



**Bedaquiline- and delamanid-
containing regimens
achieve excellent interim
treatment response without
safety concerns**

endTB interim analysis

July 2018



Acknowledgements

This interim analysis of the endTB (Expand New Drugs for TB) Observational Study was produced in a collaborative effort by the endTB team, including Sidney Atwood¹, Nana Avagyan², Mathieu Bastard³, Meredith Cain⁴, Sandra Collin², Sylvine Coutisson², Clare Flanagan⁴, Molly Franke⁵, Catherine Hewison², Helena Huerga³, Aamir Khan⁶, Palwasha Khan⁶, Uzma Khan⁶, Naira Khachatryan², Tinatin Kotrikadze², Nathalie Lachenal², Sarah McAnaw⁴, Nara Melikyan³, Carole Mitnick⁵, Nataliya Morozova⁴, Ye Yint Naing², Elna Osso⁵, Michael Rich^{1,4,5}, Nazgul Samieva², K.J. Seung^{1,4,5,7}, Megan Striplin⁴, Yoseph Tassew², Francis Varaine², Stephen Wanjala², and Askar Yedilbayev⁴.

- | | |
|--------------------------------|-------------------------------|
| 1 Brigham and Women's Hospital | 5 Harvard Medical School |
| 2 Médecins Sans Frontières | 6 Interactive Research Design |
| 3 Epicentre | 7 Eugene Bell Foundation |
| 4 Partners In Health | |

We want to thank the National TB program and the local endTB grant team members in the following countries:

- | | | |
|---|--------------|----------------|
| • Armenia | • Georgia | • Lesotho |
| • Bangladesh | • Haiti | • Myanmar |
| • Belarus | • Indonesia | • Pakistan |
| • Democratic People's Republic of Korea | • Kazakhstan | • Peru |
| • Ethiopia | • Kenya | • Viet Nam |
| | • Kyrgyzstan | • South Africa |

The endTB Project is funded by Unitaid.

This guide can be found in electronic format at <https://www.endtb.org/resources>.

Citation: Bedaquiline- and delamanid-containing regimens achieve excellent interim treatment response without safety concerns: endTB interim analysis. endTB. Boston, USA. 2018.

Table of Contents

● Executive Summary	6
● Introduction	8
● Methods	10
endTB Observational Study	10
Data quality / cleaning	11
Dependent and independent variable definitions	11
Inclusions and exclusions for the three analyses	12
Analysis	14
<i>Safety Analysis</i>	14
<i>Delamanid Analysis</i>	14
<i>Injectable Analysis</i>	15
● Results	16
Results of Safety Analysis	16
Results of Delamanid Analysis	19
Results of Injectable Analysis	22
● Discussion	26
Safety Analysis	26
Delamanid Analysis	27
Injectable Analysis	28
● Conclusion	29

Figure 1.	endTB countries and enrollment periods	10
Figure 2.	Inclusions and exclusions in the endTB interim analyses	13
Table 1.	Adverse events of clinical relevance	12
Table 2.	Characteristics of 1,244 RR-TB patients initiating bedaquiline or delamanid, 1 April 2015 – 30 June 2017	16
Table 3.	General incidence of clinically relevant AE	18
Table 4.	Relative incidence of clinically relevant AE	18
Table 5.	Characteristics of patients initiating a delamanid-containing regimen with a positive baseline sputum culture	19
Table 6.	Culture conversion within six months among patients receiving delamanid, overall and in subgroups	21
Table 7.	Relative odds of conversion within six months with a baseline regimen containing delamanid relative to one containing bedaquiline	21
Table 8.	Characteristics of patients initiating a bedaquiline- or delamanid-containing regimen with a baseline positive culture and susceptibility testing to SLIs	22
Table 9.	Percentage of patients who had culture converted by six months stratified by resistance to SLIs at baseline	24
Table 10.	Association of being on an SLI at time of initiation of bedaquiline or delamanid with culture conversion at six months stratified by baseline drug-susceptibility to SLI	25
Table 11.	Culture conversion in endTB and other cohorts	27

Executive Summary

Each year, there are an estimated 600,000 new cases of rifampicin-resistant (RR) or multidrug resistant tuberculosis (MDR-TB) patients. Globally, the cure rate for MDR-TB is only 54%. Bedaquiline and delamanid were approved for use in MDR-TB patients in 2012 and 2013 respectively, the first two new drugs for TB developed in 50 years. Despite the dire need for improved treatment for MDR-TB, there has been surprisingly little uptake of delamanid and bedaquiline globally. endTB was established to address barriers to access of these two drugs, such as lack of country registration, high price, and lack of clinician and National TB Programme experience. It is funded by Unitaid and implemented by a consortium of non-governmental organizations—Partners In Health (PIH), Médecins Sans Frontières (MSF), and Interactive Research and Development (IRD)—in partnership with National TB Programmes around the world.

One of the main activities of endTB is a multi-centre observational study of the effectiveness and safety of delamanid and bedaquiline. The endTB observational study follows patients who receive treatment regimens containing bedaquiline or delamanid in 17 countries on four continents. This is the largest closely followed cohort of patients receiving bedaquiline or delamanid in the world. This study started in April 2015 and continues to enroll patients currently.

This interim analysis presents the results of three different analyses:

- Safety Analysis** | What types of adverse events are observed in patients receiving multidrug regimens including bedaquiline or delamanid?
- Delamanid Analysis** | What is the evidence for or against the use of delamanid in multidrug regimens for RR/MDR-TB?
- Injectable Analysis** | What is the evidence for or against the use of injectable-sparing regimens for RR/MDR-TB when bedaquiline or delamanid are available?

The entire primary research cohort (consisting of 1,244 RR-TB patients initiating bedaquiline or delamanid between 1 April 2015 and 30 June 2017) was included for the **Safety Analysis**. While QT interval prolongation is a concern with the new drugs, in the endTB observational study, clinically relevant QT interval prolongation was found to be much less frequent than clinically relevant AEs associated with conventional second-line TB drugs. Only 2.7% of patients experienced a QTcF > 500 ms, while AEs associated with injectables or linezolid were much more common. 35.6% of patients who received an injectable were estimated to experience at least one injectable-related toxicity (hearing loss, acute renal failure, or hypokalaemia/hypomagnesemia). 19.9% of patients receiving an injectable experienced new or worsening hearing loss. 11.0% of patients receiving linezolid experienced at least one toxicity commonly attributed to linezolid (peripheral neuropathy, optic neuritis or myelosuppression).

Executive Summary

A total of 658 patients were included in the **Delamanid Analysis**. In general, patients receiving delamanid had a high rate of comorbidities, including HIV (18%), diabetes (18%) and hepatitis C (21%). A majority had bilateral disease and cavitory disease apparent on their baseline chest X-ray and one-third had XDR-TB. Overall, 79% (95% CI: 73%-85%) experienced culture conversion within six months. Conversion probabilities were similar for HIV-negative patients, those with XDR-TB, those with XDR-TB or pre-XDR-TB with fluoroquinolone resistance and those receiving five likely effective drugs, but were notably lower for the 32 patients living with HIV (63%; 95% CI: 31%-82%).

The **Injectable Analysis** included 633 patients, of which 353 were on a second-line injectable (SLI) at initiation of bedaquiline or delamanid. Patients with strains susceptible to injectables had higher odds of culture conversion at six months when receiving an injectable compared to those who did not receive an injectable, although this finding was not statistically significant. In contrast, there was no added benefit of an injectable in patients with injectable-resistant strains.

Overall, there is no evidence of any major safety issue with either delamanid or bedaquiline. QT interval prolongation is known to be associated with both drugs, but in the endTB cohort, clinically relevant prolongation was not very common. All deaths and other serious AEs were reviewed by the MSF PV unit—no unexpected safety signals have been found to date. While clearly there is a role for ECG screening in MDR-TB treatment, more resources and energy should be allocated to screening for more common and potentially more deadly AEs that are associated with other drugs.

The endTB data is consistent with previous studies showing that delamanid is an effective drug in the treatment of MDR-TB. Culture conversion within six months in patients who receive delamanid-containing regimens appears to be quite good in this cohort of highly chronic and very resistant MDR-TB patients. Delamanid also has very few safety or tolerability issues; it should be strongly considered as an effective and safe drug when constructing an MDR-TB regimen.

When deciding to replace the injectable in individual patients, clinicians and patients need to weigh the benefits and the risks. The endTB interim results suggest a benefit of improved six-month culture conversion in patients with non-injectable-resistant strains. The endTB data also clearly shows that toxicities related to injectables and linezolid are more common than toxicities related to either of the new TB drugs, bedaquiline or delamanid.

Overall, the efficacy and safety data presented in this report supports elevation of bedaquiline and delamanid in the hierarchy of MDR-TB drugs. The effectiveness of delamanid in treatment of MDR-TB is supported by a high rate of culture conversion within six months. Both delamanid and bedaquiline appear to be safer than commonly used drugs such as injectables or linezolid. These findings suggest that both bedaquiline and delamanid are likely to play an expanded role in achieving improved treatment response in MDR-TB.

