Shorter treatment for minimal TB in children (SHINE)

A phase III randomised open trial comparing 4 vs 6 months treatment in children (+/- HIV) with smear-negative non-severe TB in Africa and India

Medical Research Council Clinical Trials Unit, University College London

Di Gibb
Diana.gibb@ucl.ac.uk
Why have children been left out of TB trials?

• Less infectious; therefore ‘less of a priority’
• Difficulties in confirming the diagnosis and measuring endpoints
• Generally effective therapy for drug-susceptible TB
• BUT:
  – *Could be over treating* the majority of childhood TB
  – *Children have the right to benefit from child-focussed research as much as adults*
### TB Natural History in Children

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*Adapted from Marais et al 2004 IJTD. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era*

**Risk of TB Disease Following primary infection**
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<tr>
<th>Age (yrs)</th>
<th>Ghon/LN</th>
<th>Bronchial</th>
<th>Effusion</th>
<th>“Adult-type”</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>1-2</td>
<td>X</td>
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**Pulmonary disease**
Question:
Can we safely reduce 6 months treatment to 4 months in children with smear-negative non-severe (minimal) TB?
Shorter treatment for minimal TB – Why Children?

A controlled trial of 3-month, 4-month, and 6-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 5 years. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council.

2% relapse rate in smear-negative culture-positive drug-sensitive TB

TB in children:
- 75% intrathoracic disease
- 85% smear-negative
- Most lymph-node disease & paucibacillary
- Recently increased TB drug doses in children
- Shorter treatment may be sufficient for drug sensitive TB

Potential benefits:
- Reduced toxicity
- Reduced drug-drug interactions with anti-retrovirals
- Reduced costs to families and health services
- Improved adherence
3405 participants from 3 adult trials of treatment shortening:

- 4-month regimens were non inferior to 6 months in individuals with <2+ sputum +
- Stratified medicine approach: regimen shortening for mild disease (? 4 months) high smear grade / cavitation may need > 6 months
Children aged <16 years with minimal TB (n=1,200)

Randomise (1:1)

Arm A, 4 month (n=600)
Intensive phase: 8 weeks HRZ(E)
Continuation Phase: 8 weeks HR

Arm B, 6 month (n=600)
Intensive phase: 8 weeks HRZ(E)
Continuation Phase: 16 weeks HR

18 months follow-up for primary outcome assessment

All anti-TB drugs prescribed as per WHO 2010 dosing guidelines using new weight bands
New fixed dose combinations

Intensive Phase:
• RMP 75mg + INH 50mg + PZA 150mg

Continuation Phase:
• RMP 75mg + INH 50 mg

H: 10mg/kg (range 10–15mg/kg) max 300mg/day;
R: 15mg/kg (range 10–20mg/kg) max 600mg/day;
Z: 35mg/kg (30–40mg/kg);
E: 20mg/kg (15-25mg/kg)
**Updated WHO weight bands**

<table>
<thead>
<tr>
<th>Weight band</th>
<th>Numbers of tablets</th>
<th>Intensive phase: RHZ 75/50/150*</th>
<th>Continuation phase: RH 75/50</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-7 kg</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>8-11 kg</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>12-15 kg</td>
<td>3</td>
<td>3</td>
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</tr>
<tr>
<td>16-24 kg</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>25+ kg</td>
<td><strong>Adult dosages recommended</strong></td>
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*Ethambutol should be added in the intensive phase for children with extensive disease or living in settings where the prevalence of HIV or of isoniazid resistance is high.*

Population

Age <16 years
Non-severe TB, smear negative; known HIV status
Decision to treat with standard 1st line regimen; no known resistance

Primary endpoints:

Efficacy:
Unfavourable outcome:
TB treatment failure
Relapse/re-infection or Death

Safety:
Grade 3/4 adverse events & SAEs

Secondary endpoints:

– Mortality
– Adverse drug reactions up to 30 days of completing treatment
– Suppressed HIV viral load at 24 and 48 weeks in HIV (+)
– Bacterial infections requiring hospitalisation
– Adherence and acceptability
– Unfavourable outcome in those with confirmed TB
The ERC (blinded to treatment arm) has three functions:

1. To determine (in a consistency and independent way) the TB diagnosis at enrolment across sites (for the key secondary analysis of those with definitive TB)
   
   **Baseline Adjudication of TB or not TB**

2. To adjudicate cause of death based on all available sources of data
   
   **Cause of Death**

3. To determine the primary endpoint classification for all patients as favourable, unfavourable or unassessable
   
   **Primary Endpoint Classification**
SHINE Clinical Sites

**PK substudies:**
- Nijmegen, Netherlands
- UTH, Cape Town, SA

**Coordination:**
- MRC CTU at UCL, London, UK
**Timelines and recruitment**

**SHINE enrolment: all sites (N=1204)**

- **First child randomised 1st July 2016**

- **Set up**
  - 2 years

- **Recruitment**
  - 2 years

- **Follow up**
  - 72 weeks

- **Close out**
Timelines and recruitment

SHINE enrolment: all sites (N=1204)

