LOPINAVIR/RITONAVIR 1:1 SUPER-BOOSTING OVERCOMES RIFAMPICIN INTERACTIONS IN CHILDREN

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Background

- LPV/r (4:1) preferred 1st line ARV regimen for infants
- TB is common in HIV-infected children
- Rifampicin (RIF) induces cytochrome (CYP) p450 3A4 and p-glycoprotein ⟶ ± 90% ⬇LPV/r
- Doubling the LPV/r dose does not work in children
- "Superboosting"- i.e. increasing the dose of ritonavir (RTV) to obtain a 1:1 LPV:RTV ratio counteracts the RIF effect in children - BUT
  - Small studies
  - RIF dose increased in revised WHO guidelines

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- Multicenter, open label, non-randomized, study
- Primary Objective:
  - To determine whether the proportion of subjects achieving modelled LPV $C_{0/\text{morning trough}}$ > 1mg/L during RTV superboosting (1:1 ratio) on RIF-based anti-TB treatment is inferior to LPV/r 4:1 without RIF
  - Non-inferiority threshold -10%
- Standard weight-band dosing
- Using liquid LPV/r and RTV

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Sample size

- Calculated to provide at least 80% power to prove that LPV/r trough levels during superboosting for RIF therapy are not inferior to those after superboosting and RIF discontinuation (critical delta 10%)

- 90 **evaluable** subjects provide adequate power to test for non-inferiority

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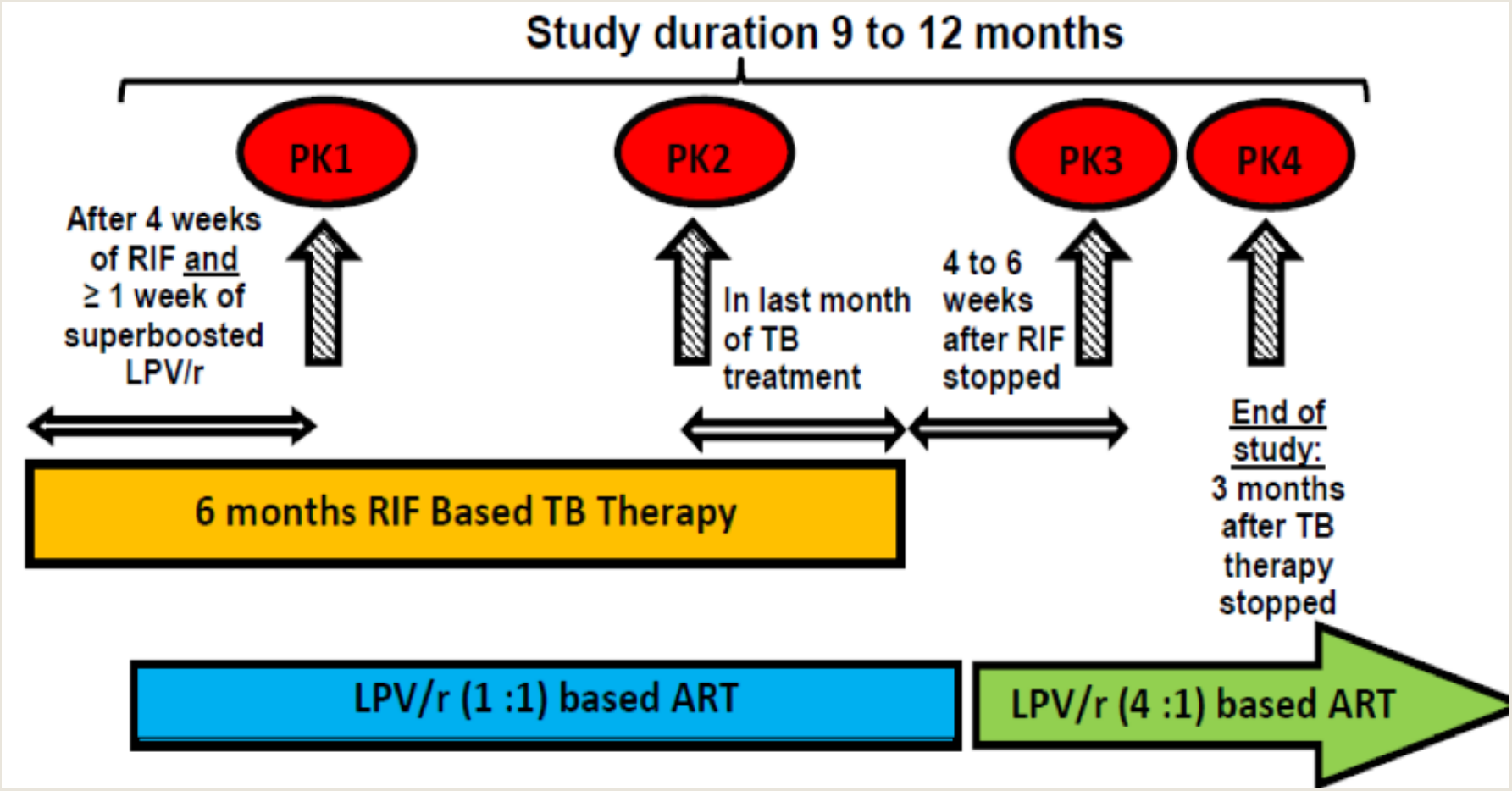
Study plan



