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endTB aims to find shorter, less toxic and more effective treatments for multidrug-resistant TB through access to new drugs, a clinical trial, and advocacy at country and global levels.

Why?

Only 11% of multidrug-resistant tuberculosis (MDR-TB) patients get successful treatment. In the absence of successful treatment, MDR-TB is transmitted among families and communities, and is often fatal.

Of the 480,000 estimated new MDR-TB patients in 2014, only 123,000 (26%) were reported as diagnosed. 110,000 (23%) ever received appropriate treatment. Even fewer received treatment with quality-assured drugs. Approximately 50% of those treated, or 11%, are expected to have successful outcomes.

Access is limited for many reasons. A key contributor is the absence of an effective, user-friendly treatment regimen. Moreover, existing structures do not facilitate development of such regimens.

MDR-TB treatment is extremely challenging to administer:

- Treatment requires a combination of at least five drugs;
- Among them, an intramuscular injection is required daily for eight months;
- The remaining drugs are oral but some have to be taken twice daily, for a total duration of 18-24 months;
- The treatment is extremely toxic and difficult to tolerate; completion demands daily support of treatment administration as well as nutritional, social, and economic support.

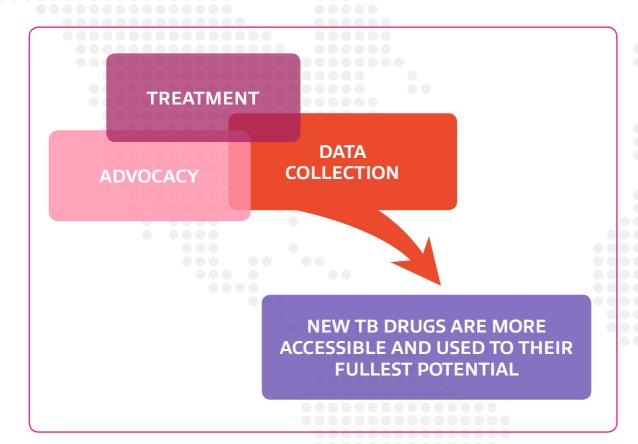
Manufacturers are motivated to test drugs, not regimens. The objective of industry is to bring single anti-TB drugs to a paying market. Although two new drugs, bedaquiline and delamanid, have been brought to market recently, the manufacturers do not have an incentive to support development of optimal regimens including one or both of these drugs.

Without concerted, externally supported efforts to test the drugs in combination, such combinations will never be evaluated.



Major gaps in regimen development for MDR-TB remain. Existing trials aim mostly to identify a single regimen, which invariably will not be adequate for all patients in all settings at all times. Few of these efforts combine new drugs in a single regimen.

Conclusion: This evidence gap leads to a market failure that prevents acceptance of new drugs and regimens by National TB Programs (NTPs).



Approach

endTB partners – Partners In Health (PIH), Médecins Sans Frontières (MSF), and Interactive Research and Development (IRD) will implement the following activities:

Introduce new drugs

We will treat at least 2,600 TB patients with new drugs and regimens in 15 countries, according to WHO guidance.

- → Establish an evidence base for broader, safe use of new MDR-TB drugs:

 Collection and analysis of data from this cohort of 2,600 patients will generate evidence for the safe, effective use of these drugs.
- → Address country-level barriers to enable access to new TB drugs:
 In each country, we will meet government requirements to authorize the import and use of these new drugs. We will work to incorporate their use in national guidelines, informed by the evidence generated by the project.

Clinical trial

The trial will evaluate five new combinations of drugs to identify those that are as good or better than the current regimen. 750 patients will be enrolled across trial sites, managed by PIH and MSF. Potential sites are: Georgia, Kazakhstan, Kyrgyzstan, Lesotho and Peru.

We will use the results to

Shape global policy and treatment practice

We will advocate for increased access to new drugs worldwide by disseminating and sharing our data with NGOs, UN agencies, Ministries of Health, pharmaceutical companies and global health donors.

Improve availability of anti-TB drugs

Using evidence from the regimens tested in our clinical trials, we will put pressure on manufacturers to supply adequate quantities of TB treatment drugs.

