UPDATE ON TB TREATMENT RESEARCH IN CHILDREN

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Every breath counts

CHALLENGES OPPORTUNITIES

- Children traditionally excluded from TB treatment trials: paucibacillary, end point definitions, perceived ethical and practical challenges, small perceived market share

- Novel drugs: Efficacy for disease not required: priority: PK, safety and formulations development (phase I, II)

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	• PK studies first-line drugs at higher doses • PK/efficacy study in children • <6 months
DR-TB	• PK/dosing second-line drugs (FQ, aminoglycosides, linezolid) • Requirement for injectables for limited disease • New drug PK and safety (bedaquiline, delamanid, PA-824, sutezolid)	• Modeling existing data, testing doses predicted to achieve PK targets • Careful clinical cohort study • PK/safety studies bedaquiline, PA-824 • Safety/QT for BDQ+ DLM in children
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

Novel TB drug candidates

Drug/class	Pharma	Target	Status
Rifapentine	Sanofi	LTBI, disease	Adult phase IIB; pediatric PK in development (TBTC)
Bedaquiline	Janssen	MDR TB	Adult phase IIB Pediatric trial in development
Delamanid PA-824	Otsuka TB alliance	MDR TB LTBI, DS/DR TB	Adult phase IIB, paediatric trials ongoing Adult phase IIB
SQ 109	Sequella	LTBI, MDR TB	Adult phase IIB
Sutezolid Tedizolid	Sequella Cubist	MDR TB MDR TB?	Adult phase I Licensed for SSTI
Moxifloxacin Levofloxacin	Bayer Generics	DS /MDR TB	Adult phase III Pediatric trials underway

DS-TB

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

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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

wellcometru

UKai from the Departmen International Develo

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=1300 children

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DAtiC

- NIHCD R01: McIlleron
- PK and safety of first-line TB drugs in paediatric populations
- HIV-infected
- Drug-drug interactions (DDI)
- Malnutrition
- PK modeling
- Interim analysis: n=47 children: low rif exposures, adequate to high INH, PZA

Infant PK study: TREAT INFANT-TB

- Infants< 12 months: DS-TB
- N=40 infants
- Intensive PK
- NCA and PK modeling
- Long term outcome: safety and treatment outcome
- DTTC, Stellenbosch University, University of Cape Town, partnership TB Alliance, Step TB Project
- Interim analysis: n=19: low rifampicin exposure

DNDi: Superbooster for HIV/TB co-infection

- Develop a stand-alone ritonavir (RTV) booster formulation to be added to the optimized LPV/r-based paediatric ARV regimen
- South Africa, Thailand; Institut Necker, France
- Ongoing; interim analyses

SURE TBM TRIAL

- Short intensive anti-tuberculosis and anti-thrombosis phase III treatment for children with TBM
- Factorial design of open-label short, intensive anti-tuberculosis treatment and double-blind, placebo-controlled anti-thrombosis therapy for children with drug-susceptible TBM.
- Compare (i) the efficacy and toxicity of a short intensive anti-tuberculosis regimen with the standard WHO-recommended regimen (open label) and (ii) low dose aspirin (double-blind placebo-controlled).
- Children <18 years with TB meningitis, with or without HIV infection

Control arm: standard first-line treatment for TB meningitis for 12 months (revised WHO guidelines):

- Once daily for two months
  - Isoniazid 7-15mg/kg
  - Rifampicin 10-20mg/kg
  - Pyrazinamide 30-40mg/kg
  - Ethambutol 15-25mg/kg
- Followed by once daily for ten months
  - Isoniazid 7-15 mg/kg
  - Rifampicin 10-20mg/kg

Intervention arm: once daily treatment for 6 months

- Isoniazid 10-20mg/kg
- Rifampicin 20-25mg/kg
- Pyrazinamide 30-40mg/kg
- Levofloxacin 15-20mg/kg

Optimizing Treatment to Improve TBM Outcomes in Children:

