Update on planned and ongoing paediatric trials

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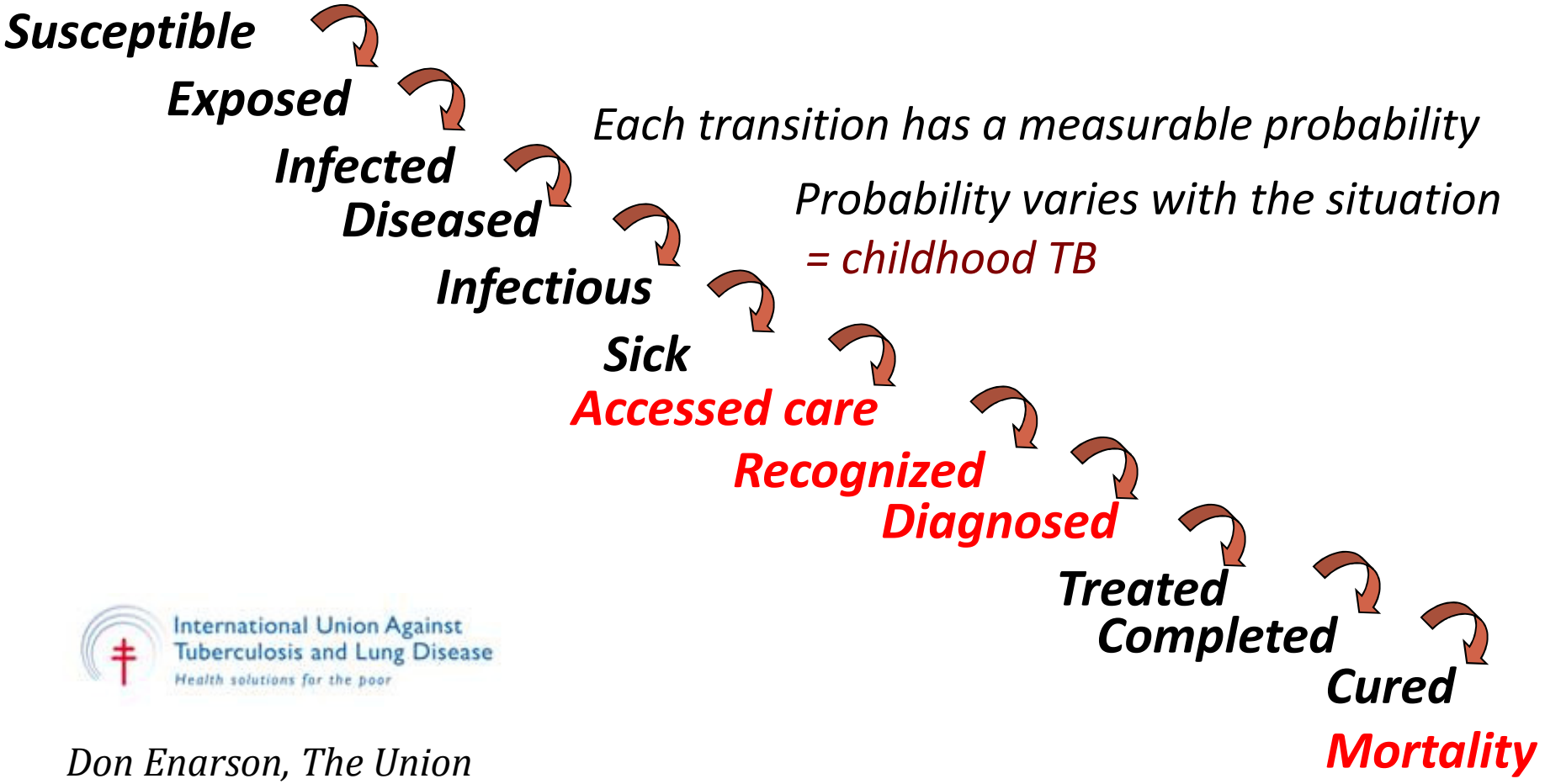
Key transitions in tuberculosis