Introduction

Each year, there are an estimated 600,000 new cases of rifampicin-resistant (RR) or multidrug resistant tuberculosis (MDR-TB) patients. Globally, the cure rate for MDR-TB is only 54%. In 2016, there were about 240,000 deaths from MDR-TB.¹ MDR-TB is not only a deadly disease but also highly infectious, with delayed diagnosis, long treatment regimens with uncomfortable and sometimes permanent side effects, and unfavourable treatment outcomes all contributing to high rates of transmission. The lack of access to effective treatment is a major driving force behind the growth of MDR-TB globally.

Hope emerged when two new drugs, bedaquiline and delamanid, were approved for use in MDR-TB patients in 2012 and 2013 respectively. But despite the dire need for improved treatment for MDR-TB, there has been surprisingly little uptake of delamanid and bedaquiline globally. endTB was established to address access barriers such as lack of country registration, high price, and lack of clinician and National TB Programme experience.² It is funded by Unitaid and implemented by a consortium of non-governmental organizations—Partners In Health (PIH), Médecins Sans Frontières (MSF), and Interactive Research and Development (IRD)—in partnership with National TB Programmes in 17 countries around the world.

One of the main activities of endTB is a multi-centre observational study that informs questions about effectiveness and safety of delamanid and bedaquiline, using a common protocol, data collection and analysis. There are many important questions about the use of bedaquiline and delamanid within multidrug regimens that also contain the repurposed drugs, linezolid and clofazimine. This report aims to address three of them:

Safety Analysis

What types of Adverse Events (AEs) are observed in patients receiving multidrug regimens including bedaquiline or delamanid?

There continues to be anxiety about the potential AEs of both bedaquiline and delamanid, particularly cardiotoxicity, at country level. Phase II trials of both drugs revealed a risk of prolonged QT interval.^{3,4} Excess death in the bedaquiline arm in post-treatment follow-up in the Phase II trial resulted in a black-box warning on the package insert. Phase III results for bedaquiline are still pending (Clinical Trials NCT02409290), but bedaquiline has been used widely in select populations without additional safety concerns, which has reduced concern about the excess mortality observed in the Phase II trial.

The Phase III trial of delamanid has been completed but is unpublished. The safety profile is very encouraging; risk of QT interval prolongation appears less pronounced than with other anti-TB drugs and initial concerns about albumin abnormalities have been tempered. Nevertheless, systematic follow-up and reporting of toxicity is rare outside the trial setting so uncertainty still exists regarding both drugs.

The endTB observational study is the largest closely followed cohort of patients receiving bedaquiline or delamanid in the world. Data on AEs are captured in a uniform manner, providing an excellent opportunity to determine the frequency of AEs in patients being treated outside of a clinical trial.

¹ World Health Organization. Global Tuberculosis Report 2016. (World Health Organization, 2017).

² Cox V, Brigden G, Crespo RH, et al. Global programmatic use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2018; 22(4): 407-412.

³ Pym AS, Diacon AH, Tang S-J, Conradie F, Danilovits M, Chuchottaworn C, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. *Eur Respir J* 2016; 47(2): 564-74.

⁴ Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, Kummik T, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. *Eur Respir J* 2013; 41(6): 1393-1400.

Introduction

Delamanid Analysis

What is the evidence for or against the use of delamanid in multidrug regimens for RR/MDR-TB?

In the Phase II trial, delamanid was found to be active both at two months and later, and subsequently received stringent regulatory authority approval.⁵ The Phase III trial reported 87.6% success at six months among patients who received delamanid. Although statistically significant differences were observed in secondary analyses of sputum-culture conversion, superiority of delamanid was not formally established on the primary endpoint of time to culture conversion. Phase II and III studies stopped delivery of bedaquiline and delamanid prior to the end of treatment, possibly reducing the benefits that may be afforded by their use. The inconclusiveness of the Phase III delamanid efficacy results, coupled with very encouraging safety results, leaves uncertainty about the role of delamanid in multidrug regimens for MDR-TB.

Globally, the uptake of delamanid has been extremely slow, even in comparison with bedaquiline. The endTB observational study has the largest cohort of delamanid patients outside of a clinical trial to date, meaning that it is uniquely positioned to answer the question of whether delamanid is an effective drug in the treatment of MDR-TB. While final outcomes for most endTB patients are not available, this analysis presents interim outcomes for patients receiving delamanid-containing regimens in the endTB observational study.

Injectable Analysis

What is the evidence for or against the use of injectable-sparing regimens for RR/MDR-TB when bedaquiline or delamanid are available?

Injectable toxicity is extremely common and can result in permanent disability (e.g. hearing loss) or death. This has led to the increasing practice of replacing the injectable, often with bedaquiline or delamanid, with or without additional drugs. Currently, injectables are recommended by the WHO for all MDR-TB regimens, so choosing to replace the injectable in MDR-TB treatment is a crucial decision that affects all MDR-TB patients. Even though this practice is increasing globally among clinicians and programmes, there is very little data about how to do this in patients receiving conventional (20-month) or shorter (9-month) MDR-TB regimens. Can the injectable simply be replaced by a single drug, or are multiple drugs required to replace the injectable? And if replacement is possible, which drug or combination of drugs is the best choice for a replacement?

Within the endTB cohort, there are a wide variety of reasons why a specific patient might not receive an injectable. Patients might be found to have TB strains that are resistant to one of the injectables and then be started on a bedaquiline or delamanid in order to strengthen the regimen. Patients might also experience toxicity related to the injectable and be switched to bedaquiline or delamanid as a replacement. These clinical decisions were not standardised, but individualized to each patient. In this analysis we compared culture conversion within six months between patients who did and did not receive an injectable.

⁵ Gler M, Skrzponoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med* 2012; 366(23): 2151-6.

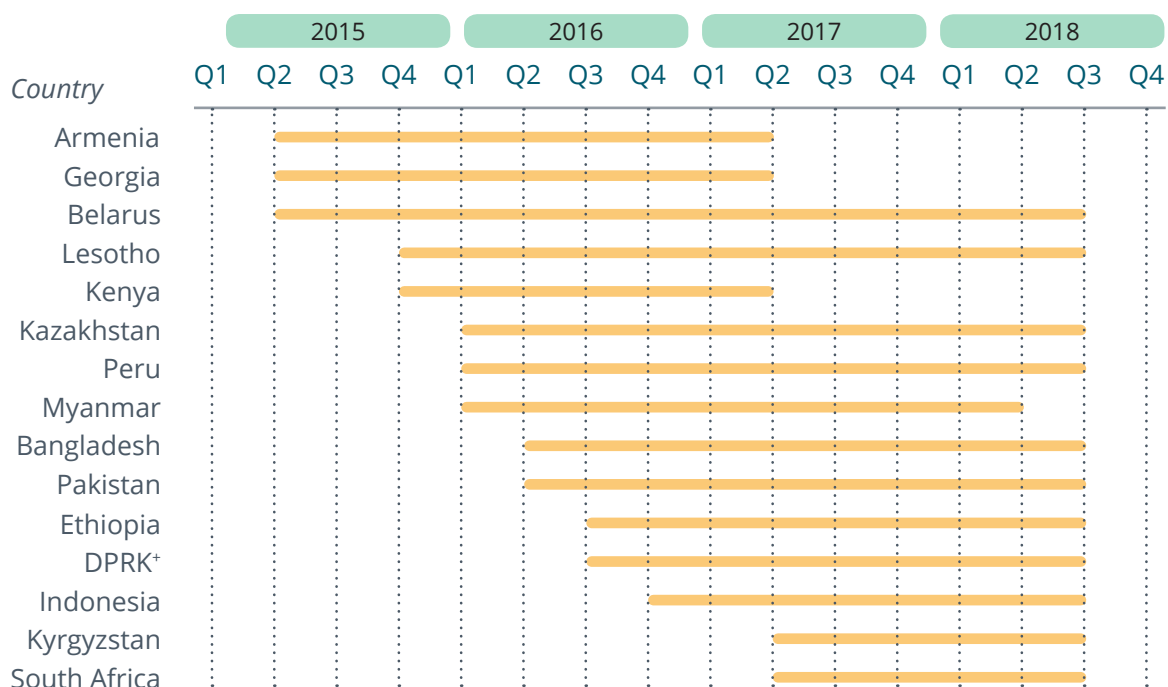
Methods

endTB Observational Study

This is an observational study of patients who received treatment regimens containing bedaquiline or delamanid through the Unitaid-funded endTB project. Patients were treated according to national and WHO guidelines under routine programmatic conditions in 17 countries on four continents (Haiti and Vietnam started after the inclusion cut-off for this interim analysis). A standard study protocol that guided data collection, but not the treatment, was approved by ethics/institutional review boards (E/IRBs) that supervise research conducted by the three consortium partners, as well as by E/IRBs in each endTB country.

Patients are eligible for inclusion in the endTB observational cohort if they receive bedaquiline or delamanid at one of the endTB sites during the life of the endTB project in that site (Figure 1). Patients consented to allow their clinical data to be included in the analysis of the observational study. For a small subset of patients who had started and stopped treatment before the research component of the project was locally approved, consent was waived by E/IRBs and data were captured for the study retrospectively. The endTB observational study is registered at www.clinicaltrials.gov (Clinical Trial NCT02754765).