The TBM-KIDS Trial

A Phase I/II Randomized, Open-label Trial to Evaluate the Pharmacokinetics, Safety, and Treatment Outcomes of High Dose Rifampicin with or without Levofloxacin versus Standard Treatment for Pediatric Tuberculosis Meningitis

NICH R01 Dooly
Malawi, India

Primary Objectives

- To characterize the PK (plasma and CSF) of rifampicin given at model-derived optimal intravenous and oral daily doses and levofloxacin given at a dose of 20 mg/kg daily in children ages 6 months to 12 years with TBM

- To evaluate the safety of TBM treatment over eight weeks, by Arm

- To assess relationship between Rif exposures and functional outcomes, adjusting for factors known to affect treatment response

Secondary Objectives

- To assess functional outcomes among children treated for TBM at end of intensive phase of TB treatment (2 months) and at end of treatment (9 months), by Arm

- To describe neurocognitive outcomes among children ages 0-6 years treated for TBM longitudinally over 18 months, by Arm

Study treatment: n=120 children

	Intensive Phase		Continuation Phase
Arm	Weeks 0-2	Weeks 3-8	Weeks 9-36
1	**R_{iv}HZE**	**R_{ho}HZE**	RH
2	**R_{iv}HZL**	**R_{ho}HZL**	RH
3 (SOC)	**R**HZE	**R**HZE	RH

*Note: During Weeks 9-36, patients will receive standard TB treatment through local TB programs. All children will receive oral steroids

Rifampin (R_{iv}):	high-dose IV rifampin once daily
Rifampin (R_{ho}):	high-dose oral rifampin once daily
Rifampin (R):	15 mg/kg once daily
Levofloxacin (L):	20 mg/kg once daily
Ethambutol (E):	20 mg/kg once daily
Isoniazid (H):	10 mg/kg once daily
Pyrazinamide (Z):	35 mg/kg once daily

MDR-TB

- Characterize PK of 2ndline TB drugs, optimize their use in current regimens
- Shorter and safer treatment: injectable sparing
- Evaluation of novel drugs (phase I/II)
- Prevention
- Inform guidelines and formulation development

Treatment outcomes in children with MDR-TB (n=149)

Outcome	N = 149 (%)
Cure	36 (24.2)
Probable cure*	101 (67.8)
Transferred out	1 (0.7)
Lost to follow up	8 (5.4)
Died	3 (2.0)

Includes 8 patients who stopped their therapy before indicated but were clinically well at follow up

Seddon, Clin Infect Dis 2013

Adverse events (n = 137)

Grade of AE	Gr 0	Gr 1	Gr 2	Gr 3-4	Any AE (%)
Joint, muscle or bone pain	122	11	2	2 (1.5)	15 (10.9)
Skin rashes	104	30	2	1 (0.7)	33 (24.1)
Itchy skin	110	24	2	1 (0.7)	27 (19.7)
Headache	120	16	1	0	17 (12.4)
Sleep/mood problem	124	9	3	1 (0.7)	13 (9.5)
Lethargy	118	17	1	1 (0.7)	19 (13.9)
Visual problem	132	5	0	0	5 (3.6)
Vomiting	113	20	3	1 (0.7)	24 (17.5)
Diarrhoea	125	10	1	1 (0.7)	12 (8.8)
Jaundice	133	1	2	1 (0.7)	4 (2.9)
↓Appetite/nausea	118	14	3	1 (0.7)	18 (13.1)
Hearing loss (n=142)					25 (17.6)
Thyroxine supplementation (n=142; ↑TSH & ↓ fT4)					32 (22.5)

Seddon, Clin Infect Dis 2013

MDR PK study: NICD R01

- To characterize the PK and toxicity of routinely used 2nd-line anti-TB drugs in children
- N=276 children
- MDR-TB disease and prevention
- HIV-infected, DDI
- Desmond Tutu TB Centre, Stellenbosch
- Collaboration with University of Cape Town
- PIs: Hesseling, Schaaf