Intensive pharmacokinetic visits: PK1, 2, and 3; PK4 trough levels only

6 samples: Hr 0 = (pre observed dose), then 1, 2, 4, 6, & 10 hours

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Inclusion / exclusion criteria

Inclusion

- Confirmed HIV-1 infection
- Weight 3.0 kg -15.0 kg
- > 42 weeks post-conception age
- On or about to start LPV/r-based ART
- Clinically diagnosed TB requiring RIF in anti-TB therapy)
- Written informed consent

Exclusion

- Concomitant-potent enzyme-inducing/inhibiting drugs
- Need for anti-TB or ARVs other than from protocol
- Anticipated anti-TB treatment duration > 9 months

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Screening, Enrollment and Follow-up

Screened 272

Enrolled 96

PK	Expected	Performed	Excluded	
1	93	92	0	254 Intensive PK performed 174 on RIF
2	84	82 (Returned late for PK2 n=2)	1	
3	80	80	0	

- Lost to follow-up N = 5
- Withdrew consent N = 6
- Death N=3
- Other N= 2

N=16

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Subjects characteristics (1)

	Enroll n=96	PK1 n=93 PK Data for 92	PK2 n=84 Data for 82	PK3 n=80 Data for 80
***Age (months)**	18.2 (9.6-26.8)	19.1 (10.4-27.6)	23.3 (15.2-34.4)	25.0 (16.7-34.3)
Female	52 (54%)			
Age <1y	30 (31%)	27 (29%)	15 (18%)	7 (9%)
***Weight (kg)**	8.4 (6.7-10.3)	8.8 (7.1-11.1)	9.8 (8.5-12.2)	10.1 (8.9-12.3)
***WAZ**	-2.15 (-3.36- -1.19)	-2.00 (-2.86- -0.87)	-1.34 (-2.15- -0.43)	-1.37 (-2.22- -0.45)
***WHZ**	-0.64 (-1.61– -0.31)			-0.26 (-1.1- 0.52)
Clinical stage 4	60 (62%)			
CD4% *	19.5 (11.6 – 25.7)		27.3 (20.5 – 32.6)	

**Median and IQR*

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Subjects characteristics (2)

- TB treatment started 1st: 70 (73%)
- < 3 Months ART Before TB: 12 (12.5%)
- TB therapy 4 drugs (including EMB): 77 (80%)
- ABC + 3TC: 91 (95%)

	Enroll n=96	PK1 n=93	PK2 n=84	PK3 n=80
***BSA**	0.39 (0.34-0.46)	0.40 (0.35-0.47)	0.44 (0.40-0.52)	0.45 (0.41-0.52)
***LPV Dose mg/m²**		322.9 (297.5 – 339.45)	309.86 287.21-330.51)	308.14 (286.37-329.12)
***RIF Dose mg/kg**		12.45 (11.1-13.48)	12.63 (11.68-13.63)	
Viral load Log	5.7 (4.6-6.3)		2.1 (<1.6-2.9)	
Viral load <Log 2.6	6 (6%)		67 (82%)	

*Median and IQR

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Model-based analysis

- PK1 was used to develop PK model
- The model was used to compare the data from PK2 (LPV/RTV superboosting with RIF) and PK3 (LPV/r normal dose)
  - Separate PK estimates for each visit
- Model-based simulations were used to compare exposures between superboosting or normal dose:
  - To account for diurnal variation overnight clearance was assumed 30% slower
  - The % of children with Cmin < 1mg/L was compared for each regimen
  - The 95% confidence interval for this difference was checked for non-inferiority

