Clinical application of emerging data antituberculosis drugs pharmacokinetics and dosing in children

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25th Annual Conference of the Union – North America

February 27, 2021

Department of Pediatrics
Division of Global Pediatrics
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Objectives

- Identify the most important results emerging from ongoing pharmacokinetic studies and trials of key antituberculosis drugs
- Apply new pediatric research data on antituberculosis drug dosing to improve the treatment outcomes of pediatric TB patients

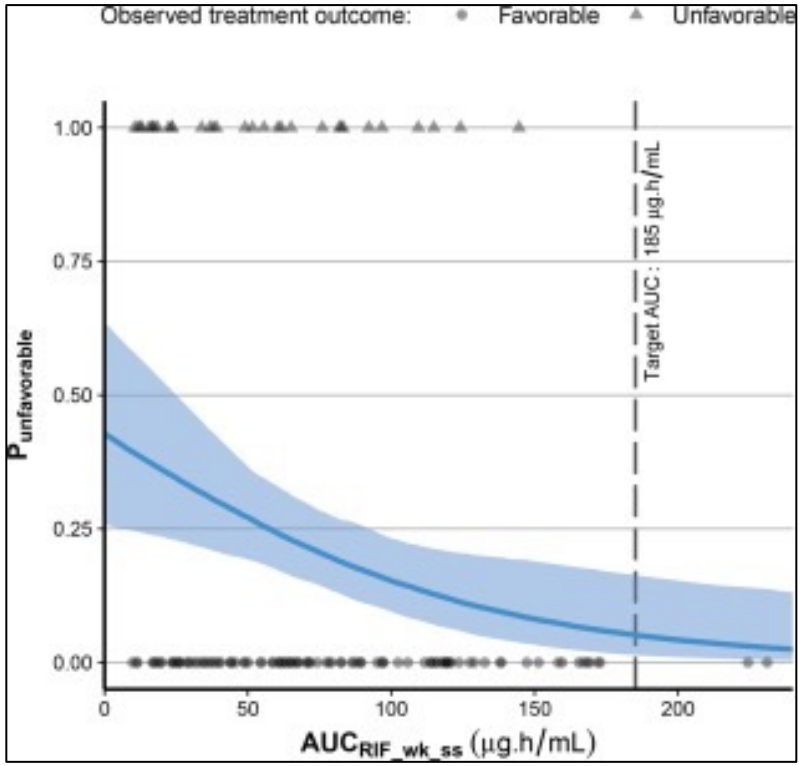
Overview

1. Emerging data, implications for practice
   - Rifampicin
   - Moxifloxcin
   - Linezolid
   - Bedaquiline
   - Delamanid
2. Ongoing studies – what to be looking for in the near future
3. Future – new drugs, optimization, challenges, ways forward
4. Formulations

Rifampicin

Key characteristics	• Rifamycin • Substantial EBA • Excellent sterilizing activity
Role in TB treatment	• Key component of first-line treatment of DS-TB • Prevention of DS-TB • TB meningitis • Treatment shortening
Gaps for children	• Exposures with newly recommended doses, FDCs • Optimal dose for special groups – TBM, malnutrition • Formulation – FDCs, some single drug formulations

Rifampicin exposure in children and TB treatment outcome

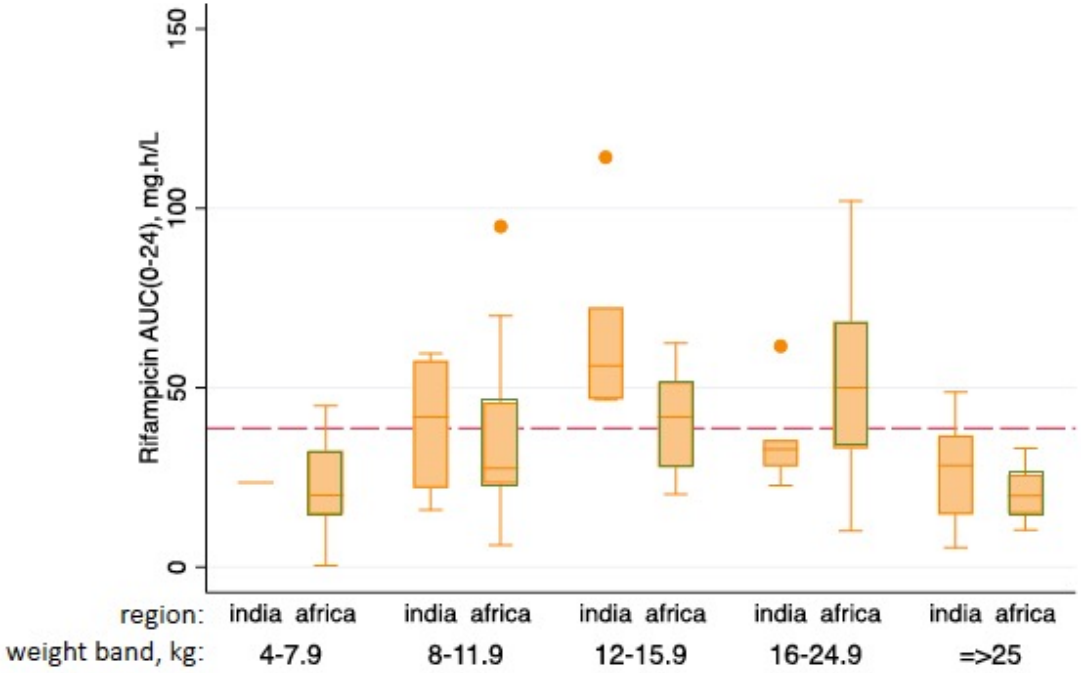


- 161 Indian children with TB or TB-HIV treated 3x/weekly
- Low rifampicin exposure was associated with unfavorable outcome
- Rifampicin exposure was lowest in children with low weight and HIV-infection

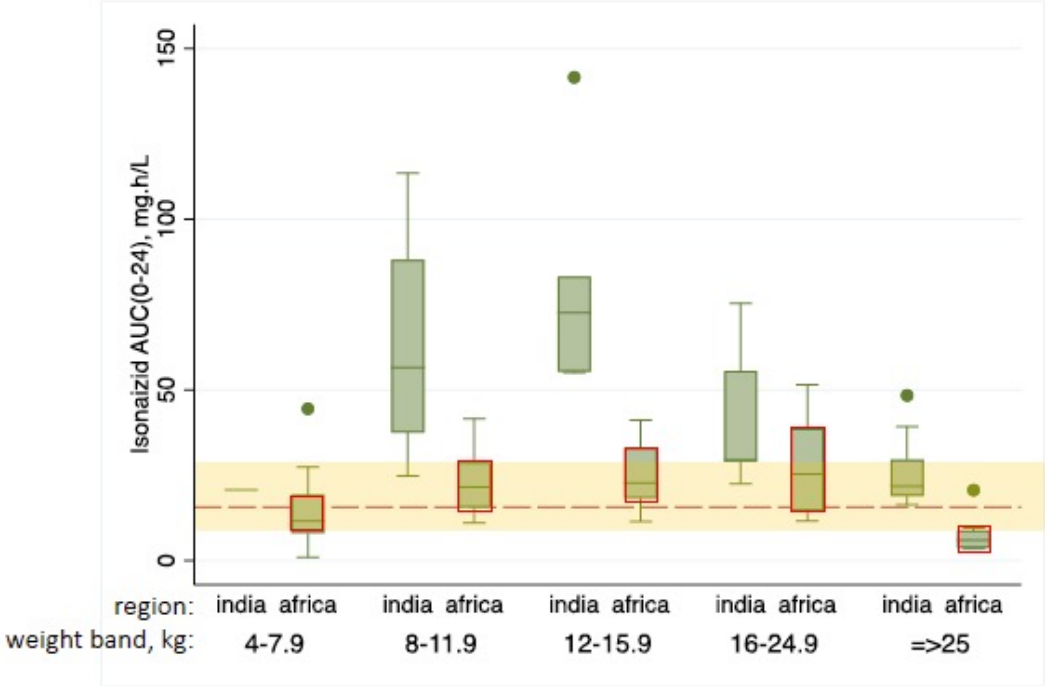
Guiastrennec B, Ramachandran G, Karlsson MO, et al. Suboptimal Antituberculosis Drug Concentrations and Outcomes in Small and HIV-Coinfected Children in India: Recommendations for Dose Modifications. *Clin Pharmacol Ther.* 2018 Oct;104(4):733-741.

