Shortened MDR-TB Regimens: Union-Supported Research

I.D. Rusen
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Outline

- MDR–TB burden and treatment limitations
- Early Union involvement in shortened MDR–TB regimens
- Bangladesh MDR–TB treatment pilot project
- STREAM clinical trial
- Observational treatment cohorts
- Conclusions
MDR-TB – burden and treatment limitations

- WHO estimates approximately 480,000 new MDR-TB cases globally in 2013
- An estimated 210,000 deaths due to MDR-TB in 2013
- Of reported MDR-TB patients treated – only 48% were successfully treated
- Currently recommended treatments are lengthy and often difficult to tolerate
Union involvement in shortened MDR-TB regimens

- Union believed/believes strongly that a more accessible and tolerable treatment for MDR–TB was/is urgently needed.

- Experience from a Damien Foundation pilot programme utilizing a nine-month treatment regimen in Bangladesh demonstrated impressive results.
‘Bangladesh’ Regimen

Daily treatment for 9 months

<table>
<thead>
<tr>
<th>Drug</th>
<th>Months**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanamycin*</td>
<td>1–4</td>
</tr>
<tr>
<td>Isoniazid (H)</td>
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</tr>
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<td>Prothionamide</td>
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<tr>
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<tr>
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* Kanamycin 3 times/week in month 4
** The intensive phase can be extended to 6 months
Sequential Cohort Approach

- Six consecutive regimens between 1997 and 2007
- Treatment outcomes and adverse drug reaction frequency directed regimen adjustments
- New regimen cohort was started when results of previous one seemed sufficiently clear
Regimen Highlights

- Removing INH from the regimen resulted in poor treatment outcomes (57% cure)

- Absence of both Prothionamide and Clofazimine in continuation phase resulted in high failure rate (13.3%) (Pto throughout regimen increased default rate)

- Clofazimine replacing Pto in continuation demonstrated best results
### Results from Bangladesh Project

#### Published cohort (206 pts)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td>82.5%</td>
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<td>Relapse</td>
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<td>Overall success rate:</td>
<td>87.9%</td>
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*Am J Respir Crit Care Med 2010*

#### Updated total (515 pts)

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<tr>
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<tr>
<td>Default</td>
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<tr>
<td>Death</td>
<td>5.6%</td>
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<tr>
<td>Failure</td>
<td>1.4%</td>
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<tr>
<td>Relapse</td>
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<td>Overall success rate:</td>
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*Int J Tuberc Lung Dis 2014*
Union involvement in shortened MDR–TB regimens

- Union requested an international review of the pilot programme in an effort to see the shortened regimen endorsed globally.

- World Health Organization/Green Light Committee–led review of Damien Foundation Project in 2007 concluded:
  - Additional data from larger studies required...this should preferably be done in randomized-controlled clinical trials conducted under Good Clinical Practice (GCP) conditions.
  - Consider using a 12 or 15-month instead of 9-month treatment regimen....with a careful (multicenter) cohort study of this approach.
Union involvement in shortened MDR–TB regimens

• The Union began to search for the necessary resources for further research of the Bangladesh regimen

• In early 2008 a USAID RFA for a new research cooperative agreement highlighted the opportunity for clinical trials on priority MDR–TB topics

• The Union developed a clinical trial protocol as part of a larger TB research proposal (TREAT TB) and was awarded a five-year cooperative agreement
A Parallel Approach

- Additional cohorts
  - Cameroon
  - Benin
  - Niger
  - Other countries

- Randomised trial
  - STREAM, a non-inferiority design RCT
A Parallel Approach

- Additional cohorts
  - Cameroon
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  - Other countries

- Randomised trial
  - STREAM, a non-inferiority design RCT
STREAM Trial Design

- STREAM is a randomised controlled trial of non-inferiority design
- The control regimen is the locally used WHO recommended regimen in the participating countries
- The study regimen is very similar to the regimen in Bangladesh with the exception that high dose moxifloxacin replaces high dose gatifloxacin
STREAM Study Partners

Funder: USAID

Sponsor: International Union Against Tuberculosis and Lung Disease

Design, Management, Analysis

Microbiology: Institute of Tropical Medicine, Antwerp

Impact Assessment: Liverpool School of Tropical Medicine

MRC Clinical Trials Unit

SOUTH AFRICA
- King Hospital, Durban
- Sizwe Tropical Diseases Hospital

VIETNAM
- Ho Chi Minh City Hospital

MONGOLIA
- NCCD, Ulaanbataar

ETHIOPIA
- Armaeuer Hansen Research Institute (AHRI)
- St. Peter’s Tuberculosis Specialised Hospital/ Global Health Committee