First child randomised 1st July 2016
Enrolment completed 20 July 2019
Baseline Data

• Median Age 3.5 years (1.5-7.0 yr)
  – India 7.4 years, IQR (4.4-10.5); Africa 3.0 years, IQR (1.3-6.3)
• 52% male
• HIV status: 131 (11%) HIV infected (Zambia and Uganda)
• 1122 (93%) had abnormal CXR (local reports) TB Symptoms:
  • 86% present with respiratory Symptoms:
    – 62% cough >2weeks
    – 51% fever
    – 52% poor feeding/appetite (5% severe malnutrition)
    – 51% had TB contact in last year, (93% with pulmonary TB)
• 77% had Mantoux test (despite world-wide shortage): 60% tested positive
  – IGRA tests done in South Africa only (n=34)
• Microbiological samples on all randomised children
  – 163 (14%) confirmed TB (GeneXpert and/or Culture)
Trial Management Committee
Lusaka, Zambia
September ‘18
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September ‘18

SHINE results in 2020
Hopefully... timing to inform new WHO guidelines
Sub-studies
Shorter treatment for minimal TB in children (SHINE)

Vidya Mave, MD, MPH & TM
BJ Government Medical College-Johns Hopkins University Clinical Research Site, Pune, India
vidyamave@gmail.com
Sub-studies

• PK sub-studies
  – PK 2: Interactions: anti-TB vs anti-HIV (South Africa, Zambia)
  – Lopinavir/ritonavir TDS PK: Modified LPV/r dosing with Rifampicin in HIV-infected children (Zambia)
  – Hair PK – INH & PZA concentration is hair samples-(All sites)

• Palatability/acceptability sub-studies (SA)
  – Explore patient, caregiver and healthcare worker experience of using FDCs
  – Explore child and caregiver experiences of the SHINE treatment and adherence

• Health Economics sub-study
  – Cost/cost effectiveness of shorter treatment

• Biomarker sub-study
• Chest X-ray sub-study
• Microbiology sub-study
• Pharmacogenetics sub-study
Sub-study Leads

**Biomarker lead:**
Anneke Hesseling, Anne-Marie Demers, DTTC South Africa

**Social Science lead:**
Graeme Hoddinott, DTTC South Africa

**CXR lead:**
Megan Palmer, DTTC South Africa

**Microbiology lead:**
Anne-Marie Demers, DTTC South Africa

**Microbiology (Xpert Ultra) lead:**
Willy Ssengooba, MUJHU Uganda

**PK lead:**
Helen McIlleron, UCT South Africa

**PK lead collaborator (India):**
Hemanth Kumar AK, NIRT Chennai

**Hair PK lead:**
Vidya Mave, BJMC-JHU CRS Pune

**LPV/r PK lead:**
Chishala Chabala, UTH Zambia
PK Sub-studies 1 and 2

• Describe PK of the first-line drugs in HIV- children <37 kg dosed according to currently recommended weight bands
  – New paediatric FDCs in recommended weight band-based doses
  – Single intensive PK (1, 2, 4, 6, 8 and 12 hours after drug intake)

• Evaluate PK interactions between anti-TB and ARVs in all ages of HIV/TB co-infected children
  – 2 intensive PK sessions of ARVs (EFV; LPV/r)
    • 1st PK during TB treatment;  2nd PK 4 weeks post TB treatment
PK 1 results in HIV negative (60 African, 25 Indian); full PK Curves

Results presented by Dr C Chabala at PK workshop (London, Sept 2019) and will also be presented by Helen McIlneron: *Session SP-20-B4 Therapeutic TB trials in children: improving knowledge and access (31/10/19 4pm)*
Lopinavir/ritonavir TDS PK (Zambia Only)

• To evaluate whether modified LPV/r from BD to TDS dosing will achieve adequate blood levels of LPV/r in children co-treated with RIF
• Evaluate acceptability and tolerability of TDS LPV/r dosing
• Methods
  – 2 intensive PK sessions of ARVs - During and Post TB treatment
  – 9 recruited of a target sample size of 20
Hair PK sub-study

• To assess the utility of hair assay for INH & PZA as a drug adherence and exposure tool
• Assess relationship between INH & PZA hair concentrations vs TB treatment outcomes.
• Method
  – Hair samples collected at 4, 8, 16 and 24 weeks
  – 414 participants consented

Advantages:
• Estimates an average level of drug exposure over weeks to months
• Non invasive and painless to collect.
• No special skills to collect or cold storage/shipment requirements.
• No bio-hazardous constraints – easy for storage and shipment.
Palatability/acceptability sub-studies
(n=20 days of observations + 14 key informant discussions)