International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

Don Enarson, The Union

Research Area	Gaps for children	Priority studies
DS-TB	• PK/safety first-line drugs at higher doses, esp. infants, HIV+ • Optimal treatment for TB meningitis • Treatment shortening DS-TB • Rifampicin dose optimization	• PK studies first-line drugs at higher doses • PK/efficacy study in children • SHINE, nested PK
DR-TB	• PK/dosing second-line drugs (FQ, aminoglycosides, linezolid) • Injectable sparing shorter regimen • New drug PK and safety (bedaquiline, delamanid, PA-824, sutezolid)	• Modeling existing data, testing doses predicted to achieve PK targets • Non-inferiority trial • PK/safety studies bedaquiline, PA-824, DLM, BDQ and combinations
Co-treatment TB/HIV	• Super boosting LPV/r in young children taking HRZE • EFV-based regimen in children < 3 years • INSTI-based ART with standard TB drugs (HRZE)	• Super-boosted PI with HRZE • EFV+HRZE in slow CYP2B6 genotype • RAL or DTG-based ART with TB drugs
LTBI	• Safety/tolerability/PK once-weekly INH/RPT regimen for youngest children • DDI with ART • MDR LTBI	• RPT dose for children under 2 for weekly INH/RPT; tolerability/bioequivalence child-friendly formulation • Efficacy and safety of long-term use of fluoroquinolones

Trial sponsor

UCL

Co-ordinating centre

MRC Clinical Trials Unit

Collaborating groups

SHINE

Shorter treatment for minimal TB in children

A randomised trial of therapy shortening for minimal tuberculosis with new WHO-recommended doses/ fixed-dose-combination drugs in African and Indian HIV+ and HIV- children

PI: Gibb, BMRC CTU

Collaborating gro

MU-JHU Care Ltd, Kampala, Uganda

Stellenbosch University, South Africa

University Teachir Hospital, Lusaka, Zambia

National Institute Research in Tuberculosis, Chennai

BJ Medical Colleg Pune, India

Funders

MRC Medical Researcl Council

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Summary Information Type	Summary Details
Short Name Title of Trial	**SHINE** (Shorter treatment for minimal TB in children)
Long Title of Trial	A randomized trial of therapy shortening for minimal tuberculosis with new WHO-recommended doses/ fixed-dose-combination drugs in African and Indian HIV+ and HIV- children
Version	1.0
Date	24-Mar-2014
ISRCTN #	ISRCTNXXXXXXXX
Study Design	Parallel group, randomised, non-inferiority, open label, 2 arm phase III clinical endpoint trial
Type of Participants to be Studied	Children < 16 years with suspected minimal (limited) TB disease, with or without HIV infection, will be screened
Setting	South Africa (Cape Town); Zambia (Lusaka); Uganda (Kampala) and India (Chennai and Pune)
Interventions to be Compared	**4-MONTH REGIMEN** The experimental arm will be standard daily first-line anti-TB treatment for 16 weeks dosed according to revised WHO dosage recommendations: intensive 8 weeks Isoniazid (H) , Rifampicin (R), Pyrazinamide (Z) with or without Ethambutol (E) according to local practice, HRZ(E), followed by continuation of 8 weeks HR. **6-MONTH REGIMEN** The control arm will be standard daily first-line anti-TB treatment for 24 weeks dosed according to revised WHO dosage recommendations: intensive 8 weeks HRZ(E), followed by continuation of 16 weeks HR.

