SUBOPTIMAL LOPINAVIR EXPOSURE ON 8-HOURLY LPV/R 4:1 IN HIV/TB CO-INFECTED CHILDREN

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BACKGROUND

- Young children with HIV/TB co-infection have limited antiretroviral treatment (ART) options.
- Lopinavir/ritonavir 4:1 (LPV/r) is widely used for first- and second-line ART but lopinavir (LPV) exposures are profoundly reduced by concomitant rifampicin.
- Recommended super-boosted lopinavir (LPV/r 1:1) is not feasible, when single-entity ritonavir is not available in low-income settings.
- A previous study in 11 children showed that model-predicted 8-hourly doses of the liquid LPV/r formulation co-administered with rifampicin achieved targeted trough concentrations of LPV ≥1 mg/L in nearly two-thirds of children, suggesting that higher LPV/r dosing could potentially be used.
- We evaluated increased 8-hourly LPV/r (4:1) doses in HIV/TB co-infected children in a substudy of the SHINE trial (ISRCTN 63579542).

METHODS

- HIV/TB co-infected Zambian children, weighing 3.0 to <20 kg, on LPV/r-based ART and rifampicin-containing TB treatment were included.
- The children received modified 8-hourly dosing using liquid LPV/r 4:1 formulation administered in weight bands (WBs) ranging from LPV 31-40 mg/kg/dose in the lowest WBs to 20-22 mg/kg/dose highest WBs.
- Dosing was switched to WHO-recommended 12-hourly LPV/r 2 weeks after stopping rifampicin-based TB treatment.
- LPV plasma concentrations were assessed on 8-hourly LPV/r and repeated 2 weeks after returning to 12-hourly dosing.
- Samples were obtained pre LPV/r dose and at 1, 2, 4, 6 and 8hrs post dose on 8-hrly dosing, as well as 12 hrs post dose on 12-hourly dosing.
- LPV plasma concentrations were measured using a validated LC-MS/MS method.

RESULTS

- 15 children (10[66%] males), with median age of 3.0 (range 1.0 to 7.0) years at enrolment, received median LPV 23 (range 21-37) mg/kg/dose during rifampicin co-treatment
- Plasma LPV exposures on 8-hourly LPV/r with rifampicin were lower compared to 12-hourly dosing (AUC24 GMR [90% CI] 0.35[0.21-0.61]) (Table 1).
- Only 7/15(45%) and 8/12(67%) children achieved target LPV C_{min} post dose trough concentrations ≥1mg/L (8hr and 12hr) with and without rifampicin respectively.
- During median 12 (IQR 4-16) weeks on 8-hourly LPV/r, 2 patients had 3 grade 3/4 adverse events (2 pneumonias, 1 urinary tract infection) deemed unrelated to the intervention. There were no treatment-related discontinuations.

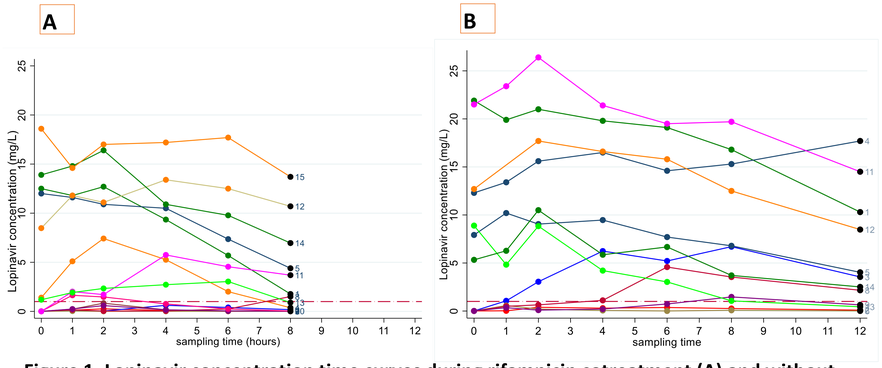

Figure 1. Lopinavir concentration time curves during rifampicin cotreatment (A) and without rifampicin (B). Horizontal line represents Lopinavir target trough concentration of 1 mg/L

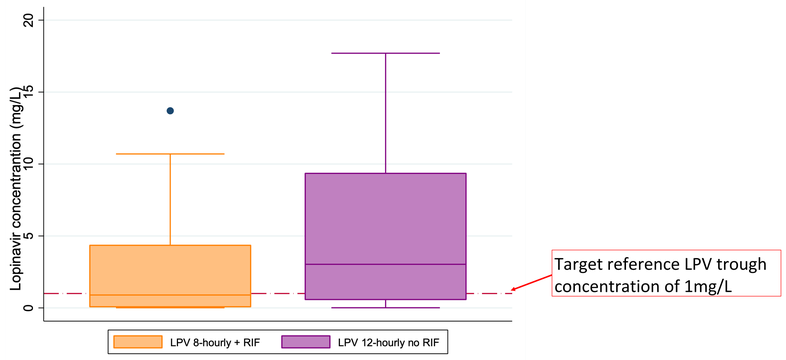

Figure 2: Median Lopinavir peak concentrations during 8-hourly dosing with rifampicin vs 12-hourly dosing without rifampicin

Table 1: Patient characteristics and pharmacokinetic measures

Patient characteristics	LPV/r 8-hourly during TB treatment, N=15	LPV/r 12-hourly after TB treatment, N=12	p-value
Age in years at PK sampling, median (IQR)	3.2 (2.3, 4.3)	4.0 (2.6, 4.7)	-
Sex, male	10 (67)	7 (58)	-
WHZ, median (IQR)	0.2 (-0.7, 0.9)	0.0 (-0.2, 1.3)	0.79

Pharmacokinetic measures	n=15	n=12	GMR (90% CI)
AUC_{24}, median (IQR), mg.hr/L	55.3 (5.6, 222.2)	121.6 (35.9, 353.8)	0.4 (0.2, 0.6)
C_{max}, median (IQR), mg/L	3.0 (0.6, 12.7)	9.5 (3.0, 17.7)	0.4 (0.2, 0.6)
C_{min}, median (IQR), mg/L	0.9 (0.0, 4.4)	3.0 (0.5, 9.4)	0.4(0.3, 0.8)
C_{min} ≥1mg/L, n (%)	7 (46.7)	8 (66.7)	p=0.44

LPV/r; Lopinavir/ritonavir, WHZ; weight-for-height z-score, GMR; geometric mean ratio with 90% confidence interval (calculated from 12 paired observations); AUC_{24}; area under the concentration-time curve from time 0 to 24 hours (calculated using 3 x AUC_{8hr} and 2 x AUC_{12hrs}), C_{max}; peak plasma concentration, C_{min}; 8 or 12 h trough concentration for the respective 8- and 12-hour dosing intervals.

CONCLUSION

- Lopinavir/ritonavir 4:1 oral solution given in increased doses 8-hourly alongside rifampicin did not reach adequate LPV concentrations, and therefore unsuitable for HIV/TB co-infected children.
- The high proportion of subtherapeutic exposures observed after TB treatment raise questions about the bioavailability of LPV/r oral solution.
- The findings support the rapid transition to dolutegravir-based ART in TB/HIV endemic with limited co-treatment options.

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