Figure 1.
endTB countries
and enrollment
periods



⁺Democratic People's Republic of Korea; North Korea

All data are collected in real-time using standard data collection forms with completion guidelines, and then entered into the endTB EMR (Bahmni v.2.2.0, built on the platform of OpenMRS v.2.0.4). The EMR provides patient-level follow-up tools, programmatic monitoring tools as well as anonymized exports. Exports are sent from each country to the central level for data cleaning/quality and merging for analysis.

Comprehensive data collection includes baseline patient characteristics (age, sex, marital status), comorbidities (HIV, Hepatitis B and C, non-infectious diseases such as renal, liver and cardiac disease), history of TB treatment, and indication for bedaquiline or delamanid

treatment. Longitudinal data collected throughout study participation include: treatment adherence, and results of biochemistry, microbiology, clinical examination, ECG and audiometry screening.

Data on AEs are routinely captured for analysis. A set of nine AEs of special interest are recorded irrespective of severity (Table 1). Other clinically important AEs are defined as those that lead to the permanent discontinuation of a TB drug or anything else of clinical interest, as determined by treating physicians. All recorded AEs are graded by the reporting physician according to the MSF Severity Scale (<http://endtb.org/resources/pharmacovigilance>), which has been specifically designed to evaluate AEs reported within MDR-TB projects. It is mainly based on the standardised and commonly used toxicity table for infectious diseases, the Division of Microbiology and Infectious Diseases (DMID) grading system, complemented with a selection of terms from the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) scale. Serious AEs are also reported within 24-hours to the MSF Pharmacovigilance (PV) unit in Geneva and are stored in a separate database. Data from the PV database are reconciled with each country EMR on a regular basis. For the purpose of this report, any AE recorded in the endTB EMR or in the PV unit database that met the definition of "clinically relevant" was included in the Safety Analysis.

— Data quality/cleaning

Data quality and data cleaning are performed both at country level and central level. Export of datasets are sent every month by the sites and consortium partners to the central data manager in Boston and data quality checks are run. A data quality report with listing of specific queries are sent to each project site for clarifications. When needed, corrections are documented and made in the EMR.

— Dependent and independent variable definitions

Baseline refers to the first date of bedaquiline or delamanid administration during the endTB project.

Culture and smear result at baseline is defined as the culture (smear) result from a sputum sample collected within 90 days preceding (and closest to) the initiation of bedaquiline or delamanid. If no culture (smear) is available in the 90 days prior to initiation, results up to 15 days after initiation of bedaquiline or delamanid are considered.

Culture conversion within six months was determined for patients with a positive baseline sputum culture and defined as two consecutively negative cultures collected at least 15 days apart. Because baseline culture status was determined up to 15 days following the delamanid or bedaquiline start date, conversion could occur as early as day 16 of treatment. Patients were followed for up to 210 days after bedaquiline or delamanid initiation for the second consecutive negative culture result. Patients who had no follow-up cultures or who died or were lost to follow-up before conversion during the first 180 days of treatment were considered not to have converted.

Date of culture conversion was defined within 180 days of bedaquiline or delamanid initiation as the date of the first of the two consecutive negative cultures.

Resistance profile at baseline was assessed according to local standards and generally included testing for resistance to at least isoniazid, rifampicin, injectables, and fluoroquinolones. Resistance at initiation of bedaquiline or delamanid is defined as any documented resistance from sputum samples collected any time before initiation of bedaquiline or delamanid and up to 15 days after treatment start. Resistance tests included: phenotypic drug-susceptibility testing, Hain line probe assay (MTBDRplus and MTBDRsl) and

Xpert. Resistance on any one of these tests is sufficient to classify a strain as resistant to the drug tested; susceptibility could only be established if all tests reported susceptible results. Patient resistance patterns were classified in the following mutually exclusive, exhaustive groups: RR/MDR-TB without injectable or fluoroquinolone resistance, RR/MDR-TB with injectable resistance, RR/MDR-TB with fluoroquinolone resistance and RR/MDR-TB with injectable and fluoroquinolone resistance (XDR-TB), or missing.

Likely effective drug: A drug was considered likely effective if (1) all reported testing to that drug confirmed susceptibility, or (2) no resistance to the drug was reported and the patient had not previously received the drug for one month or more. Otherwise the drug was not considered likely effective.

AEs of clinical relevance: For all AEs included in this analysis, a severity grade for determining clinical relevance was identified. For most AEs, the clinically relevant grade is the grade at which the MSF Severity Scale recommends a TB drug treatment change; if the reported grade meets or exceeds the threshold for a treatment change, the event was considered to be clinically relevant. For hypothyroidism and hypokalaemia/hypomagnesaemia, the clinically relevant grade was the grade that requires supplementation.

Table 1.
Adverse events
of clinical
relevance

AE term	Threshold grade for clinically relevant AEs and definitions [†]	
	Grade(s)	Comment
QT prolongation	3 or 4	QTcF \geq 501 msec, no symptoms.
Peripheral neuropathy	2, 3 or 4	Moderate discomfort; BPNS sensory score 4-6 or worse.
Optic neuritis	1, 2, 3 or 4	Any clinical diagnosis, irrespective of visual acuity.
Myelosuppression*	Anaemia: 3, 4	Hemoglobin \leq 7.9 g/dL.
	Platelets Decreased: 3, 4	Platelet count < 50,000/mm ³ .
	White Blood Cell Decreased: 3, 4	White blood cell count < 2000/mm ³ .
	Lymphocyte Count Decreased: 3, 4	Lymphocyte count < 500/mm ³ .
	Absolute Neutrophil Count Low: 2, 3, 4	Absolute neutrophil count < 750/mm ³ .
Hearing loss	1, 2, 3 or 4	Threshold shift of \geq 15-25 dB at 2 or more contiguous test frequencies.
Acute renal failure	2, 3 or 4	Serum creatinine \geq 2-3 times above baseline
Hypokalemia / Hypomagnesaemia	1,2, 3 or 4	Serum K < 3.4 mmol/L or serum Mg: < 1.4 mmol/L.
Hepatotoxicity	3 or 4	ALT or AST > 5 times upper limit of normal.
Hypothyroidism	2, 3 or 4	Symptomatic; thyroid replacement indicated.

[†]MSF Severity scale and all PV documents available at: <http://www.endtb.org/resources/pharmacovigilance>

*Also included pancytopenia, defined as any combination of the specific measures of myelosuppression.

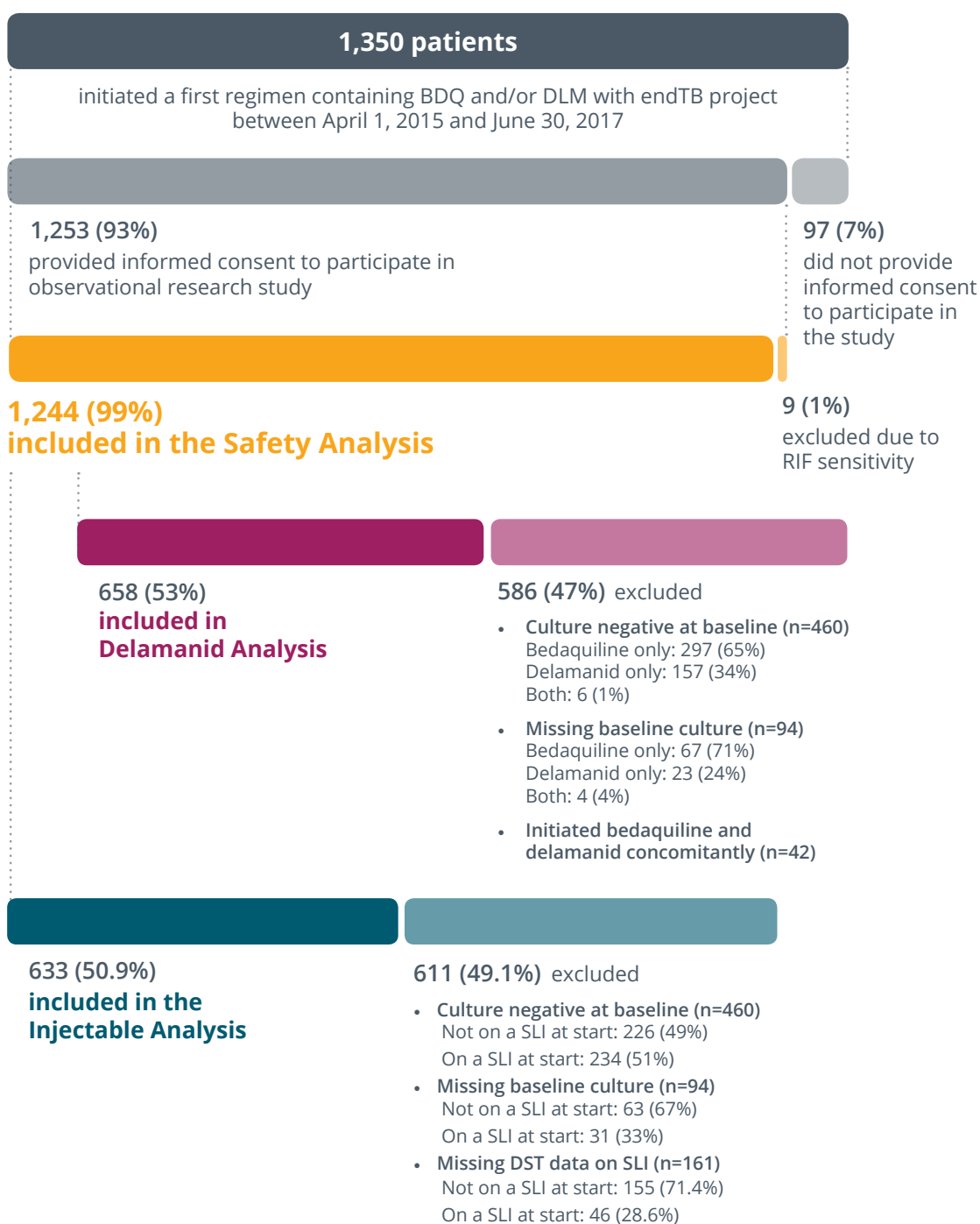
— Inclusions and exclusions for the three analyses

The primary research cohort comprised 1,244 TB patients who consented to participate in the endTB observational study and initiated bedaquiline or delamanid, or both, within a multidrug regimen between 1 April 2015 and 30 June 2017. Patients with rifampicin-susceptible strains (n=9) were excluded. Only the first treatment registration was considered for patients who had

more than one treatment registration in the endTB project during the study period. During the study period, eight patients initiated a second regimen with endTB containing bedaquiline or delamanid; these second regimens were excluded from analyses.