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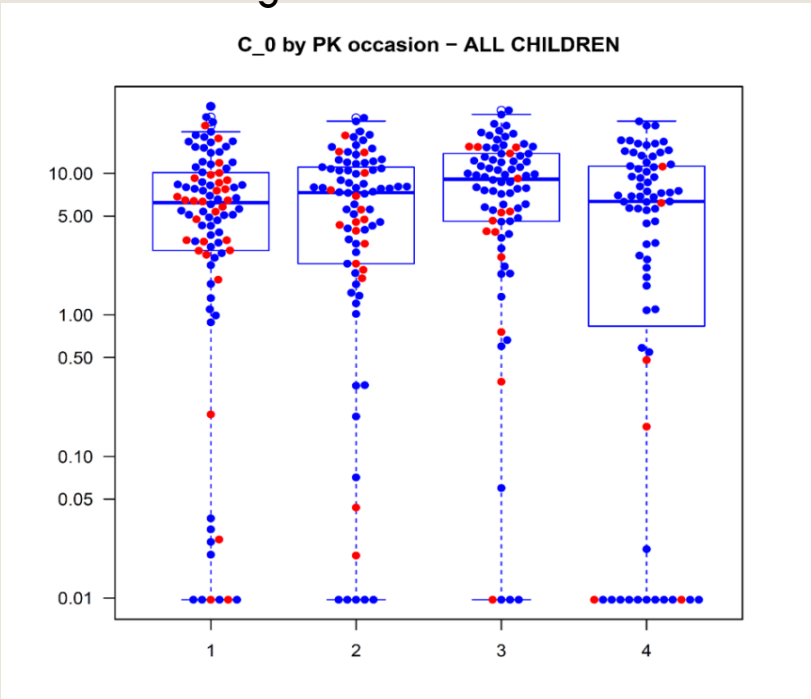
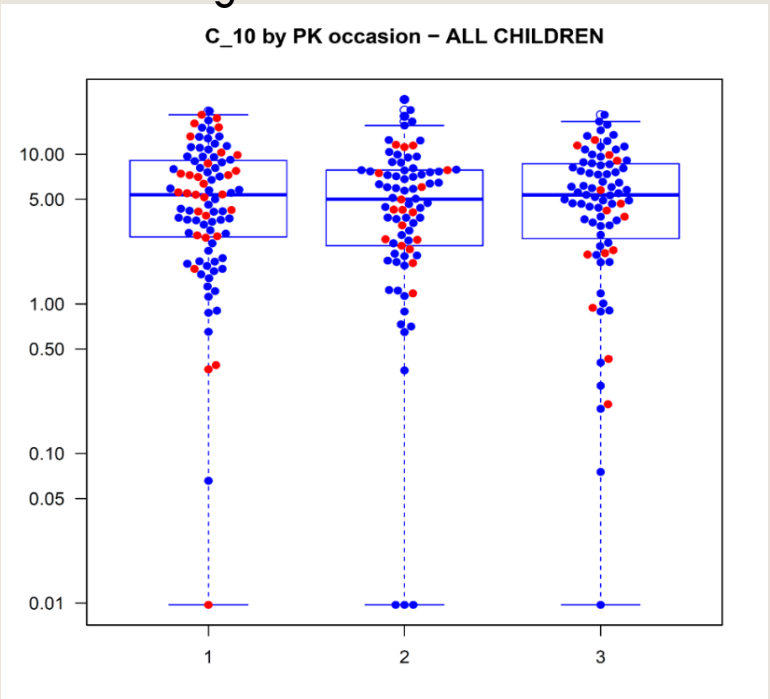
Observed LPV C_0 and C_{10} levels