Low rifampicin exposures in young children (SHINE Trial)

Rifampicin exposures by weight-band



Isoniazid exposures by weight-band



McIlleron H, Chisala Chaballa, Hemanth Kumar AK. *Evidence-based dosing of first-line TB drugs in African and Indian children: the SHINE and DATIC studies.* Union World Conference on Lung Health, Hyderabad, India, 2019.

High rifampicin doses for treatment shortening (adults)

- PanACEA HIGHRIF1[1] and extension trial[2]
  - *Design* – Dose ranging study: PK, safety, extended EBA of 14 days of escalating doses of RMP
  - RMP dosing: 10, 20, 25, 30, 35, 40 and 50 mg/kg once daily
  - *Efficacy* - Increasing bactericidal activity associated with increasing RMP dose and exposure

1 Boeree MJ, et al. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. Am J Respir Crit Care Med. 2015 May 1;191(9):1058-65.
2 Te Brake LHM, et al. Increased bactericidal activity but dose-limiting intolerability at 50 $mg \cdot kg^{-1}$ rifampicin. Eur Respir J. 2021 Feb (ahead of print).

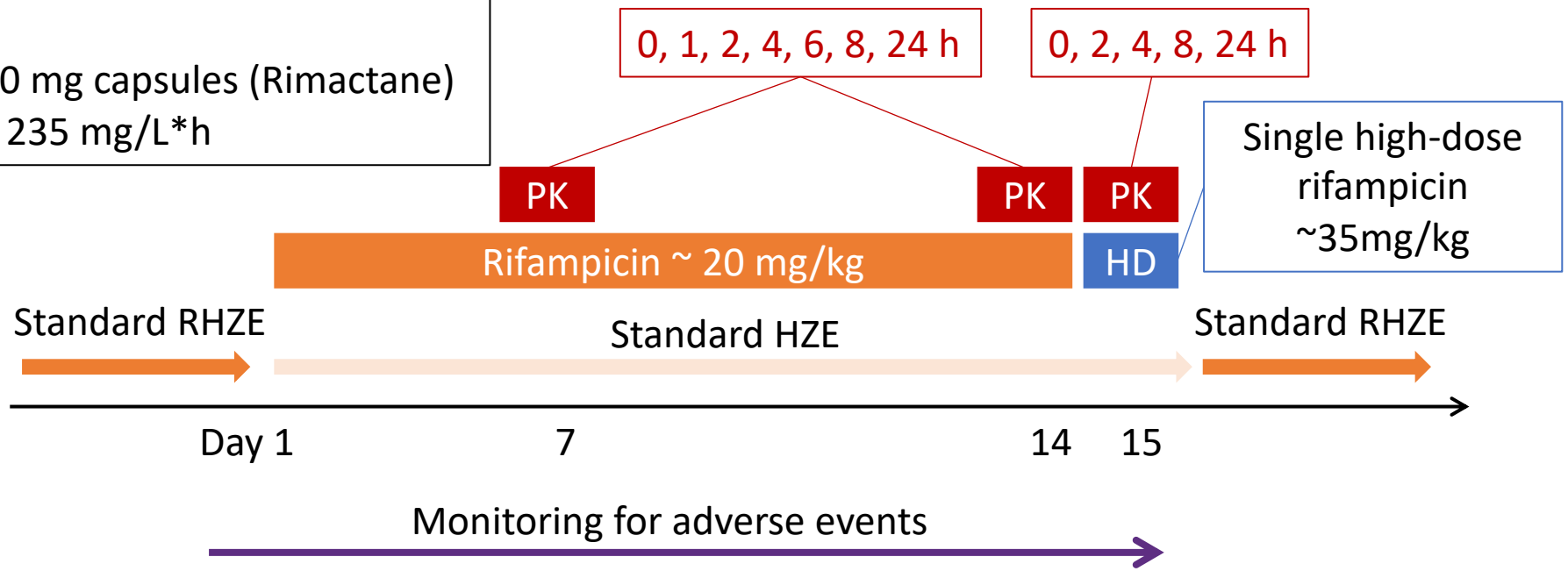
Table 2| Total number of adverse events per severity, dose group and treatment period.

	10-30 mg/kg RIF	35 mg/kg RIF	40 mg/kg RIF	50 mg/kg RIF
AE monotherapy	*n=53*	*n=15*	*n=15*	*n=17*
Total, n	46	25	36	93*
Not specified	0	0	0	10
Unrelated	13	4	9	10
Possibly related	28	19	19	24
Related	5	2	8	49
Grade 1, n	38	18	26	60
Grade 2, n	6	7	9	21
Grade 3, n	2	0	1	1
SAE, n	0	0	0	0

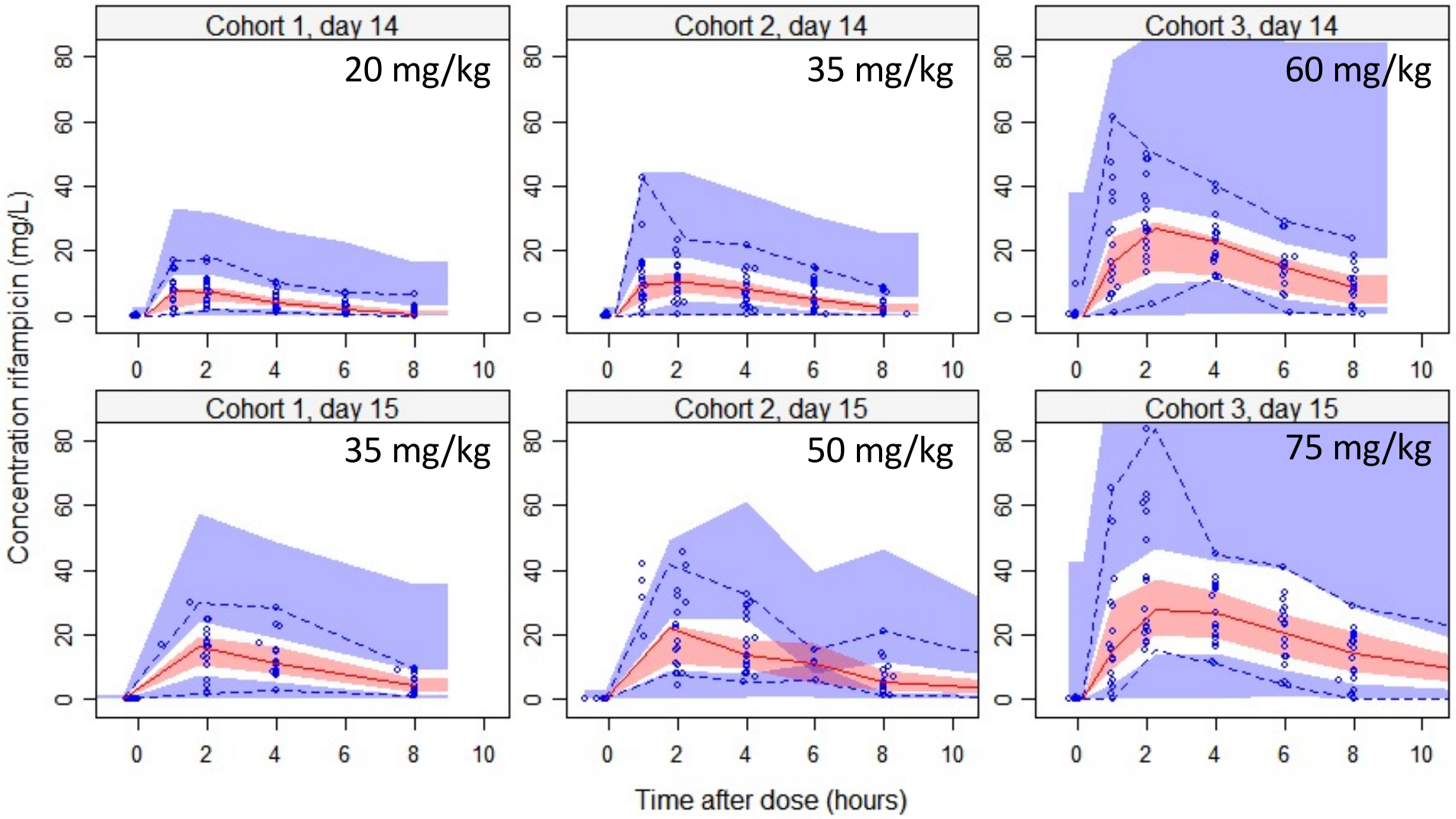
- Most frequent events were GI (nausea, vomiting, elevated bilirubin, jaundice)
- Tolerability – there were 9 early withdrawals from 50 mg/kg dosing group