The entire primary research cohort was included for the Safety Analysis. For the Delamanid Analysis, we excluded from the primary research cohort 586 (47%) patients who did not have a positive baseline culture and those who initiated a baseline regimen containing both bedaquiline and delamanid. For the Injectable Analysis, we excluded from the primary research cohort 611 (49.1%) patients who did not have a positive baseline culture or were missing data on baseline drug-susceptibility to injectables. More details about exclusions are shown in Figure 2.

Figure 2.
Inclusions and exclusions in the endTB interim analyses



— Analyses

Analyses were performed using Stata 15.1 software (Stata Corporation, College Station, Texas, USA) and SAS v. 9.4 software (Cary, North Carolina, USA).

Safety Analysis

For each of the identified AEs at a specified severity grade, we calculated the frequency of patients with at least one occurrence of the event, the median [interquartile range, IQR] time to the first occurrence of the AE in months and the incidence of the AE /100 person-months of treatment and its 95% confidence interval. In the case of a single type of AE occurring more than once in a single patient, only the first clinically relevant event was counted. However, a single patient could experience multiple different AEs and the first instance of each clinically relevant event was counted, regardless of when it occurred. However, a single patient could experience multiple different AEs and the first instance of each clinically relevant event was counted, regardless of when it occurred.

To calculate the general incidence of AEs, the period of exposure was the days with any TB drug exposure starting from the first day of new drug prescription (delamanid, bedaquiline or both) until the event or until treatment outcome or censoring date for those who did not experience an event. To calculate the relative incidence of AEs, the period of exposure was calculated from the start date of the initial regimen containing the drug in question until the first event or until the first treatment change of the drug in question, whichever came first. Only events occurring in this period (+2 days) were considered for the calculation of the specific incidence.

Delamanid Analysis

The primary objective was to provide estimates of sputum conversion within six months and 95% confidence intervals among patients who initiated a delamanid-containing regimen at baseline. To account for clustering at the country level, we conducted mixed effects logistic regression analyses with an intercept-only model and a random intercept for each country and derived predicted probabilities and corresponding 95% confidence intervals. In addition to the overall proportion who experienced culture conversion, we provide conversion estimates for the following subgroups: patients with and without HIV infection; patients with XDR-TB or RR/MDR-TB with fluoroquinolone resistance at baseline; and patients receiving at least five likely effective drugs as part of their baseline regimen.

As a secondary objective we compared the relative odds of conversion among patients who initiated a delamanid-containing regimen to those who initiated a bedaquiline-containing regimen. We used a mixed effects logistic regression model with a random intercept for each country to account for clustering at the country level. We adjusted for biologically plausible confounders (Table 5) that were associated both with receipt of delamanid (versus bedaquiline) and with six-month sputum culture conversion at a p-value of <0.20. Only two covariates included in the final multivariable model had any missing data: HIV status and history of incarceration. We opted to use the missing indicator method to account for missing covariate data for two reasons. First, <3% of patients lacked data on HIV status and therefore residual confounding by this variable is likely to be minimal. Second, history of incarceration was not collected at all sites and therefore could not be reliably imputed for those countries.

The TB drugs comprising a regimen may change throughout the course of treatment, and these changes may occur as a result of sputum culture conversion (or lack thereof). Therefore, for both primary and secondary objectives, we conducted sensitivity analyses to account for patients who, within the first 180 days of treatment, either switched from delamanid to bedaquiline (or vice versa) or who had the other drug added to their regimen. For patients who experienced these changes, we evaluated their conversion status at the time of the change.

Injectable Analysis

The association of baseline characteristics with injectable use was examined using the chi-squared test. The association of potential confounders with culture conversion within six months was examined by univariate logistics regression with random effects to adjust for clustering at country level. Any variable with evidence of an association ($p < 0.2$) with the outcome was further explored in the multivariable model.

We compared the relative odds of culture conversion within six months among patients who received an injectable-containing regimen to those who received an injectable-sparing regimen, stratified by baseline resistance to the second-line injectable (SLI). We used a mixed effects logistic regression model with a random intercept for each country to account for clustering at the country level. We adjusted for a priori covariates, age, and sex, and then iteratively introduced biologically plausible confounders (shown in Table 8) to assess association both with receipt of the injectable and with culture conversion within six months, reflected by a change in the odds ratio by $\geq 10\%$. Each confounder was fitted as a continuous and then as a categorical variable where appropriate to establish which approach altered the odds ratio from the unadjusted to a greater degree and thereby more efficiently controlled for its confounding effects.

Results

Results of Safety Analysis

The entire primary research cohort was included in the Safety Analysis. Characteristics of these patients, separated by use of bedaquiline or delamanid, are shown in Table 2.

Table 2.
Characteristics
of 1,244 RR-TB
patients initiating
bedaquiline or
delamanid, 1 April
2015 – 30 June 2017

Characteristic	Total n (%) ^a	BDQ only n (%) ^a	DLM only n (%) ^a	BDQ & DLM n (%) ^a
Demographic	N=1244	N=848	N=354	N=42
Median age at treatment initiation (IQR; range)	35 (27-46; 14-82)	35 (27-45; 15-71)	37 (29-48; 14-82)	37 (29-45; 17-67)
Female	415 (33.4)	298 (35.1)	107 (30.2)	10 (23.8)
Country				
Armenia	106 (8.5)	47 (5.5)	50 (14.1)	9 (21.4)
Bangladesh	113 (9.1)	77 (9.1)	33 (9.3)	3 (7.1)
Belarus	51 (4.1)	30 (3.5)	19 (5.4)	2 (4.8)
DPRK	17 (1.4)	17 (2.0)	0 (0)	0 (0)
Ethiopia	31 (2.5)	18 (2.1)	11 (3.1)	2 (4.8)
Georgia	290 (23.3)	213 (25.1)	77 (21.8)	0 (0)
Indonesia	7 (0.6)	7 (0.8)	0 (0)	0 (0)
Kazakhstan	275 (22.1)	177 (20.9)	75 (21.2)	23 (54.8)
Kenya	5 (0.4)	2 (0.2)	3 (0.8)	0 (0)
Kyrgyzstan	6 (0.5)	6 (0.7)	0 (0)	0 (0)
Lesotho	96 (7.7)	46 (5.4)	49 (13.8)	1 (2.4)
Myanmar	20 (1.6)	13 (1.5)	7 (2.0)	0 (0)
Pakistan	141 (11.3)	109 (12.8)	30 (8.5)	2 (4.8)
Peru	82 (6.6)	82 (9.7)	0 (0)	0 (0)
South Africa	4 (0.3)	4 (0.5)	0 (0)	0 (0)
Married or lives with partner (N=1232)	690 (56.0)	473 (56.4)	193 (55.0)	24 (57.1)
History of incarceration (past or present) (N=1034) ^b	170 (16.4)	101 (15.0)	63 (19.7)	6 (15.0)
Comorbidities				
Diabetes mellitus (N=1187)	135 (11.4)	85 (10.5)	43 (12.8)	7 (17.7)
HIV infection (N=1223)	143 (11.7)	69 (8.3)	72 (20.4)	2 (4.8)
Hepatitis B serology positive (N=1227)	49 (4.0)	31 (3.7)	16 (4.6)	2 (4.8)
Hepatitis C serology positive (N=1231)	167 (13.6)	95 (11.3)	61 (17.4)	11 (26.2)
At least one other comorbidity ^c	136 (10.9)	83 (9.8)	48 (13.6)	5 (11.9)
Tuberculosis-related				
Indication for bedaquiline or delamanid (N=1241)				
Regimen of four likely effective second-line drugs could not be constructed	1194 (96.2)	829 (98.0)	323 (91.5)	42 (100)
<i>If yes, this regimen could not be constructed solely due to toxicity</i>	210 (17.6)	94 (11.3)	115 (35.6)	1 (2.4)
Other high risk of unfavourable outcome	47 (3.8)	17 (2.0)	30 (8.5)	0 (0)
Prior TB treatment (N=1063)				
No prior treatment	148 (11.9)	90 (10.6)	57 (16.1)	1 (2.4)