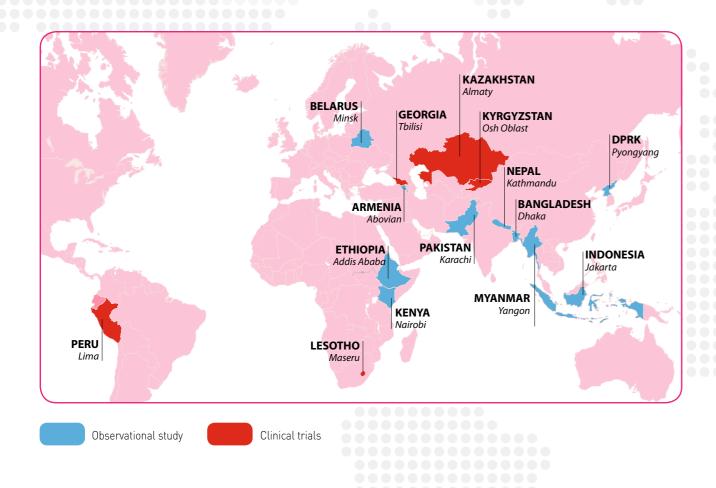
Negotiate fair TB drug pricing

The **endTB** partnership, will negotiate with suppliers to make new (and re-purposed) TB drugs affordable.



Countries

endTB is implemented in 15 countries struggling with serious MDR-TB epidemics. Thirteen rank among the 30 countries with the highest burdens of MDR-TB worldwide.

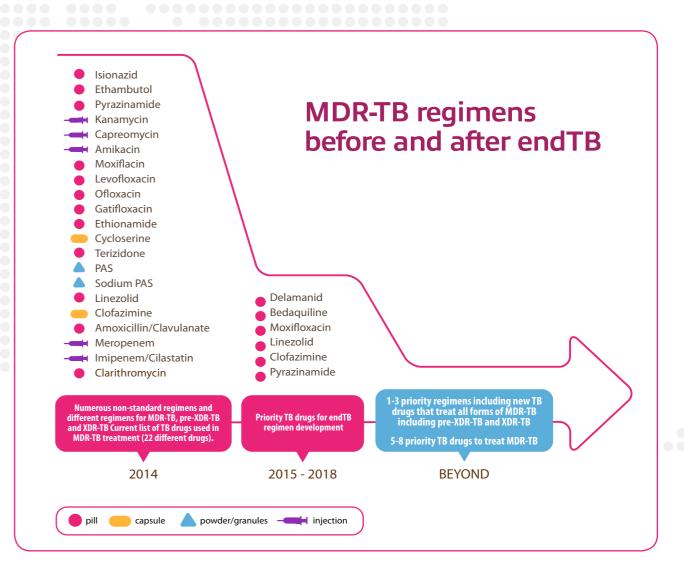


endTB countries are home to a range of patients who face many challenges beyond MDR-TB including extreme poverty, HIV, hepatitis C, alcohol and substance addiction, and social and political disruption. Implementing **endTB** in these varied settings provides important information about the use of new drugs in the full range of patients afflicted by MDR-TB.

Country requirements

endTB countries were selected on the following criteria:

- → endTB activities are implemented through close collaboration between NTPs and other national authorities and an NTP partner: PIH, MSF or IRD.
- endTB partners have already been working with NTPs on compassionate use treatment protocols, which include using delamanid and bedaquiline.
- → A formal NTP "Project Acceptance Form" was signed by the appropriate authorities.
- endTB partners obtain separate approvals for the observational study and the clinical trial preparation.
- Countries implement the consent processes required for receipt of new drugs and participation in studies.



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Treating and closely monitoring a large cohort of patients with new TB drugs

Approximately 2,600 patients will receive new TB drugs in the 15 **endTB** countries. The project will meet all WHO conditions¹ for the use of new TB drugs.

Procure new and companion TB drugs

endTB procurement will focus on five WHO Group 5 drugs² in the table below:

Classification	TB Treatment Drug	Abbreviation	
New	Bedaquiline	Bdq	
	Delamanid	Dlm	
Re-purposed	Linezolid	Lzd	
	Clofazimine	Cfz	
	Imipenem/Cilastatin	Imp/Cln	

- → New drugs: Bdq and Dlm are considered to be "new" TB drugs as they have recently been granted conditional approval for MDR-TB treatment by a stringent regulatory authority³.
- Repurposed drugs: Lzd, Cfz and Imp/Cln are considered TB "re-purposed" drugs. They have been developed to treat other diseases but are also used by clinicians to treat MDR-TB and extensively drug-resistant tuberculosis (XDR-TB). In countries where these drugs are not yet approved, we will find the best ways to ensure these drugs can be procured and imported according to country regulations.

