SURE trial update

and challenges with recruitment and diagnosis

WHO child and adolescent TB annual meeting
14th November 2023, Paris

Julie Huynh
On behalf of the SURE trial team
Shorter intensified anti-tuberculosis therapy for children with TBM?

**WHO-recommended regimen**

2HRZE/ 10HR

- Long treatment
- Poor penetration of R and E into CSF
- After 2 months only H is in CSF
- No effective drugs in H-resistant TB

**Emerging evidence**

- Higher doses R associated with quicker culture conversion in PTB
- Intensified treatment with 4 drugs given for **6 months** may be at least as effective
- Fluoroquinolones may have a place in regimen

3. Sulis et al. OFID 2021
Shorter intensified anti-tuberculosis therapy for children with TBM?

**WHO-recommended regimen 12 months**

- **H** 7-15 mg/kg, max 300mg
- **R** 10-20 mg/kg, max 600mg
- **Z** 30-40 mg/kg
- **E** 15-25 mg/kg

**'Cape Town regimen' 6 months**

- **H** 20 mg/kg, max 400mg
- **R** 20 mg/kg, max 600mg
- **Z** 40 mg/kg, max 2g
- Ethionamide 20mg/kg, max 750mg

Strong recommendation
Low quality of evidence

Conditional recommendation
Very low certainty of evidence
Shortened intensified anti-tuberculosis therapy for children with TBM?

**WHO-recommended regimen 12 months**

H 7-15 mg/kg, max 300mg  
R 10-20 mg/kg, max 600mg  
Z 30-40 mg/kg  
E 15-25 mg/kg

**'Cape Town regimen' 6 months**

H 20 mg/kg, max 400mg  
R 20 mg/kg, max 600mg  
Z 40 mg/kg, max 2g  
*Ethionamide* 20mg/kg, max 750mg

**Modified ‘Cape Town regimen’ 6 months = SURE trial**

H 20 mg/kg, max 400mg  
R 30 mg/kg, max 600mg  
Z 40 mg/kg, max 2g  
*Levofloxacin* 20mg/kg, max 1g
Host directed therapy – adjuvant aspirin?

PHASE 2 RCT
- HIV neg adults with TBM
Placebo vs Aspirin 81mg vs 1000mg
   (8 week duration)
- in addition to SOC

MAIN FINDINGS
- in grade 3/4 bleed or deaths/new infarcts
- Subanalysis: ↓ deaths/infarcts in aspirin treated with confirmed TBM

ANCILLARY FINDINGS
- High dose aspirin assoc. with
  Better resolution infarcts
  CSF: ↓ inflammatory mediators + ↑ pro-resolving mediators

Mai et al. eLife 2018
SURE trial questions

Is 6 months of intensified ATT as good as the 12-month standard for TBM?

AND

Does high-dose aspirin improve neurofunctional outcomes in children with TBM?
SURE trial design

A phase III, multi-centre, international, partially-blinded factorial randomised controlled trial of TBM treatment in children

Factorial trial: all patients enter the two randomisations 1, 2 simultaneously

1. RANDOMIZATION – OPEN LABEL
   - Intensified 6-month Arm (6H^HD^R^HD^ZL)
   - Standard 12-month Arm (2HRZE 10HR)

2. RANDOMIZATION – DOUBLE BLIND
   - Aspirin 20mg/kg for 8 weeks
   - Placebo for 8 weeks

Non-trial treatment required for ALL patients
1. Corticosteroids for 8 weeks (SOC)
2. Ranitidine prophylaxis for 8 weeks (Prevention of the bleeding risk of Aspirin)

Children aged between 29 days and under 18 years with TBM disease, with or without HIV infection

N = 400

Total follow-up 72 weeks for each patient

H = isoniazid, R = rifampicin, Z = pyrazinamide, L = levofloxacin, E = ethambutol, HD = high-dose
SURE trial sites

TB incidence per 100,000 population

CDC yellow book 2023
SURE trial design

A phase III, multi-centre, international, partially-blinded factorial randomised controlled trial of TBM treatment in children

PATIENT INCLUSION CRITERIA
1. Age
2. Weight: ≥3kg
3. Parent/legal carer giving informed, written consent
4. Agree for a CSF sample to be collected and processed
5. Diagnosis:
   - Symptoms compatible with TBM
   - CSF result with abnormalities compatible with TBM

