ORIGINAL ARTICLE

Culture Conversion in Patients Treated with Bedaquiline and/or Delamanid
A Prospective Multicountry Study

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Abstract

Rationale: Bedaquiline and delamanid offer the possibility of more effective and less toxic treatment for multidrug-resistant (MDR) tuberculosis (TB). With this treatment, however, some patients remain at high risk for an unfavorable treatment outcome. The endTB Observational Study is the largest multicountry cohort of patients with rifampin-resistant TB or MDR-TB treated in routine care with delamanid- and/or bedaquiline-containing regimens according to World Health Organization guidance.

Objectives: We report the frequency of sputum culture conversion within 6 months of treatment initiation and the risk factors for nonconversion.

Methods: We included patients with a positive baseline culture who initiated a first endTB regimen before April 2018. Two consecutive negative cultures collected 15 days or more apart constituted culture conversion. We used generalized mixed models to derive marginal predictions for the probability of culture conversion in key subgroups.

Measurements and Main Results: A total of 1,109 patients initiated a multidrug treatment containing bedaquiline (63%), delamanid (27%), or both (10%). Of these, 939 (85%) experienced culture conversion within 6 months. In adjusted analyses, patients with HIV had a lower probability of conversion (0.73; 95% confidence interval [CI], 0.62–0.84) than patients without HIV (0.84; 95% CI, 0.79–0.90; $P = 0.03$). Patients with both cavitary disease and highly positive sputum smear had a lower probability of conversion (0.68; 95% CI, 0.57–0.79) relative to patients without either (0.89; 95% CI, 0.84–0.95; $P = 0.0004$). Hepatitis C infection, diabetes mellitus or glucose intolerance, and baseline resistance were not associated with conversion.

Conclusions: Frequent sputum conversion in patients with rifampin-resistant TB or MDR-TB who were treated with bedaquiline and/or delamanid underscores the need for urgent expanded access to these drugs. There is a need to optimize treatment for patients with HIV and extensive disease.

Keywords: multidrug-resistant tuberculosis; rifampicin-resistant tuberculosis; sputum conversion; interim outcome; extensively drug-resistant tuberculosis

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

At a Glance Commentary

Scientific Knowledge on the Subject: Few large studies have reported the frequency of unfavorable treatment outcomes and associated factors from patients receiving bedaquiline and/or delamanid for rifampin-resistant (RR) or multidrug-resistant (MDR) tuberculosis (TB) treatment.

What This Study Adds to the Field: The endTB Observational Study comprises the largest multicountry cohort of patients receiving bedaquiline or delamanid as part of a regimen for RR-TB or MDR-TB and includes broad representation from patients known to be at high risk for unfavorable treatment outcomes. Among 1,106 patients treated programmatically in one of 16 countries on five continents, we found that 85% of patients experienced a favorable interim outcome (i.e., conversion of sputum from positive to negative) within 6 months. Patients living with HIV and those who presented with both a high smear grade and cavitary disease were at higher risk of no sputum culture conversion within 6 months. Patients with extensively drug-resistant TB, hepatitis C virus infection, and/or diabetes mellitus or glucose intolerance experienced a similar frequency of sputum conversion relative to patients without these conditions. Continued work is needed to optimize RR-TB or MDR-TB treatment for patients with TB characterized by high smear grade and cavitary disease and for patients living with HIV infection.

Multidrug-resistant (MDR) tuberculosis (TB) is catastrophic to patients, communities, and health systems. Defined as disease caused by *Mycobacterium tuberculosis* that is resistant to rifampin and isoniazid, the two most potent drugs used in standard first-line therapy, MDR-TB, together with rifampin-resistant (RR) TB, sickens more than 500,000 people annually (1). Historically, patients endured a grueling 18- to 24-month MDR-TB treatment regimen that cured only 55%. Among patients whose TB was caused by *M. tuberculosis* also resistant to a fluoroquinolone and a second-line aminoglycoside or polypeptide (i.e., extensively drug-resistant [XDR] TB), only 34% were cured (2). Debilitating side effects limited patients' ability to complete treatment and had lasting social and economic consequences (3–7).