Patients enrolled in Output 1 will also need additional drugs for a complete treatment regimen; these companion drugs will be supplied by existing mechanisms.

Evaluate MDR-TB patients for eligibility for new TB drugs

Inclusion criteria

Two types of patients will be considered for inclusion in the study

- newly diagnosed patients with MDR-TB
- → patients whose MDR regimen is failing or who are experiencing excessive toxicity who would benefit from a new regimen with new TB drugs.

Patients who have already started second-line MDR regimens⁴ without new drugs and are doing well will generally not be evaluated for initiation of new TB drugs.

Lab support

Second-line drug susceptibility testing (see text box on following page) will be important to the evaluation of MDR-TB patients enrolled in **endTB.** As such, access to a quality-assured/ quality-controlled (QA/QC) laboratory will be needed at all sites. In sites where there is no such access, samples will be sent to a supra-national reference laboratory.

Treatment guidelines

Output 1 will follow WHO TB treatment guidelines, as operationalized in the **endTB Guide for New TB Drugs**. This document describes indications for the new TB drugs, developed jointly by in-country and central experts. This guide will serve as a "how-to" manual to evaluate patients for new TB drugs specific to the site's individual MDR-TB program.

Conduct an observational study

Using data from routine treatment and follow-up of MDR-TB patients receiving one of the new anti-TB drugs, we will evaluate the safety and effectiveness of treatment with the new drugs. A standard protocol will guide the collection of data for evaluation.

Every patient who receives Bdq or Dlm at an **endTB** project site will be invited to participate in the observational study. Inclusion requires signing of an informed consent form for study participation. Any patient who declines to participate in the observational study will receive the same quality of care as study participants, but their data will not be included in the collection or analysis.

Initiate and monitor MDR-TB treatment with new drugs

Enrollment totals per site: The **endTB** goal is to enroll a minimum of 2,600 patients on MDR-TB treatment with new drugs. The country-specific targets (see map in Project Countries section) reflect that an estimated 30% of MDR-TB patients in each catchment area will meet

^{1 -} WHO conditions for the use of new TB drugs: 1) Proper patient inclusion; 2) Adherence to the principles of designing a WHO-recommended MDR-TB regimen; 3) Close monitoring of patients; 4) Active pharmacovigilance and proper management of adverse drug reactions; and 5) Patient consent.

^{2 -} Group 5 drugs are those on the list of drugs with limited data on efficacy and/or long-term safety in WHO guidelines for the programmatic management of MDR-TB.

^{3 -}Bedaquiline by the U.S. Food and Drug Administration (FDA) in 2012 and European Medicines Agency (EMA) in 2013; and Delamanid by EMA in 2013.

^{4 -} A second-line MDR regiment is one that is given when the initial MDR treatment regiment (also known as first-line therapy) doesn't work, or stops working.



the criteria for prescription of a new TB drug. Program capacity to enroll and closely monitor patients at each site was also considered.

Individual patient treatment decisions

Local physicians will prescribe the treatment regimen for each patient. Site physicians and staff will receive training on the *endTB Guide for New TB Drugs*. The Guide will be updated on a regular basis throughout the duration of the project.

Patient monitoring

Each enrolled patient will be monitored according to the schedule outlined in the *endTB Guide for New TB Drugs*. Monitoring will measure response to treatment (e.g. through sputum culture) and screen for potential adverse events. Although the new drugs were found to be relatively safe in the trials leading to their approval, these trials were small and rare events may have been missed. Routine screening is therefore critical to identifying such events.

Drug susceptibility testing

Drug susceptibility testing: Testing to determine which drugs are effective against the bacteria causing disease.

Clinical decisions will rely on drug susceptibility testing (DST) for drugs that have a reliable, pre-established testing method at laboratories with a proper QA/QC system.

