

MDR-TB RCTs: Bridging the evidence gap

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Status of MDR-TB world-wide

- In 2013 an estimated **480,000** people developed MDR-TB
- Approximately **300,000** of all notified cases
- Of these an estimated **136,000** were diagnosed and notified
- Of these **97,000** were started on treatment (**~ 1 in 5**)
- Of patients in the 2011 cohort of detected cases:
 - 48%** were successfully treated
 - 16%** died
 - 12%** failures of treatment
 - 24%** interrupted/no outcome reported

Status of MDR-TB world-wide

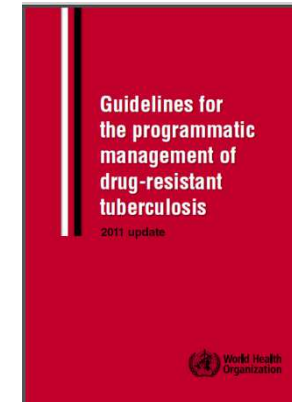
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**Only 1 in 10
cases**

Current Guidance on duration

4. Duration of second-line anti-tuberculosis regimens



Recommendations

- 4.1 In the treatment of patients with MDR-TB, an intensive phase of at least 8 months' duration is recommended (conditional recommendation, ⊕○○○/very low quality evidence).
- 4.2 In the treatment of patients with MDR-TB, a total treatment duration of at least 20 months is recommended in patients without any previous MDR-TB treatment (conditional recommendation, ⊕○○○/very low quality evidence).

Why STREAM?

- Results from the last of six successive cohorts of patients with MDR-TB in Bangladesh treated with a shortened regimen suggested there are better options even without the introduction of new drugs

Results of the regimen used in Bangladesh

Published cohort (206 pts)

Cure 82.5%

Completion 5.3%

Default 5.8%

Death 5.3%

Failure 0.5%

Relapse 0.5%

Overall success rate:

87.9% (95% CI 82.7, 92.6)

Cohort update (515 pts)

81.2%

3.3%

7.8%

5.6%

1.4%

0.8%

Overall success rate:

84.5% (95% CI 0.81, 0.88)

A parallel approach to assessing the effectiveness of the Bangladesh regimen

Cohort studies

- Cameroon
- Benin
- Niger
- Swaziland
- Other African countries
- Uzbekistan

Randomised trial

- STREAM

STREAM study design

- STREAM is a randomised controlled trial of **non-inferiority design** currently being conducted in Ethiopia, South Africa, Vietnam and Mongolia
- The control regimen **(A)** is the locally used WHO recommended regimen in the participating countries
- The study regimen **(B)** is closely similar to the regimen used in Bangladesh with the exception that high dose moxifloxacin replaces high dose gatifloxacin

The 9-month regimen (B)

Drug	Weeks	Drug doses by weight group		
		< 33 kg	33 - 50 kg	> 50 kg
Kanamycin*	1 - 16	15 mg per kilogramme body weight		
Isoniazid (H)	1 - 16	300 mg	400 mg	600 mg
Prothionamide	1 - 16	250 mg	500 mg	750 mg
Clofazimine	1 - 40	50 mg	100 mg	100 mg
Moxifloxacin	1 - 40	400 mg	600 mg	800 mg
Ethambutol	1 - 40	800 mg	800 mg	1200 mg
Pyrazinamide	1 - 40	1000 mg	1500 mg	2000 mg

- Kanamycin 3 times/week after week 12

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

STREAM Study Population

- Adults (18 years or older) who has given consent for treatment and follow-up
- Smear-positive pulmonary tuberculosis, or if HIV positive may be smear negative
- Evidence of initial resistance to rifampicin on line-probe assay, GeneXpert or other DST
- No evidence of initial resistance to fluoroquinolone or 2nd-line injectables on line-probe assay
- No pre-existent QT prolongation >500msec
- If pre-menopausal woman, not pregnant or breast feeding and agrees to use effective barrier contraception/IUCD during treatment

Stage 1: current status

- Enrolment to Stage 1 commenced: July 2012
- Sites: Ethiopia (2), South Africa (3), Viet Nam and Mongolia
- 424 of initial target of 400 patients enrolled
- Intake closed: June 30th 2015
- Primary endpoint at 30 months
- Last patient visit: Q4 2017
- Results from Stage 1 expected: Q1/2 2018

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 STREAM trial in its present form?
 - if so, what would be the appropriate regimens to evaluate?