Characteristic	Total n (%) ^a	BDQ only n (%) ^a	DLM only n (%) ^a	BDQ & DLM n (%) ^a
Prior treatment only with first-line drugs	132 (10.6)	64 (7.5)	68 (19.2)	0 (0)
Prior treatment with second-line drugs	964 (77.5)	694 (81.8)	229 (64.7)	41 (97.6)
Extra-pulmonary disease	13 (1.0)	12 (1.4)	1 (0.3)	0 (0)
Radiographic findings				
Bilateral disease (N=1111)	733 (66.0)	489 (64.9)	210 (66.5)	34 (82.9)
Cavitary disease (N=1061)	622 (58.6)	410 (57.1)	177 (58.6)	35 (85.4)
Bacteriologically confirmed tuberculosis disease	1237 (99.5)	843 (99.5)	352 (99.4)	42 (100)
Positive baseline culture (N=1150) ^d	690 (60.0)	484 (62.0)	174 (52.6)	32 (84.2)
Positive baseline smear (N=1195) ^d	557 (46.6)	394 (48.6)	135 (39.4)	28 (68.3)
Resistance profile				
RR/MDR-TB without any injectable or fluoroquinolone resistance	313 (25.2)	163 (19.2)	147 (41.5)	3 (7.1)
RR/MDR-TB with any injectable resistance	161 (12.9)	100 (11.8)	60 (16.9)	1 (2.4)
RR/MDR-TB with any fluoroquinolone resistance	316 (25.4)	255 (30.1)	58 (16.4)	3 (7.1)
XDR-TB ^e	419 (33.7)	310 (36.6)	79 (22.3)	30 (71.4)
No result for RR/MDR-TB	35 (2.8)	20 (2.4)	10 (2.8)	5 (11.9)
Body mass index <18.5 (N=968)	283 (29.2)	188 (29.5)	80 (27.6)	15 (37.5)
Baseline regimen characteristics				
Drugs included in the baseline regimen				
Moxifloxacin or levofloxacin	778 (62.5)	491 (57.9)	278 (78.5)	9 (21.4)
Amikacin	156 (12.5)	130 (15.3)	25 (7.1)	1 (2.4)
Kanamycin	90 (7.2)	66 (7.8)	24 (6.8)	0 (0)
Capreomycin	397 (31.9)	295 (34.8)	96 (27.1)	6 (14.3)
Linezolid	1020 (82.0)	728 (85.8)	251 (70.9)	41 (97.6)
Clofazimine	839 (67.4)	601 (70.9)	200 (56.5)	38 (90.5)
Imipenem/cilastatin or meropenem/cilastatin	232 (18.6)	154 (18.2)	58 (16.4)	20 (47.6)
Prothionamide / ethionamide	446 (35.8)	292 (34.4)	153 (43.2)	1 (2.4)
Cycloserine	851 (68.4)	569 (67.1)	270 (76.3)	12 (28.6)
P-Aminosalicylic Acid	462 (37.1)	340 (40.1)	116 (32.8)	6 (14.3)
Pyrazinamide	690 (55.5)	486 (57.3)	191 (53.9)	13 (30.9)
Median number of drugs included in baseline regimen (IQR)	6 (5-7)	6 (5-7)	6 (5-6)	5 (5-6)
Median number of likely effective drugs included in baseline regimen (IQR) ^f	4 (4-5)	4 (4-5)	5 (3-5)	4 (3-5)

a. Unless otherwise noted.

b. This variable was not routinely collected in all countries.

c. Other comorbidities include cirrhosis, chronic renal insufficiency, chronic obstructive pulmonary disease, cancer, heart disease, seizures, depression or seizures.

d. Based on the most recent result within 90 days preceding the initiation of bedaquiline or delamanid. If no result was available in the 90 days prior to initiation, results up to 15 days after initiation of bedaquiline or delamanid were considered.

e. Resistance to any fluoroquinolone and any injectable.

f. Can include bedaquiline or delamanid.

The proportion of patients with at least one occurrence of a clinically relevant AE, the time to the occurrence of AE and the incidence is shown in Table 3. Clinically relevant hypokalaemia/hypomagnesemia was most frequent, followed by hearing loss, peripheral neuropathy, hepatotoxicity, and myelosuppression. QTcF interval prolongation was not associated with HIV serostatus (HIV negative: 30/1,080 [2.8%]; HIV-positive: 4/143 [2.8%]; $p = 0.67$). nor with use of bedaquiline or delamanid (bedaquiline: 21/848 [2.5%]; delamanid: 12/354 [3.4%]; bedaquiline and delamanid: 1/42 [2.4%]; $p = 0.67$).

Table 3.
General incidence
of clinically
relevant AE

AE term	Patients with at least one occurrence of AE with specific grade N (%)	Time to first occurrence of AE with specific grade in months Median [IQR]	Incidence of AE with specific grade / 100 person-months (95% CI)
QTcF interval prolongation	34 (2.7)	2.0 [0.7-6.4]	0.18 (0.13-0.26)
Peripheral neuropathy	107 (8.6)	4.1 [2.0-7.5]	0.60 (0.50-0.73)
Optic neuritis	30 (2.4)	7.2 [3.6-13-1]	0.16 (0.11-0.23)
Myelosuppression	49 (3.9)	1.9 [0.6-4.9]	0.27 (0.20-0.35)
Hearing loss	211 (17.0)	3.7 [2.0-6.9]	1.29 (1.13-1.47)
Acute renal failure	52 (4.2)	1.9 [0.9-5.2]	0.28 (0.22-0.37)
Hypokalaemia/hypomagnesemia	327 (26.3)	3.0 [1.0-8.0]	2.15 (1.93-2.40)
Hepatotoxicity	71 (5.7)	2.1 [1.0-7.0]	0.38 (0.30-0.49)
Hypothyroidism	59 (4.7)	4.0 [2.9-7.3]	0.32 (0.25-0.42)

Table 4 shows the relative incidence of AEs or groups of AE among patients taking specific drugs that commonly cause those AEs. Among patients receiving injectables, the incidence of hearing loss was 3.36 (95% CI: 2.83%-4.00%) occurrences per 100 person-months of treatment with injectable. In addition, incidence of any occurrence of hearing loss, acute renal failure and hypokalaemia/hypomagnesemia was 6.16/100 person-months (95% CI: 5.46%-6.93%). Among those who received linezolid at baseline, incidence of any occurrence of peripheral neuropathy, optic neuritis and myelosuppression was 0.94/100 person-months (95% CI: 0.78%-1.13%).

Table 4.
Relative incidence
of clinically
relevant AE

AE term	Patients with at least one occurrence of AE with specific grade N (%)	Incidence of AE with specific grade / 100 person-months (95% CI)
Hearing loss all grade <i>Among those receiving an injectable</i>	128/643 (19.9)	3.36 (2.83-4.00)
Hearing loss or acute renal failure or hypokalaemia/hypomagnesemia <i>Among those receiving an injectable</i>	229/643 (35.6)	6.16 (5.46-6.93) ^a
Peripheral neuropathy or optic neuritis or myelosuppression <i>Among those receiving linezolid</i>	112/1020 (11.0)	0.94 (0.78-1.13) ^b

a. Total number of events n=261; person-months of treatment on injectables PM=4235.93

b. Total number of events n=120; person-months of treatment on linezolid PM=12715.5

Results of Delamanid Analysis

Of the 658 patients with a positive baseline culture, 174 (26%) initiated a delamanid-containing regimen and were included in primary objective analyses of sputum culture conversion. Table 5 provides the characteristics of these patients. Seventy-five percent of patients receiving delamanid resided in four countries: Georgia (27%), Kazakhstan (20%), Armenia (17%), and Lesotho (11%). In general, patients receiving delamanid had a high rate of comorbidities, including HIV (18%), diabetes (18%) and hepatitis C (21%). A majority had bilateral disease and cavitary disease apparent on their baseline chest X-ray and one-third had XDR-TB.

