Evaluating Newly Approved Drugs for MDR-TB: A Clinical Trial

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Co-PI endTB Clinical Trial
Founding Member, RESIST-TB Steering Committee
Summary

• Magnitude of MDR-TB problem
• MDR-TB treatment outcomes and access
• Bedaquiline and delamanid & short regimens
• endTB
  – Treatment per current guidance
  – Novel, shorter regimens
• Trial design
• Trial timeline
MDR-TB Treatment Access & Success Relative to Burden

- Estimated # of MDR-TB cases among prevalent TB patients
- Estimated # of MDR-TB cases among notified TB patients
- # of reported MDR-TB patients 2014
- # of MDR-TB patients started on treatment 2014
- Estimated # of MDR-TB patients started on treatment in 2014 who will be successfully treated
Outcomes on existing MDR-TB treatment

Percentage cured or completed treatment

Reference

1. WHO Global Report, 2013
2. Orenstein, Lancet, 2009
4. Diacon, AAC, 2012

* % with favorable outcome (95% CI)
Frequency of AEs (or AE indicating drug removal) on existing MDR-TB treatment

- FDA AIAC briefing, bedaquiline, Nov 2012
- Gler et al, 2012, supplementary material
- Nathanson, IJTLBD, 2004
### Typical Daily Pill Burden for MDR-TB/HIV Co-infected Patient >60 kg

<table>
<thead>
<tr>
<th>Morning dose</th>
<th>Evening dose</th>
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<tbody>
<tr>
<td>Pyrazinamide: 4 tablets</td>
<td>Ethionamide: 2 tablets</td>
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<tr>
<td>Kanamycin: 1 g IM</td>
<td>Cycloserine: 2 capsules</td>
</tr>
<tr>
<td>Levofloxacin: 2 tablets</td>
<td>PAS: 1 sachet</td>
</tr>
<tr>
<td>Ethionamide: 1 tablet</td>
<td>Pyridoxine: 4 tablets</td>
</tr>
<tr>
<td>Cycloserine: 1 capsule</td>
<td></td>
</tr>
<tr>
<td>PAS: 1 sachet</td>
<td></td>
</tr>
<tr>
<td>AZT/3TC combination: 1 tablet</td>
<td>AZT/3TC combination: 1 tablet</td>
</tr>
<tr>
<td>Cotrimoxazole: 1 tablet</td>
<td>EFV (600 mg): 1 tablet</td>
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</tbody>
</table>

Photo: Daily MDR-TB regimen in Mozambique. Why we're investing w/ @PIH, IRD & @MSF for better treatment! pic.twitter.com/j7zovDfiQ3 (UNITAID Twitter feed May 7, 2014)
<table>
<thead>
<tr>
<th>Regimen description</th>
<th>Drugs</th>
<th>Price Range for Regimens Using Quality-Assured Products</th>
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</thead>
<tbody>
<tr>
<td>Conventional Regimen for MDR-TB in Settings with No SLD Resistance</td>
<td>pyrazinamide, kanamycin, levofloxacin, ethionamide, cycloserine</td>
<td>USD $1,344 - $2,222</td>
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<tr>
<td>Regimen for Patients with SLD Resistance</td>
<td>pyrazinamide, capreomycin, moxifloxacin, ethionamide, cycloserine, PAS</td>
<td>USD $5,267 - $7,339</td>
</tr>
<tr>
<td>Regimen for XDR-TB or Failures of MDR-TB Treatment</td>
<td>capreomycin, moxifloxacin, cycloserine, clofazimine, linezolid, meropenem</td>
<td>USD $14,244 - $15,356</td>
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</tbody>
</table>
Randomized Pilot Trial of Eight Weeks of Bedaquiline (TMC207) Treatment for Multidrug-Resistant Tuberculosis: Long-Term Outcome, Tolerability, and Effect on Emergence of Drug Resistance

The Diaryquinoline TMC207 for Multidrug-Resistant Tuberculosis

Proportion of Culture-Positive Patients

Days to Culture Conversion

No. at Risk
Placebo
TMC207

19
18
16
22
21
13
11

Fig. 2. The Proportion of Patients with Positive Sputum Cultures and Time to Conversion.

Weeks to culture conversion
Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

A Mycobacterial Growth Indicator Tube System

Cumulative Proportion of Patients with Sputum-Culture Conversion

Days

Delamanid, 100 mg, twice daily

Delamanid, 200 mg, twice daily

Placebo
Outcomes on existing and new MDR-TB treatments

Reference

1. WHO Global Report, 2014
2. Orenstein, Lancet, 2009
4. Diacon, NEJM, 2014
5. Skriponoca, ERJ, 2013
7. Bonnet, IJTL, 2016
8. Diacon, NEJM, 2014-A
9. Skriponoca, ERJ, 2013-A
10. Aung, IJTL, 2014
11. Piubello, IJTL, 2015
12. Kuaban, IJTL, 2014
“...when an effective and reasonably well tolerated regimen can be composed...routine addition of delamanid may not be warranted and the implications of additional health services costs should be considered”
“treatment protocols are ...approved by the relevant national ethics authority...”
“...pharmacovigilance techniques...will be needed to improve the early detection of adverse drug reactions...”