In 2012 and 2013, on the basis of promising phase II trial data (8–10), stringent regulatory authorities approved the first new TB drugs in 50 years, bedaquiline (BDQ) and delamanid (DLM), offering hope for more effective and less toxic MDR-TB treatment. Since then, evidence generated from both randomized trials and observational studies has continued to support a role for these two drugs in MDR-TB treatment (11–20); the World Health Organization (WHO) has endorsed their use, gradually broadening the populations in which they might be used (21–23). Patients with MDR-TB often experience conditions that increase the risk of unfavorable treatment outcomes (e.g., HIV and/or hepatitis C virus [HCV] coinfection, diabetes mellitus [DM], and/or XDR-TB) (24–30). It is critical to understand whether WHO-conforming regimens containing BDQ and/or DLM can produce successful outcomes in these vulnerable subgroups in routine care. Because such patients are often excluded from trials, we undertook the endTB Observational Study in a diverse prospective cohort of patients treated for MDR-TB with BDQ- or DLM-containing regimens in 17 countries (Armenia, Bangladesh, Belarus, Democratic People's Republic of Korea, Ethiopia, Kenya, Georgia, Haiti, Indonesia, Kazakhstan, Kyrgyzstan, Lesotho, Myanmar, Pakistan, Peru, South Africa, and Vietnam) (31). Here, we 1) report interim effectiveness outcomes (i.e., sputum culture conversion within 6 mo of treatment initiation) overall and among high-risk patients underrepresented in studies published to date and 2) examine which subgroups experienced a higher risk of an unfavorable interim effectiveness outcome.

Methods

Study Design and Patient Population
The endTB Observational Study (NCT02754765) comprises a prospective cohort of patients with RR-TB or MDR-TB who were treated with BDQ and/or DLM (31) according to WHO indications at the time (22, 23). A common study protocol guided data collection across participating sites (31). Treatment comprised longer (18 mo or more) individualized treatment regimens composed according to national TB program guidelines and informed by the endTB clinical guide (32). Data collection was standardized across sites and organized by the endTB consortium partners. For this analysis, we included patients who received a first endTB treatment regimen for RR-TB or MDR-TB between April 1, 2015, and March 31, 2018, and had a positive baseline sputum culture. Patients living with HIV and HCV comprised key subgroups; therefore, we excluded all 16 patients in the Democratic People's Republic of Korea, where HIV testing was not conducted and quality control assessments suggested that early HCV test results were invalid.

Outcome
The outcome of interest was sputum culture conversion within the first 6 months of treatment, which correlates with end of treatment outcomes (33, 34) and is used as a standard interim endpoint in studies of MDR-TB treatment (8, 10, 13).

Definitions

Culture conversion within 6 months was defined as two consecutive negative cultures collected at least 15 days apart, the first occurring before 180 days of treatment and the second occurring before 210 days of treatment. We classified patients into subgroups based on HIV infection, HCV infection, DM or glucose intolerance (GI), TB drug resistance category, and a composite variable considering sputum smear grade (3+ vs. <3+) and the presence of cavitation on chest radiograph (yes or no). Baseline HIV and HCV infection as well as DM or GI were determined foremost by laboratory testing. We also considered information in the clinical chart regarding the presence or explicit absence of these conditions. Baseline drug resistance category (i.e., RR-TB or MDR-TB, pre–XDR-TB with fluoroquinolone resistance, pre–XDR-TB with injectable resistance, and XDR-TB) was determined based on all prior available drug susceptibility test results. Extensive disease was established by the presence of both a 3+ positive baseline sputum smear and cavitary disease. This definition was derived from a recent study that found that patients with these characteristics may require longer or more intensive treatment (35).

Statistical Analyses

We estimated the proportion of patients who experienced the outcome of interest. We also calculated the frequency of conversion in the subgroups described above and examined whether these characteristics were associated with conversion. To do this, we conducted multivariable regression analyses using generalized mixed models with a log link (or logit link if the model did not converge) and a random intercept for country. We derived the marginal predictions of the probability of conversion for each subgroup (36) and compared them using χ^2 tests.

Secondary analyses examined effect modification of HIV by CD4 (cluster of differentiation 4) cell count and the effect modification of DM by glycemic control. To examine whether any increased risk of nonconversion among patients with HIV was due to death or loss, we reran analyses excluding deaths and losses occurring in the first 6 months and before conversion. The online supplement includes information on sensitivity analyses, including another multivariable analysis in which we adjusted for additional covariates.

Research Ethics

The endTB Observational Study protocol was approved by central ethics review committees for each consortium partner, and local ethical approval was obtained in all endTB countries. Participants provided written informed consent for inclusion in the observational cohort.

Additional information regarding study methods, including eligibility criteria, definitions, and statistical analyses, can be found in the online supplement.

Results

Overview

Of 2,195 patients initiating a first regimen for RR-TB or MDR-TB with endTB during the study period, 2,071 (94%) consented to participate in the observational study. This analysis included the 1,109 patients with a positive sputum culture within the 90 days before the earliest initiation of BDQ or DLM (Figure 1). Patients living with HIV commonly had no positive culture and were, therefore, included less often in conversion analyses than patients without HIV (43% vs. 56%, respectively). In contrast, patients with HCV, DM or GI, and XDR-TB were more often included than patients without these conditions (62% vs. 54%, 62% vs. 53%, and 64% vs. 54%, respectively).