Dosing unobserved



Dosing observed at clinic



- Younger than 12 months

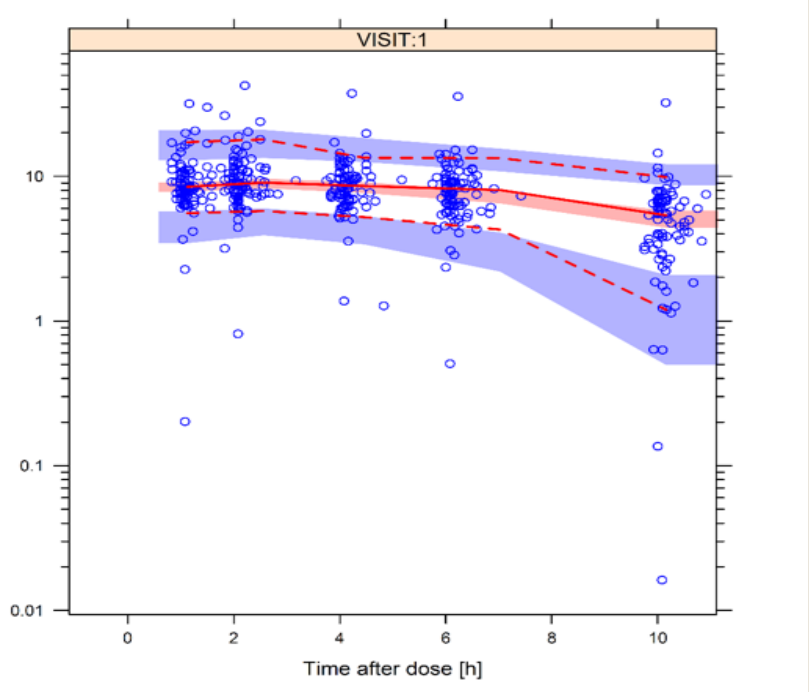
PK	Median (IQR) LPV C_0, mg/L	n
1	6.21 (2.86 – 10.1)	92
2	7.34 (2.43 – 11.0)	81
3	9.12 (4.60 – 11.4)	80
4	6.33 (0.957 - 11.2)	72

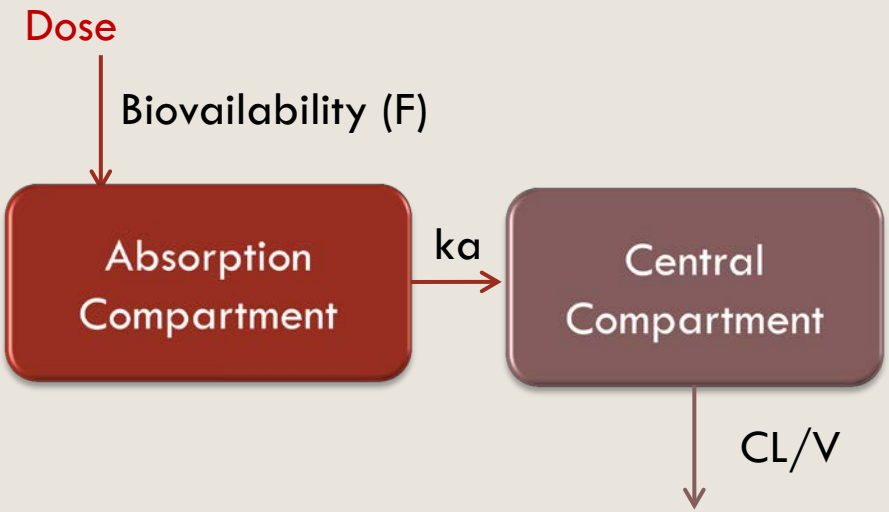
PK	Median (IQR) LPV C_0, mg/L	n
1	5.38 (2.81 – 9.12)	91
2	5.01 (2.45 – 7.84)	81
3	5.35 (2.82 – 8.62)	80

Visual predictive check – Model PK 1

The percentiles are consistently within the 90% confidence intervals

Log Scale





- Observed concentrations
- 5th & 95th centile observed value
- 50th centile observed value
- 5th & 95th centile modeled value
- 50th centile modeled value