Opti-Rif Study: Rifampicin dose escalation study in children

n = 20 per cohort x 3-5
Age: 0-12 years
Formulation: 150 mg capsules (Rimactane)
Target: $AUC_{0\text{-}24}$ = 235 mg/L*h



Opti-Rif: Rifampicin dose escalation in children: PK Results



Opti-Rif Safety: Summary

	Cohort 1 (n=20) (~20 mg/kg)	Cohort 2 (n=22) (~35 mg/kg)	Cohort 3 (n=20) (~60 mg/kg)
Number with any AE (%)	13 (65)	20 (91)	17 (85)
Number with any Gr 1 or 2 AE (%)	12 (60)	20 (91)	17 (85)
Number with any Gr 1 or 2 AE at least possibly related (%)	7 (35)	9 (41)	12 (60)
Number with any Gr 3 or 4 AE (%)	1 (5)	2 (9)	0 (0)
Number with any Gr 3 or 4 AE at least possibly related (%)	0 (0)	0 (0)	0 (0)
Number discontinuing RMP due to safety or tolerability (%)	0 (0)	2 (9)	0 (0)
Number with SAEs (%)	1 (5)	0 (0)	0 (0)
Deaths (%)	0 (0)	0 (0)	0 (0)

Rifampicin: Summary

Key findings	• *PK:* Rifampicin exposures at current WHO recommended doses still below targets • *Safety:* Safe, even at much higher doses; GI intolerability
Clinical application	• For DS-TB treatment, dose rifampicin at higher end of the range as able (formulation)

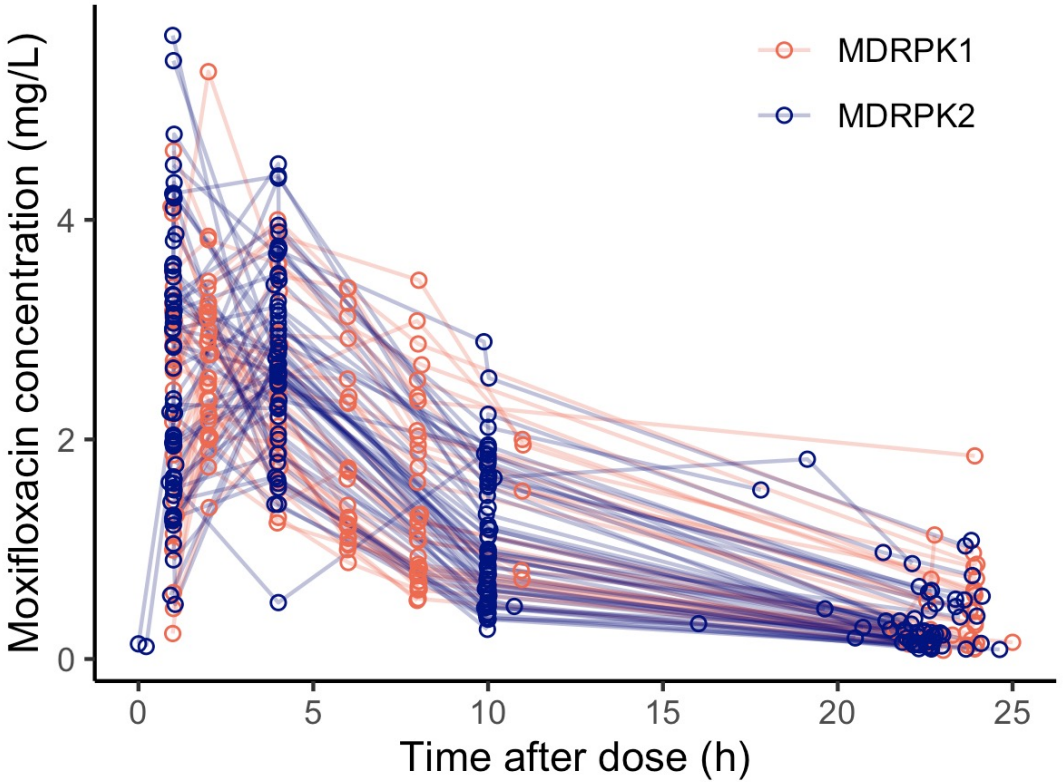
Future priorities	• Optimal dosing for routine DS-TB treatment, formulation
	• Watch for emerging data, recommendations
	  • TB meningitis
	  • Malnutrition
	  • Treatment shortening

Moxifloxacin

Key characteristics	• Fluoroquinolone • Good EBA • QT prolongation
Role in TB treatment	• Second-line TB drug, DR-TB treatment • S31 – 2HPZM/2HPM*
Gaps for children	• Recommended peds dose – 7.5-10 mg/kg once daily • Limited PK data, esp young children • Limited safety data in children • Formulation – 400 mg tab, 100 mg disp tab • Poor palatability

Moxifloxacin PK, safety

- Observational PK studies – MDRPK1, MDRPK1 – DTTC/SU, South Africa
- Children 0–17y with RR-TB
- MFX ~10 mg/kg once daily
- NLME (Radtke, Savic)
- N=85, age 4.6y (0.4, 15), 9% HIV infected
- Increased CL/F in HIV-infection



