Update on planned and ongoing paediatric trials
Key transitions in tuberculosis

Susceptible → Exposed → Infected → Diseased → Infectious → Sick

Each transition has a measurable probability

Probability varies with the situation = childhood TB

Accessed care → Recognized → Diagnosed → Treated → Completed → Cured → Mortality

Don Enarson, The Union
<table>
<thead>
<tr>
<th>Research Area</th>
<th>Gaps for children</th>
<th>Priority studies</th>
</tr>
</thead>
</table>
| 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 |
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
<table>
<thead>
<tr>
<th><strong>Summary Information Type</strong></th>
<th><strong>Summary Details</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Name Title of Trial</td>
<td>SHINE (Shorter treatment for minimal TB in children)</td>
</tr>
<tr>
<td>Long Title of Trial</td>
<td>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</td>
</tr>
<tr>
<td>Version</td>
<td>1.0</td>
</tr>
<tr>
<td>Date</td>
<td>24-Mar-2014</td>
</tr>
<tr>
<td>ISRCTN #</td>
<td>ISRCTNXXXXXXXXXX</td>
</tr>
<tr>
<td>Study Design</td>
<td>Parallel group, randomised, non-inferiority, open label, 2 arm phase III clinical endpoint trial</td>
</tr>
<tr>
<td>Type of Participants to be Studied</td>
<td>Children &lt; 16 years with suspected minimal (limited) TB disease, with or without HIV infection, will be screened</td>
</tr>
<tr>
<td>Setting</td>
<td>South Africa (Cape Town); Zambia (Lusaka); Uganda (Kampala) and India (Chennai and Pune)</td>
</tr>
<tr>
<td>Interventions to be Compared</td>
<td><strong>4-MONTH REGIMEN</strong>&lt;br&gt;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.</td>
</tr>
</tbody>
</table>
| 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
DEFINITION OF TARGET PK DRIVERS OF TREATMENT RESPONSE

<table>
<thead>
<tr>
<th>RIFAMPICIN</th>
<th>PYRAZINAMIDE</th>
<th>ISONIAZID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>AUC</td>
<td>Cmax</td>
</tr>
</tbody>
</table>

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

Department of Paediatrics and Child Health, Desmond Tutu TB Centre,
Faculty of Medicine and Health Sciences, Stellenbosch University
RIFAMPICIN
N=39

| Formulation 1 | 13 mg/kg | $C_{\text{max}}$ | 4.1 | AUC 16.8 |
| Formulation 2 | 17 mg/kg | $C_{\text{max}}$ | 2.2 | AUC 9.5 |
Children with suspected TB Meningitis

TBM workup

Definite TBM or probable TBM

Enroll & randomize 1:1:1

Arm 1: $R_{\text{high}}$ HZE x 8 weeks

Arm 2: $R_{\text{high}}$ HZL x 8 weeks

Arm 3: $R_{\text{standard}}$ HZE x 8 weeks

Follow for safety and outcomes

Week 1: Plasma and CSF PK sampling

Week 6 +/- 2: Plasma and CSF PK sampling

STANDARD CONTINUATION PHASE TREATMENT: 10 months of daily HR

Follow-up to complete 18 months on-study

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

<table>
<thead>
<tr>
<th></th>
<th>&lt;2 years</th>
<th></th>
<th>2-5 years</th>
<th></th>
<th>≥ 5 years</th>
<th></th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV +*</td>
<td>HIV -</td>
<td>HIV +*</td>
<td>HIV -</td>
<td>HIV +*</td>
<td>HIV -</td>
<td></td>
</tr>
<tr>
<td>MDR</td>
<td></td>
<td></td>
<td>MDR</td>
<td></td>
<td>MDR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pr</td>
<td></td>
<td></td>
<td>Pr</td>
<td></td>
<td>Pr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre/XDR</td>
<td></td>
<td></td>
<td>Pre/XDR</td>
<td></td>
<td>Pre/XDR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target enrolment</td>
<td>10 10 2</td>
<td>36 30 2</td>
<td>14 10 2</td>
<td>52 32 2</td>
<td>16 2 54 2</td>
<td>276</td>
<td></td>
</tr>
</tbody>
</table>

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 16 34 32 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 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
- Group 1: Adolescents 12 to 17 years
  - (100 mg BID, n=6)

- Group 2: Children 6 to 11 years
  - (50 mg BID; n=6)
  Pediatronic 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
ERROR: stackunderflow
OFFENDING COMMAND: ~
ERROR: stackunderflow