Projects will be asked to freeze baseline cultures from all Output 1 participants. For patients with positive cultures after four months of treatment, sites will be asked to ship baseline and a late positive culture to the Institute of Tropical Medicine (ITM) in Antwerp. ITM is a supranational reference laboratory working to develop drug susceptibility testing for the new TB drugs, will be the primary reference lab for **endTB**.

Establish an endTB care management system/open-source electronic medical record and a pharmacovigilance system

Data management systems are an essential part of any MDR-TB program. Generally, they allow clinicians quick and secure access to a patient's complete health history without having to locate the patient's paper chart; reduces medical errors by restricting entry to only plausible value ranges; can alert clinicians to missing data and abnormal or dangerous signals; provide indications that the patient is not responding to therapy, and can be used to compile aggregate statistics and reports.

Existing data systems used by national TB programs to record and report information about MDR-TB treatment cohorts are often very basic and seldom facilitate monitoring and evaluation or data analysis. **endTB** will use its partners' extensive experience with electronic medical record (EMR) systems to improve clinical care and conduct operational research. (See next heading.)

Electronic Medical Records (EMR)

EMRs are generally used as an electronic data entry system for clinicians who are directly managing patients. **endTB** will maximize the capabilities of its EMR system so that it meets the needs of clinical, research, and reporting purposes. Once developed, this system will be available for free to all other TB treatment sites and countries outside of the **endTB** program. It will also allow national TB programs to continue the work after the **endTB** project ends.

The endTB EMR system will include:

- data capture
- secure storage of all study variables
- > collection and storage of additional valuable clinical information for MDR-TB treatment
- adverse event tracking (of key importance to pharmacovigilance component)
- a safety module that will facilitate reporting and interface with the dedicated pharmacovigilance database.



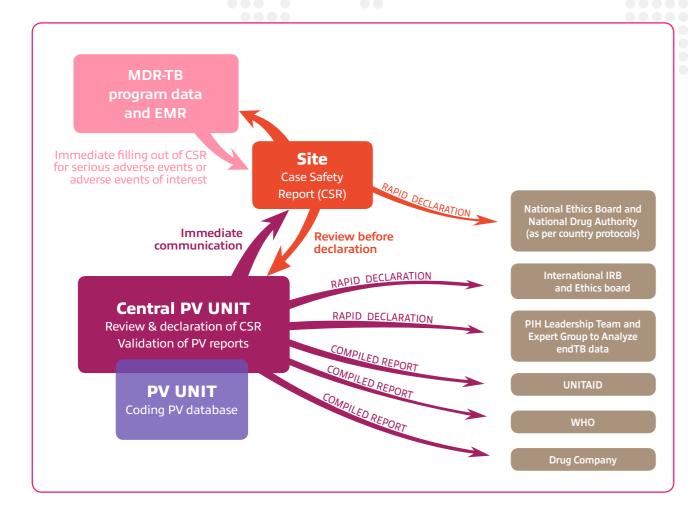
Pharmacovigilance (PV)

adverse drug reaction = any response to a drug which is noxious and unintended, including when a drug is not effective in its intended use

Pharmacovigilance is a proactive, medically-driven, safety risk management system that focuses on adverse drug reactions. A good pharmacovigilance system requires training and a real-time communication system with the central **endTB** PV unit (see diagram below). While this means that staff have an increased workload, we believe it is essential for a responsible and responsive TB treatment program.

Individual Case Safety Reports must be filed for serious adverse events (SAEs). The **endTB** project pharmacovigilance component is diagrammed in below.

endTB Pharmacovigilance Reporting of serious adverse events



Central PV Unit: A central **endTB** PV unit will serve both Outputs 1 and 2 for two primary functions:

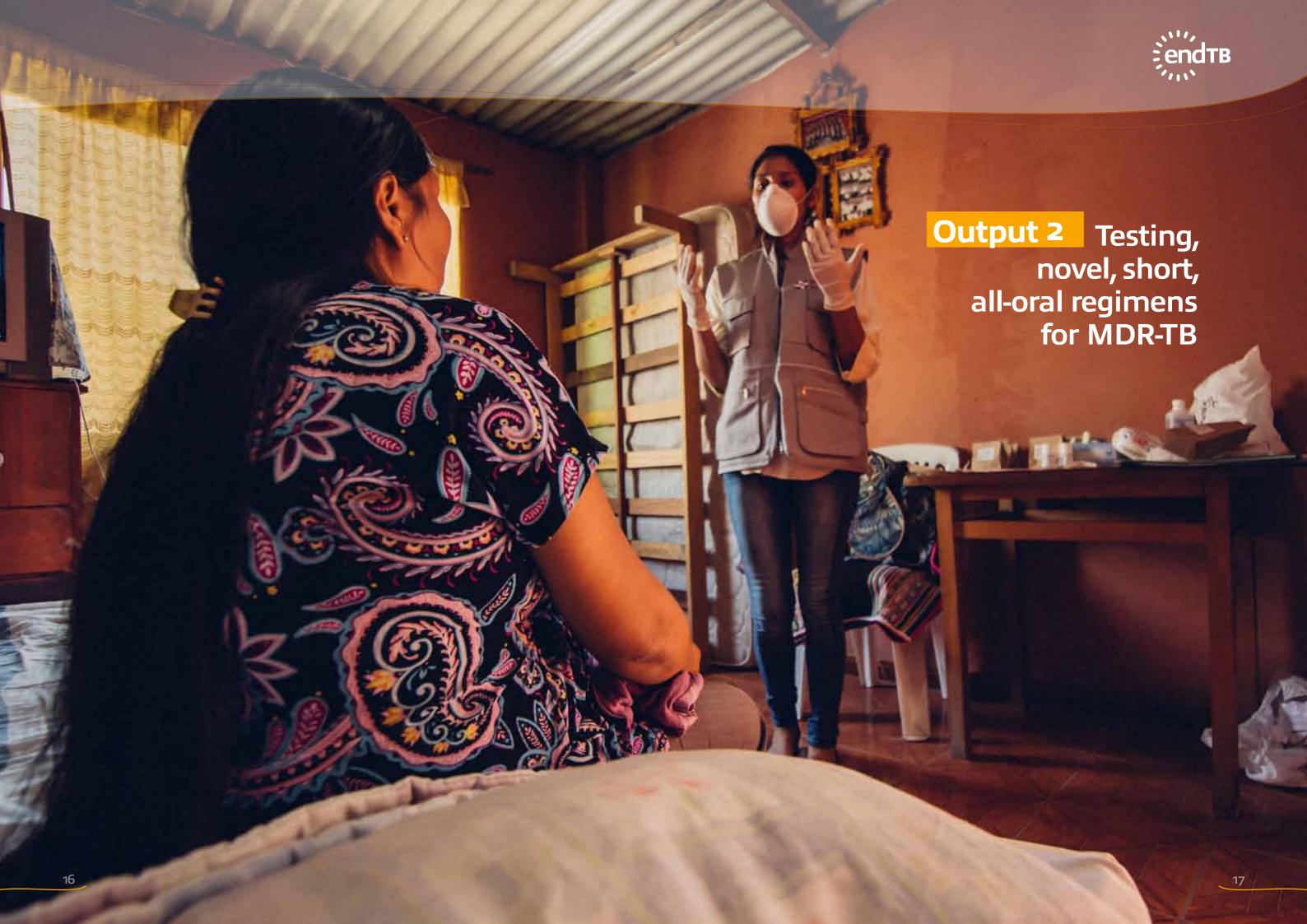
- → SAE reporting SAEs and suspected unexpected serious adverse reactions (SUSAR)⁵ will be reported to the relevant national authorities, in accord with national regulations concerning the timing and content of adverse event reporting. In addition, during Output 2, staff will also report any adverse events to the endTB central PV unit. This unit will ensure the quality and completeness of the information and contact the clinician for additional or clarifying information, when needed. This will facilitate standardized reporting of SAEs to all relevant authorities.
- → SAE database SAE reports will be entered in a central PV database⁶ for immediate analysis.