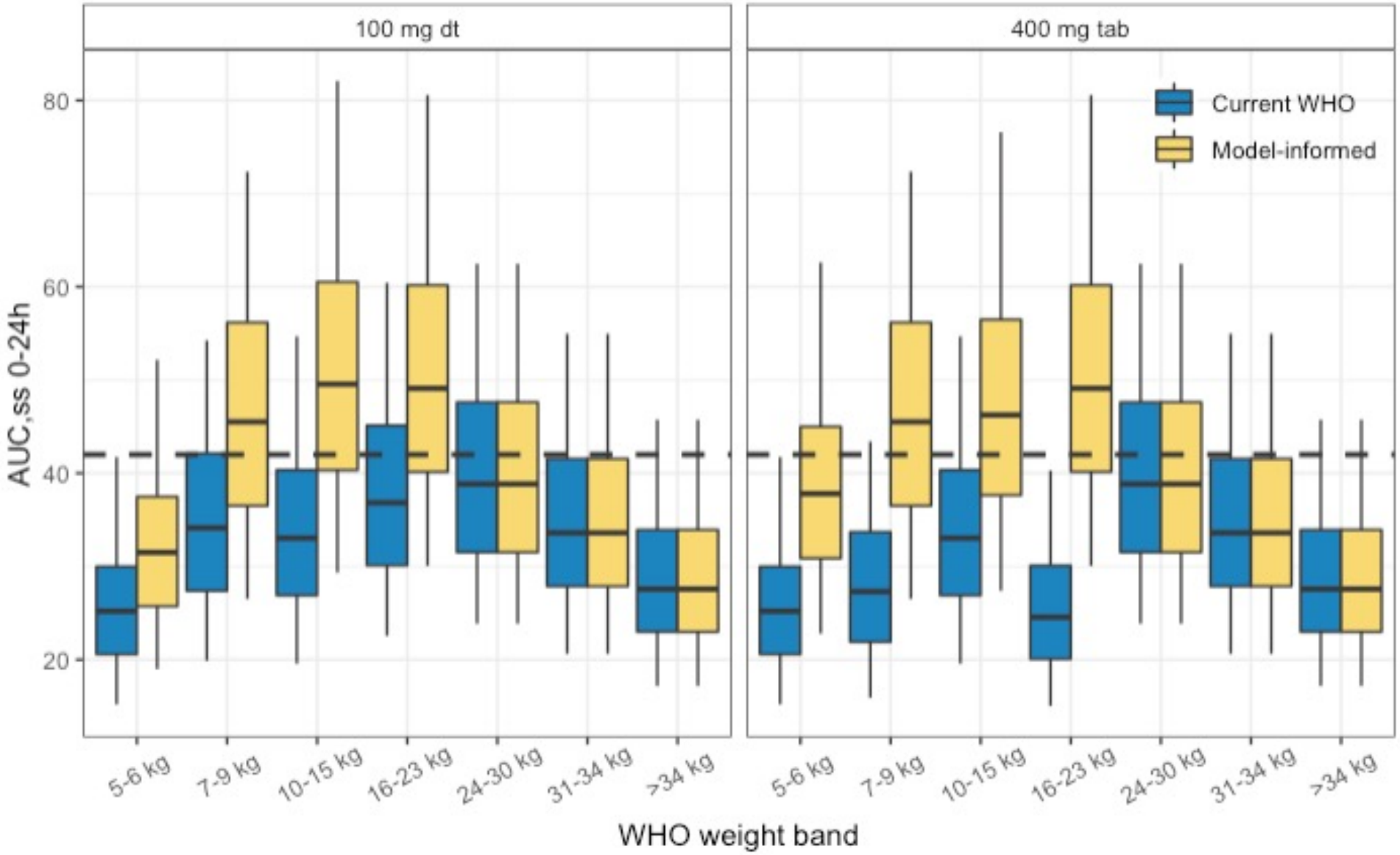


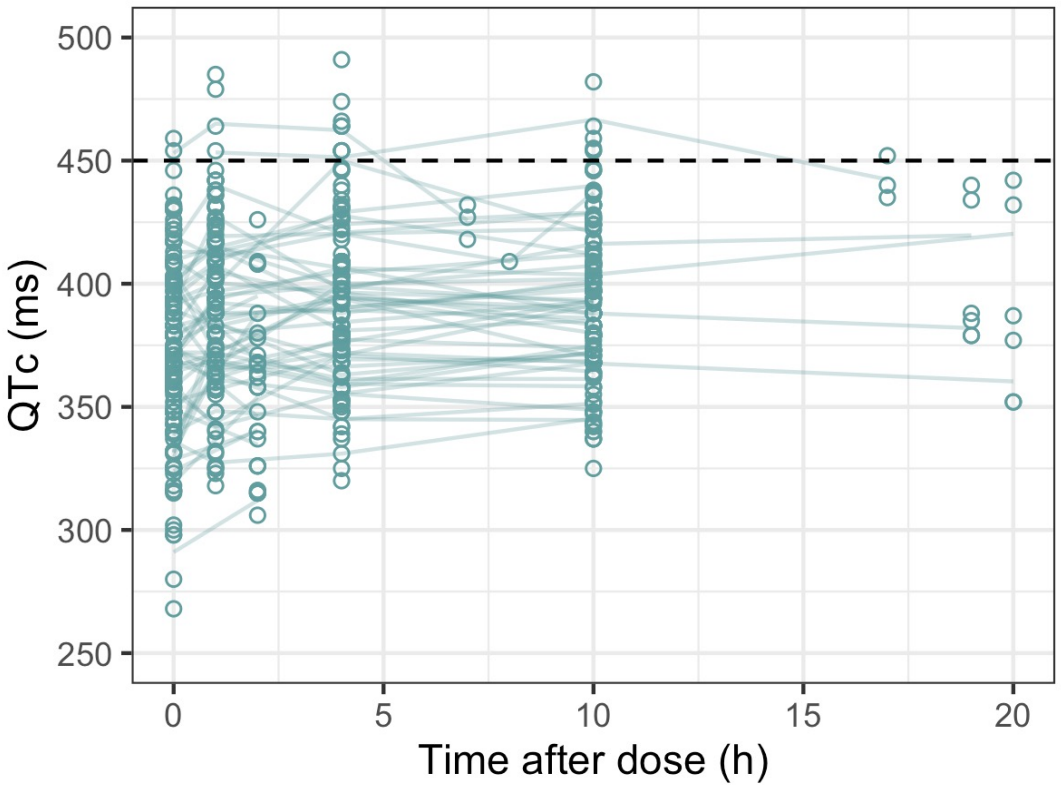
Fig. Simulated moxifloxacin AUC with WHO and model-informed weight band dosing.

Moxifloxacin proposed dosing in children

	Current WHO Dosing				Model-informed Optimized Dosing			
	100 mg dt		400 mg tab		100 mg dt		400 mg tab	
Weight band	Tabs	Dose	Tabs	Dose	Tabs	Dose	Tabs	Dose
5-6 kg	0.8	80 mg	2 mL*	80 mg	1	100 mg	4 mL*	120 mg
7-9 kg	1.5	150 mg	3 mL*	120 mg	2	200 mg	5 mL*	200 mg
10-15 kg	2	200 mg	5 mL*	200 mg	3	300 mg	7 mL*	280 mg
16-23 kg	3	300 mg	0.5	200 mg	4	400 mg	1	400 mg
24-30 kg	4	400 mg	4	400 mg	4	400 mg	1	400 mg
31-34 kg	4	400 mg	4	400 mg	4	400 mg	1	400 mg
>34 kg	4	400 mg	4	400 mg	4	400 mg	1	400 mg

Moxifloxacin: cardiac safety

- N=57
- Mean (SD) max QTcF= 408 ms (33)
  - >500 ms = 0
  - 480 to <500 = 2 (2.9%)
  - 450 to <480 = 3 (4.5%)
- Median (range) ΔQTcF (dosing interval) = 13.7 ms (-11.8, 61.3)
  - 30 to <60 ms = 11 (17%)
  - >60 ms = 1 (1.6%)
- Effect of CFZ



Moxifloxacin: Summary

Key findings	• *PK:* 10 mg/kg results in exposures below targets, esp for <24 kg • *Safety:* QT prolongation but minimal in most children; few musculoskeletal AEs
Clinical application	• *Dose:* Utilized revised wt banded doses (10-15 mg/kg once daily dose) • Important for pediatric use of 2HPMZ/2HPM • Palatability a continued issue
Future priorities	• Formulation (100 mg disp tab), improved taste masking (BENEFIT Kids, Unitaid/TBA/SU) • Confirm PK with disp tab formulation • Confirm safety with higher doses

Linezolid

Key characteristics	• Oxazolidinone
	• Effective antimycobacterial - XDR-TB, BPaL
	• Dose- and duration-dependent adverse effects
	  • Common: cytopenias, neuropathy
	  • Rare: lactic acidosis, optic neuropathy

Role in TB treatment	• WHO Group A 2nd-line TB drug, DR-TB treatment • TB meningitis
Gaps for children	• Limited PK data, dosing recommendations for TB treatment • In practice: 10 mg/kg/dose, given twice daily if <10y (30 kg), once daily if >10y or 30 kg) (max 600 mg daily) • Limited safety data in children with long-term dosing • Formulation – 600 mg tab, 20 mg/mL susp, (100 mg disp tab)

Linezolid PK: Results[1]

