The endTB Project:
Expanding New Drugs for TB

PARTNERS IN HEALTH (PIH)
MÉDECINS SANS FRONTIÈRES (MSF)
INTERACTIVE RESEARCH & DEVELOPMENT (IRD)

April 29th, 2015
Geneva, Switzerland
• endTB = Expanding New TB drugs
• The funding partner is UNITAID.
• The 3 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
endTB Overview

• The fundamental problem limiting access to MDR-TB treatment is the absence of an effective, user-friendly treatment regimen.

• The endTB Project is UNITAID’s strategy to re-shape the market for MDR-TB treatment.
Two new TB-drugs:

**Bedaquiline**  
(Trade name = Sirturo®)

**Delamanid**  
(Trade name = Deltyba®)

Also assures proper companion anti-TB drugs are available, including linezolid, clofazimine, and imipenem.
Objectives

1) Generate evidence of safety and efficacy of new TB drugs.
2) Accelerate uptake of new TB drugs and novel MDR-TB regimens.
3) Facilitate change in evidence-based WHO recommendations.
endTB Project Activities

- Expand access to new TB drugs in 16 countries and provide capacity to NTPs to incorporate new TB drugs in MDR regimens according to WHO policy. (Multi-country cohort = 2600);

- Perform a clinical trial with novel regimens that include the new TB drugs bedaquiline and/or delamanid (Five countries only; trial cohort = 600);

- Produce evidence on new TB drugs for normative agencies to help inform recommendations.
Uses WHO Interim Policy Guidance on Bedaquiline and Delamanid as basis of implementation for the multi-country cohort (2600 patients)

June 2013
WHO
Bedaquiline Guidance

October 2014
WHO
Delamanid Guidance

2014
WHO Policy Package for new drug implementation

2015 (pending)
Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis
What will endTB do?

Large, multi-country patient cohort
• 2600 patients on new drugs
• 16 countries
• Monitored closely for side effects
• Enough patients to detect rare side effects that may have been missed in small clinical trials

<table>
<thead>
<tr>
<th>Site</th>
<th>Implementing Partner</th>
<th>Patients enrolled</th>
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<tr>
<td>Peru</td>
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<td>Lesotho</td>
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<tr>
<td>TOTAL</td>
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<td><strong>2,600</strong></td>
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What will endTB do?

**Groundbreaking clinical trial**

- 5 countries (subset of the 16)
- 600 additional patients
- Testing new ‘user-friendly’ treatment regimens
- Will identify regimens that are:
  - Effective
  - Short
  - Contain no injectable drug
  - Manageable side effects
- Will start in Year 2 of the project.
Current list of TB drugs used in MDR-TB treatment (22 different drugs) - Resulting in numerous non-standard regimens and different regimens for MDR-TB, pre-XDR-TB and XDR-TB:

- Isoniazid (high-dose)
- Ethambutol
- Pyrazinamide
- Kanamycin (injection)
- Capreomycin (injection)
- Amikacin (injection)
- Moxifloxacin
- Levofloxacin
- Ofloxacin
- Gatifloxacin
- Ethionamide
- Prothionamide
- Cycloserine
- Terizidone
- PAS
- Sodium PAS
- Linezolid
- Clofazimine
- Amoxicillin/Clavulanate
- Meropenem
- Imipenem/Cilastin
- Clarithromycin
- Bedaquiline
- Delamanid

Possible priority TB drugs for regimen development during END-TB intervention (7-9 different drugs)

- Delamanid
- Bedaquiline
- Moxifloxacin/Levofloxacin
- Linezolid
- Clofazimine
- Pyrazinamide
- New investigational agents (such as PA-824, Stulezolid).

Possible inclusion of one of the Group 4 drugs?

5-8 priority TB drugs to treat MDR-TB.

1-3 regimen priority regimens involving new TB Drugs that can treat MDR-TB including pre-XDR-TB and XDR-TB.
Traditional TB Drug Development Paradigm

- Drugs rolled out individually
- 6 years for each drug

New Regimen Development Paradigm

- All drugs rolled out simultaneously
- Full novel regimen in $\frac{1}{4}$ the time

Stage 1: Optimizing regimens containing new drugs for fluoroquinolone susceptible (Fq-susceptible) strains

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<th>Cfz</th>
<th>Lzd</th>
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Control: OBR per WHO +/- BDQ or DLM as indicated by interim guidance

Bdq=bedaquiline; Dlm=delamanid; Cfz=clofazimine; Lzd=linezolid; FQ=fluoroquinolone, Mfx=moxifloxacin, Lfx=levofloxacin; Z=pyrazinamide
Stage 2: Optimizing regimens containing new drugs for fluoroquinolone resistant (Fq-resistant) strains

• Stage 2 will explore combinations of bedaquiline and delamanid if studies planned and underway do not contraindicate their combination.
What will endTB do?

Facilitate scale-up of use of new TB drugs.

• Assist with drug importation.
• Adapt national guidelines to include new drugs.
• Work with country programs on financing of new drugs.
• Ultimately change WHO guidelines to include new TB drugs.
Pharmacovigilance (PV) and operational research are important components.

PV focuses on adverse drug reactions.

The PV will take place in multiple forms:

✓ Use of Individual Case Safety Reports (ICSRs) that are filed for serious adverse events (SAEs), 3200 patients.
✓ An observational study of the 2600 patients will serve as Cohort Event Monitoring.
✓ In the Clinical trial of 600 patients.
THANK YOU

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