Emerging data

- Moxifloxacin, levofloxacin, ofloxacin
- Amikacin
- Ethionamide
- High dose INH
- Terizidone
- Clofazamine

AMIKACIN BY AGE AND HIV STATUS (N=28)

	C_{max} (µg/ml)			T_{max} (h)			AUC_{0-8} (µg·h/ml)		
	N	Median (IQR)	p-value	N	Mean (SD)	p-value	N	Median (IQR)	p-value
Age group									
0-2 years	6	43.65 (42.20 - 49.20)		6	1.00 (0.00)		6	103.85 (96.80 - 119.10)	
2-5 years	7	49.10 (40.70 - 59.20)		7	1.14 (0.38)		7	124.15 (97.75 - 162.05)	
6-15 years	15	49.60 (40.30 - 56.40)	0,845	15	1.13 (0.35)	0,593	14	159.25 (124.20 - 179.48)	0,016
HIV status									
HIV-infected	10	47.05 (42.20 - 54.40)		10	1.10 (0.31)		9	151.00 (109.40 - 162.05)	
HIV-uninfected	18	46.85 (40.70 - 53.00)	0,719	18	1.11 (0.32)	0,931	18	128.65 (112.50 - 174.95)	0,918

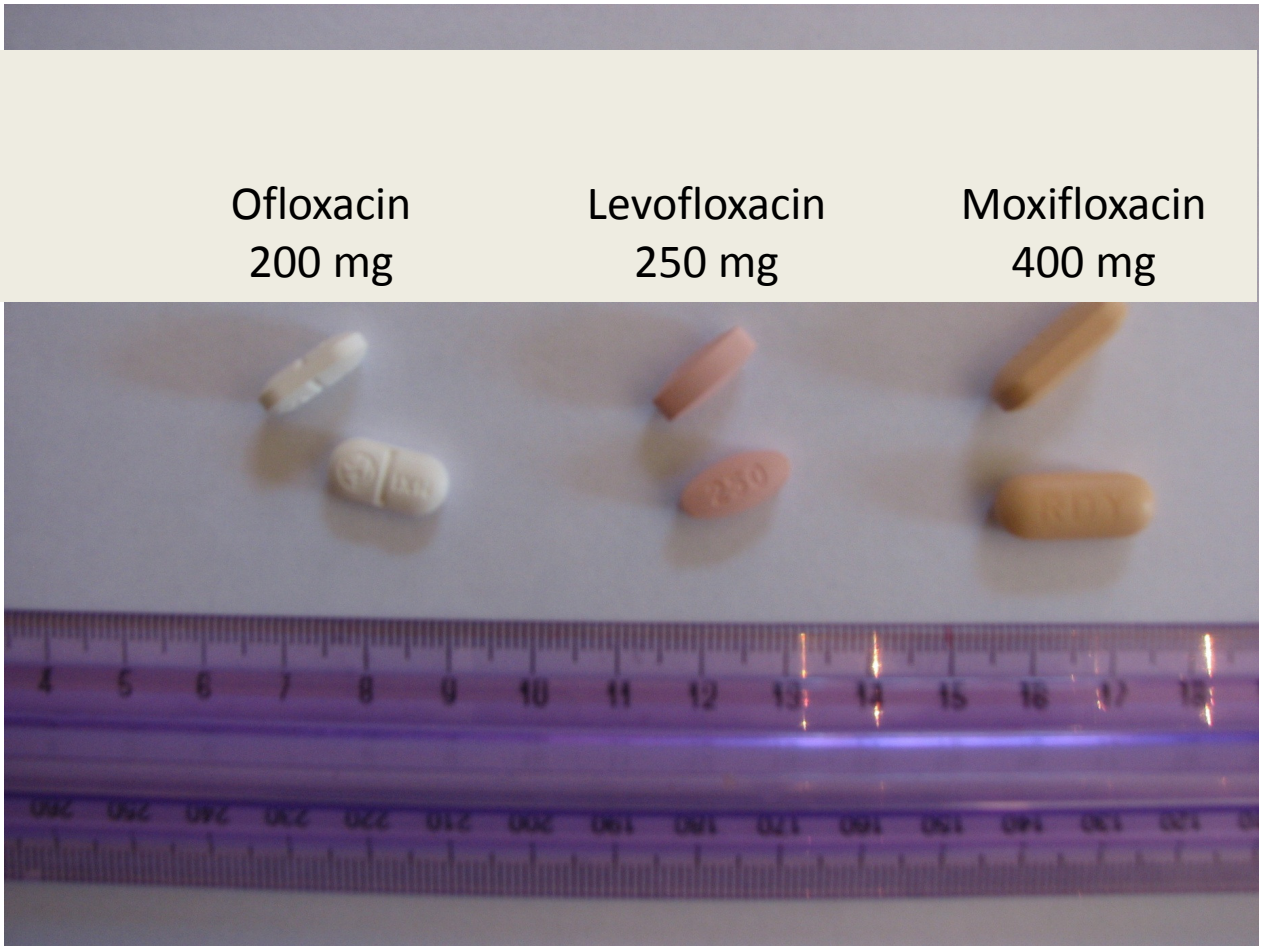
Adult target values:
C_{max}: 35-45 ug/ml