PATIENT EXCLUSION CRITERIA
1. Resistance to rifampicin
2. On ATT for >21 days
3. Known (or pending confirmation of) HIV status
4. Compliance Assessment
   - Resistance to rifampicin
   - On ATT for >21 days
   - Severely moribund
   - Pregnancy
   - Specific medical history:
     - Known allergy or other contraindication to any first-line ATT, corticosteroids, or aspirin
     - GI bleeding or bleeding diathesis
5. Pre-existing medical conditions:
   - Active clinical infection with influenza or varicella
   - Grade 4 liver toxicity
   - Other contraindications

N = 400

Children aged between 29 days and under 18 years with TBM disease, with or without HIV infection
### RANDOMISATION 1 – Open Label

<table>
<thead>
<tr>
<th>Intensiﬁed 6-month ATT Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(6H^{HDR}HDZL)</td>
</tr>
</tbody>
</table>

Non-inferior?*

<table>
<thead>
<tr>
<th>Standard 12-month ATT Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2HRZE 10HR)</td>
</tr>
</tbody>
</table>

### PRIMARY OUTCOMES

All-cause mortality at 48 weeks

*Detect 10% non-inferiority* assuming mortality of 20% in control arm and 3% absolute reduction
SURE trial design

RANDOMISATION 2 – Double Blind

Aspirin 20mg/kg for 8 weeks

Superior?*

Placebo for 8 weeks

PRIMARY OUTCOMES

Modified Rankin Scale (mRS) measuring functional outcome at 48 weeks

The paediatric Modified Rankin Scale

*mRS 0: No symptoms
*mRS 1: Nonsignificant disability
*mRS 2: Slight disability
*mRS 3: Moderate disability
*mRS 4: Moderately severe disability
*mRS 5: Severe disability
*mRS 6: Death

*Detect 16% superiority assuming mortality and disability of 50% in placebo arm.
SURE trial design

**SECONDARY OUTCOMES**

1) **mRS outcomes** at W24, W48 (for randomisation 1) and W72
2) **All-cause mortality** at W72
3) Clinical or microbiological **relapse of TBM and/ or TB disease** by W72
4) **Specific adverse events (AEs):**
   - Any new Grade 3 and Grade 4
   - Leading to treatment modification (any grade)
   - Any gastrointestinal bleeding (any grade)
   - Drug-induced liver injury (DILI) of Grade 2 or more
   - Development of obstructive hydrocephalus
5) **Acquired drug resistance**
6) **Adherence** to treatment
7) **Acceptability** to treatment
8) **Assessment of HIV viral load** for HIV patients

**RANDOMIZATION 1 – Open Label**

- **Intensified 6-month ATT Treatment (6HRZL)**
  - Non-inferior?
- **Standard 12-month ATT Treatment (2HRZE 10HR)**

**RANDOMIZATION 2 – Double Blind**

- **Aspirin 20mg/kg for 8 weeks**
  - Superior?
- **Placebo for 8 weeks**
Enrolment

*Preliminary Data: 1st Oct 2023 data extraction

Pre-Screened
N=3643

Screened
N=290

Randomised
N=266

Allocations

Intervention arm (Short)
Aspirin

Control arm (Long)
Placebo

24 Screening failures (not randomised)
Main reasons for not randomising
A5. CSF result does not display abnormalities compatible with TBM (n=16; 67%)

Other, miscellaneous reasons (n=8; 23%)

3329 Pre-Screening failures (not randomised)
Top 3 main reasons for not randomising:
A4. Does not display symptoms compatible with TBM (n=1549; 47%)
A5. CSF result does not display abnormalities compatible with TBM (n=544; 16%)
B4. The child is severely moribund (n=153; 5%)

Other, miscellaneous reasons (n=1083; 33%), top 2 including:
A7. Parent or Child unwilling for a CSF sample to be collected.
C4. Alternative diagnosis of bacterial meningitis found
## Total participants randomised by centre