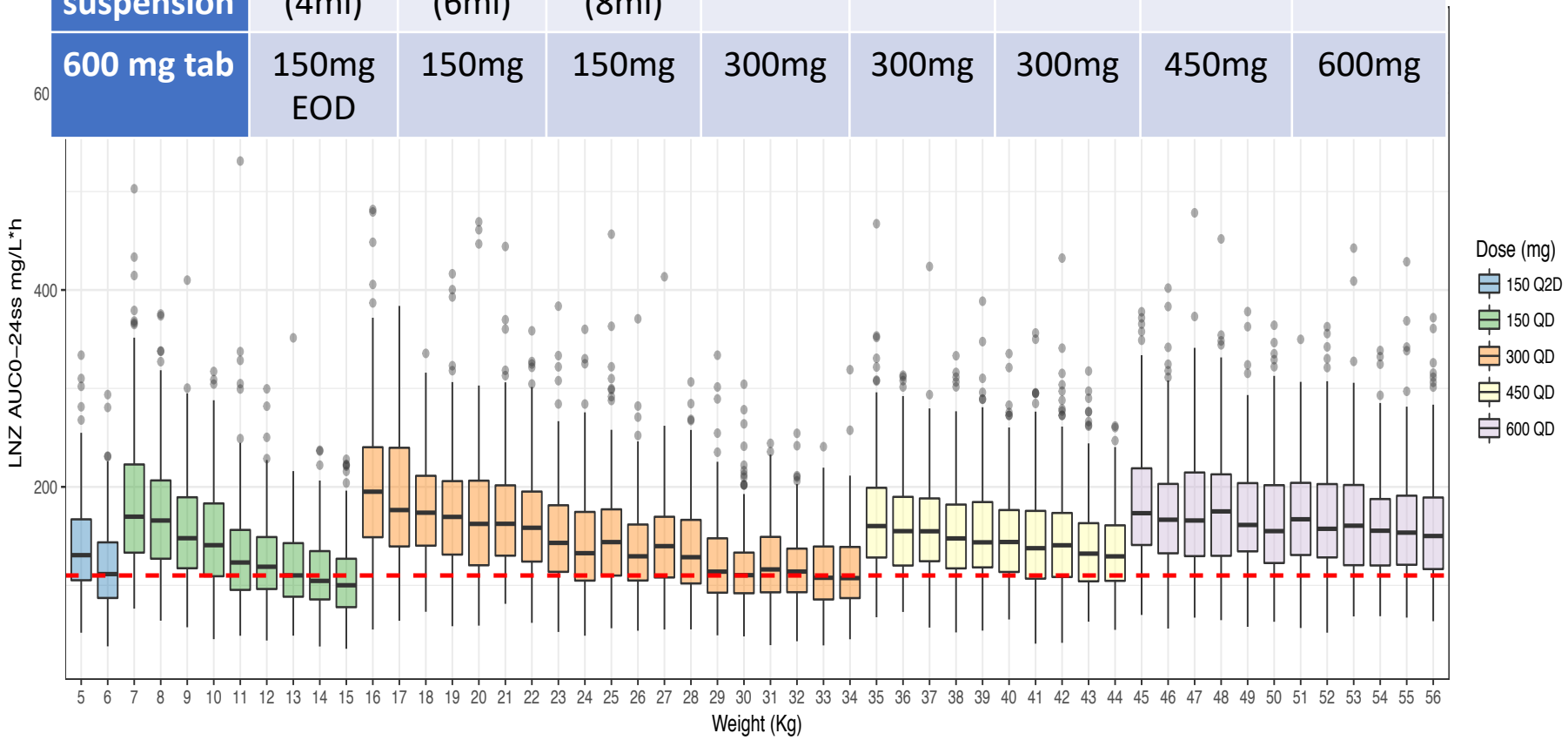
Design	Observational PK studies – MDRPK1, MDRPK2 (DTTC/SU, South Africa)
Population	Age 0-17 years, RR-TB
Analysis	NLME modelling (Garcia-Cremades, Savic) Target AUC_{0-24} after 600 mg dose – 110 mcg/L*h

Age	Dose	Number (Total n=48)	Median AUC_{0-24ss} (range) mg/L*h
<10 years	<10 mg/kg	16	78.5 (56.6, 158)
	10 to <20 mg/kg	16	128 (59.2, 243)
	>20 mg/kg	5	190 (139, 216)
≥10 years	<10 mg/kg	7	98.9 (75.3, 322)
	10 to <20 mg/kg	4	114 (102, 271)
	>20 mg/kg	0	--

1 Garcia-Prats AJ, et al. (2019) Pharmacokinetics, optimal dosing, and safety of linezolid in children with multidrug-resistant tuberculosis: Combined data from two prospective observational studies. PLOS Medicine 16(4): e1002789.

Linezolid results: Dosing, simulated AUCs

	5-6 kg	7-9kg	10-15kg	16-23kg	24-30 kg	31-34 kg	35-44 kg	>44 kg
OPTIMAL DOSE	80 mg	120mg	150mg	220mg	280mg	300mg	400mg	600mg
20 mg/ml suspension	80mg (4ml)	120mg (6ml)	160mg (8ml)	-	-	-	-	-
600 mg tab	150mg EOD	150mg	150mg	300mg	300mg	300mg	450mg	600mg



Linezolid Safety Results

N=17

Median age: 6.1y (0.6, 15.3)

Median time on LZD: 17.7m (IQR 7.5, 19.7)

# of Events: 10/17 (59%)

LZD dose adjust : 4 (23.5%)

LZD temp interrupt: 5 (29.4%)

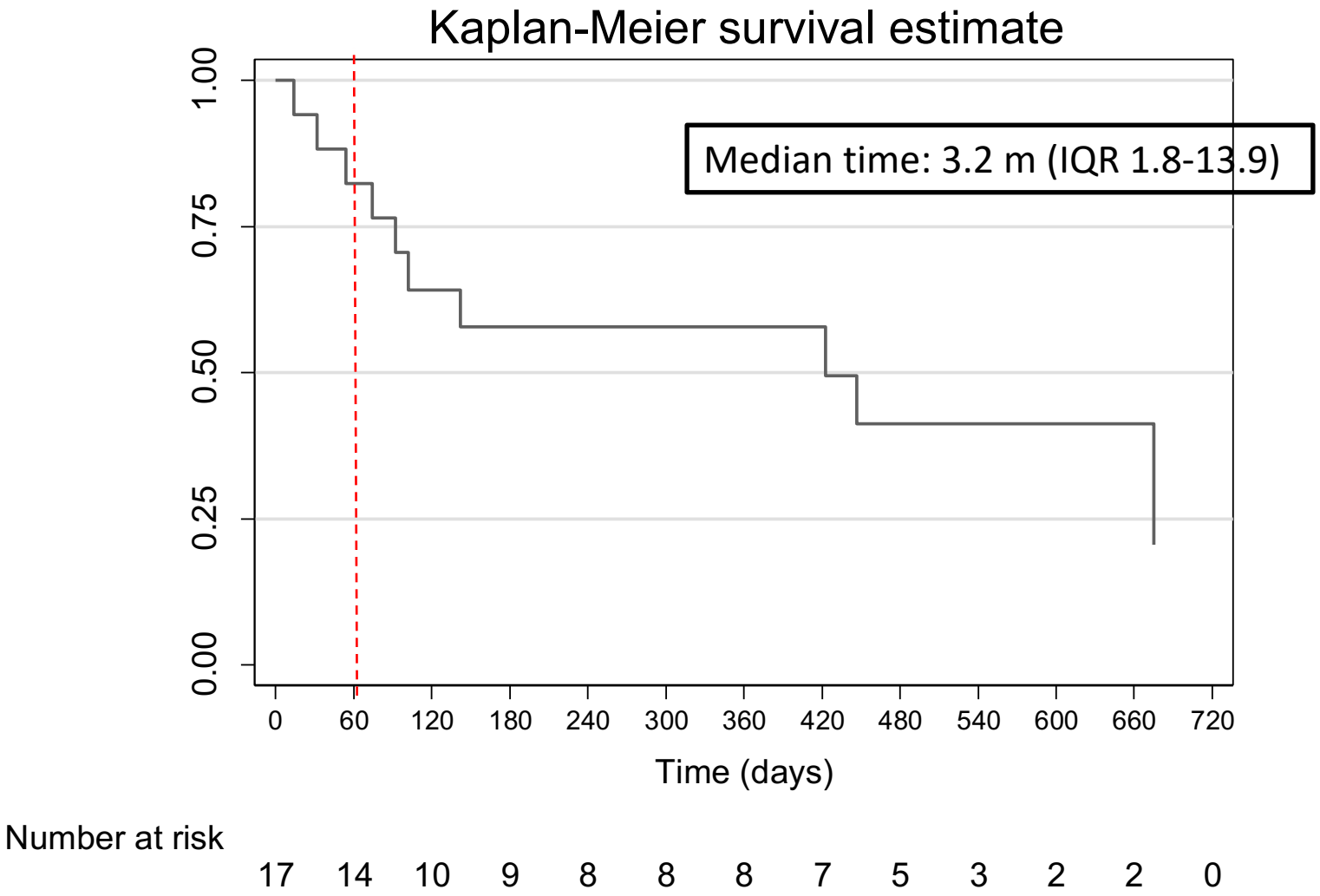
LZD discontinued: 4 (23.5%)