Levofloxacin for children: 15 mg/kg daily

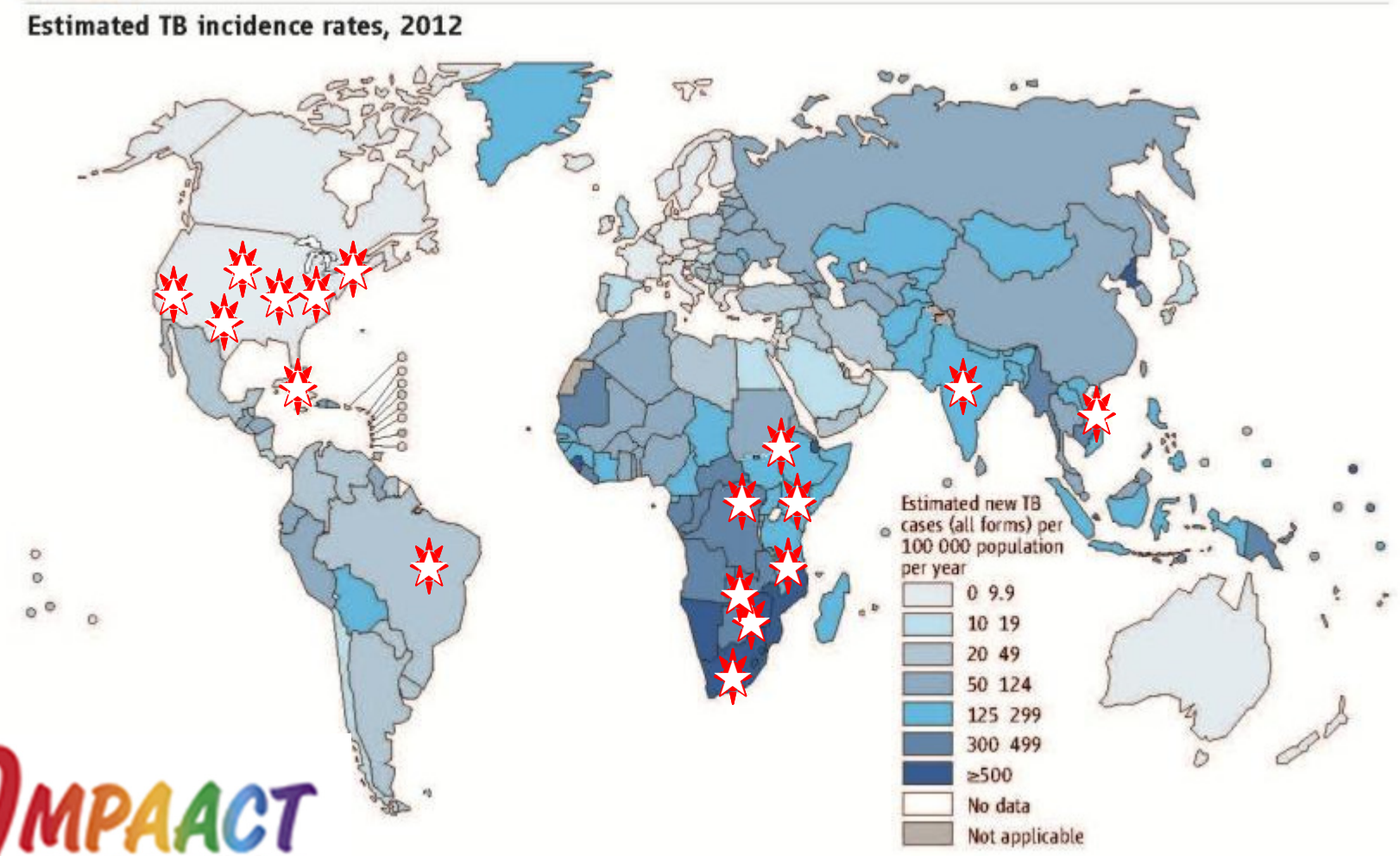
Parameter	Median (IQR) PK value (n=23)
C_{max} (µg/ml)	6.71 (4.69 - 8.06)
AUC_{0-8} (µg·h/ml)	29.89 (23.81 - 36.39)