Additional regimens studied in Stage 2

- 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 (regimen **C**)
 - a 6-month simplified regimen (regimen **D**)
- Both of these regimens include bedaquiline
- Funding USAID, sponsor The Union, trial management and analysis MRC Clinical Trials Unit, London

Primary objectives of STREAM Stage 2

- The primary objectives of Stage 2 are to assess whether the **fully oral regimen (C)** and the **6-month regimen (D)** are as effective as regimen B at 18 months after randomisation

STREAM Stage 2 timescale

- Enrolment to begin end Q3/4 of 2015
- Plan to complete enrolment to Stage 2 in 3 years
- Last patient enrolled Q3/4 of 2018 (approx time of Stage 1 results)
- Last patient reaches 18 months post-randomisation Q2 of 2020
- Last patient completes long term follow-up Q2 of 2021

Other phase III trials

Delamanid Phase III

- Placebo controlled trial:
 - Delamanid + optimum background regimen (OBR)
 - OBR + placebo

Delamanid and placebo are given for 6 months

Primary endpoint: time to sputum culture conversion

Secondary endpoint: durability of sputum culture conversion
18 months post-randomisation

Enrolment complete

Sites in Eastern Europe, Asia, South America, South Africa

STAND – a universal regimen (TB Alliance)

- The STAND trial includes both drug-sensitive (DS) and MDR-TB patients; the experimental arms do not include either rifampicin or isoniazid
- DS patients are randomised to one of three regimens of different durations each containing **moxifloxacin, pretonamid (two dose schedules) and pyrazinamide**
- **300 MDR-TB patients are to be enrolled, all will receive six months of moxifloxacin, pretonamid and pyrazinamide**
- Enrolment started in Q1 2015

PRACTECAL – trial regimens

24 week intervention (TBC):

- bedaquiline + pretomanid + linezolid + moxifloxacin
- bedaquiline + pretomanid + linezolid + clofazimine
- bedaquiline + pretomanid + linezolid

Control

- Locally accepted standard of care consistent with the WHO recommendations for the treatment of M/XDR-TB.

Patients with XDR are also eligible

END TB

(UNITAID, Partners in Health, MSF)

- An adaptive design; based on progress in the regimens, poorly performing regimens may be dropped early and the best performing regimen, as defined by culture negativity in the early months of treatment will be allocated a higher proportion of patients
- Treatment experimental regimens include bedaquiline, delamanid, linezolid and clofazamine
- Patients eligibility requires fluoroquinolone sensitive MDR-TB

NIX-TB (new investigational drugs for XDR TB) **(TB Alliance)**

- The investigational regimen is comprised of **bedaquiline, pretomanid, and linezolid**
- Potential to be used as a relatively simple and affordable universal regimen.
- The NIX-TB regimen will first be tested in XDR-TB patients because it may be more toxic than current MDR-TB therapy, but if the regimen proves safe and effective, that will pave the way for expanding the study to MDR-TB patients and then potentially to drug-sensitive TB patients

NExT trial

South African MRC

- Open label RCT of a 6-9 month injection free regimen containing bedaquiline, linezolid, levofloxacin, ethionamide, high dose isoniazid, and PZA
- To enrol in South African sites

The DDI trial (ACTG 5343)

- None of the current studies include bedaquiline and delamanid given together
- Before combining these two drugs we need the results of the drug-drug interaction study which assesses the safety, tolerability and pharmacokinetics when these are given in the same regimen
- Trial expected to begin recruitment in Q4 of 2015

Not forgetting the children

- There is a widespread recognition that if possible children should be included earlier in clinical trials than has been the case in the past
- It is hoped that it will be possible to include children in Stage 2 of STREAM when information from PK studies becomes available
- In the meantime an application to EDCTP is being prepared in which a delamanid based regimen will be assessed in children

In conclusion

After years of inaction

- There are some exciting initiatives in progress
- This includes the prospect of injection-free regimens and universal regimens of six months or less duration
- BUT the earliest phase III results are not expected before 2018

