (4.1–10.24)	6.6 (5.6–9.9)
Baseline viral load (log_{10} copies/mL)	6.3 (5.7–6.5)	6.5 (6.3–6.8)
LPV/r dose	Regular dose as per local guidelines (5)	Double-dosed (5) Semisuperboosted (4)
Lopinavir PK parameters		
Proportion Ctrough <1.0 mg/L	1/5 (20.0%)	6/9 (67%)
C_{trough} (mg/L)	3.44 (1.27–18.9)	0.197 (0.0293–3.92)
$AUC_{0–12h}$ (h*mg/L)	64.2 (44.5–265)	40.3 (5.72–115)
C_{max} (mg/L)	8.21 (4.91–25.0)	7.57 (1.48–14.8)
T_{max} (h)	4.0 (3.0–5.0)	4.0 (2.0–4.0)
t_{half} (h)	8.26 (3.54–25.2)	1.60 (0.937–3.62)
Cl/F	1.25 (0.374–2.88)	4.14 (1.72–42.9)
Vd/F (L)	15.4 (5.7–23.3)	12.9 (5.33–99.4)

Area-under-curve 0–12 hours ($AUC_{0–12h}$), half-life (T_{half}), maximum concentration (C_{max}), oral clearance (Cl/F), time to C_{max} (T_{max}), trough concentration (C_{trough}), volume of distribution (Vd/F). Reported: median (IQR).