Parameter	Target value	Mean (sd) PK value/MIC if MIC is 0.5	Mean (sd) PK value/MIC if MIC is 1.0
C_{max} /MIC	8-10	13.1 (4.0)	**6.5 (2.0)**
AUC/MIC	100	**65.3 (18.4)**	**32.6 (9.2)**

Thee, Antimicrob Agents Chemother, 2013


Ofloxacin
200 mg
Levofloxacin
250 mg
Moxifloxacin
400 mg

International Maternal Pediatric AIDS Clinical Trials (IMPAACT) Network



Priority IMPAACT TB treatment protocols

Goals	Status
Preventive Therapy 1) IPT in HIV-infected pregnant women 2) Ultra short Rifapentine-based regimen in adults and adolescents 3) Preventive therapy for MDR TB in children and adolescents 4) INH/RFP weekly in pregnancy	 P1078; open ACTG 5279: co-endorsed; open Phoenix with ACTG* P2001
Treatment 1) Bedaquiline PK/safety HIV+/- MDR-TB 2) DDI TB/HIV in pregnancy 3) PK of ART TB therapy in LBW infants 4) Dose finding RAL with TB 5) Delamanid ART co-treatment: MDR-TB 6) Maternal TB treatment registry	 P1108 P1026 P1106 P 1101 CAP 406 (Otsuka) CAP

IMPAACT P1108

In HIV-uninfected infants, children and adolescents with MDR-TB

1. To evaluate the safety and tolerability of bedaquiline over 24 weeks
2. To evaluate the PK of bedaquiline over 24 weeks