<table>
<thead>
<tr>
<th>Country</th>
<th>India</th>
<th>Vietnam</th>
<th>Uganda</th>
<th>Zambia</th>
<th>Zimbabwe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. randomised</td>
<td>90</td>
<td>120</td>
<td>2</td>
<td>31</td>
<td>23</td>
<td>266</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Site name</th>
<th>Date site opened to recruit</th>
<th>No. randomised by site</th>
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<tbody>
<tr>
<td>PGI Chandigarh</td>
<td>11/02/22</td>
<td>40</td>
</tr>
<tr>
<td>LHH Delhi</td>
<td>25/03/22</td>
<td>50</td>
</tr>
<tr>
<td>PNTH HCMC</td>
<td>22/02/21</td>
<td>67</td>
</tr>
<tr>
<td>CH2 HCMC</td>
<td>01/06/22</td>
<td>26</td>
</tr>
<tr>
<td>NLH Hanoi</td>
<td>19/04/21</td>
<td>13</td>
</tr>
<tr>
<td>VNCH Hanoi</td>
<td>13/06/22</td>
<td>14</td>
</tr>
<tr>
<td>MU-JHU Uganda</td>
<td>07/04/21</td>
<td>2</td>
</tr>
<tr>
<td>UTH Zambia</td>
<td>19/03/21</td>
<td>31</td>
</tr>
<tr>
<td>UZCRC Zimbabwe</td>
<td>22/02/21</td>
<td>23</td>
</tr>
</tbody>
</table>

VNCH: Vietnam National Children’s Hospital  
UZCRC: University of Zimbabwe Clinical Research Centre  
MU-JHU: Makerere University – Johns Hopkins University  
PGI: Post Graduate Institute of Education and Medical Research  
LHH: Lady Hardinge Hospital (Kalawati Saran Children’s Hospital)  
CH2: Children Hospital 2  
NLH: National Lung Hospital  
PNTH: Pham Ngoc Thach Hospital  
UTH: University Teaching Hospital
SURE Recruitment - All Sites

- **COVID-19**: Oct 1, 2023
- **No. of Patients Randomised**

**African + main sites in Vietnam open**

**Indian + satellite sites Vietnam open**

**Vietnamese + Uganda close**

**Zambian authorities stopped recruitment**

- **N=400, 90% power**
- **N=300, 80% power**
- **N=266, Oct 1, 2023**

- **Target (14/Mth)**
- **Actual**
## Participant retention

<table>
<thead>
<tr>
<th>Visit</th>
<th>India</th>
<th>Uganda</th>
<th>Zambia</th>
<th>Zimbabwe</th>
<th>Vietnam</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. Randomised</strong></td>
<td>90</td>
<td>2</td>
<td>31</td>
<td>23</td>
<td>120</td>
<td>266</td>
</tr>
<tr>
<td><strong>Week 48 Attendance/Expected</strong></td>
<td>24/25</td>
<td>1/1</td>
<td>12/12</td>
<td>2/2</td>
<td>54/55</td>
<td>93/95 (98%)</td>
</tr>
<tr>
<td><strong>Week 72 Attendance/Expected</strong></td>
<td>3/4</td>
<td>1/1</td>
<td>8/8</td>
<td>1/1</td>
<td>26/29</td>
<td>40/43 (93%)</td>
</tr>
</tbody>
</table>
## Demographics

**No. randomised = 266**

<table>
<thead>
<tr>
<th>Gender</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>144</td>
<td>(54%)</td>
</tr>
<tr>
<td>Female</td>
<td>122</td>
<td>(46%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV status</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>252</td>
<td>(95%)</td>
</tr>
<tr>
<td>Positive</td>
<td>12</td>
<td>(5%)</td>
</tr>
</tbody>
</table>

On ART at randomisation

<table>
<thead>
<tr>
<th>Years</th>
<th>Percentage of participants %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>20</td>
</tr>
<tr>
<td>1 - &lt;2</td>
<td>12</td>
</tr>
<tr>
<td>2 - &lt;5</td>
<td>18</td>
</tr>
<tr>
<td>5 - &lt;12</td>
<td>35</td>
</tr>
<tr>
<td>12 - &lt;18</td>
<td>16</td>
</tr>
</tbody>
</table>

Median 5.0 years (1.2, 9.9)
Baseline TBM Symptoms

- Fever: 91%
- Lack of playfulness/energy: 80%
- Poor feeding/appetite: 70%
- Vomiting: 60%
- Weight loss/Failure to thrive: 50%
- Headache: 40%
- Neck stiffness: 30%
- Seizures: 25%
- Cough: 20%
- Anoxia: 15%
- Night sweats: 10%
- Light sensitivity/Photophobia: 5%
- Bulging fontanelle: 2.5%
- Sunsetting eyes: 1%
- Other: 0.5%
- Focal symptoms: 0.5%

