Suboptimal lopinavir exposure in infants 1-12 months on rifampicin treatment receiving double-dosed or semi-superboosted lopinavir/ritonavir; results from the EMPIRICAL trial

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Introduction

- Lopinavir (LPV) is co-administered with ritonavir, a potent inhibitor of cytochrome p450 3A (CYP3A) in a 4:1 ratio to achieve higher (effective) lopinavir exposure.
- LPV trough concentrations (C_{trough}) below 1.0 mg/L were found to correlate with a higher chance of virological failure.[1]
- Rifampicin is a strong inducer of CYP3A, leading to large decreases in plasma concentrations of LPV.
- Super-boosted LPV/r to a 4:4 ratio was found to an appropriate dosing strategy for infants to overcome the interaction with rifampicin.[3]
- Double-dosing of LPV/r (8:2 ratio) in infants and young children receiving rifampicin resulted in subtherapeutic LPV trough concentrations (<1.0mg/L) in 60% of children.[2] Only four infants <12 months old participated in that study.[2]
- In clinical practice, double-dosed LPV/r is frequently given to infants receiving rifampicin due to limited availability of single formulation ritonavir syrup.
- We evaluated plasma LPV concentrations in infants with HIV receiving LPV/r according to local dosing guidelines with or without rifampicin-based TB-treatment

Methods

- This is a 2-arm pharmacokinetic sub-study of the EMPIRICAL randomized controlled trial (#NCT03915366) to evaluate whether empirical treatment against cytomegalovirus and tuberculosis improves survival of infants living with HIV and severe pneumonia.[4]
- Infants aged 1-12 months receiving LPV/r with or without (control) rifampicin-based TB-treatment, were recruited from hospitals in Mozambique, Zambia, and Zimbabwe.
- LPV/r dosages were prescribed following local guidelines. Infants received double-dosed or semi-superboosted LPV/r during rifampicin co-treatment (table 1). All provided dosages for PK included morning doses.
- Six blood samples were taken (predose and 2, 4, 6, 8, and 12 hours after drug intake).
- This project is part of the EDCTP2 programme supported by the European Union (GA RIA2017MC-2013 Acronym EMPIRICAL)

Results

- In total, 13/15 included infants had evaluable pharmacokinetic curves.
- 5/8 infants in the rifampicin arm had LPV Ctrough <1.0mg/L (equally divided over those receiving double-dosed and semi-superboosted LPV/r)
- LPV oral clearance was 4-fold higher for infants receiving rifampicin

Table 2. Patient demographics and main PK parameters for LPV in the EMPIRICAL substudy

Demographics	Control arm (n=5)	Rifampicin arm (n=8)
Male/Female	5/0	4/4
Weight (kg)	6.4 (5.3-6.6)	6.1 (5.3-6.8)
Age (months)	5.7 (5.1-7.6)	7.5 (6.1-10.1)
LPV/r dose	Regular dose (5)	Double-dosed (5) Semi superboosted (3)
C_{trough} (mg/L)	3.35 (1.56-15.8)	0.250 (0.062-2.79)
AUC_{0-12h} (h*mg/L)	64.2 (61.8-237.2)	47.6 (7.7-96.1)
C_{max} (mg/L)	8.2 (6.2–23.6)	8.7 (2.0 – 12.9)

Reported: Median(IQR)

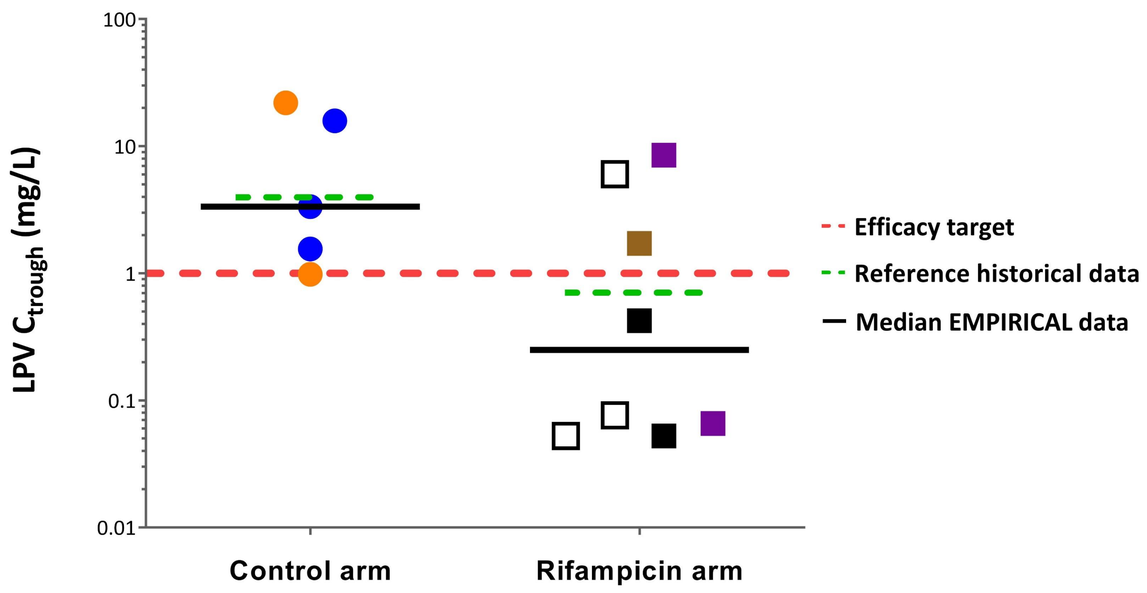

Figure 1. LPV trough concentrations in infants using LPV/r without rifampicin (control arm) or with rifampicin (rifampicin arm)