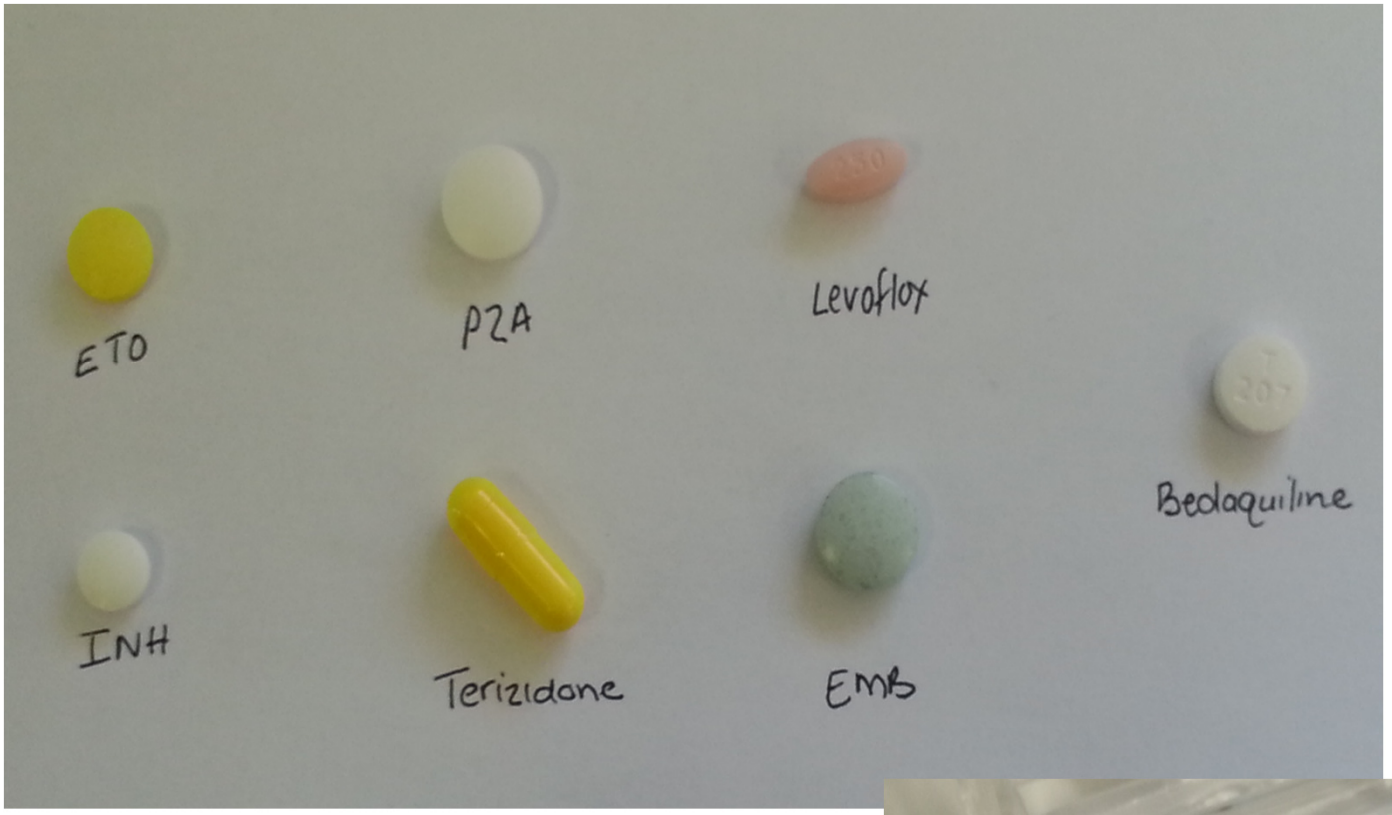
ARV regimens:

