Designing a MDR-TB Injectable Sparing Regimen in Children: Research Priorities, Design Considerations and Discussion

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Outline

• Background
• Who to include
• Composition of control arm
• Composition of intervention arm
• Other questions and challenges
Considerations for study

• **Entry points**
  - how to diagnose TB disease
  - how to diagnose “MDR-TB”
  - disease severity (deciding treatment regimen and treatment duration)

• **End points/Treatment response (Outcomes)**
  - Culture-confirmed or not (bacteriological cure vs. Rx completion)
  - Favourable vs. unfavourable outcomes

• **Safety/tolerability**
  - Adverse effects of drugs - monitoring

• **Microbiology**
  - Which lab bacteriology to use and how/when (e.g. Xpert only initial diagnosis)
Entry points – who should be included (1a)

Certainty of diagnosis and DST-patterns

• **DR-TB disease**: Clinical, radiological, or microbiological pathology, in combination with diagnosis of confirmed, probable, (or possible) DR-TB disease (*Seddon et al JPIIDS 2013*)

• **Not TB infection only**, which should include children with positive bacteriology who have no clinical or radiological disease
Entry points – who should be included (1b)

Certainty of diagnosis and DST-patterns

• For research into paediatric DR-TB, it is important to describe the precise drug susceptibility test (DST) result:
  – **Confirmed** DR-TB: DST pattern of child’s isolate
  – **Presumed (probable)** DR-TB: DST pattern of the likely source case(s)
  – Therefore not only the “category” (MDR/Pre-XDR/XDR) but full available DST result
  – Should possible DR-TB be included? (no DST result of child or source)

• **Only MDR-TB** and more, or also RIF-mono-resistant? What about incomplete results (GXP only)
Entry points – who should be included (2)

Age: 0-17 years

• Important to include adolescents – different types of pulmonary disease, rarely studied
• Important to include infants – immune system developing and different pharmacokinetics

HIV status

• Both HIV-uninfected and HIV-infected children should be included
Entry points – who should be included (3)

Types of TB

• Pulmonary TB – yes
• Extrapulmonary TB – yes, but not TB meningitis / miliary TB (?) unless certainty about regimen’s drugs penetrating CSF?

Disease severity

• Very important consideration: severe and non-severe TB disease – could definitely influence treatment duration and treatment outcome
• Classification by Wiseman et al. (PIDJ 2013) or Shine-trial classification for non-severe disease
Who to include - options

- MDR-TB
  - MDR-TB with susceptibility to flq and inj
    - Probable
    - Confirmed
  - MDR-TB with susceptibility to the flq
    - Probable
    - Confirmed
  - Any MDR-TB irrespective of flq and inj susceptibility
Who to include and how to treat them - options

MDR-TB

- Same regimen
  - All children
  - Children with limited disease
  - Children with severe disease
  - Children with confirmed disease

- Variable regimens
  - Different regimens for severe vs. limited disease
  - Different regimens for confirmed vs. limited disease
**Control Arm – options**

- Standard traditional 18 month ‘WHO’ regimen where every child receives the same regimen for the same duration
  - 6Am/Mfx or Lfx/Cyc or Tzd/Eth/Z/H 12Mfx/Cyc/Eth/Z/H
- Clinician designed regimen based on WHO principles (4 active drugs plus Z) – variable regimens for
  - Variable types of resistance
  - Variable types of severity
  - Treatment response
- 9-12 month regimen
  - 4-6Am/H/Eth/Clof/Mfx/E/Z +5-6Clof/Mfx/E/Z
**Intervention arm principles**

- In designing a regimen we need to consider the following when thinking about which drugs to include
  - Different mechanisms of action
  - Different mechanisms of resistance
  - Toxicity (also similar toxicity other drugs, e.g. mitochondrial tox with LNZ, BDQ, ARVs)
  - Distribution (penetration)
  - Interaction (other drugs)
  - Ease of use (children and healthcare programs)
Intervention arm thoughts (no injectable)

- E / Z / H
- Mfx / Lfx
- Eth / Cyc
- Lnz / Cfz
- Dlm

Duration?
Other Questions (to get more out of study)

• Drugs
  – Aspirin
  – Steroids
  – NAC (N-acetyl-cysteine)
  – Ibuprofen
  – Efflux pump inhibitors
  – Vitamin D
• Delivery
  – Inhaled therapy
• Other
  – Nutritional support
  – Psychosocial support
Possible Trial 1

All children with MDR-TB

Intervention
6-9Lfx/Lnz/Clz/Dlm/H/Z/Eth

Control
9-12 month regimen

NAC
Placebo

Opt out for individual children; Lnz or Lfx change to PAS or BDQ if intolerable/resistance?
Possible Trial 2

All children with MDR-TB

Limited Disease
- Intervention: 6 Lfx/Del/Z/Clz
- Control: 9 month regimen (omitting injectable?)