Sponsor: International Union Against Tuberculosis and Lung Disease
STREAM Trial Sites

- Ethiopia (Addis Ababa)
- Mongolia (Ulan Bataar)
- Vietnam (Ho Chi Minh)
- South Africa (Sizwe, Durban, Pietermaritzburg)

* MDR-TB: multidrug-resistant tuberculosis (resistance to, at least, isoniazid and rifampicin)
Primary Objectives

1. To compare the proportion of patients with a favourable outcome in the study regimen and a standardised control regimen.

2. To compare the proportion of patients who experience grade 3 or greater adverse events at any time during follow-up on the study regimen as compared to the control regimen.
## STREAM Trial Regimen

### Daily treatment for 9 months

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<tr>
<td><strong>Moxifloxacin</strong></td>
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</tr>
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* Kanamycin 3 times/week in month 4
** The intensive phase can be extended to 6 months
Selected Reasons for Ineligibility

1. Extra-pulmonary TB only (i.e. no pulmonary tuberculosis)

2. Resistance to second-line injectables by line probe assay

3. Resistance to fluoroquinolone by line probe assay

4. Critically ill, and unlikely to survive more than 4 months

5. Known to be pregnant or breast-feeding

6. Pre-existent QT prolongation (QTc > 500ms) on ECG prior to randomisation
## STREAM timelines

<table>
<thead>
<tr>
<th>Event</th>
<th>Actual</th>
<th>Planned</th>
</tr>
</thead>
<tbody>
<tr>
<td>First patient randomised:</td>
<td>27\textsuperscript{th} July 2012</td>
<td></td>
</tr>
<tr>
<td>Enrolled</td>
<td>389</td>
<td>400</td>
</tr>
<tr>
<td>Completion of recruitment:</td>
<td></td>
<td>Q2 2015</td>
</tr>
<tr>
<td>Final patient follow-up visit:</td>
<td></td>
<td>Q3 2017</td>
</tr>
<tr>
<td>Results expected:</td>
<td></td>
<td>Q4 2017</td>
</tr>
</tbody>
</table>
STREAM Stage 2

- Early in 2013 in recognition of the progress made to date in STREAM and noting the provisional licensing of the first new drug for TB for almost 50 years we were asked to consider:
  - is it possible to include additional regimens to the current STREAM trial?
  - if so, what would be the appropriate regimens to evaluate?
After extensive discussions between the study team, the local investigators and other experts it was agreed that the primary interest to patients and programmes would be:

- a fully oral 9-month regimen
- a 6-month simplified regimen

Both of these regimens would include bedaquiline as part of a broader agreement for support with Janssen Pharmaceuticals.
STREAM Treatment Regimens

Regimen A
- Locally used WHO-approved MDR-TB regimen

Regimen B
- (Stage 1 study regimen)
  - 16 weeks
  - 40 weeks
  - Clofazimine
  - Ethambutol
  - Moxifloxacin
  - Pyrazinamide
  - Isoniazid
  - Kanamycin
  - Prothionamide

Regimen C
- (modified Stage 1 study regimen, all oral)
  - 16 weeks
  - 40 weeks
  - Bedaquiline added
  - Moxifloxacin replaced by levofloxacin
  - Kanamycin dropped
  - Bedaquiline
  - Clofazimine
  - Ethambutol
  - Levofloxacin
  - Pyrazinamide
  - Isoniazid
  - Prothionamide

Regimen D
- (modified Stage 1 study regimen, shortened)
  - 8 weeks
  - 28 weeks
  - Bedaquiline added
  - Moxifloxacin replaced by levofloxacin
  - Prothionamide dropped
  - Ethambutol dropped
  - Bedaquiline
  - Clofazimine
  - Pyrazinamide
  - Levofloxacin
  - Isoniazid
  - Kanamycin
In Regimen C, the fully oral regimen, kanamycin is replaced by bedaquiline and moxifloxacin by levofloxacin.