N=266
Median duration:
- Fever: 15 days (8,26)
- Lack of playfulness/energy: 14 days (7,23)
- Poor feeding/appetite: 14 days (7,22)
TBM Staging

Grade 1: 47%
Grade 2: 38%
Grade 3: 15%

N=266
# TB Microbiology

<table>
<thead>
<tr>
<th>N = 266</th>
<th>Smear</th>
<th>GeneXpert/ GeneXpert Ultra</th>
<th>MGIT culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients with sample collected</td>
<td>256</td>
<td>249</td>
<td>212</td>
</tr>
<tr>
<td>No. with MTB detected/ with results</td>
<td>43 / 224 * (17%)</td>
<td>110 / 249 ** (34%)</td>
<td>46/212 *** (22%)</td>
</tr>
</tbody>
</table>

* 76% positive on CSF / CSF + respiratory, 24% negative on CSF negative but positive elsewhere
** 80% positive on CSF / CSF + respiratory, 20% negative CSF negative but positive elsewhere
*** 85% positive on CSF / CSF + respiratory, 15% negative on CSF negative but positive elsewhere
## Chest X-Ray (CXR)

<table>
<thead>
<tr>
<th>No. Baseline CXR</th>
<th>248</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR result</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>125 (54%)</td>
</tr>
<tr>
<td>Normal</td>
<td>106 (46%)</td>
</tr>
<tr>
<td>Missing</td>
<td>17</td>
</tr>
<tr>
<td>Typical of TB</td>
<td>82 (66%)</td>
</tr>
<tr>
<td>Not typical of TB</td>
<td>43 (34%)</td>
</tr>
</tbody>
</table>

**Most common abnormalities**

1. Uncomplicated lymph node disease (35%)
2. Miliary TB (26%)
3. TB Bronchopneumonia (14%)
Cerebral imaging

- **Meningeal enhancement**: 64%
- **Hydrocephalus**: 57%
- **Tuberculomas**: 37%
- **Infarcts**: 33%

**N=189**

- **138 MRI**
- **51 CT**

171 (90%) abnormal
18 (10%) normal
## Baseline TBM Categorisation

<table>
<thead>
<tr>
<th>No. Randomised</th>
<th>266</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. with Baseline TBM Categorisation</td>
<td>257 *</td>
</tr>
<tr>
<td>Definite</td>
<td>101 (39%)</td>
</tr>
<tr>
<td>Probable</td>
<td>93 (36%)</td>
</tr>
<tr>
<td>Possible</td>
<td>61 (24%)</td>
</tr>
<tr>
<td>Not categorised</td>
<td>2 (1%) **</td>
</tr>
</tbody>
</table>

* 9 cases not classified (pending further information, pending queries or CSF Score=0 & No Imaging)
** No CSF

Diagnostic challenges and opportunities

**CHALLENGES**

- LP refusal by parents and staff
- Limited CSF microscopy skill, delayed processing
- Diagnosis dependent on clinical; junior staff with limited experience
- Early diagnosis is difficult, ideally MRC grade 1 when benefit (if any) is most likely

**OPPORTUNITIES**

- Animated video on LP procedure for parent/carer
  [https://www.picturinghealth.org/lumbar-puncture/](https://www.picturinghealth.org/lumbar-puncture/)
  Led by Susan Abarcar Salazar
- LP education and practical workshops
- Diagnostics substudy which recruited controls desensitised parents to LP
- Unexpected TBM cases captured through diagnostics substudy

_Explaining LP: A guide for parents in Africa_
[https://vimeo.com/638617138](https://vimeo.com/638617138)
SURE trial is the largest TBM trial in children and adolescents

Challenging diagnosis, < 35% identified on rapid molecular diagnostics on CSF

Diagnostic substudy embedded in trial augmented participant recruitment

75% of children with confirmed and probable TBM

Half of children affected by TBM were < 5 years

More than 50% of children enrolled have moderate–severe disease

Reached 70% of target recruitment, complete recruitment Jun 2024, end follow up Dec 2025
Susan Abarcar Salazar

Peruvian Infectious Diseases Specialist
PhD candidate (London School Hygiene and Tropical Medicine)
SURE trial management group member
Daughter, sister, aunty, friend