Table 5. Adverse events in children treated for multidrug-resistant tuberculosis with linezolid (n=17)

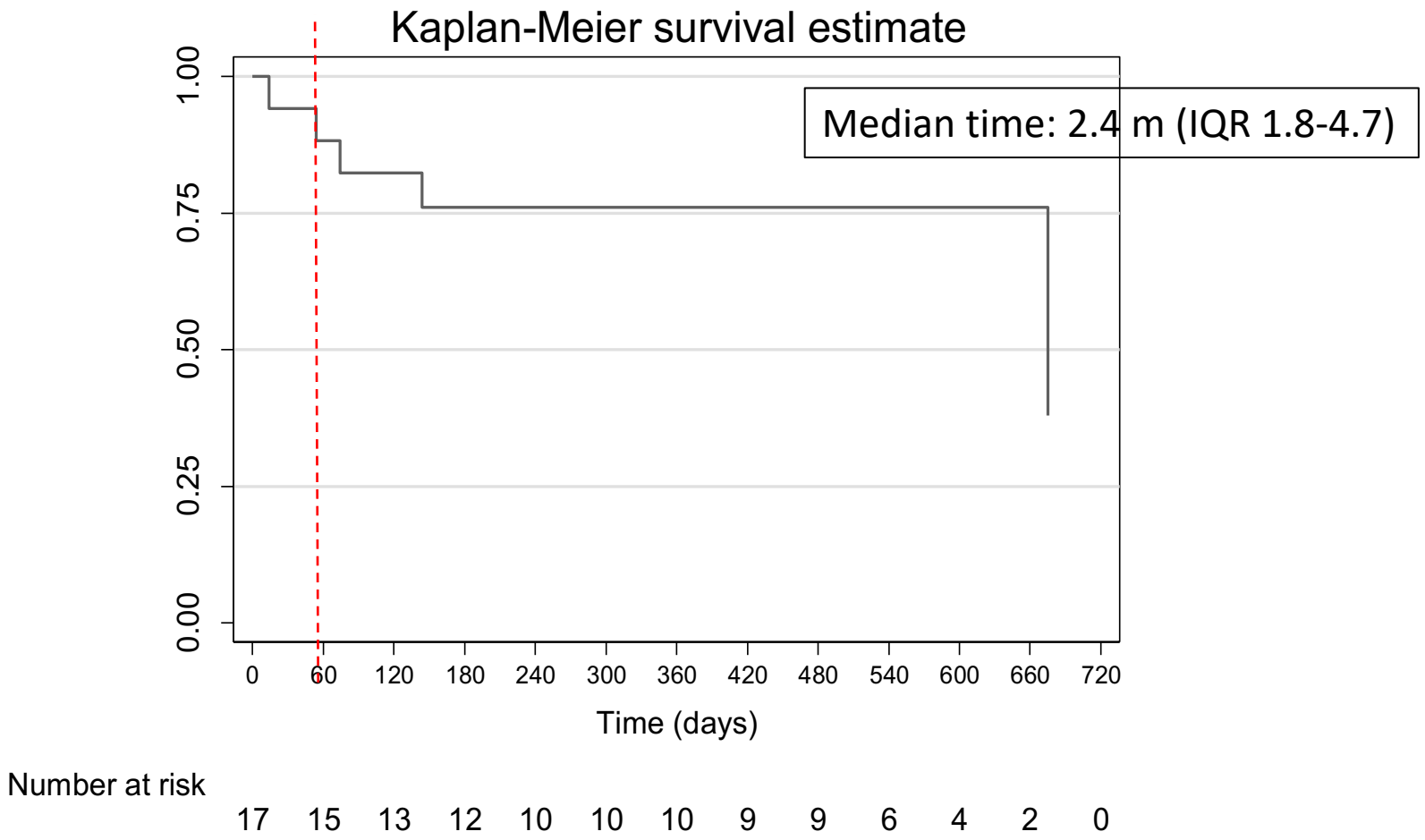
	Adverse events possibly, probably or definitely attributed to linezolid by grade						
Adverse Event	# of patients with event	Grade 1	Grade 2	Grade 3	Grade 4	Total # of events	Event Rate (per 100 person-yrs)
Peripheral neuropathy	1	1	0	0	0	1	4.8
Low haemoglobin	10	5	2	3	2	12	57.2
Low platelets	2	1	1	0	0	2	9.5
Low white blood cell count	1	1	0	0	0	1	4.8

17 patients followed for a median time of 17.7 months (IQR: 7.5 - 19.7 months); total person years = 21.0.

Linezolid safety results: Time (days) to a linezolid-related adverse event of any grade



Linezolid safety results: Time (days) to a LZD-related Grade 3/4 event



Linezolid: Summary

Key findings	• *PK:* Lower mg/kg doses appropriate compared to previous • *Safety:* Adverse events frequent (anemia), can be severe and occur early
Clinical application	• WHO Group A drug - use for most DR-TB cases, individualize duration • Utilize newly recommended doses – WHO weight-banded doses, ~10-15 mg/kg once daily • Monitor safety closely – regular blood counts
Future priorities	• Formulation • Optimized dosing strategy (ZeNix, TB-PRACTECAL, endTB) • Optimal duration • Therapeutic drug monitoring • Novel oxazolidinones

Bedaquiline

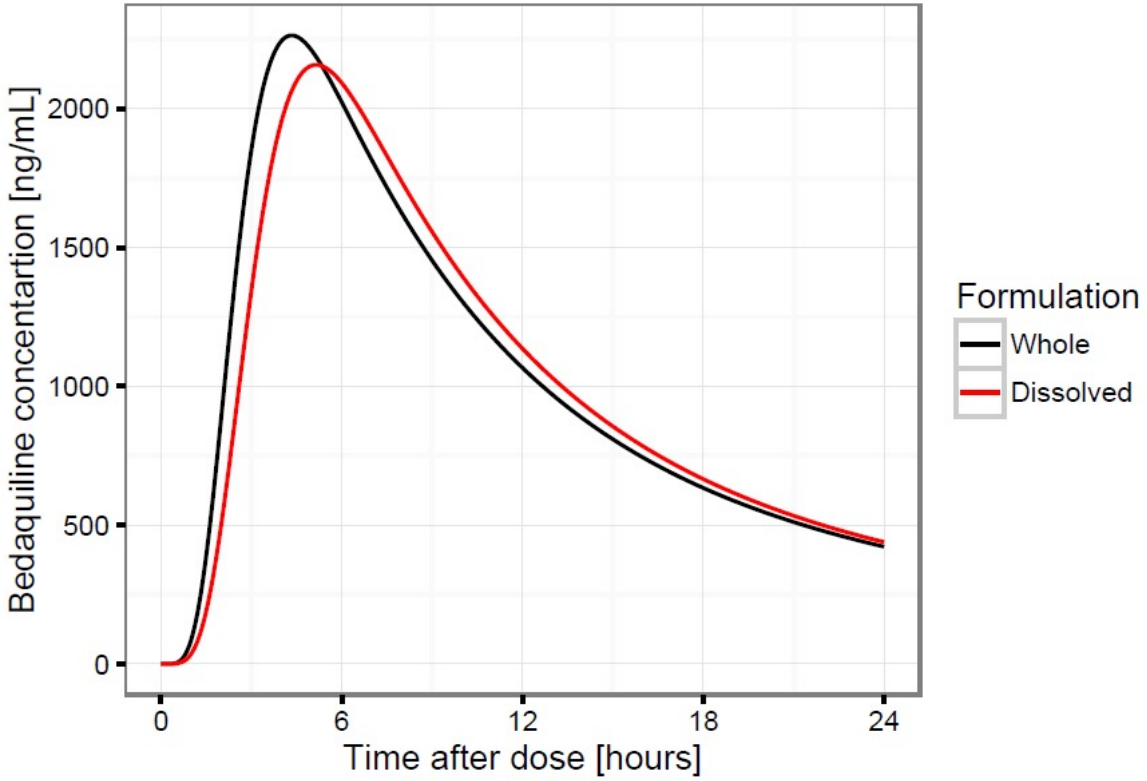
Key characteristics	• Diarylquinoline
	• Highly effective – reduced mortality, BPaL, treatment shortening potential
	• Safety
	  • QT prolongation
	  • Arthralgia/arthritis, hepatotoxicity