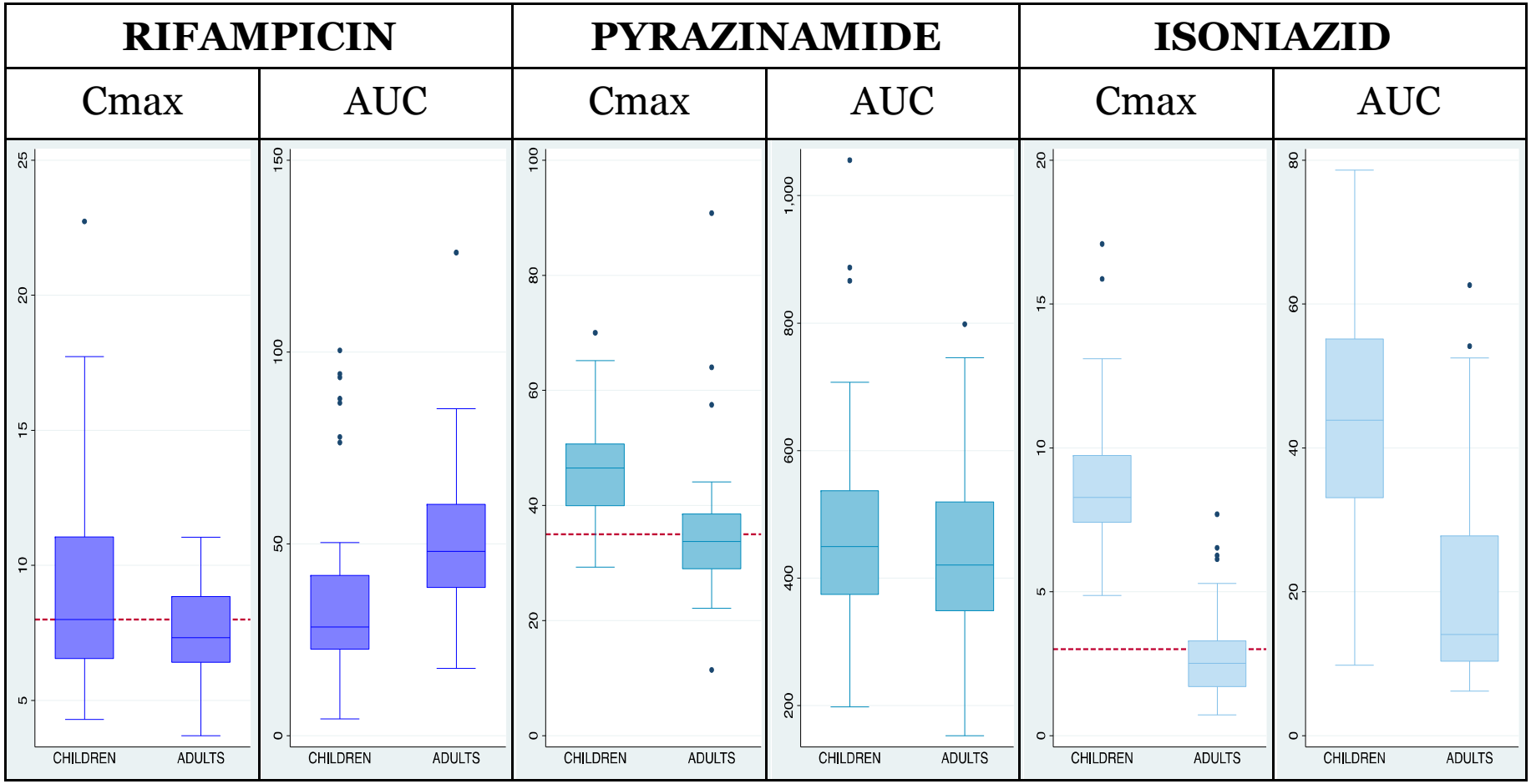
Primary Outcome Measure(s)	**Main Trial:** Efficacy: Unfavourable outcome, defined by the composite endpoint of TB treatment failure, relapse (or re-infection) or death Safety: Grade 3/4 adverse events **Pharmacokinetic Studies:** Pharmacokinetic (PK) parameters (AUC, Cmin, Cmax) of HRZ(E) and of antiretrovirals (ARVs), from full pharmacokinetic curves determined per age group and by HIV status

N=1200 children
New FDC; 75, 50, 150 (McCleods)
Opening: April 2016

Slide 6

1 Anneke Hesseling, 27/10/2014

DEFINITION OF TARGET PK DRIVERS OF TREATMENT RESPONSE



Model-based Cmax and AUC estimates in first 47 children enrolled to the DATiC study (Zvada et al. 7th Int WS TB Pharm 2014; Chigutsa et al. AAC 2015).