Rifampicin arm
- 160/40mg LPV/r (3-10kg WB), semi-superboosted
- 160/40mg LPV/r (3-6kg WB), double-dosed
- 240/60mg LPV/r (6-10kg WB), double-dosed
- 320/80mg LPV/r (3-6kg WB), double-dosed with different evening dose

Control arm
- 80/20mg LPV/r (3-6kg WB)
- 120/30mg LPV/r (6-10kg WB)

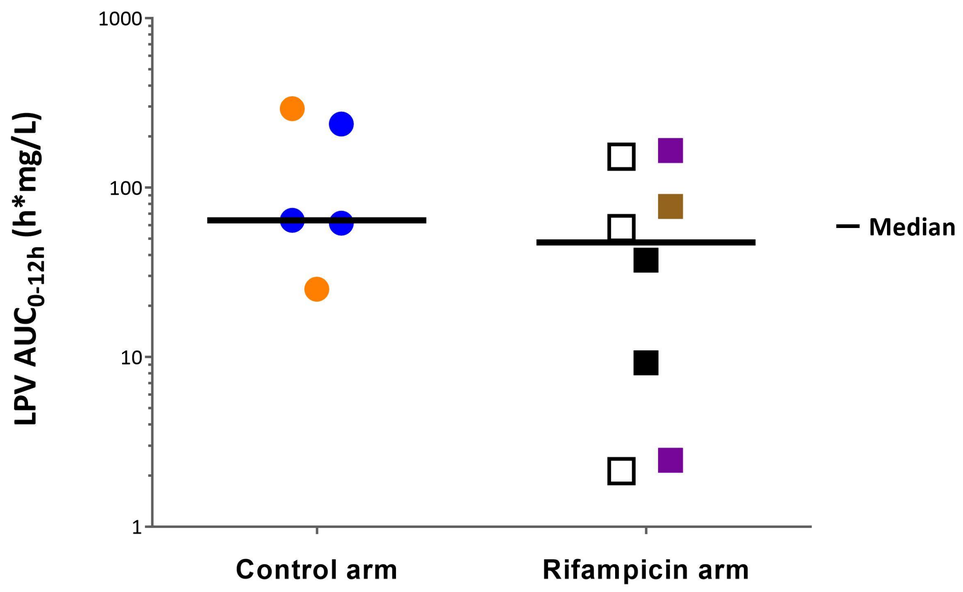

Figure 2. LPV AUC_{0-12h} in infants using LPV/r without rifampicin (control arm) or with rifampicin (rifampicin arm)

Rifampicin arm
- 160/40mg LPV/r (3-10kg WB), semi-superboosted
- 160/40mg LPV/r (3-6kg WB), double-dosed
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- 320/80mg LPV/r (3-6kg WB), double-dosed with different evening dose

Control arm
- 80/20mg LPV/r (3-6kg WB)
- 120/30mg LPV/r (6-10kg WB)

Conclusion

- Double-dosed and semi-superboosted LPV/r for infants 1-12 months old receiving rifampicin resulted in substantial proportions of subtherapeutic lopinavir levels. This is in line with historical data.[2]
- There is an urgent need for data on alternative antiretroviral agents in infants living with HIV receiving rifampicin-based TB treatment, such as twice-daily dolutegravir.
- Later this year, we expect the results from an ongoing EMPIRICAL pharmacokinetic substudy looking at twice-daily dolutegravir in infants receiving concomitant rifampicin.

Table 1. Lopinavir/ritonavir local dosing guidelines

Weight band	Mozambique guidelines		Zambia guidelines		Zimbabwe guidelines	
	Regular LPV/r dosing	LPV/r dosing with rifampicin	Regular LPV/r dosing	LPV/r dosing with rifampicin	Regular LPV/r dosing	LPV/r dosing with rifampicin
3-6kg	80/20mg BID	N/A, switch LPV/r to AZT	80/20mg BID	160/40mg BID (double-dosed)	Morning: 160/40mg Evening: 80/20mg	As regular +100mg RTV evening dose (semi-superboosted)
6-10kg	120/30mg BID	N/A, switch LPV/r to AZT	120/30mg BID	240/60mg BID (double-dosed)	Morning: 160/40mg Evening: 80/20mg	As regular +100mg RTV evening dose (semi-superboosted)

References

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