Role in TB treatment	• WHO Group A 2nd-line TB drug, DR-TB treatment • Component of multiple shortened, all-oral regimens for DR-TB
Gaps for children	• PK, safety data in children • Formulation

Phase I/II pediatric bedaquiline trials

	C211: Bedaquiline PK and safety in HIV-uninfected children (n=60)	P1108: PK, safety and tolerability of bedaquiline with OBR in HIV-infected and uninfected children with MDR-TB (n=54-72)
Sponsor	Janssen Pharmaceuticals	NIH (DAIDS, IMPAACT)
Design	Age de-escalation	Modified age de-escalation
Inclusion	0-<18y, HIV-uninfected only	0-<18y; both HIV-infected and uninfected
Accrual	Open 2016, South Africa, Philippines, Russia, India, Mozambique	Open 2018 – South Africa, India, Haiti
Other	Adult, pediatric formulations	Adult formulation, (pediatric formulation)
Progress	Cohorts 1 (12-17y) and 2 (5-<12y) complete; Cohort 3 (3-5y) open, Cohort 4 (<3y) after completion of Cohort 3	Data from cohort 1 (6-17y) shared with WHO; Cohorts 2 (3-<5y) and 3 (<3y) to open in parallel

BDQ CRUSH Results: Impact of dissolving on a typical BDQ PK profile



- Mean absorption time slightly longer for dissolved tablets: +23% (p=0.03, $CI_{95\%}$ 2.1-48%)
- T_{max}: 4.3 to 5.2h
- C_{max}: ↓ 5%

- Difference in bioavailability dissolved vs whole tablets not statistically significant (p=0.92, $CI_{95\%}$ 94-108%)
  → **Bioequivalence criteria fulfilled**

Analysis and slide courtesy of Elin Svensson

Bedaquiline: Summary

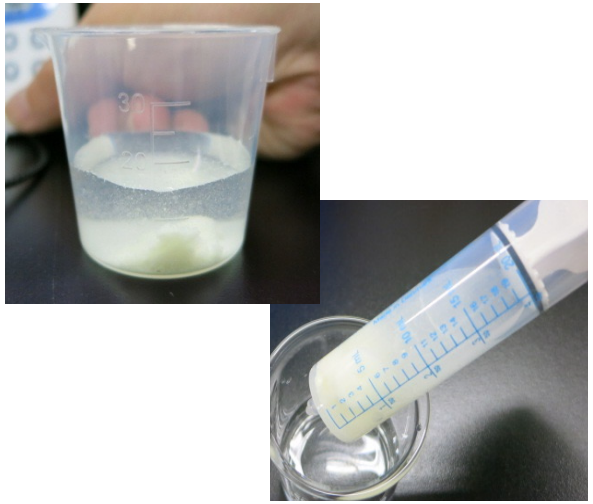
Key findings	• *PK:* FDA approved dose for children ≥5 years, including 20 mg disp tab • ”Dissolved/crushed” 100 mg tab bioequivalent to whole
Clinical application	• Use routinely for >5y of age with RR-TB • <5y, not routinely use, weigh risks and benefits in special cases
Future priorities	• PK, dose, safety – children <5 years • Formulation – disp tab • Alternative dosing strategies (daily dosing)

Delamanid

Key characteristics	• Nitroimidazole • Pre-clinical data - potential for treatment shortening • PK: Long half-life of Dlm and DM-6705 • Safety: QT prolongation
Role in TB treatment	• WHO Group C 2nd-line TB drug, DR-TB treatment • Under evaluation for DR-TB preventive therapy • Component of multiple trials of shortened, all-oral RR-TB regimens
Gaps for children	• PK, dosing, safety data in children • Formulation – 50 mg tablet, (25 mg, 5 mg dispersible tablets)

Otsuka trials 232 and 233

- 232 – Phase 1 (10d DLM); 233 – Phase 2 (6m DLM)



- Current Tablet Formulation
  - Group 1: Adolescents 12 to 17 years
    - (100 mg BID; n=6)
  - Group 2: Children 6 to 11 years
    - (50 mg BID; n=6)
- Pediatric formulation
  - Group 3: Children 3 to 5 years
    - (25 mg BID; n=12)
  - Group 4: Newborns and infants 0 to 2 years
    - [10mg BID (>10kg), 5mg BID (>8 to 10 Kg), 5mg QD(5.5 to 8Kg]
    - (n=12)
- Overall sample size = 36 children (HIV-uninfected)
- Status: Completed all Groups

Slide provided by Jeff Hafkin, Otsuka Pharmaceuticals

Table. Median delamanid and DM-6705 plasma PK parameters for Groups 1-3 in pediatric trial 232

	Group 1 (12 – 17y) (n=7)	Group 2 (6-11y) (n=6)	Group 3 (3-5y) (n=12)	Group 4 (0-2y) (n=12)	Adults
Median **DLM** AUC_{0-24} (ng*h/mL)	9730	12000	9085	--	6811
Median **DM-6705** AUC_{0-24} (ng*h/mL)	1780	1870	1374	--	2411

*Day 10 values from 232 for Groups 1 and 2; Day 14 values from adult trials

Delamanid in children: WHO guidance

- ≥34 kg – 100 mg (2 tabs) twice daily*
- ≥24 to <35 kg – 50 mg (1 tab) twice daily*
- ≥16 to <24 kg – 25 mg twice daily**
- <16 kg - ???

- *(WHO: 12 - <18y, 6 - <12y, 3 - <6y)
- **Formulation issues (dose based on paeds formulation [Disp tabs, DT], not available)
  - DT not bioequivalent (~85% BA) vs adult tabs
  - No evidence on crushing, suspending adult tabs
  - Manipulation may reduce bioavailability
  - Can use, must be aware of uncertainty, balance risks/benefits

Other delamanid pediatric trials

	IMPAACT 2005	Delamanid Crush study	PHOENIx (A5300/I2003)
Sponsor	NIH/DAIDS (IMPAACT)	Stellenbosch University (Unitaid)	NIH/DAIDS (ACTG/IMPAACT)
Design	Phase II – PK, safety of Dlm	Rdmzd crossover, relative BA: whole vs crushed Dlm 50 mg	Phase III cluster randomized trial – delamand vs INH
Participants	Children 0-17y with RR-TB	Healthy adult volunteers (n=24)	High-risk RR-TB HHCs, including children
Expected results	1) Model-informed dosing strategy across ages; 2) Dose in children <3y	Inform rationale use of “crushed” 50 mg solid tabs, for use in children	1) Efficacy, safety of delamanid for preventing TB in RR-TB exposed persons; 2) PK OD delamanid in children
Timing	Open, on pause, results in 2024	Open, results expected 2021	Opened 2019

Delamanid: Summary

Key findings	• *PK:* Recommended doses for >6y, 3-6y recommended doses with DT, <3y no doses currently • DT formulation not available outside CU
Clinical application	• Use as needed for >6y of age • In 3-6y, weigh risks and benefits of using 50 mg tab • Monitor safety carefully
Future priorities	• Formulation – disp tablets • Dosing of “crushed” 50 mg tabs • Optimized dosing strategy (IMPAACT 2005)