Aim: To explore the various aspects of using the FDCs; understandings of TB, treatment adherence with regard to the patient, caregiver and healthcare worker experience

Wademan D, et al. IJTLD manuscript in press
• In general, the FDC was adequately palatable
• The FDC compares favourably to TB treatment caregivers have seen other people use in their family context

• Additional analysis
  – **Planned outcome analyses:
  – Risks “change in acceptability”
  – Acceptability as a predictor of adherence
Biomarker sub-study

- To test host markers in serum and whole blood RNA to predict early and late treatment outcomes

- Samples collected at wk 0, 2, 8, 16 and 24 and at relapse/recurrence/early exit
  - serum collected on 995 children
  - samples in Paxgene tubes collected in only in South Africa

- Assays include:
  - cytokine and metabolite measurements in serum
  - multiplex qPCR on ex vivo RNA
  - microRNA in serum and whole blood
  - collaboration with Tony Hu (Tulane University) and other collaborators to evaluate different biomarkers
Microbiology

• Microbiology: TB testing harmonized across laboratories using key elements in TB laboratory procedures that:
  – Have the greatest impact on microbiology endpoints of clinical trials
  – Allow for comparison of results among all trial sites (or from one study to another)
  – Provide accurate test results to ensure safety of trial participants

• Analysis of baseline TB microbiology ongoing

Willy Ssengooba et al. Accuracy of Xpert Ultra in the diagnosis of pulmonary TB among children in Uganda:

*SOA-17-C10 Finding the missing with TB: many paths to the same truth, 2\textsuperscript{nd} November, 2PM*
Chest X-ray sub-study

- Investigate CXR interpretation between clinicians and experts
  - Experts are double or triple reading all CXRs at baseline for ERC adjudication of TB diagnosis

- CXR features of children diagnosed with non-severe PTB on the SHINE trial
  - By age / by HIV status / by microbiological confirmation status / by country
  - Methodology of CXR reading on clinical trials for paediatric TB
  - Image library as reference
Pharmacogenetics substudy

- Evaluate genetic differences in drug metabolic pathways affecting individual responses to drugs in terms of therapeutic and adverse effects.

- To determine if there are differences between African and Indian ethnic groups.

- Sample collection complete:
  - 149 / 149 India
  - 904 / 1055 Africa
Acknowledgements

SHINE study participants and study teams in Zambia, Uganda, South Africa, and India:

- **University Teaching Hospital, Children’s Hospital, Lusaka, Zambia**: C. Chabala, V. Mulenga, J. Lungu, M. Kapasa, K. Zimba, K. Zymbo, C. Tembo, S. Kunda, E. Shingalili, T. Chipoya, F. Mwanakalanga, E. Chambula, J. M. Hankombo, M. Malama Kalumbi

- **Makerere University - Johns Hopkins University Research Collaboration, Kampala, Uganda**: E. Wobudeya, P. Musoke, R. Mboizi, W. Nansamba, G. Businge

- **Desmond Tutu TB Centre, Stellenbosch University, South Africa**: A. C. Hesseling, M. Palmer, M. M. van der Zalm, J. Workman, A. M. Demers, H. S. Schaaf, E. Walters, W. Zimri, G. Hoddinott

- **Byramjee Jeejeebhoy Government Medical College, Pune, India**: A. Kinikar, V. Mave, A. P. Raichur, A. Nijampurkar, S. Khan

- **Indian Institute of Research in Tuberculosis, Chennai, India**: S. Hissar, J. Bency, P. K. Bhavani, G. Prathiksha, D. Baskaran, V. Mythily, H. Kumar, S. Elilarasi, S. Balaji, M. A. Aravind, J. Ganesh

Division of Clinical Pharmacology, University of Cape Town: H. McIlleron

Radboud University Medical Center, Nijmegen, The Netherlands: R. Aarnoutse

MRC CTU at UCL: D. M. Gibb, A. Turkova, A. Crook, L. Choo, G. Wills, K. LeBeau, C. McGowan

Endpoint Review Committee: S. Welch, S. Graham, J. Seddon, E. Whittaker, S. Anderson, L. Grandjean

Independent Data Monitoring Committee: T. Peto, A. Mwinga, K. Fielding

Trial Steering Committee: P. Mugyenyi, J. Darbyshire, P. Clayden, P. Donald, V. Singh, M. Grzemska, S. Swaminathan

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Sponsor: University College London, UK

Trial drugs: Manufactured by Macleods Pharmaceuticals Ltd.
Thankyou

Any Questions?
Sample size

- Assumptions on mortality and TB recurrence in HIV(-) and HIV(+) children - overall 8%
- 6% non-inferiority margin
- 90% power, 5% two-sided alpha
- 10% loss to follow-up
- Plus assumption that ~20% of children will not actually have TB as adjudicated by blinded independent ERC (secondary analysis excluding children with non-TB)

= 1200 children