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Pharmacokinetics of lopinavir/ritonavir in second-line treatment of children living with HIV in the CHAPAS-4 trial

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Abstract

Objective

Lopinavir/ritonavir (LPV/r) remains a much-used drug combination for treatment of children with HIV, but pharmacokinetic data when the adult formulation (LPV/r 200/50 mg) is used for children weighing 25-34.9 kg, or when combined with tenofovir alafenamide/emtricitabine (TAF/FTC), is currently lacking.

Design

We aim to provide this data by an intensive LPV/r pharmacokinetic sub-study nested within the CHAPAS-4 trial (#ISRCTN22964075).

Methods

Children (3-15 years), weighing 14-24.9 kg received 200/50 mg LPV/r orally twice daily; those weighing 25-34.9 kg received 400/100 mg LPV/r in the morning and 200/50 mg in the evening; and those weighing ≥35 kg received 400/100 mg LPV/r twice daily. LPV/r was used in combination with either TAF/FTC or standard-of-care backbone

(abacavir/lamivudine or zidovudine/lamivudine). Pharmacokinetic parameters were compared to those reported in children receiving WHO-recommended dosages.

Results

We enrolled 40 children from Uganda, Zambia and Zimbabwe. The geometric mean (GM) area under the concentration-time curve ($AUC_{0\text{-}12h}$) for LPV was 116.2 h*mg/L (coefficient of variation [CV%], 37%), comparable to children receiving WHO-recommended dosages. The GM trough concentration was 7.7 mg/L (52%), 57% higher than the reference value of 4.9 mg/L (95% confidence interval, 4.14–5.80), mainly caused by higher exposure in children 25-34.9 kg. There were no differences in LPV $AUC_{0\text{-}12h}$ or C_{trough} between backbones.

Conclusions

Children (3-15 years), weighing ≥14 kg and taking LPV/r in second-line treatment achieve adequate exposure of LPV within limits reported to be safe and well tolerated. These data support the use of a LPV/r based regimen and the adult formulation of 200/50 mg in children 25-34.9 kg.

Key-words:

Lopinavir/ritonavir, pharmacokinetics, HIV, children, second-line

1. Introduction

In recent years, the number of children with HIV initiating treatment with antiretroviral therapy (ART) has risen. Improved access to HIV and viral load testing is increasing detection of first-line treatment failure as well.[1, 2] Children with virological failure on an integrase strand transfer inhibitor (INSTI)-based regimen are recommended to switch to a protease inhibitor (PI) boosted by ritonavir.[3] Lopinavir/ritonavir (LPV/r) and atazanavir/ritonavir (ATV/r) are currently the recommended PIs as second-line treatment for children with HIV.[3] Although there are some disadvantages of LPV/r compared to ATV/r and darunavir/ritonavir (DRV/r), such as more gastrointestinal side-effects, higher risk of lipid abnormalities, poorer growth and virological outcomes[4-6], LPV/r remains in many places the only available PI in a paediatric formulation and was still being used by ~25% of children on ART in 2022.[7]

WHO dosing recommendations for LPV/r are based on weight bands. When treated with fixed dose combination tablets (available as 200/50 mg and 100/25 mg LPV/r), children 14-24.9 kg receive 200/50 mg twice daily, while those 25-34.9 kg receive 300/75 mg twice daily. The latter requires 100/25 mg tablets, as the film-coated tablets cannot be split or crushed, although limited availability in some countries raises questions about the

utility and sustainability of this formulation.[8] A backbone of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) remains universally recommended for first- and second-line ART. Abacavir (ABC) and zidovudine (ZDV) are still most commonly recommended in children in combination with lamivudine (3TC).[3] Tenofovir alafenamide (TAF) combined with 3TC or emtricitabine (FTC) is listed as an alternative agent,[3] although it was recently shown to be superior over 'standard-of-care' backbones in second-line.[3, 6]

Pharmacokinetic data of LPV/r in children 25-34.9 kg treated with the adult 200/50 mg formulation, i.e. 400/100 mg in the morning and 200/50 mg in the evening, as well as pharmacokinetic data when combined with TAF/FTC are lacking. Demonstrating adequate exposure with this dosing scheme facilitates use of adult LPV/r tablets in children 25-34.9 kg, simplifying procurement. We aim to close this information gap by an intensive LPV/r pharmacokinetic sub-study within the CHAPAS-4 trial (#ISRCTN22964075).