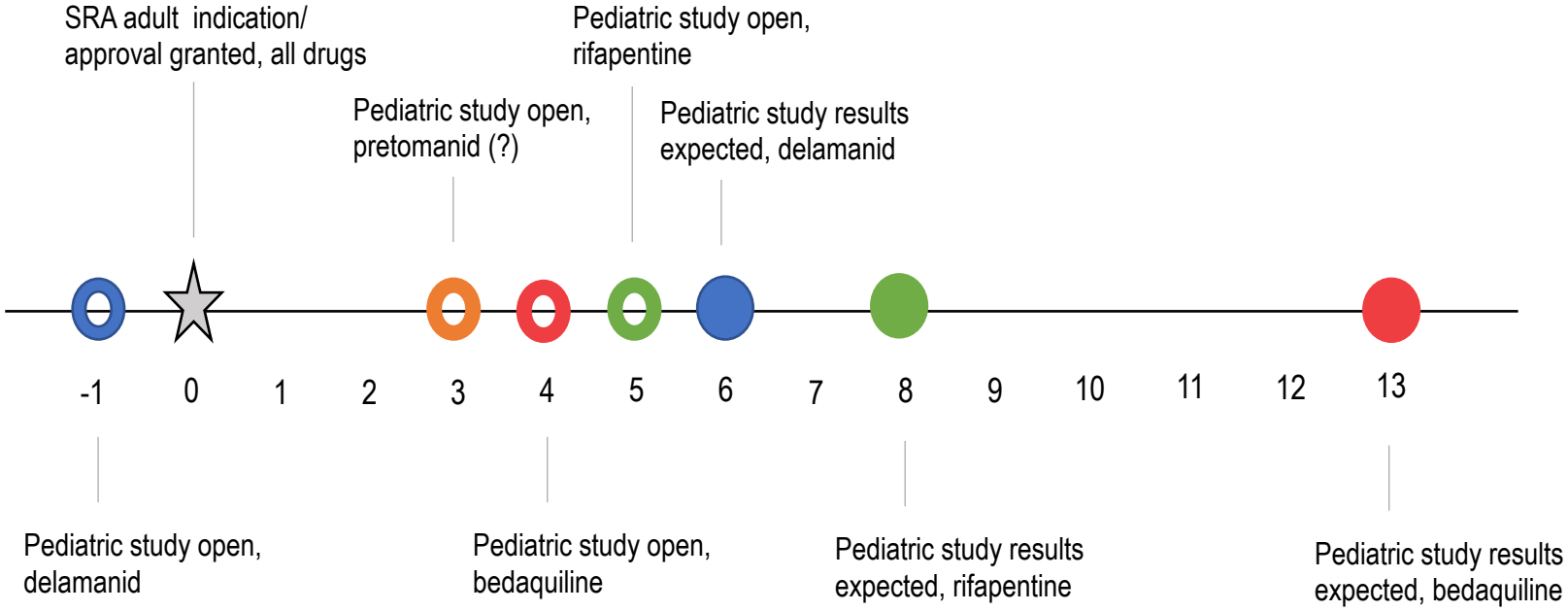
Other ongoing studies to watch

	Ongoing trials
Rifapentine	• S35 – PK, safety 3HP, RPT disp tabs • IMPAACT 2024 – PK, safety 1HP • ??? PK, safety RPT (approxaimte RPT 1200 mg daily)
Clofazimine	• Clofaz Kids (SU, Novartis): PK, safety 50 mg gel caps • CATALYST (SU, Unitaid): PK, safety 50 mg tabs (Macleods)
Pretomanid	• Awaiting male fertility study • Single dose PK, safety in children (TBA/IMPAACT 2034) • ??? Multiple dose PK, safety in children

Playing Catch Up: Anticipated Pediatric TB Treatment Research Gaps for Existing Medicines at Optimized Doses (Slide courtesy Lindsay McKenna, TAG)

Drug	Current Adult Dose/Dosing Schedule Established or Under Investigation [Relevant Pediatric Studies]	New Adult Dose/Dosing Schedule Under Investigation or Planned [Relevant Adult Studies]	Anticipated Pediatric PK Research Gaps
Bedaquiline (B)	400 mg daily for 2 weeks, then 200 mg thrice weekly [P1108; C211]	200 mg daily for 8 weeks, then 100 mg daily [SimpliciTB; ZeNix]	**Lower bedaquiline doses administered daily**
Delamanid (D)	100 mg twice daily [232/233; P2005]	200 mg daily [PHOENIx]	**Once daily delamanid dosing** [PHOENIx; P2020]
Clofazimine (Cfz)	100 mg daily [MDR PK; P2020]	300 mg daily for 2 weeks, then 100 mg daily [A5362; A5356]	**Loading clofazimine doses**
Isoniazid (H)	300–600 mg daily [MDR PK]	500–1000 mg daily [NEXT; A5312; STREAM; A5373]	**Higher isoniazid doses**
Levofloxacin (Lx)	11–14 mg/kg daily [MDR PK; TB CHAMP]	17–20 mg/kg daily [TBTC S32]	**Higher levofloxacin doses**
Linezolid (Lz)	300–600 mg daily [MDR PK; P2020]	600–1200 mg daily or intermittently [ZeNix; TB-PRACTECAL; endTB]	**Higher and lower linezolid doses**
Moxifloxacin (Mx)	400 mg daily [MDR PK]	400–800mg daily [STREAM I]	**Higher moxifloxacin doses**
Pretomanid (Pa)	200 mg daily [CAP 556]		
Rifampin (R)	10–35+ mg/kg daily [OptiRif Kids]	10–55+ mg/kg daily [HR; TRUNCATE-TB; RIFASHORT]	**Higher rifampin doses**
Rifapentine (P)	P:900 mg/H:900 mg once weekly P:600 mg/H:300 mg daily [TBTC S35; P2024]	P:600 mg daily [TBTC S37] P:1200 mg daily [TBTC S31/A5349; TRUNCATE-TB]	**Higher rifapentine doses administered daily**

Timelines for Pediatric TB Research & Development Remain Too Long (Slide courtesy Lindsay McKenna, TAG)



	Rifapentine	Delamanid	Bedaquiline	Pretomanid
SRA adult indication/ approval	2014	2014	2012	2019
Pediatric study open	2019	2013	2016	2022 ?
Pediatric study results	2022	2020	2025	???
Time from adult indication until children of all ages can benefit	8 years	6 years	13 years	To be determined

Future Ped TB Treatment Research Gaps (Slide courtesy Lindsay McKenna, TAG)

		telacebec (Q203)		
TBAJ-587	BTZ-043			
pyrifazimine (TBI-166)	macozinone (PBTZ-169)			
TBI-223	OPC-167832			
TBAJ-876			SQ109	bedaquiline
SPR720		TBA-7371	delpazolid (LCB01-0371)	delamanid
GSK2556286 (GSK-286)		GSK3036656 (GSK-656)	sutezolid (PNU-100480)	pretomanid
PHASE IA	**PHASE IB**	**PHASE IIA**	**PHASE IIB/C**	**PHASE III**
IMI ERA4TB				
		IMI UNITE4TB		
GMRI				
			PAN-TB	
			CDC TBTC	
		NIH ACTG		
		EDCTP PanACEA		
Pharmaceutical Companies (e.g., Otsuka, Janssen, GlaxoSmithKline, Qurient, LegoChem)				
Product Development Partnerships (i.e., TB Alliance)				

- 15 compounds in clinical development for TB
  - 8 with novel targets/ mechanisms of action
  - + 3 oxazolidinones, 1 riminophenazine, and 2 diarylquinolines, of interest as potential advantaged alternatives to existing TB medicines, linezolid, clofazimine, and bedaquiline, respectively
- Product sponsors with compounds in IIa: Qurient/Janssen, University of Munich, iM4TB, Otsuka, GMRI, GlaxoSmithKline, TB Alliance, LegoChem

TAG
Treatment Action Group

Child-friendly formulations

Child-friendly Formulations

- Progress: Child-friendly formulations being developed, becoming available
  - RHZ and RH FDCs
  - BDQ, MFX, LFX, ETO, CS, EMB
- Challenges:
  - Gaps: RPT, CFZ, DLM
  - Access in high-income countries?
- Evidence to inform use of manipulated formulations
  - BDQ, DLM ”Crush” studies
- Extemporaneous formulations - BENEFIT Kids (Unitaid)
  - TB Alliance
  - Bdq, Dlm, Cfz, Lzd
  - High, low-middle income settings

Acknowledgments

Anneke Hesseling
Rada Savic
Kendra Radtke
Maria Garcia-Cremades
Elin Svensson
Paolo Denti
Heather Draper
Simon Schaaf
Lindsay McKenna
Helen McIlleron
Lubbe Wiesner
Jennifer Norman
Desmond Tutu TB Centre
TB Alliance
NICHD/DAIDS
IMPAACT
Unitaid