“...bedaquiline may be added... when an effective treatment regimen containing 4 2nd-line drugs in addition to PZA according to WHO recommendations cannot be designed; or, when there is documented evidence of resistance to FQ”
Using delamanid, program conditions

Awaiting bedaquiline, program conditions

Distribution of BDQ & DLM Testing and Use, April 2016

Using bedaquiline, program conditions

Bedaquiline tested in clinical trials

endTB = Expanding New TB drugs
The funding partner is UNITAID.
The Consortium partners are:
- Partners In Health (PIH)
- Doctors Without Borders (MSF)
- Interactive Research and Development (IRD)
Project duration is 4 years.
Project budget = $60.4 million USD
• Expand access to new TB drugs in 15 countries (2600 patients) according to WHO guidance;

• Perform a clinical trial with novel regimens that include bedaquiline and/or delamanid (5 countries, 750 participants);

• Produce evidence on new TB drugs to inform policy and clinical decisionmaking.
Facilitate scale-up of new TB drugs

Facilitate drug availability in countries.

Adapt national guidelines to evidence around new drugs.

Work with countries on financing of new drugs.

Adapt WHO guidelines to evidence around new TB drugs.
Large, multi-country patient cohort

<table>
<thead>
<tr>
<th>Site</th>
<th>Implementing Partner</th>
<th>Target enrollment</th>
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<tbody>
<tr>
<td>Peru</td>
<td>PIH</td>
<td>420</td>
</tr>
<tr>
<td>Lesotho</td>
<td>PIH</td>
<td>150</td>
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<td>Kazakhstan</td>
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<td>573</td>
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<td>Ethiopia</td>
<td>PIH</td>
<td>30</td>
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<td>Kenya</td>
<td>MSF</td>
<td>46</td>
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<td>Georgia</td>
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<tr>
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<td>Eugene Bell Foundation</td>
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<tr>
<td>Nepal</td>
<td>Nepal Anti-TB Association</td>
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<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>2,600</strong></td>
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</table>

2600 patients on new drugs

15 countries

Monitored closely for side effects

May detect rare side effects missed in small clinical trials
Principles for designing future regimens for multidrug-resistant tuberculosis

Grania Brigden, a Bern-Thomas Nyang'wa, b Philipp du Cros, b Francis Varaine, c Jennifer Hughes, d Michael Rich, e C Robert Horsburgh Jr, f Carole D Mitnick, g Eric Nuermberger, h Helen McIleron, i Patrick PJ Phillips j & Manica Balasegaram a

- At least one new drug class
- At least 3 and max 5 effective drugs
- Effective against MDR and XDR strains
- 6 months
- Oral
- Simple dosing schedule
- Good side effect profile, limited monitoring
- Minimal interaction with antiretrovirals
endTB Project

endTB Trial
Stages 1 & 2

MSF Clinical Trial Initiative
MDR-TB
• Randomized, controlled, Bayesian response-adaptive, non-inferiority
  – Identify ALL non-inferior regimens
• FQ-susceptible, pulmonary RIF-R DR-TB
• 5 39-week experimental regimens vs. conventional, 20-month control
• 73-week favorable outcome primary endpoint
• 750 participants
Trial Stage 1 Objectives

- **Primary**: assess whether the efficacy of (5) experimental regimens at 73 weeks is non-inferior to that of the control

- **Secondary efficacy**: Compare to control
  - Culture conversion in experimental regimens
  - Efficacy of experimental regimens at 39 weeks
  - Efficacy of experimental regimens at 104 weeks, including failure & relapse

- **Secondary safety**: Compare to control
  - At 73 and 104 weeks: death; grade 3 or higher AEs, SAEs, QTc prolongation in experimental arms
Study Population: Inclusion

- Pulmonary TB, RIF-resistant & FQ-susceptible, by validated rapid molecular test;
- ≥ 15 years of age;
- Negative pregnancy test & willingness for (men & women) to use appropriate contraception;
- Informed consent by participant (& guardian);
- Intends to remain accessible to study
Study Population: Exclusion

- Allergy or hypersensitivity to study drugs
- Exposure/resistance to bedaquiline, delamanid, linezolid, clofazimine (last 5 years)
- Pregnant, breastfeeding
- Unable or unsafe to comply with study
- Hematology/chemistry/electrolyte abnormalities
- Cardiac risk factors
- Participating in other trial
- Must take disallowed medications
Choice of drugs

- Rely on new or repurposed drugs w/ limited prior population exposure:
  - Bedaquiline
  - Delamanid
  - Linezolid
  - Clofazimine

- Existing drugs considered key to MDR-TB treatment
  - Fluoroquinolone: Moxifloxacin or Levofloxacin
  - Pyrazinamide
New, Repurposed Drugs with Limited Population Exposure