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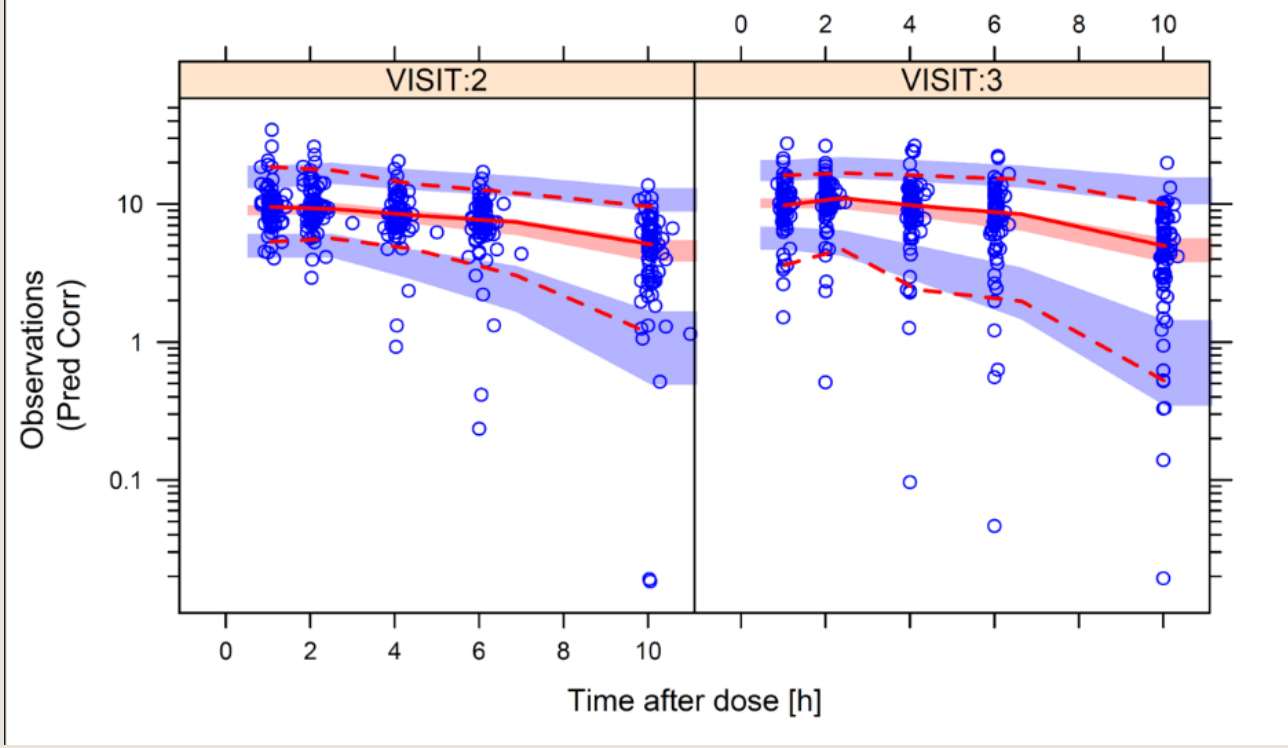
Visual predictive check – Model PK 2-3

The percentiles are consistently within the 90% confidence intervals

Log Scale



- Observed concentrations
- 5th & 95th centile observed value
- 50th centile observed value
- 5th & 95th centile modeled value
- 50th centile modeled value

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Percentage modeled C_0 below target

- **Superboosting %** Cmin < 1 mg/L = **7.6% (0.4% -16.2%)**
- **Standard dose** % Cmin < 1 mg/L = **8.8% (0.6%- 19.8%)**
- **Difference: -1.1% (-6.9% to 3.2%)**

- The 10% delta threshold is outside the 95% confidence interval for the difference, confirming non-inferiority

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Adverse events and safety

- 29 Serious adverse events
  - 3 deaths
  - 16 infections (7 respiratory tract infections)
  - 1 obstructive jaundice (temporary discontinuation of therapy all reintroduced)
  - 4 neutropenia (no therapy changes required)
  - 1 type 1 Diabetes (islet cell antibody positive)
- No ECG abnormalities requiring therapy change

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Hepatic enzymes monitoring

	Baseline	PK1	PK2	PK3	Exit
ALT (U/L) Median (IQR)	25.0 (18.0 - 40.0)	25.0 (19.0 - 32.0)	26.0 (19.5 - 35.5)		20.0 (16.0 - 26.0)
Normal	68 (72%)	79 (86%)	62 (78%)	72 (91%)	
ALT Gr 1 1.5-2.5 ULN	21 (22%)	9 (10%)	13 (16%)	6 (8%)	
ALT Gr 2 2.6-5 ULN	6 (6%)	4 (4%)	5 (6%)		

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Virologic response

- At PK 2
  - 69 (84%) < Log 3
  - 67 (82%) < log 2.6
- 22 resistance test performed
  - 7 No mutations
  - No lopinavir resistance
  - M184V in 10/15 children
  - NNRTI mutations seen in 10/15 children (9/10 significant)

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Discussion and conclusion

- LPV trough levels on superboosting were NOT inferior to those on standard LPV/r without RIF
- Viral suppression <400 copies was comparable to published cohort data
  - No major LPV/r resistance documented
  - 9 of 15 children with resistance had significant NNRTI resistance
- Logistical complexity and tolerability may remain obstacles – Mothers assessment and children reactions do not necessarily match
- Taste masked LPV/r granules and RTV powder may help

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