2. Methods

CHAPAS-4 evaluated safety, efficacy and pharmacokinetics of dolutegravir (DTG), DRV/r, LPV/r and ATV/r in combination with an NRTI backbone (ZDV/3TC, ABC/3TC or TAF/FTC) in children (3-15 years) from Zambia, Uganda and Zimbabwe. The trial was approved by local and national ethical committees. Caregivers and participants (as applicable), provided informed consent and assent, respectively. Here, we report results of the LPV/r pharmacokinetic sub-study within CHAPAS-4. Results of the main trial, and other pharmacokinetic sub-studies have been reported elsewhere.[6, 9-11]

Children weighing 14-24.9 kg received 200/50 mg LPV/r twice daily; those 25-34.9 kg received 400/100 mg in the morning and 200/50 mg in the evening; those ≥35 kg received 400/100 mg LPV/r twice daily. LPV/r tablet formulations and quantities administered are shown in the table in Supplemental Digital Content (SDC) 1, http://links.lww.com/QAD/D646. Tablets could not be split or crushed. Dosing of NRTI backbones is shown in the table in SDC 2, http://links.lww.com/QAD/D647.

After 6 weeks of treatment (at steady-state) the intensive 12-hour pharmacokinetic assessment was performed. A standardized breakfast (~250 kcal, 5% fat) was provided 10 minutes before intake of the LPV/r morning dose. Co-medications that could influence the pharmacokinetics were not allowed within 2 hours after ART intake. Blood samples were collected at t=0 (pre-dose) and 1, 2, 4, 6, 8 and 12-hours post-dose. Volumes of blood samples were within safety limits.[12] Details on laboratory procedures are described in SDC 3, http://links.lww.com/QAD/D648.

Pharmacokinetic parameters were calculated using non-compartmental analysis (Phoenix 8.4 WinNonlin®). Primary pharmacokinetic parameters were $AUC_{0\text{-}12h}$ (area under the

concentration-time curve) and C_{trough} (12-hours post-dose concentration), which is related to LPV antiviral activity. We also reported the pre-dose concentration (C_0) as it may reflect the lowest level in children 25-34.9 kg. Other parameters determined were C_{max} (maximum plasma concentration), T_{max} (time to reach the maximum concentration), CL/F (apparent oral clearance), CL/F/kg (apparent oral clearance corrected for body weight), V_d/F (apparent volume of distribution) and $T_{1/2}$ (apparent elimination half-life).

The aim was to achieve pharmacokinetic parameters comparable to those in children who received WHO-recommended dosages in the KONCERT trial (see table, SDC 1, http://links.lww.com/QAD/D646), in which treatment with LPV/r BID demonstrated efficacy and low rates of viral rebound.[13, 14] The target C_{trough} for LPV was 1.0 mg/L.[15]

$AUC_{0\text{-}12h}$ and C_{trough} levels were compared between weight bands and NRTI backbones by one-way ANOVA on log-transformed values with Tukey post hoc analysis. Lipid elevation differences between weight bands were assessed by comparing changes in total, low density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol and triglycerides between week 0 and week 48 by one-way ANOVA. In addition, the correlation between LPV and RTV $AUC_{0\text{-}12h}$ and C_{trough}-levels and changes in lipids levels was assessed.

3. Results

Between February 2019 and September 2020, 51 children from Uganda, Zambia and Zimbabwe were enrolled in this sub-study. Eleven children were excluded from analysis (for additional details, see description SDC 3, http://links.lww.com/QAD/D648). Of the children included in analysis, 11 received a backbone of ABC/3TC, 20 received TAF/FTC and 9 received ZDV/3TC. Other demographic data are presented in Table 1.

LPV pharmacokinetic parameters for all children are summarized in Table 1. The geometric mean (GM) $AUC_{0\text{-}12h}$ and GM C_{max} are comparable to that of children in KONCERT.[13] The GM C_{trough} is ~57% higher than the GM value of children in KONCERT. The GM LPV plasma concentration versus time profile for all children in this sub-study and for KONCERT are shown in Figure 1(I).

LPV pharmacokinetic parameters for each weight band are summarized in Table 1. $AUC_{0\text{-}12h}$ values did not significantly differ by weight band (one-way ANOVA, p=0.189). Comparison of C_{trough} values did show a difference between weight bands (p=0.015). The C_{trough} was higher in children weighing 25-34.9 kg compared to children in the lowest and highest weight band (Tukey post hoc analysis, p=0.021 and 0.048, respectively). Despite differences, all 40 individual C_{trough} values were above the target of 1.0 mg/L. C_0-values of LPV did not differ by weight band (p=0.674). One participant weighing 25-34.9 kg had a C_0-value below the target of 1.0 mg/L. GM LPV plasma concentrations versus time

profiles by weight band and for KONCERT are shown in Figure 1(II). Changes in total, HDL, LDL cholesterol and triglycerides between week 0 and week 48 did not differ by weight band (p=0.230, 0.395, 0.462 and 0.612, respectively) (see figure, SDC 4, http://links.lww.com/QAD/D649). In addition, no correlation was found between $AUC_{0\text{-}12h}$ or C_{trough}-values of LPV or RTV and lipid changes between week 0 and 48.