- **Bedaquiline and Delamanid**
- **Linezolid (Lzd)**
  - Meta-analyses
  - Improved conversion in XDR-TB trial
  - Toxicity concerns (600mg → 300mg)

- **Clofazimine**
  - Active in acute and chronic mouse models
  - Observational studies support contribution in MDR & XDR
  - Inapparent EBA
Drugs “critical” to MDR-TB treatment

- ** Fluoroquinolones (FQ)**
  - Lfx or Mfx: cornerstone of MDR treatment

- ** Pyrazinamide**
  - Important to shortening TB treatment
  - Potent combined with BDQ and other drugs
  - ~50% resistance in MDR
Selection of Combination Regimens

- Finite combinations possible
- Selected combinations supported by mouse models

Principles
- Injectable sparing
- Fluoroquinolone & PZA
- 4-5 drugs, >=3 likely effective drugs
- BDQ or DLM, combined in 1 arm
- <=2 important QT-interval prolongers (clofazimine, bedaquiline, moxifloxacin)
## Experimental 9-month Regimens (Stage I)

<table>
<thead>
<tr>
<th></th>
<th>Bdq</th>
<th>Dlm</th>
<th>Cfz</th>
<th>Lzd</th>
<th>FQ</th>
<th>Z</th>
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<tr>
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</table>

Standard of care control, per WHO Guidelines, may include Dlm or Bdq.

Bdq=bedaquiline, Dlm=delamanid, Cfz=clofazamine, Lzd=linezolid, FQ=fluoroquinolone (Mfx=moxifloxacin, Lfx=levofloxacin), Z=pyrazinamide
<table>
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<tr>
<th>Drug</th>
<th>Weight Band (kg)</th>
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<tr>
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<tr>
<td>Bedaquiline (Be)</td>
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<tr>
<td></td>
<td>400 mg QD x 2 weeks followed by 200 mg 3x/week</td>
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<tr>
<td>Delamanid (De)</td>
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</tr>
<tr>
<td></td>
<td>100 mg BID</td>
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<tr>
<td>Moxifloxacin (Mo)</td>
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<td></td>
<td>400 mg</td>
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<tr>
<td>Levofloxacin (Le)</td>
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<tr>
<td></td>
<td>750 mg</td>
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<tr>
<td>Linezolid (Li)</td>
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<tr>
<td></td>
<td>600 mg QD for up to 4 months (followed by 300 mg QD or intermittent dosing for 5 months)</td>
</tr>
<tr>
<td>Clofazimine (C)</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>800 mg</td>
</tr>
</tbody>
</table>
Randomize to 6 arms

Observe & predict response-8 & 39 weeks

Adapt randomization

Drop inferior arms, end trial early, adjust sample size

Produce results

Arm 1

Arm 2

Arm 3

Arm 4

Arm 5

Arm 6
- Control Response = 70%
- Response non-inferior experimental arm = 75%
- $\Delta = 12\%$
- 80% power
- One-sided $\alpha = 0.025$
- Detect 1-3 non-inferior arms in mITT
- Detect 1-2 non-inferior arms in PP

- ITT: all randomized participants with $\geq 1$ dose
- mITT: ITT, culture positive, confirmed MDR/FQ-S
- PP: mITT without deviation that affects endpoint assessment
Sample scenarios: Non-Inferiority Margin=0.12
Summary: Frequentist Analysis

- Primary, secondary: pairwise experimental vs. comparator, or descriptive
  - Proportion & 97.5% CI calculated & compared
- Covariates: comorbidities, prior exposure, PZA (& other) resistance, extent of disease, etc.
Relative Sample Size to Detect Non-Inferior Arms Adaptive (BAR) vs. Balanced (BR) Randomization
Expansion of MDR-TB trial site capacity
endTB Exchange: Peru-Armenia
Trial Summary-Stage 2

- Randomized, controlled, balanced, non-inferiority
- FQ-resistant, RIF-resistant TB
- 2 39-week experimental regimens vs. conventional, 20-month control
- 73-week favorable outcome primary endpoint
- ~400 participants
## endTB Timeline

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<td>Central IRB approval - stage 1</td>
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<td>Local IRB approval - stage 1</td>
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<td>Enroll stage 1</td>
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</tr>
</tbody>
</table>
On behalf of endTB Central Trial Investigators

- Francis Varaine, Co-PI, MSF (France)
- Michael Rich, Co-I, PIH
- Maryline Bonnet & Elisabeth Baudin, Co-Is, Epicentre
- Alex Telnov, Co-I, MSF (Switzerland)
- Bouke de Jong, Co-I, ITM (Antwerp)
- Protocol Committee: Patrick Phillips (UKMRC), Helen McIlneron (UCT), Lorenzo Trippa (DFCI), Peter Zimetbaum (BIDMC)
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- Division of Global Health Equity, Brigham & Women’s Hospital
- Interactive Research & Development/Indus Hospital
- Partners In Health/Socios En Salud
- Institute of Tropical Medicine
- Global TB CAB
- MSF MDR-TB Clinical Trial Scientific Advisory Committee

Ministries of Health: Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru, (S. Africa, Pakistan)