A set of **endTB** guides, tools and forms will be provided to all collaborators to help standardize project operations:

- endTB Guide for New TB Drugs
- endTB Pharmacovigilance guidelines
- Study participant consent forms
- Standard clinical chart that includes enrollment and follow-up pharmacovigilance forms

^{5 -} A suspected unexpected serious adverse reaction (SUSAR) is an adverse reaction that is both unexpected (not among the known adverse reactions caused by the drug or treatment regimen so far) and also meets the definition of a Serious Adverse Event (SAE). The term "adverse reaction" implies that a causal relationship between the event and the drug or treatment regimen is at least a reasonable possibility.

^{6 -} Database will utilize the Medical Dictionary for Regulatory Activities (MedDRA).





Testing, novel, short, all-oral regimens for MDR-TB

Study design

This is a randomized, controlled, trial of five new, all, oral, 9-month regimens compared to the current standard of care. Randomization will be outcome adapted, rather than fixed. This means that the probability of being randomized to regimens changes as the outcomes are reported: more patients will be assigned to regimens that are producing better outcomes.

Study treatment regimens

Each experimental regimen will contain at least one new drug, in combination with up to four companion drugs. The control regimen will be composed according to local interpretation of WHO guidance and may include a new drug if indicated.

Trial Regimens	Bedaquiline	Delamanid	Clofazimine	Linezolid	Fluoroquinolone	Pyrazinamide
endTB 1 BeLiMoZ	Be			Li	Мо	Z
endTB 2 BeCLiLeZ	Ве		С	Li	Le	Z
endTB 3 BeDeLiLeZ	Ве	De		Li	Le	Z
endTB 4 DeCLiLeZ		De	С	Li	Le	Z
endTB 5 DeCMoZ		De	С		Мо	Z
endTB 6 Control	Standard of care control, composed according to WHO Guidelines, including the possible use of De or Be					

Study oversight

Several independent groups will provide formal external oversight of the study protocol implementation, operation and analysis:

- → Institutional Review Boards or Ethics Committees at Harvard Medical School, MSF, ITM and in each country participating in Output 2
- → Independent Scientific Advisory Committee (SAC)
- Global Community Advisory Board, convened by the Treatment Action Group
 - → Data Safety and Monitoring Board (DSMB)

These groups will continue to assure the relevance of the trial for clinical care and policy, its safety for participants, and that global standards for clinical research are met or exceeded.







Breaking down local barriers to accessing new drugs

Facilitate importation of new and re-purposed drugs in **endTB** countries

In most of the countries where **endTB** projects will be implemented, quality-assured Lzd, Cfz, Imp, Bdq and Dlm are neither marketed nor registered. **endTB** seeks to change this.

In the short term, **endTB** will seek importation waivers (exceptions) to allow these drugs to reach patients. This strategy has been used for other second-line TB drugs that have not been registered in country; the process for seeking importation waivers is different in each country and depends on local laws.

In the long term, endTB partners will negotiate three main issues with manufacturers:

- → Country-level, TB-specific registration of these products
- → Affordable pricing to match MDR-TB-affected countries' resources
- Volume of each drug to be manufactured.

Progress in these areas will alleviate importation constraints for **endTB** organizations and secure a sustainable supply beyond the project. These negotiations are part of a long-term strategy that can be assisted by **endTB** and other partners and stakeholders, such as the WHO.

Update national TB guidelines in all endTB countries to include new TB drugs

Most country TB treatment guidelines don't currently include new TB drugs, since some WHO recommendations were only recently released (November, 2014). As such, clinicians at **endTB** sites will use the **endTB** Guide on New TB Drugs for guidance during the initial phase of the project (Output 1). **endTB** country staff will meet regularly with the national TB program in each operating country. These meetings will allow them to provide technical assistance for updating the national guidelines based on the evidence generated from the **endTB** cohort, as well as continuing WHO updates.

Improve transparency and accountability of national and nongovernmental TB programs aimed at accessing new TB drugs

endTB staff will formalize and present ongoing data on the progress countries are making in increasing access to more effective TB drugs and regimens through continually updated Web-based progress reports.

endTB will produce its own TB-related progress report starting 2017. This dashboard report will cover at least six endTB country data, including:

- drug registration
- inclusion of new TB drugs in national guidelines
- assessment of the use of, and access to, new technologies for diagnostics
- national and donor funding support to implement new testing and treatment strategies.

The dashboard will be available on the endTB and MSF-AC websites.