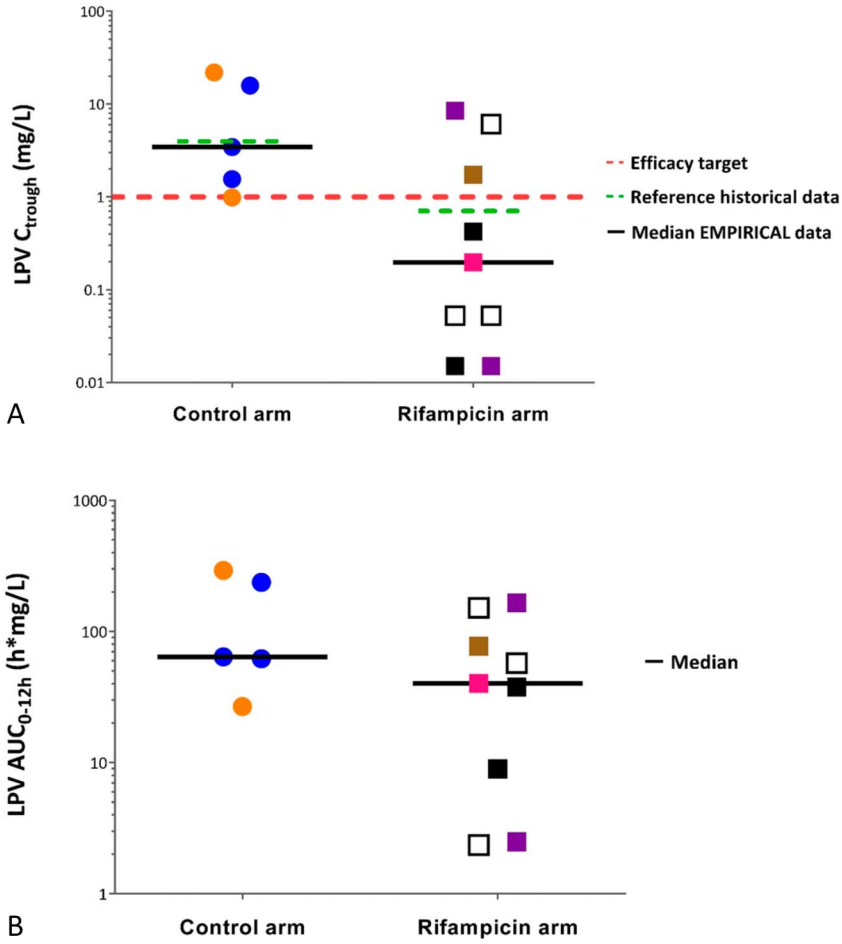

FIGURE 1. LPV trough concentrations (A) and AUC0-12h (B) in infants using LPV/r without rifampicin (control arm) or with rifampicin (rifampicin arm). Reference data for LPV C_{trough} in children on LPV/r without rifampicin and with rifampicin receiving double-dosed LPV/r: Mcilleron et al 2011.[7] The dot types reflect the various dosages that were administered; control arm: orange: 80/20 mg LPV/r (3–6kg WB); blue 120/30 mg LPV/r (6–10 kg WB). Rifampicin arm: pink: semisuperboosted 80/20 mg LPV/r (3–6kg WB); white: semisuperboosted 160/40 mg LPV/r (3–10 kg WB); black: double-dosed 160/40 mg LPV/r (3–6kg WB); purple: double-dosed 240/60 mg LPV/r (6–10 kg WB); brown: double-dosed with different evening dose 320/80 mg LPV/r (3–6kg WB). full color online

Rabie et al[5] have shown that superboosting of LPV/r provides an adequate strategy to overcome rifampicin's inducing the effect of CYP3A4 in infants. Hence, this strategy has been widely adopted by national and international guidelines.[6] However, pediatric ritonavir formulations for superboosting are not readily available.

Limited HIV treatment options are available and acceptable for infants receiving rifampicin-based TB treatment. ARVs that have been studied include efavirenz, raltegravir, and nevirapine.[4] Efavirenz can be dosed as usual during rifampicin cotreatment to achieve therapeutic exposure in children living with HIV.[15] However, CYP2B6 genotype–directed dosing, which is critical for children younger than 3 years old receiving efavirenz, is not feasible in TB-endemic settings. Double-dosed raltegravir was found to achieve pharmacokinetic targets safely in infants receiving concomitant rifampicin.[16] Yet, large interpatient pharmacokinetic variability of raltegravir and difficulties with the administration of oral granules could result in some infants being underdosed,[17] and availability of raltegravir in TB-endemic countries is limited. Adequacy of nevirapine dosing during rifampicin treatment is questionable,[18] and it is currently being phased-out for treatment of HIV across all ages. In previous WHO guidelines, switching the anchor drug to a third NRTI during concomitant rifampicin treatment was recommended as a suitable option for CLHIV who require TB treatment.[19] This was based on the ARROW trial showing that a triple NRTI regimen resulted in a short-term virologic suppression similar to NNRTI-based therapy.[20] Of note, this strategy has not been studied in children with HIV/TB coinfection.[4]

Recent research has shown dolutegravir-based ART to be superior to nondolutegravir-based ART for pediatric HIV treatment.[21] Subsequently, pediatric dolutegravir tablets have been rolled out rapidly in resource-limited settings. Moreover, increasing the dosing interval of dolutegravir from once daily to twice daily was shown to be safe and sufficient to overcome its interaction with rifampicin in children with HIV/TB coinfection.[22] However, pharmacokinetic data were available for only 3 children <6 year old, and no evaluable data were available for infants less than 1 year old.[22] More data are needed to confirm twice-daily dolutegravir dosing in infants with HIV/TB.

This study has various limitations. First, the sample size was small because of decreased enrolment during the COVID-19 pandemic and with the recent introduction of pediatric dolutegravir tablets; many EMPIRICAL infants were switched from LPV/r to dolutegravir-based ART. Due to the small sample size, we were not able to link the pharmacokinetic findings to treatment failure or success.

Also, the large variability of national LPV/r dosing strategies when combined with rifampicin used for our study population complicated the pharmacokinetic analysis. On the other hand, the large variability in dosing also shows the complexity of dosing LPV/r in clinical practice and lack of consensus on how to overcome the drug–drug interaction with rifampicin and, therefore, contributes to the recommendation to move away from using LPV/r for infants on rifampicin.

CONCLUSIONS

Double-dosed or semisuperboosted LPV/r for infants 1–12 months old receiving rifampicin resulted in substantial proportions of subtherapeutic LPV levels. There is an urgent need for data on alternative ART options for infants with HIV/TB coinfection using rifampicin, such as twice-daily dolutegravir.

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