There were no differences in LPV $AUC_{0\text{-}12h}$ and C_{trough} between backbones (one-way ANOVA, p=0.331 and 0.293, respectively). GM LPV plasma concentrations versus time profiles by NRTI backbone are shown in Figure 1(III).

RTV $AUC_{0\text{-}12h}$ values for all children and each weight band are summarized in Table 1. The GM $AUC_{0\text{-}12h}$ was comparable to what was observed in KONCERT. $AUC_{0\text{-}12h}$-values of RTV did not differ by weight band (one-way ANOVA, p=0.106).

4. Discussion

This study demonstrated that a dose of 200/50 mg LPV/r twice daily in children 14-24.9 kg, 400/100 mg LPV/r in the morning and 200/50 mg LPV/r in the evening in children 25-34.9 kg and 400/100 mg LPV/r twice daily in children ≥35 kg, in combination with a backbone of TAF/FTC or SOC, achieve $AUC_{0\text{-}12h}$ levels of LPV comparable to reference values found to be safe and effective in children.[13-16] The GM C_{trough} observed in this sub-study is ~57% higher compared to the reference value.

These results are reflected by the LPV plasma concentration time curves (Figure 1 – I). The higher overall C_{trough} is mainly caused by higher concentrations measured in children 25-34.9 kg, although C_{trough}-values in the other weight bands are also slightly higher than observed in KONCERT (Figure 1 – II). In addition, the T_{max} of LPV is later compared to the reference value. Children in this sub-study received LPV/r after breakfast, while children in KONCERT received LPV/r before breakfast or under fasting conditions. This might cause LPV absorption to be delayed in children in this sub-study, resulting in a later T_{max} and higher C_{trough}-values compared to the KONCERT trial.

Although not statistically significant, the $AUC_{0\text{-}12h}$ seems slightly higher in children 25-34.9 kg compared to the other weight bands. This could be explained by the relatively higher milligram per kilogram body weight dosing in this weight band in the morning, i.e. 400/100 mg LPV/r. Results from the main trial showed that treatment with LPV/r was associated with less favourable lipid profiles compared to treatment using DTG, DRV/r or ATV/r.[6] The higher LPV exposure during the day in children 25-34.9 kg might raise concerns for increased risk of toxicity compared with the other weight bands. However, comparison of lipid changes between week 0 and 48 within this sub-study revealed no differences between weight bands. Additionally, no correlation was found between $AUC_{0\text{-}12h}$ or C_{trough}-values of both LPV and RTV and the extent of lipid changes, indicating no increased risk of lipid abnormalities in children weighing 25-34.9 kg

compared with the other weight bands. Studies in adults show conflicting results, as some did not find an association between LPV levels and lipid elevations [17, 18], while others showed a correlation between LPV C_{trough}-levels and increased lipid levels.[19, 20] Of note, in CHAPAS-4 lipids were not measured during the same visit as the pharmacokinetic assessments. Additionally, a paediatric study on pharmacokinetics of high-doses LPV/r reported a median C_{12h} of 12.4 mg/L (range, 2.88-12.6) and a median AUC_{0-12h} of 162.2 h*mg/L (range, 63.8-185.7) in children on LPV/r with ≥2 NRTIs, which is comparable to values in children 25-34.9 kg observed in this sub-study.[16] The high doses were well tolerated, with no withdrawals for gastrointestinal side-effects, no gastrointestinal toxicity >grade 2, and no relationship between drug concentrations and heart rate or QTc. A more detailed pharmacokinetic/pharmacodynamic (PK/PD) analysis will be conducted to evaluate the relationship between lopinavir exposure and the occurrence of adverse events.

Given LPV levels in this sub-study are within limits reported to be safe and well tolerated, these data support use of the 200/50 mg LPV/r formulation in children 25-34.9 kg. Considering low availability of 100/25 mg LPV/r in some countries,[8] this is a potential advantage that could overcome issues regarding stock-outs of paediatric formulations and consequently treatment disruption.

AUC_{0-12h} and C_{trough}-values of LPV did not differ between NRTI backbones, indicating that TAF/FTC does not affect the pharmacokinetics of LPV after administration of LPV/r. This is consistent with a study in adults investigating potential drug interactions between TAF and several ARVs.[21]

RTV AUC_{0-12h} observed in children in this sub-study is comparable to the AUC_{0-12h} observed in KONCERT. Although not statistically significant, RTV AUC_{0-12h} seems slightly higher in children 25-34.9 kg compared to the other weight bands. This is in line with observations for LPV and is explained by the higher milligram per kilogram body weight morning dose of RTV in this weight band.