<table>
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<tr>
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<th>Weeks</th>
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<tr>
<td></td>
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<td>Less than 33 kg</td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>1 – 40</td>
<td>400 mg once daily for first 14 days/200 mg thrice weekly thereafter</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1 – 40</td>
<td>750 mg</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>1 – 40</td>
<td>50 mg</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>1 – 40</td>
<td>800 mg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1 – 40</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>1 – 16</td>
<td>300 mg</td>
</tr>
<tr>
<td>Prothionamide</td>
<td>1 – 16</td>
<td>250 mg</td>
</tr>
</tbody>
</table>

The intensive phase can be extended by 4 or 8 weeks if smear conversion has not occurred by 16 or 20 weeks respectively.
Regimen D

- In Regimen D prothionamide is replaced by bedaquiline, moxifloxacin is replaced by levofloxacin, ethambutol is removed, the dose of isoniazid is increased and the total duration is reduced from 40 to 28 weeks.

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<tr>
<td>Pyrazinamide</td>
<td>1 - 28</td>
<td>1000 mg</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>1 – 8</td>
<td>400 mg</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>1 – 8</td>
<td>15 mg per kilogram body weight (maximum 1g)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>600 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>800 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>900 mg</td>
</tr>
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The intensive phase can be extended by 4 or 8 weeks if smear results is 2+ or more at 8 or 12 weeks respectively.
Primary objectives in Stage 2

– To assess whether the proportion of patients with a favourable efficacy outcome on Regimen C, the fully oral regimen, is not inferior to that on Regimen B at 76 weeks (18 months)

– To assess whether the proportion of patients with a favourable efficacy outcome on Regimen D, the 6-month regimen, is not inferior to that on Regimen B at 76 weeks (18 months)
Parallel primary objective in Stage 2

– To assess whether the proportion of patients with a favourable efficacy outcome on Regimen C, the fully oral regimen, is superior to that at on Regimen B at 76 weeks (18 months)
Health Economics Evaluation

• In Stage 2 (as in Stage 1) comprehensive health economics evaluation to be undertaken assessing both patient and health system cost components with respect to all four treatment regimens
Community Engagement

- STREAM Stage 1 had varying levels of community engagement
- STREAM Stage 2 protocol reviewed by Global TB CAB
- STREAM Stage 2 to include strengthened community engagement with external training and support
- Appointment of community representative from a site Community Advisory Board as voting member of TSC
Stage 2 timeframe

- We plan to complete enrolment to Stage 2 in 3 years (1155 patients)
- If enrolment begins in Q2 of 2015
- Last patient enrolled Q2 of 2018 (approx time of Stage 1 results)
- Primary endpoint results of Stage 2 Q2 of 2020
- Last patient completes long term follow-up Q4 of 2020
A Parallel Approach

**Additional cohorts**
- Cameroon
- Benin
- Niger
- Other countries

**Randomised trial**
- STREAM, a non-inferiority design RCT
Initial African Treatment Cohort

- Observational cohort study of 173 patients in Benin and Cameroon
- Modified Bangladesh regimen
  - 12 months treatment
  - normal dose gatifloxacin
  - prothionamide throughout treatment
- 91% treatment success (90% cured)
• Observational cohort study of 65 patients

• Modified Bangladesh regimen
  • 12 months treatment
  • normal dose gatifloxacin
  • prothionamide limited to intensive phase

• 89.2% cured

Int J Tuberc Lung Dis 2014
Current West African Cohort Study

- Observational cohort study of 1000 patients on a modified Bangladesh regimen
- Utilizing normal dose moxifloxacin in place of gatifloxacin
- Prothionamide during intensive phase only
- As of end of 2014 – 870 patients recruited in nine countries in West Africa
An increasing number of countries/projects utilizing shortened treatment regimens under observational research conditions will likely be initiated in the near future:

- Kazakhstan
- Laos
- The Philippines
Outstanding issues in treatment shortening research

- Observational cohort research
- Comparison requirements
- Regimen composition
- Site availability and capacity
Conclusions

• The Union supports further evaluation of the shortened regimens to find the optimal regimen for patients and programmes

• As new medicines become available their potential impact on treatment shortening must be evaluated in programme settings

• Capacity of programmes to evaluate regimens in both observational and RCT studies must be strengthened
Acknowledgements

• STREAM Trial Management Group – Prof Andrew Nunn and Dr. Sarah Meredith

• STREAM trial site staff and patients

• Union project coordinating team

• Trial funders: USAID, DFID/MRC, Janssen Pharmaceuticals