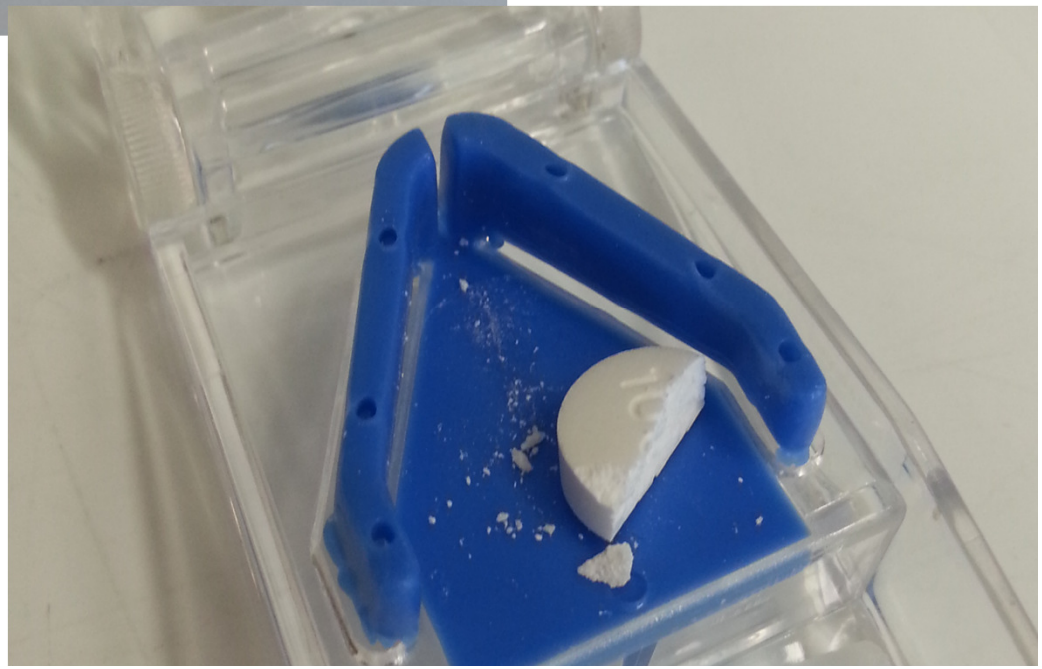
- Triple NRTI-based regimen: Zidovudine, Lamivudine (3TC) and Abacavir (ABC) only
- Nevirapine (NVP) and 2 NRTI

Secondary objectives

1. Long-term safety and tolerability of BDQ over 30 months
2. PK of BDQ between Week 24 and Week 120 on study (following completion of 24 weeks of bedaquiline)
3. Treatment response during up to 30 months
4. Safety and tolerability of BDQ in combination with selected HAART regimens over 24 weeks

- International sites, including South Africa
- Bedaquiline licensed by MCC October 2014


ETO
PZA
Levoflox
Bedaquiline
INH
Terizidone
EMB



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

Otsuka

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)