In conclusion, results of this sub-study show that children 3–15 years, taking LPV/r in second-line treatment, achieve adequate concentrations of LPV. This is in line with main efficacy and safety results of CHAPAS-4.[6] If DTG, ATV/r and DRV/r are not available or indicated, these data support the use of a LPV/r-based regimen as second-line treatment for children from ≥14 kg, including the adult formulation of 200/50 mg LPV/r in children 25-34.9 kg and in combination with TAF/FTC.

5. Acknowledgements

D.M.G. conceived the study, the CHAPAS-4 trial team conducted the clinical trial, A.S. managed the trial data. A.C., D.M.B. and H.W. led the pharmacokinetic sub-study. A.E.M., T.K. and A.C. conducted the non-compartmental analysis. C.C., M.B., S.M. J.N. V.Mul. and

V. Mus. carried out the trial activities. H.W., A.B., S.N.W, A.C. and D.M.B. critically reviewed and provided input on the manuscript. All authors read and approved the final manuscript.

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Figure 1. *Geometric mean lopinavir plasma concentrations versus time profiles of the CHAPAS-4 pharmacokinetic sub-study compared to the KONCERT trial (I); the CHAPAS-4 sub-study by weight band (II); and the CHAPAS-4 sub-study by NRTI backbone (III). The horizontal dotted line indicates the LPV target* C_{trough} *of 1.0 mg/L. LPV denotes lopinavir, FTC/TAF emtricitabine/tenofovir alafenamide, ABC/3TC abacavir/lamivudine and ZDV/3TC zidovudine/lamivudine.*