Table 5.
Characteristics of patients initiating a delamanid-containing regimen with a positive baseline sputum culture

Characteristic	n (%) ^a
Demographic	
Median age at treatment initiation (IQR; range)	40 (30 - 52; 16 - 84)
Female	42 (24.1)
Country	
Armenia	29 (16.7)
Bangladesh	11 (6.3)
Belarus	13 (7.5)
Ethiopia	4 (2.3)
Georgia	47 (27.0)
Kazakhstan	34 (19.5)
Kenya	1 (0.6)
Lesotho	20 (11.5)
Myanmar	1 (0.6)
Pakistan	14 (8.0)
Married or lives with partner (N=173)	97 (56.1)
History of incarceration (past or present) (N=159) ^b	39 (24.5)
Comorbidities	
Diabetes mellitus (N=164)	30 (18.3)
HIV infection (N=173)	32 (18.5)
Hepatitis B serology positive (N=173)	6 (3.5)
Hepatitis C serology positive (N=173)	37 (21.4)
At least one other comorbidity ^c	26 (14.9)
Tuberculosis-related	
Indication for bedaquiline or delamanid	
Regimen of four likely effective second-line drugs could not be constructed	155 (89.6)
<i>If yes, this regimen could not be constructed solely due to toxicity (N=155)</i>	23 (14.8)
Other high risk of unfavourable outcome	19 (10.9)
Prior TB treatment	
No prior treatment	25 (14.4)
Prior treatment only with first-line drugs	24 (13.8)
Prior treatment with second-line drugs	125 (71.8)
Extra-pulmonary disease	6 (3.4)
Radiographic findings	
Bilateral disease (N=158)	110 (69.6)
Cavitary disease (N=152)	101 (66.4)

Characteristic	n (%) ^a
Bacteriologically confirmed tuberculosis disease	174 (100)
Positive baseline smear ^d	105 (60.3)
Resistance profile	
RR/MDR-TB without any injectable or fluoroquinolone resistance	53 (30.5)
RR/MDR-TB with any injectable resistance	24 (13.8)
RR/MDR-TB with any fluoroquinolone resistance	38 (21.8)
XDR-TB ^e	57 (32.8)
No result for RR/MDR-TB	2 (1.1)
Body mass index <18.5 (N=172)	67 (39.0)
Baseline regimen characteristics	
Drugs included in the baseline regimen	
Moxifloxacin or levofloxacin	118 (67.8)
Amikacin	14 (8.0)
Kanamycin	11 (6.3)
Capreomycin	49 (28.2)
Linezolid	132 (75.9)
Clofazimine	117 (67.2)
Imipenem/cilastatin or meropenem/cilastatin	48 (27.6)
Prothionamide / ethionamide	68 (39.1)
Cycloserine	125 (71.8)
P-Aminosalicylic Acid	52 (29.9)
Median number of drugs included in baseline regimen (IQR; range)	6 (5 – 6; 2 – 9)
Median number of likely effective drugs included in baseline regimen (IQR; range) ^f	5 (4 – 5; 2 – 7)

a. Unless otherwise noted.

b. This variable was not routinely collected in all countries.

c. Other comorbidities include cirrhosis, chronic renal insufficiency, chronic obstructive pulmonary disease, cancer, heart disease, seizures, depression or seizures.

d. Based on the most recent result within 90 days preceding the initiation of bedaquiline or delamanid. If no result was available in the 90 days prior to initiation, results up to 15 days after initiation of bedaquiline or delamanid were considered.

e. Resistance to any fluoroquinolone and any injectable.

f. Can include bedaquiline or delamanid.

Primary delamanid analyses. Sputum culture conversion within six months, overall and in subgroups, is shown in Table 6. Ten of 174 patients (6%) lacked a follow-up culture and were therefore presumed not to have converted. Adjusting for clustering at the country level, the probability of conversion was 0.82 (95% CI: 0.68-0.91). Conversion probabilities were similar for HIV-negative patients, those with XDR-TB, those with XDR-TB or RR/MDR-TB with fluoroquinolone resistance and those receiving five likely effective drugs, but were notably lower for the 32 patients living with HIV (0.63; 95% CI: 0.31-0.82). Of the patients with HIV who did not experience sputum conversion within six months, 7 died during this period with deaths typically occurring within the first few months of treatment (median 61 days; range 8 to 101 days). Eleven of 174 (6%) patients receiving delamanid either switched to bedaquiline or had bedaquiline added to their regimen during the first six-months of treatment. Of these, seven had already experienced conversion at the time of change, and of the remaining four, only two

subsequently went on to convert after the change. Therefore, results from sensitivity analyses in which we considered conversion status at the time of the change were similar to the primary findings (predicted probability, adjusted for clustering by site: 0.80; 95% CI: 0.65-0.9).

Table 6.
Culture conversion within six months among patients receiving delamanid, overall and in subgroups

Population	Number converted	Crude proportions, unadjusted for clustering by site [95% CI]	Predicted probabilities, adjusted for clustering by site [95% CI]
Overall (N=174)	138	0.79 [0.73 - 0.85]	0.82 [0.68 - 0.91]
HIV-positive patients (N=32)	20	0.63 [0.46 - 0.79]	0.63 [0.31 - 0.82]
HIV-negative patients (N=141)	117	0.83 [0.77 - 0.89]	0.83 [0.70 - 0.91]
XDR or pre-XDR FQ (N=95)	76	0.80 [0.72 - 0.88]	0.80 [0.67 - 0.88]
XDR (N=57)	45	0.79 [0.68 - 0.90]	0.77 [0.50 - 0.92]
At least five likely effective drugs (N=89)	68	0.76 [0.68 - 0.85]	0.77 [0.64 - 0.86]

Secondary delamanid analyses. 658 patients, 174 receiving a delamanid-containing baseline regimen and 484 receiving a bedaquiline-containing baseline regimen, were analysed to compare sputum culture conversion within six months in these two groups (Table 7). In univariable analyses, a baseline regimen containing delamanid, relative to a baseline regimen containing bedaquiline, was not significantly associated with sputum culture conversion within six months (OR: 0.72; 95% CI: 0.44-1.16). Results were similar in the final multivariable model, which adjusted for XDR-TB, history of incarceration, HIV infection, linezolid included in the baseline regimen, amikacin or kanamycin included in the baseline regimen, and clofazimine contained in the baseline regimen (OR: 0.76; 95% CI: 0.44-1.31). Twenty-seven of 658 (4%) patients switched to the other drug or had the other drug added to their regimen. Of these, 14 had already experienced conversion at the time of change, and of the remaining 13, eight subsequently went on to convert after the change. Adjusted results from sensitivity analyses in which we considered conversion status at the time of the change were similar to the primary findings (0.77; 95% CI: 0.46-1.30).

Table 7.
Relative odds of conversion within six months with a baseline regimen containing delamanid relative to one containing bedaquiline

Analysis	Delamanid (N=174) n converted (%)	Bedaquiline (N=484) n converted (%)	Adjusted for clustering by site (no covariates)	Adjusted for clustering by site and covariates ^a
Main analysis	138 (79)	418 (86)	0.72 [0.44, 1.16]	0.76 [0.44, 1.31]
Sensitivity analysis ^b	136 (78)	412 (85)	0.74 [0.46, 1.18]	0.77 [0.46, 1.30]

a. The following baseline covariates were included: XDR-TB, history of incarceration, HIV infection, linezolid included in regimen, amikacin or kanamycin included in regimen, clofazimine included in regimen.

b. Sensitivity analyses considered the culture status at the time that a patient experienced a switch to the other “new” tuberculosis drug or the addition of the other “new” drug to their regimen, if applicable.

— Results of Injectable Analysis

Of 633 patients included in the Injectable Analysis, 280 were not on a SLI at initiation of bedaquiline or delamanid; of these, 23 patients (8.2%) were subsequently started on a SLI during the course of treatment. Median time to starting a SLI in this group was 58 days (IQR 8 – 204).

Of the 353 patients who were on a SLI at initiation of bedaquiline or delamanid, 92 (26.1%) stopped the SLI after two months of treatment; 132 (37.4%) stopped the SLI after three months of treatment; 171 (48.4%) stopped the SLI after four months; and 221 (62.6%) stopped the SLI after six months. Median time to stopping a SLI in this group was 124 days (IQR 59 – 237).

Characteristics of patients included in this analysis stratified by injectable use and baseline resistance to SLIs are shown in Table 8. Of note, 81.9% (227/277) that had no evidence of resistance to a SLI on drug-susceptibility testing at baseline had prior treatment with second-line drugs. Of those with evidence of resistance to a SLI at baseline, 88.2% (314/356) had prior treatment with second-line drugs.

Table 8.
Characteristics of patients initiating a bedaquiline- or delamanid-containing regimen with a baseline positive culture and susceptibility testing to SLIs

Characteristic	No resistance to at least one SLI (N=277)		Resistance to at least one SLI (N=356)	
	No SLI at start n (%) ^a	Received SLI at start n (%) ^a	No SLI at start n (%) ^a	Received SLI at start n (%) ^a
Demographic	N=66	N=211	N=214	N=142
Median age at treatment initiation (IQR; range)	36 (28 – 51; 15 – 82)	35 (26 – 47; 15 – 71)	38 (29 – 47; 17 – 70)	34 (28 – 45; 16 – 68)
Female	19 (28.8)	66 (31.3)	99 (31.7)	67 (30.7)
Country				
Armenia	4 (6.1)	25 (11.9)	31 (14.5)	8 (5.6)
Bangladesh	22 (33.3)	12 (5.7)	4 (1.9)	5 (3.5)
Belarus	0 (0)	2 (1.0)	28 (13.1)	7 (4.9)
Ethiopia	2 (3.0)	6 (2.8)	0 (0)	0 (0)
Georgia	9 (13.6)	55 (26.1)	51 (23.8)	45 (31.7)
Indonesia	1 (1.5)	0 (0)	1 (0.5)	0 (0)
Kazakhstan	5 (7.6)	25 (11.9)	69 (32.2)	32 (22.5)
Kenya	0 (0)	1 (0.5)	0 (0)	2 (1.4)
Kyrgyzstan	0 (0)	1 (0.5)	0 (0)	2 (1.4)
Lesotho	12 (18.2)	9 (4.3)	5 (2.3)	2 (1.4)
Myanmar	0 (0)	0 (0)	1 (0.5)	1 (0.7)
DPRK	0 (0)	4 (1.9)	1 (0.5)	7 (4.9)
Pakistan	10 (15.2)	64 (30.3)	10 (4.7)	9 (6.3)
Peru	0 (0)	7 (3.3)	13 (6.1)	22 (15.5)
South Africa	1 (1.5)	0 (0)	0 (0)	0 (0)
Married or lives with partner (No SLI resistance: N=273; SLI resistance: N=356)	39 (60.0)	114 (54.8)	110 (51.4)	83 (58.5)
History of incarceration (past or present) (No SLI resistance: N=191; SLI resistance: N=319) ^b	5 (10.0)	30 (21.3)	48 (24.5)	25 (20.3)