("TREAT INFANT TB")
PHARMACOKINETICS OF FIRST-LINE ANTI-TUBERCULOSIS DRUGS IN INFANTS

A Bekker , HS Schaaf, HR Draper, L van der Laan, S Murray, L Wiesner,
PR Donald, HM McIlleron, AC Hesseling

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Faculty of Medicine and Health Sciences, Stellenbosch University

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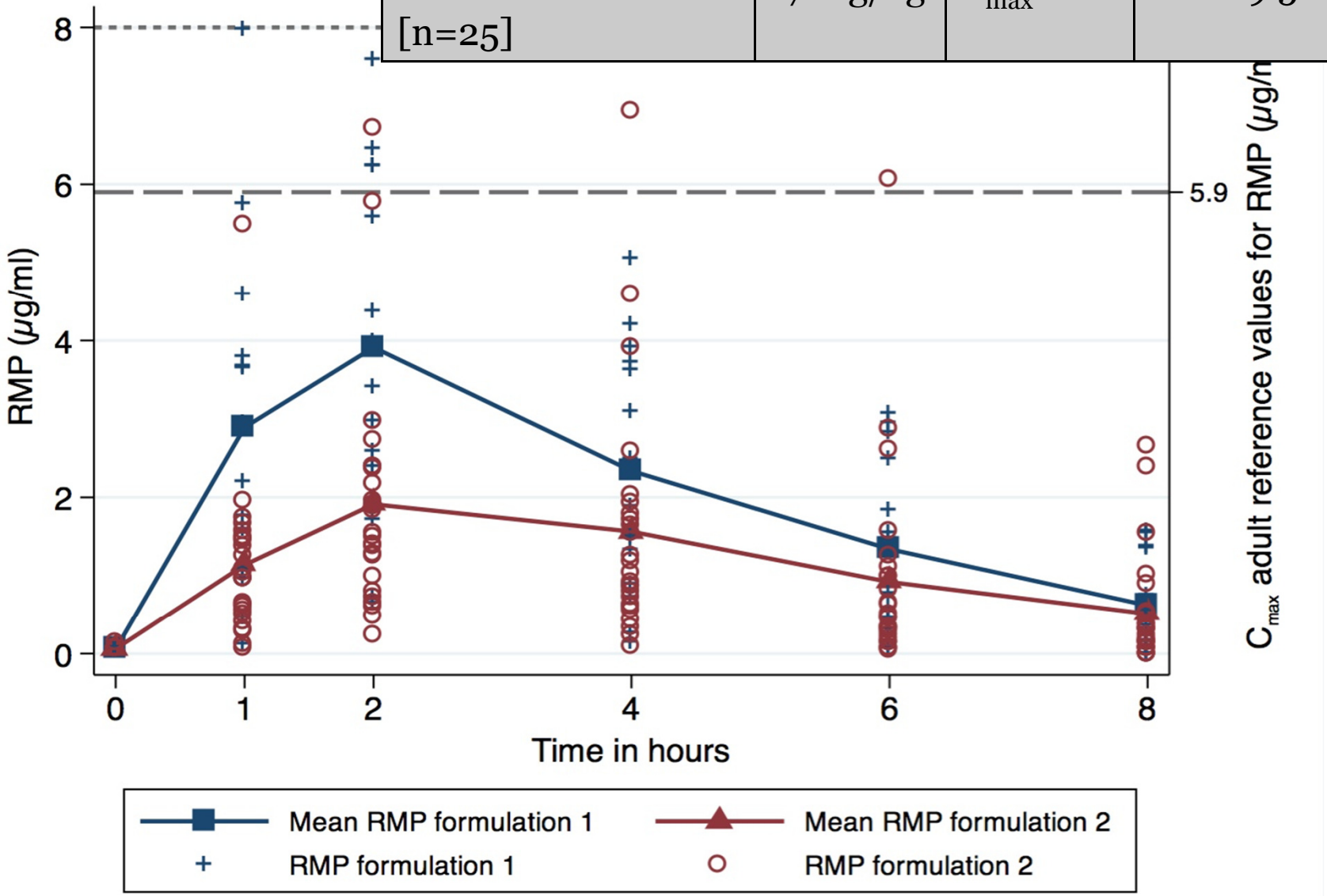
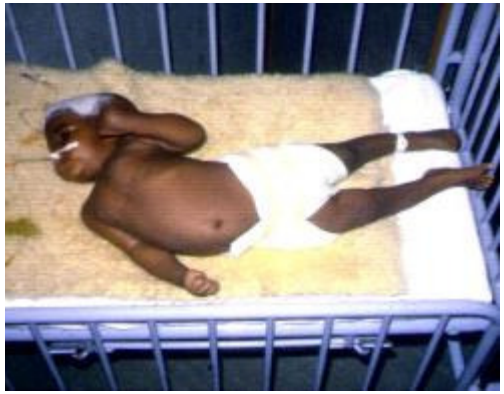
Every breath counts