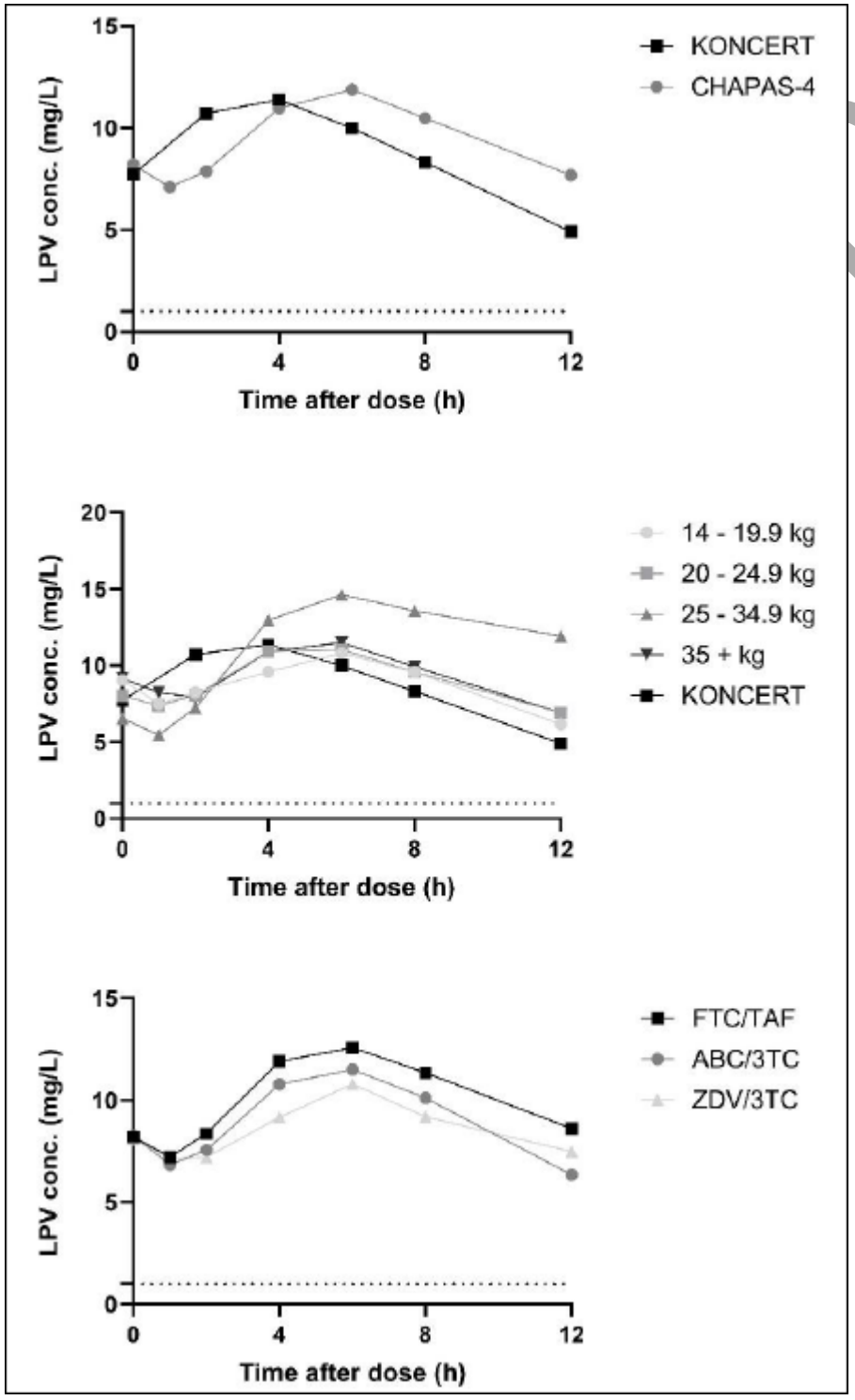

Table 1. Patient demographics and summary of LPV pharmacokinetic parameters in children within CHAPAS-4 and reference values.

	Total CHAPAS-4 sub-study	**Weight band**				**KONCERT**
		14 – 19.9 kg 200/50 mg LPV/r, BID	**20 – 24.9 kg** 200/50 mg LPV/r, BID	**25 – 34.9 kg** 400/100 mg LPV/r AM, 200/50 mg LPV/r PM	**35+ kg** 400/100 mg LPV/r, BID	
Number of participants, N	40	9	10	9	12	53
Age, years	10.3 (4.3-14.7)	5.9 (4.3-7.7)	9.7 (6.9 -12.8)	10.2 (8.1-13.0)	13.7 (10.6-14.7)	11.0
Weight, kg	25.4 (14.2-49.5)	18.0 (14.2-19.1)	22.8 (20.0-24.2)	27.0 (25.0 - 30.6)	43.6 (36.5-49.5)	31.0
Number of girls (% in WB)	17 (57%)	4 (44%)	7 (70%)	5 (56%)	7 (58%)	
LOPINAVIR						
AUC_{0-12h} (h*mg/L)	116.2 (37)	104.3 (38)	110.3 (33)	145.1 (40)	109.7 (32)	106.9 (97.8-116.9)

C_{trough} (mg/L)	7.7 (52)	6.2 (55)	6.9 (45)	11.9 (39)	7.0 (46)	4.9 (4.14-5.80)
C_0 (mg/L)	8.1 (76)	9.1 (34)	8.0 (48)	6.5 (178)	8.9 (49)	n.a.
C_{max} (mg/L)	12.5 (32)	11.5 (30)	11.7 (32)	15.4 (44)	12.1 (28)	12.0 (11.1-12.9)
T_{max}, h	4 (0 – 12)	4 (0 – 6)	4 (0 – 12)	6 (0 – 12)	4 (0 – 6.03)	n.a.
$T_{1/2}$, h	10.5 (60)	10.5 (72)	9.0 (52)	15.1 (56)	8.3 (40)	n.a.
CL/F (L/h)	2.4 (46)	1.92 (38)	1.81 (33)	2.55 (38)	3.64 (32)	n.a.
CL/F/kg (L/h/kg)	0.09 (38)	0.11 (37)	0.08 (37)	0.09 (40)	0.09 (32)	0.089 (0.081-0.097)
V_d/F (L)	38.4 (66)	27.4 (50)	23.9 (57)	72.7 (50)	49.3 (33)	n.a.
RITONAVIR						
$AUC_{0\text{-}12h}$ (h*mg/L)	5.8 (56)	4.6 (60)	4.8 (44)	7.8 (55)	6.2 (54)	5.9 (5.28-6.65)

Age and weight are presented as medians (range). Pharmacokinetic data are presented as geometric means (coefficient of variation for CHAPAS-4, 95% confidence interval for KONCERT), except for T_{max} which is presented as median (IQR). LPV/r denotes lopinavir boosted ritonavir, BID twice daily, WB weight band, $AUC_{0\text{-}12h}$ the area under the concentration-time curve from 0 to 12 hours, C_{trough} concentration 12 hours after dosing, C_0 pre-dose concentration, C_{max} maximum plasma concentration, T_{max} time to reach the maximum plasma concentration, $T_{1/2}$ elimination half-life, CL/F apparent oral clearance, CL/F/kg apparent oral clearance corrected for body weight and V_d/F apparent volume of distribution.