The information provided on this dashboard will guide MSF-AC's ongoing work to improve transparency and accountability in the global rollout of new TB-drug use. This will provide MSF-AC and other advocacy organizations invaluable information about the pace of the rollout of new TB drugs in each country so they can adapt their strategy accordingly.

Work toward sustainable financing for transitioning to new TB drugs and regimens in endTB countries

Each endTB site implementation plan will include:

- Assistance to national TB programs to include new TB drug financing in existing MDR-TB program budgets (including existing national budgets, Global Fund budgets, etc.)
- Assistance in measuring funding gaps for MDR-TB programs
- > Estimation of future new TB drug consumption to national TB programs
- A smooth transition to new TB drugs and regimens (including monitoring & evaluation and reporting) once the targeted number of endTB patients from Output 1 is reached.





Support development of WHO guidelines for Programmatic Management of Drug-resistant Tuberculosis (PMDT)

Disseminate endTB clinical and programmatic findings globally

The **endTB** team will regularly review the results from Output 1 and 2 and present this data, as needed, to stakeholders such as the WHO, that would like to use it to develop TB treatment guidelines. For this purpose, the **endTB** website will share updates on **endTB** activities and provide access to **endTB** guidance on use of new TB drugs. In addition, tools for staff training, pharmacovigilance, using the EMR, and the **endTB** Guide to Use of New TB Drugs manual will all be available for download.

Collaborate with other groups promoting use of new TB drugs and novel regimens

endTB will collaborate with other stakeholders to create a Network of Early Implementers of New TB Drugs under the Global Drug-resistant TB Initiative (GDI), hosted by WHO. Key stakeholders promoting uptake of new TB drugs include:

- → WHO Task Force for New Drug Policy Development
- Global Drug-resistant TB Initiative (GDI)
- → Bill & Melinda Gates Foundation
- → USAID (and USAID sponsored NGO's such as KNCV, URC and others)
- Organizations doing research with new TB drugs (TB Alliance, Critical Path to TB Drug Regimens [CPTR])
- → Clinton Health Access Initiative (CHAI).

The network will also be open to any national TB program or other stakeholder in any country that is treating TB with new drugs.

Disseminate market intelligence information⁷ for new TB drugs and key companion TB drugs

MSF-AC will write and disseminate publications that report on DR-TB drug prices and other key barriers to scaling use of DR-TB drugs, focusing on the new TB drugs and highlighting

7- Market intelligence is the information companies gather and analyze to make production decisions.

lessons learned from endTB sites⁸. MSF-AC will disseminate information related to patent barriers on new TB drugs through an existing online patent opposition database. As part of its core work outside of this proposal, MSF-AC will engage in patent oppositions to remove secondary patents⁹, negotiate with manufacturers, and potentially work with key affected countries to leverage flexible aspects of Trade-Related Aspects of Intellectual Property Rights (TRIPS).

endTB organization

The endTB leadership team is responsible for overseeing Outputs 1, 3 and 4.

Clinical trial (Output 2) activities across PIH and MSF will be linked via the endTB coordinating Principal Investigators, Drs. Carole Mitnick (HMS) and Francis Varaine (MSF). The clinical trial is sponsored by MSF.

The full endTB team includes staff at PIH, MSF and IRD, as well as clinicians, researchers, epidemiologists, pharmacists and other experts drawn from leading institutions.

Project Leaders

Dr. Aamir Khan (Interactive Research & Development)

Dr. Michael Rich (Partners In Health)

Dr. KJ Seung (Partners in Health)

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Dr. Alex Telnov (Médecins sans Frontières)

^{8 -} For example, MD-TB Drugs Under The Microscope: http://www.msfaccess.org/content/dr-tb-drugs-under-microscope3rd-edition.

^{9 - &}quot;Secondary" patents are patents used for new developments or improvements of an initial, basic patent. They are used to extend the term of protection around the product of interest. When secondary patents are active, TB drugs can't be produced by other companies at cheaper prices.