Severe Disease
- Intervention: 9Lfx/Del/Lnz/Clz/Z/H
- Control: 9 month regimen

Role of BDQ if becomes available for children?
Trial implementation and uptake considerations

- Effective
- Safe
- Child friendly and program friendly (once daily dosing)
- Simplicity of regimen
- Monitoring for AE
STREAM: Regimens for Stage 2

Regimen A

Locally used WHO-approved MDR-TB regimen

Regimen B
(Stage 1 study regimen)

- Clofazimine
- Ethambutol
- Moxifloxacin
- Pyrazinamide
- Isoniazid
- Kanamycin
- Prothionamide

16 weeks
40 weeks

Regimen C
(modified Stage 1 study regimen, all oral)

- Bedaquiline
- Clofazimine
- Ethambutol
- Moxifloxacin
- Pyrazinamide
- Levofloxacin
- Isoniazid
- Prothionamide

16 weeks
40 weeks

- Bedaquiline added
- Moxifloxacin replaced by levofloxacin
- Kanamycin dropped

Regimen D
(modified Stage 1 study regimen, shortened)

- Bedaquiline
- Clofazimine
- Pyrazinamide
- Levofloxacin
- Isoniazid
- Kanamycin

8 weeks
28 weeks

- Bedaquiline added
- Moxifloxacin replaced by levofloxacin
- Prothionamide dropped
- Ethambutol dropped
Table 1. Planned or ongoing Phase 2 or 3 trials of MDR-TB treatment or preventive therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>MDR-TB Treatment trials</th>
<th>Components of intervention arm</th>
<th>Trial</th>
<th>MDR-TB Preventive therapy trials</th>
<th>Components of intervention arm</th>
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<tbody>
<tr>
<td>NC005</td>
<td>PZA, BDQ, PTA</td>
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<td>VQUIN</td>
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<td>LFX</td>
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<td>Opti-Q</td>
<td><strong>LFX</strong> + standard of care</td>
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<td>TB-CHAMP</td>
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<td>LFX</td>
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<td>STREAM II</td>
<td>BDQ, CFZ, EMB, PZA, <strong>LFX</strong>, INH, PTO</td>
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<td>PHOENIx</td>
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<td>DLM</td>
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<td>NIX-TB</td>
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<tr>
<td>STAND</td>
<td>PZA, MFX, PTA</td>
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<td>NEXT-TB</td>
<td>PZA, <strong>LFX</strong>, ETO/hdINH, <strong>LZD</strong>, BDQ</td>
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<td>C208</td>
<td>BDQ + standard of care</td>
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<td>Trial 213</td>
<td>DLM + standard of care</td>
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<td>endTB</td>
<td>Combinations including <strong>LZD</strong>, BDQ, CFZ</td>
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PZA-pyrazinamide; BDQ-bedaquiline; PTA-pretomanid; LFX-levofloxacin; EMB-ethambutol; MFX-moxifloxacin; PTO-prothionamide; CFZ-clofazimine; hdINH-high dose isoniazid; LZD-linezolid; ETO-ethionamide; DLM-delamanid

Slide: courtesy Anthony Garcia-Prats
Data gaps/Challenges

• Optimal and safe use of FQNs across age spectrum – PK studies in progress: LFX and MFX (0-8 yrs)
• Optimal and safe use of LNZ (PK data pending) – toxicity concerns – full duration of treatment (replace if AEs)
• Clofazimine PK and safety (planned IMPAACT capsule) Role of BDQ? (P1108 and Janssen study) – as data available to replace other drugs for resistance/toxicity?
• Role of BDQ/DLM co-treatment (planned IMPAACT capsule)
• Changing landscape: MDR-TB treatment guidelines, access programs
• Timing of inclusion wrt adult trials (adolescents)
• Formulations - including clofazimine (gelcaps), FQNs
Questions?