Characteristic	No resistance to at least one SLI (N=277)		Resistance to at least one SLI (N=356)	
	No SLI at start n (%) ^a	Received SLI at start n (%) ^a	No SLI at start n (%) ^a	Received SLI at start n (%) ^a
Comorbidities				
Diabetes mellitus (No SLI resistance: N=264; SLI resistance: N=342)	12 (20.0)	25 (12.3)	26 (12.5)	8 (6.0)
HIV infection (No SLI resistance: N=273; SLI resistance: N=346)	10 (15.2)	14 (6.8)	15 (7.0)	9 (6.8)
Hepatitis B serology positive (No SLI resistance: N=273; SLI resistance: N=353)	2 (3.1)	4 (1.9)	9 (4.2)	2 (1.4)
Hepatitis C serology positive (No SLI resistance: N=274; SLI resistance: N=355)	4 (6.3)	28 (13.3)	46 (21.5)	25 (17.7)
At least one other comorbidity ^c	5 (7.6)	22 (10.4)	33 (15.4)	13 (9.2)
Tuberculosis-related				
Primary indication for bedaquiline or delamanid				
Regimen of four likely effective second-line drugs could not be constructed	62 (93.9)	203 (96.2)	214 (100)	141 (99.3)
<i>If yes, this regimen could not be constructed solely due to toxicity (No SLI resistance: N=37; SLI resistance: N=6)</i>	23 (62.2)	14 (37.8)	4 (66.7)	2 (33.3)
Other high risk of unfavourable outcome	4 (6.1)	8 (3.8)	0 (0)	1 (0.7)
Prior TB treatment				
No prior treatment	9 (13.6)	19 (9.0)	11 (5.1)	19 (13.4)
Prior treatment only with first-line drugs	9 (13.6)	13 (6.2)	6 (2.8)	6 (4.2)
Prior treatment with second-line drugs	48 (72.7)	179 (84.8)	197 (92.1)	117 (82.4)
Extra-pulmonary disease	0 (0)	1 (0.5)	2 (0.9)	1 (0.7)
Radiographic findings				
Bilateral disease (No SLI resistance: N=253; SLI resistance: N=328)	37 (61.7)	133 (68.9)	157 (78.1)	77 (60.6)
Cavitary disease (No SLI resistance: N=421; SLI resistance: N=315)	32 (57.1)	113 (61.1)	147 (76.2)	77 (63.1)
Bacteriologically confirmed tuberculosis disease	66 (100)	211 (100)	214 (100)	142 (100)
Positive baseline smear (No SLI resistance: N=273; SLI resistance: N=352) ^d	32 (48.5)	146 (69.2)	145 (69.1)	102 (71.8)
Resistance profile				
RR/MDR-TB without any injectable or fluoroquinolone resistance	32 (48.5)	41 (19.4)	0 (0)	0 (0)
RR/MDR-TB with any injectable resistance	0 (0)	0 (0)	42 (19.6)	27 (19.0)
RR/MDR-TB with any fluoroquinolone resistance	34 (51.5)	170 (80.6)	0 (0)	0 (0)
XDR-TB ^e	0 (0)	0 (0)	172 (80.4)	115 (81.0)
Body mass index <18.5 (No SLI resistance: N=276; SLI resistance: N=353)	28 (42.4)	97 (46.2)	77 (36.2)	49 (35.0)
Baseline regimen characteristics				
Drugs included in the baseline regimen				
Bedaquiline alone	65 (48.5)	262 (74.4)	135 (63.1)	122 (85.9)

Characteristic	No resistance to at least one SLI (N=277)		Resistance to at least one SLI (N=356)	
	No SLI at start n (%) ^a	Received SLI at start n (%) ^a	No SLI at start n (%) ^a	Received SLI at start n (%) ^a
Delamanid alone	67 (50.0)	85 (24.2)	54 (25.2)	18 (12.7)
Bedaquiline and delamanid	2 (1.5)	5 (1.4)	25 (11.7)	2 (1.4)
Moxifloxacin or levofloxacin	110 (82.1)	221 (62.8)	108 (50.5)	61 (43.0)
Linezolid	46 (69.7)	181 (85.8)	202 (94.4)	134 (94.4)
Clofazimine	36 (54.6)	128 (60.7)	193 (90.2)	121 (85.2)
Imipenem/cilastatin or meropenem/ cilastatin	8 (12.1)	18 (8.5)	121 (56.5)	30 (21.1)
Prothionamide / ethionamide	91 (67.9)	134 (38.1)	25 (11.7)	28 (19.7)
Cycloserine	53 (80.3)	158 (74.4)	105 (49.1)	83 (58.5)
P-Aminosalicylic Acid	39 (29.1)	132 (37.5)	80 (37.4)	53 (37.3)
Median number of drugs included in baseline regimen (IQR; range)	6 (5 - 6; 2 - 8)	6 (6 - 7; 4 - 9)	5 (5 - 6; 2 - 9)	6 (6 - 7; 3 - 10)
Median number of likely effective drugs included in baseline regimen (IQR; range) ^f	4 (3 - 5; 2 - 7)	5 (4 - 6; 2 - 8)	4 (3 - 5; 1 - 7)	4 (4 - 5; 1 - 8)

a. Unless otherwise noted

b. This variable was not routinely collected in all countries.

c. Other comorbidities include cirrhosis, chronic renal insufficiency, chronic obstructive pulmonary disease, cancer, heart disease, seizures, depression or seizures.

d. Based on the most recent result within 90 days preceding the initiation of bedaquiline or delamanid. If no result was available in the 90 days prior to initiation, results up to 15 days after initiation of bedaquiline or delamanid were considered.

e. Resistance to any fluoroquinolone and any injectable.

f. Can include bedaquiline or delamanid.

Overall 83.9% (531/633) of patients culture converted by six months. Eighty-eight percent (244/277) of patients with no evidence of resistance to a SLI had culture converted by six months and 80.6% (287/356) of those with evidence of resistance to at least one SLI had culture converted by six months. Table 9 shows the percentage of patients who had culture converted by six months stratified by resistance to SLIs at baseline, with 95% confidence intervals adjusted for clustering at the country level.

Table 9.
Percentage of patients who had culture converted by six months stratified by resistance to SLIs at baseline

	No resistance to at least one SLI (N=277)		Resistance to at least one SLI (N=356)	
	n/N	Percent (95% CI)*	n/N	Percent (95% CI)*
No SLI use	54/66	81.8% (48.3 - 95.6)	170/214	79.4% (65.4 - 88.8)
SLI use	190/211	90.1% (82.8 - 94.5)	117/142	82.4% (70.7 - 90.1)

* adjusted for clustering at country-level

In the unadjusted analysis, among patients resistant to at least one SLI and who were on an injectable containing regimen at the start of treatment with bedaquiline or delamanid there was a 2.8-fold increased odds of culture conversion compared to those patients who were on an injectable-free regimen (95% CI: 1.13 - 7.01). After adjusting for age, sex, baseline resistance profile, use of bedaquiline, use of delamanid and combined use of bedaquiline or delamanid at the start of the regimen, and clustering at country-level, the strength of the association reduced to an odds ratio of 2.31 (95% CI: 0.85 - 6.27) with the 95% confidence interval including an odds ratio of 1.0. In patients who had resistance to at least one SLI, there appeared to be no association between whether they received an injectable or not and the odds of culture conversion at six months in the unadjusted and the adjusted analysis.

Table 10.
Association of being on an SLI at time of initiation of bedaquiline or delamanid with culture conversion at six months stratified by baseline drug-susceptibility to SLI

No resistance to at least one SLI (N=277)						Resistance to at least one SLI (N=356)					
Crude odds ratio ^a			Adjusted odds ratio ^b			Crude odds ratio ^a			Adjusted odds ratio ^c		
OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
2.82	1.13 - 7.01	0.026	2.31	0.85 - 6.27	0.11	1.10	0.61 - 1.98	0.75	0.98	0.53 - 1.8	0.94

a. adjusted for clustering by site

b. adjusted for age, sex, baseline resistance profile, bedaquiline use, delamanid use, combined use of bedaquiline and delamanid and clustering by site

c. adjusted for age, sex, at least five effective drugs in the regimen, prior tuberculosis treatment and clustering by site

Discussion

Safety Analysis

In this analysis of patients in the endTB observational study, clinically relevant QTcF interval prolongation was not common. QT interval prolongation is known to be associated with the new TB drugs, bedaquiline and delamanid, and has been a major cause of concern globally; regular ECG monitoring is recommended by the WHO and was performed for most patients in the endTB cohort. But clinically relevant QTcF interval prolongation was found to be much less frequent than other AEs associated with conventional second-line TB drugs, such as the injectables. Only 2.7% of patients experienced a QTcF > 500 ms (Grade 3 or 4). QTcF interval prolongation was not associated with HIV serostatus, nor with use of delamanid or bedaquiline.