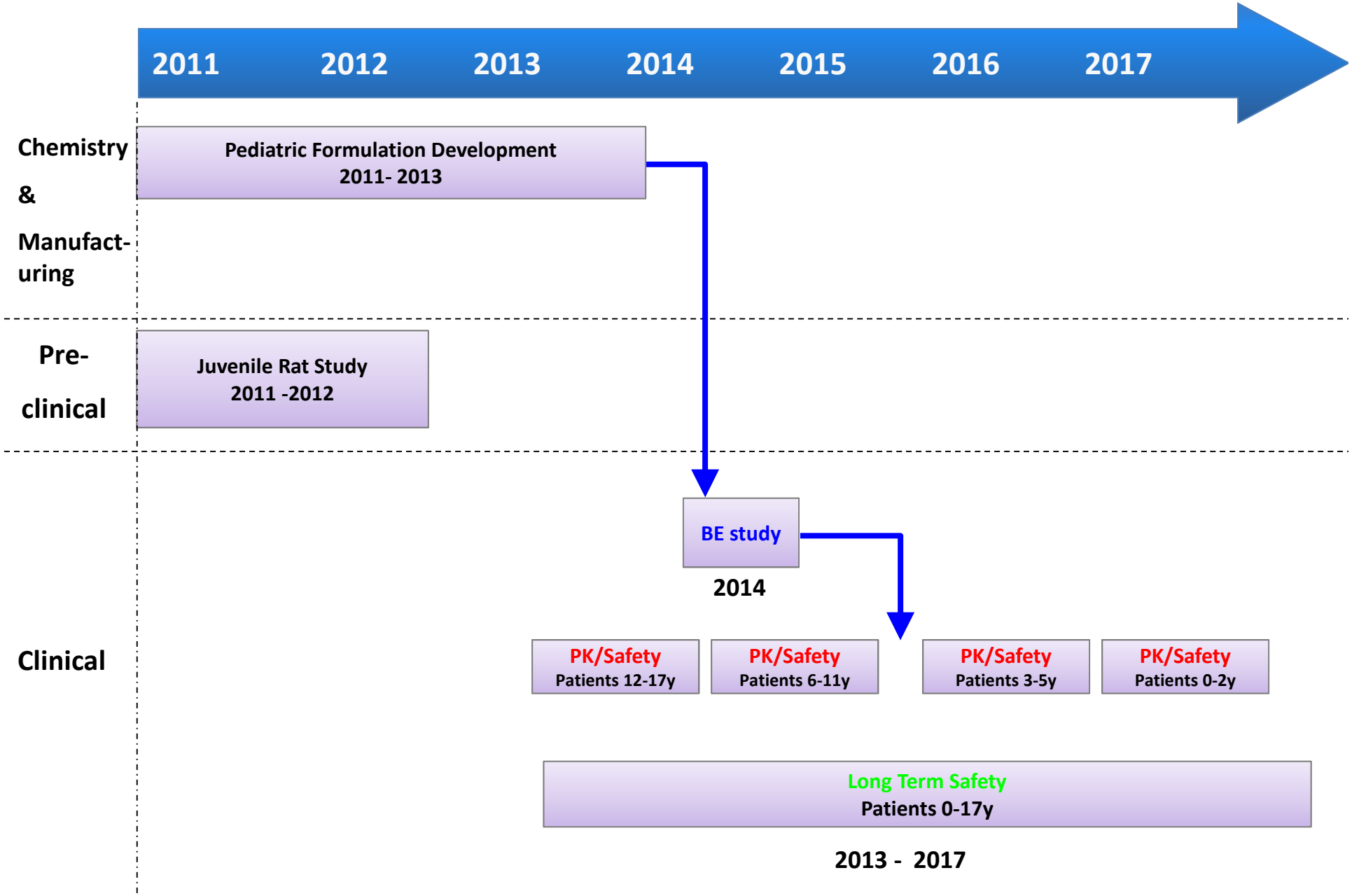
Pediatric formulation

- Group 3: Children 3 to 5 years
  - (25 mg BID; n=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

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

Delamanid Pediatric Development Timeline



NiX-TB: XDR-TB

- Randomized, open-label trial assessing bedaquiline plus PA-824 plus linezolid plus pyrazinamide or bedaquiline plus PA-824 plus linezolid in subjects with pulmonary infection with extensively drug-resistant tuberculosis (XDR-TB)
- TB Alliance
- J-L-Pa--Z
- Including adolescents (>14 years)


Damien Schum

MDR-TB CHAMP

1. Is levofloxacin (LFX), given daily for 6 months, effective to prevent MDR-TB in high-risk child and adolescent household contacts of MDR-TB cases?
2. Does LFX have acceptable toxicity and tolerability in children?
3. Is there a difference in mortality between study arms?
4. Is adherence similar between study arms?
5. Are there differences in LFX resistance between study arms for children developing incident TB?
6. Is LFX cost-effective and acceptable to prevent MDR-TB in child and adolescent HHC?

Nested economic and qualitative feasibility sub-studies will evaluate the cost, impact and acceptability of the preventive strategies

Design

- Community-based, multicentre, cluster randomised phase III superiority trial of LFX vs. placebo for the prevention of MDR-TB in HIV-infected and uninfected child household contacts of confirmed adult MDR-TB source cases
- N=1680; children 0-5 years
- Primary outcome: incident TB disease by 12 months post-randomisation
- South African sites
- Funded: BMRC/Wellcome Trust, SA MRC
- In partnership with BMRC CTU

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