RIFAMPICIN N=39

Formulation 1 [n=14]	13 mg/kg	C_{max} 4.1	AUC 16.8
Formulation 2 [n=25]	17 mg/kg	C_{max} 2.2	AUC 9.5





TBM-KIDS trial, Dooley, NICHD

MDR-TB treatment

PAEDIATRIC MDR-TB

Individual Patient Data Meta-Analysis

Anneke Hesseling, Simon Schaaf, Tony Garcia-Prats, Jennifer Furin &James Seddon
as part of the
Desmond Tutu TB Centre; Stellenbosch University; Cape Town, South Africa
are seeking collaborators for a

Evidence synthesis to inform the paediatric component of revised WHO guidelines on the management of multidrug-resistant tuberculosis

If you have individual patient data regarding treatment outcomes for paediatric MDR-TB and are interested in collaborating on this very exciting project, for more information please contact:
Elizabeth Harausz at epharausz@gmail.com

Data collected on approx 1000 children with MDR-TB (2015):

Novel MDR-TB treatment regimen

- Injectable sparing shorter regimen (STREAM)
- Smear negative TB
- Optimizing safe and effective SLD: FQN, PK and modeling
- Role of clofazamine, PAS, Linezolid
- Adult PK targets
- Inclusion of novel drugs: DMD, BDQ, others
- 9 months
- Multicentre trial, non-inferiority

MDR-PK 1: Pharmacokinetics and safety of secondline TB drugs in children with MDR-TB

Hesseling, Schaaf
NICHD R01

To characterize the pharmacokinetics and toxicity of all routinely used existing 2nd-line anti-TB drugs for the treatment and prevention of drug-resistant TB in HIV-infected and -uninfected children

Target numbers of children recruited by age and HIV

	<2 years						2-5 years						≥ 5 years				Total*
	HIV +*			HIV -			HIV +*			HIV -			HIV +*		HIV -		
	MDR	Pr	Pre/XDR	MDR	Pr	Pre/XDR	MDR	Pr	Pre/XDR	MDR	Pr	Pre/XDR	MDR	Pre/XDR	MDR	Pre/XDR	
Target enrolment	***10***	***10***	***2***	***36***	***30***	***2***	***14***	***10***	***2***	***52***	***32***	***2***	16	2	54	2	**276**
Ethio	12	6	2	40	16	2	16		2	56		2	18		58	2	232
Terizidone	12		2			2	16		2			2	18	2	58	2	116
Oflox/levo/ moxi	12	6		40	16		16	12		56	32		18		58		266
Amik	12						16						18		58		104
INH	10	12		34	32		12	12		34	32		18		58		254
PAS			2			2			2			2		2		2	12
Linezolid			2			2			2			2		2		2	12
Capreo			2			2		*	2			2		2		2	12

***clofazamine**

Age matched HIV-infected children not on TB therapy will be enrolled (42 for EFV and 22 on LPV as concurrent controls);

***Allowing for inflation due to assumptions for NCA analysis and 5% loss to follow-up. The total sample size is 276+ 42 HIV-infected controls=318 children*

DELAMANID

- **Trial 232: Phase 1 PK Age De-escalation study**
  - Define dose of delamanid in children resulting in AUC comparable to the effective AUC observed in adult MDR-TB trials

- **Trial 233: Phase 2 Safety Study**
  - Investigate the safety, tolerability, and PK of delamanid administered for six months in a pediatric population receiving concomitant OBR

Enrolling: Philippines, South Africa

Otsuka

- 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=6) and (50 mg BID; n=6)
- Group 4: Newborns and infants 0 to 2 years
  - (5 mg BID; n=6) and (25 mg BID; n =6)

IMPAACT: HIV co-infection study planned

N= 36 HIV+ children: DDI, PK and safety; PK modeling

Bedaquiline

- Paediatric PK and safety study planned
- Confirmed and probable MDR-TB
- Age de-escalation, 4 age cohorts
- Sites in Peru, Russia, South Africa
- HIV-uninfected children only (n=60)
- Janssen, TB Alliance


Damien Schum

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