These findings are consistent with the unpublished data from the Phase III trial of delamanid, which also found a low incidence of QT interval prolongation. The incidence of QT interval prolongation would be expected to be higher in the endTB observational cohort because patients were generally in poor clinical condition, and almost all of them were taking multiple drugs known to prolong the QT interval, such as clofazimine and fluoroquinolones. QT interval was not as intensely monitored as in a clinical trial, and not by cardiologists, but ECG screening was performed at least monthly in most countries during the entire length of treatment with bedaquiline or delamanid. Doctors and nurses responsible for measuring QT intervals have received specific in-country practical training.

QTcF > 500 ms is clinically relevant but only a very small proportion of these patients will go on to experience a serious cardiac arrhythmia such as torsades de pointes. Most of these patients can be managed safely by suspending one or more QT interval-prolonging drugs. In subsequent analyses, it will be important to determine how many of these patients were unable to tolerate bedaquiline or delamanid.

AEs possibly caused by the injectable were extremely common in the endTB cohort. 35.6% of patients who received an injectable were estimated to experience at least one injectable-related toxicity (hearing loss, acute renal failure, or hypokalaemia/hypomagnesaemia), with an estimated incidence of 6.16 per 100 person-months of injectable. This is far greater than the incidence of QTcF interval prolongation of 0.18 per 100 person-months of treatment. Hearing loss was quite common in the endTB cohort, which is particularly worrisome because it is irreversible. Injectables are the only TB drugs known to cause hearing loss, and were responsible for new or worsening hearing loss in 19.9% of the patients who received an injectable. Most endTB sites screened patients monthly for hearing loss with some form of audiometry. Portable audiometry can be done in resource-limited settings by doctors and nurses; it is not as accurate as an evaluation by an audiologist, but is much more sensitive at picking up high-frequency hearing loss than relying solely on patient reporting or clinician impression. If the injectable is not suspended, high-frequency hearing loss is almost always followed by low-frequency and clinically apparent hearing loss. Prospective studies from the southern Africa region show even higher rates of hearing loss than found in endTB; this region is arguably underrepresented in the endTB cohort.⁶

Hypokalaemia/hypomagnesaemia and acute renal failure are other important toxicities often related to the injectable that are commonly seen in this cohort. In contrast to

⁶ Modongo C, Sobota RS, Kesenogile B, Ncube R, Sirugo G, et al. Successful MDR-TB treatment regimens including amikacin are associated with high rates of hearing loss. *BMC Infect Dis* 2014; 14: 542.

hearing loss, however, there are other causes of hypokalaemia/hypomagnesemia and acute renal failure, meaning that the incidence rates reported here should be considered an overestimate of toxicity caused by the injectable. Nevertheless, these are important toxicities that complicate the treatment of MDR-TB immensely, and were both more common than QT interval prolongation.

Linezolid-associated AEs such as peripheral neuropathy, myelosuppression and optic neuritis were also common in the endTB cohort. Both peripheral neuropathy and myelosuppression can be caused by other drugs or factors, but optic neuritis is almost certainly caused by linezolid in the endTB cohort. Linezolid-induced peripheral neuropathy was actually lower in the endTB cohort compared to that reported in previous clinical trials.⁷ Linezolid-induced myelosuppression is generally reversible but it can be difficult to detect in resource-limited settings. Linezolid-induced optic neuritis was not common in the endTB cohort, but its clinical impact cannot be underestimated, as it can result in permanent blindness if the linezolid is not stopped in time. Overall, the high incidence rate of linezolid-associated AEs emphasizes the importance of close monitoring when using this important drug.

The incidence of clinically relevant hepatotoxicity was also high, but this could be related to the unexpectedly high rate of hepatitis B and C co-infection. Almost any drug can potentially cause drug-induced hepatotoxicity; pyrazinamide, for example, was used by 55.5% of patients in this cohort. Another possible factor for hepatotoxicity, however, was the high rate of hepatitis B and C disease. A positive antibody for hepatitis C was found in 13.6%; overall 17.0% had hepatitis B, C or both. Active chronic hepatitis B or C could both result in elevated liver enzymes, but could also be a risk factor for drug-induced hepatotoxicity. Future analysis in this cohort should allow quantification of these patient-related risk factors.

Delamanid Analysis

In the endTB cohort, 79% of patients who received delamanid as part of a multidrug regimen converted their sputum culture within six months. This culture conversion rate was not only consistent with the Phase III trial, but also with other observational cohorts (Table 11). Of note, the population was heterogeneous, treated in 10 countries. A significant percentage of the endTB cohort had comorbidities or social risk factors for compromised treatment response.

Table 11.
Culture conversion
in endTB and
other cohorts

Cohort	Number of patients	Culture conversion
Delamanid Phase III trial (unpublished)	226	88%
endTB interim analysis	174	79%
Compassionate use ⁸	78	80%
MSF ⁹	53	68%
South Korea ¹⁰	32	94%

⁷ Lee M, Lee J, Carroll MW, Choi H, Min S et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med* 2012; 367(16): 1508-18.

⁸ Hafkin J, Hittel N, Martin A, Gupta R. Early outcomes in MDR-TB and XDR-TB patients treated with delamanid under compassionate use. *Eur Respir J* 2017; 50(1).

⁹ Hewison C, Ferlazzo G, Avaliani Z, Hayrapetyan A, Jonckheere S, et al. Six-month response to delamanid treatment in MDR TB patients. *Emerg Infect Dis* 2017; 23(10).

¹⁰ Mok J, Kang H, Hwang SH, Park JS, Kang B, et al. Interim outcomes of delamanid for the treatment of MDR- and XDR-TB in South Korea. *J Antimicrob Chemother* 2018; 73(2): 503-508.

Culture conversion within six months with delamanid-containing regimens was also good in subgroups with higher resistance patterns. For example, culture conversion within six months was 80% (95% CI: 72%-88%) in patients with fluoroquinolone-resistant strains, almost exactly the same as in the complete cohort. Delamanid was used as part of a multidrug regimen, making it difficult to determine the relative contribution of other drugs such as linezolid, clofazimine and imipenem/cilastatin. Overall, however, the findings suggest that delamanid can contribute to achieving improved treatment response in MDR-TB.

Secondary analysis reveals no statistically significant difference in culture conversion within six months between those who received delamanid- and bedaquiline-containing regimens. Effect estimates, however, were consistently less than one. Controlling for confounding always brought the effect estimate toward null, raising the possibility that residual, unmeasured confounding persists. Patients who received delamanid often had comorbidities or medical contraindications to bedaquiline. Determining the relative effectiveness of delamanid and bedaquiline is likely to be beyond the scope of the endTB observational study; ongoing clinical trials (including the endTB clinical trial) are more likely to provide useful data in this regard.

Injectable Analysis

In the endTB cohort, patients with strains susceptible to injectables had higher culture conversion at six months when receiving an injectable compared to those who did not receive an injectable, although this finding was not statistically significant. In contrast, there was no added benefit of an injectable in patients with injectable-resistant strains. Currently there is much interest in the relative effectiveness within the injectable class (kanamycin, amikacin, capreomycin). A stratified analysis of the endTB data by specific aminoglycoside/polypeptide is planned. However, there are a number of limitations that need to be considered before any firm conclusions are drawn. This study was not designed to answer the question we have examined in the Injectable Analysis, and this is a highly selective cohort of patients—more than 80% had had prior MDR-TB treatment. Although controlling for confounding brought the effect estimate toward null, there remains the possibility of residual confounding by unmeasured or complex confounders.

Conclusion

Overall, there is no evidence of any major safety issue with either delamanid or bedaquiline.

QT interval prolongation is known to be associated with both drugs, but in the endTB cohort, clinically relevant prolongation was not very common. All deaths and other serious AEs were reviewed by the MSF PV unit—no unexpected safety signals have been found to date. While clearly there is a role for ECG screening in MDR-TB treatment, more resources and energy should be allocated for screening of more common and potentially more deadly AEs that are associated with other drugs.

The endTB data is consistent with previous studies showing that delamanid is an effective drug in the treatment of MDR-TB.

Culture conversion within six months in patients who receive delamanid-containing regimens appears to be quite good in this cohort of highly chronic and very resistant MDR-TB patients. Delamanid also has very few safety or tolerability issues; it should be strongly considered as an effective and safe drug when constructing an MDR-TB regimen.

When deciding to replace the injectable in individual patients, clinicians and patients need to weigh the benefits and the risks.

The endTB data is consistent with a benefit of receiving injectables with respect to culture conversion at six months, in patients with non-injectable-resistant strains. The endTB data also clearly shows that toxicities related to injectables and linezolid are more common than toxicities related to either of the new TB drugs, bedaquiline or delamanid.

Overall, the efficacy and safety data presented in this report supports elevation of bedaquiline and delamanid in the hierarchy of MDR-TB drugs.

The effectiveness of delamanid in treatment of MDR-TB is supported by a high rate of culture conversion within six months. Both delamanid and bedaquiline appear to be safer than commonly used drugs such as injectables or linezolid. These findings suggest that both bedaquiline and delamanid are likely to play an expanded role in achieving improved treatment response in MDR-TB.