Annex I: abbreviations

AE Adverse Event
Bdq Bedaquiline
Cfz Clofazimine
Cln Cilastatin
Dlm Delamanid

DPRK Democratic People's Republic of Korea

DR-TB Drug-resistant TuberculosisDST Drug Susceptibility TestingECG Electrocardiogram

EBF Eugene Bell Foundation

EMR Electronic Medical Record

endTB Expand New Drug Markets for TB

FQ Fluoroquinolone

Imp Imipenem

IRB Institutional Review Board

IRD Interactive Research and Development

KNCV Koninklijke Nederlandse Chemische Vereniging

Lfx Levofloxacin
Lzd Linezolid

MDR-TB Multidrug-resistant Tuberculosis

MedDRA Medical Dictionary for Regulatory Activities

Mfx Moxifloxacin

MOH Ministry of Health

MSF Médecins Sans Frontières

MSF-AC Médecins Sans Frontières Access Campaign

NATA Nepal Anti-Tuberculosis Association

NIH National Institutes for Health
NTP National Tuberculosis Program

OCA Operational Centre Amsterdam/MSF Holland
OCG Operational Center Geneva/MSF Switzerland

OCP Operational Center Paris/MSF France

PIH Partners In Health
PV Pharmacovigilance

SAC Scientific Advisory Committee

SAE Serious Adverse Event

SRA Stringent Regulatory Authority
URC University Research Co., LLC

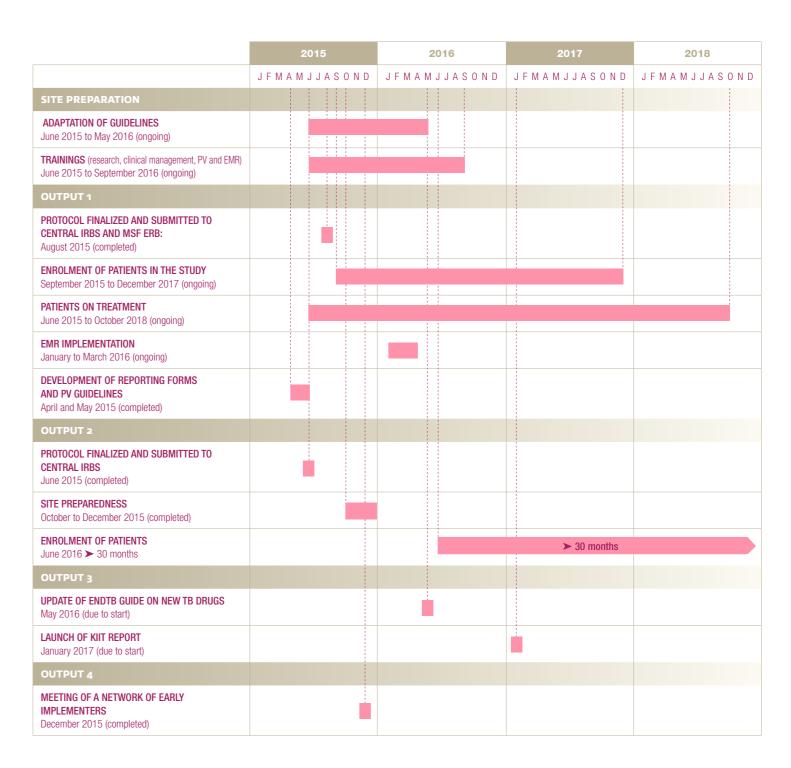
USAID United States Agency for International Development

WHO World Health Organization

XDR-TB Extensively Drug-resistant Tuberculosis

Z Pyrazinamide

Annex II: endTB Project Timeline



Crédits photos

P. 8-9: Dickens, who has HIV and MDR-TB, sorts his daily dose of tablets. MDR-TB clinic, Homa Bay district hospital, Kenya. (Photo by: Jane Linekar / Médecins Sans Frontières)

P. 16-17: Mrs. Flor*, an XDR-TB patient, receives medication from Gaby Merlin Contreras, a PIH field technician, at Flor's home in the Ate District of Lima, Peru.
*Name has been changed. (Photo by: William Castro Rodríguez / Partners In Health)

P. 20-21: Daily dose of pills for Hekim, 40, a XDR-TB patient from Myanmar. (Photo by: Sami Silva / Médecins Sans Frontières)

P. 24-25: A female MDR-TB patient waiting at the TB area entrance at MSF's Myitkyina clinic, Myitkyina, Kachin State, Myanmar. (Photo by: Aye Pyae Sone / Médecins Sans Frontières)