The 1,109 included patients were treated in 16 endTB countries (Table E1 in the online supplement) and initiated a multidrug regimen containing BDQ (63%), DLM (27%), or both (10%) (Table 1). Linezolid and clofazamine were commonly used, with 82% and 73% of patients receiving these repurposed drugs in their baseline regimen. One-third of the cohort were female, and the median age was 36 years (interquartile range, 27–46) (Table 1). Comorbidities were common; 119 patients (11%) were living with HIV, 144 (13%) were living with HCV, and 181 (17%) met the definition of DM or GI. XDR-TB was found in 389 (36%) patients. Thirteen percent of patients had extensive disease, and 75% had received prior treatment with second-line TB drugs. Among patients living with HIV, 72% (86/119) were known to be on antiretroviral treatment (ART) at the time of BDQ or DLM initiation, and of those with a baseline CD4 cell count, 52% had a value <200 cells/ml. Relative to patients without HIV, patients living with HIV were more likely to be smear negative (44% vs. 26%, respectively). Eighty percent of patients with DM or GI (n = 145) had a baseline HbA1c result; DM was poorly controlled in 57%.

Sputum Culture Conversion

Overall, 939 (85%) patients experienced sputum culture conversion within 6 months. Excluding contaminated cultures, the median number of cultures per person was 5 (interquartile range, 4–6). Fifty-four patients (5%) had no follow-up cultures and were considered not to have experienced culture conversion. Of these, the majority (64%, n = 34) died or were lost to follow-up, and 90% of these outcomes occurred during the first 3 months of treatment. In univariable analyses, living with HIV or HCV or having extensive disease were risk factors for not experiencing culture conversion within 6 months (Table 2). In contrast, the proportion of patients who experienced sputum culture conversion within 6 months did not differ according to baseline resistance category or whether the patient had DM or GI. In the multivariable analyses, only HIV infection and extensive disease were independent risk factors for not experiencing culture conversion within 6 months (Figure 2 and Table E2). Adjusting for resistance category, HCV infection, DM or GI, extensive disease, and year of enrollment, patients living with HIV had a marginal predicted probability of conversion of 0.73 (95% confidence interval [CI], 0.62–0.84) compared with a probability of 0.84 (95% CI, 0.79–0.90) among patients without HIV infection (P = 0.03). Extensive disease was associated with a lower probability of conversion (0.68; 95% CI, 0.57–0.79) relative to patients who had neither cavitary disease nor a sputum smear result of 3+ (0.89; 95% CI, 0.84–0.95; P = 0.0004).

Secondary analyses suggested that HIV infection was a more important risk factor for patients with a CD4 cell count of 200 cells/ml or more relative to those with a CD4 cell count <200 cells/ml (Table 3). HIV remained similarly associated with nonconversion after excluding 71 patients who died or were lost to follow-up before conversion (adjusted odds ratio for full
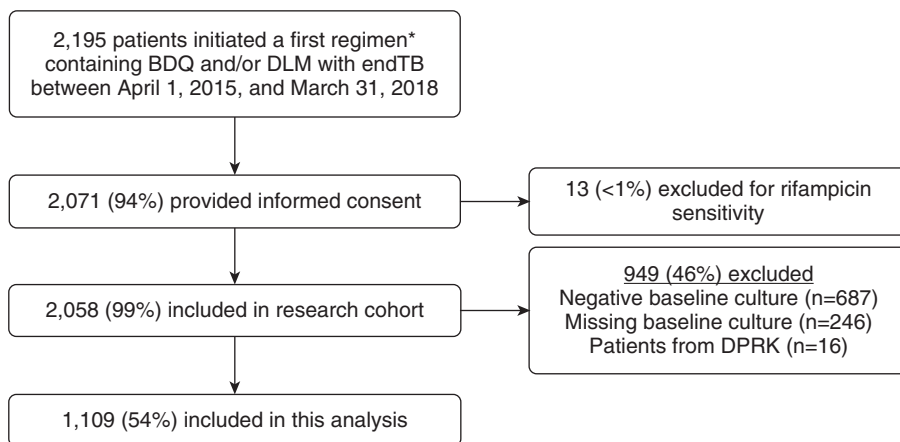
Figure 1. Overview of the analysis cohort. *During the study period, 12 patients initiated a second regimen with endTB containing bedaquiline and/or delamanid. These second regimens were excluded from analyses. BDQ = bedaquiline; DLM = delamanid; DPRK = Democratic People's Republic of Korea; TB = tuberculosis.

cohort of 1,103, 2.12 [95% CI, 1.13–3.97] vs. 2.09 [95% CI, 0.90–4.85] with 71 exclusions). The effect of DM or GI on culture conversion was similar among patients with and without glycemic control at baseline (Table 3).

Results from a multivariable model in which we adjusted for additional covariates were qualitatively similar to results from the primary model (Table E2). Results of other sensitivity analyses did not change the interpretation of findings (Table E3).

Discussion

When national TB programs and partners used BDQ and DLM alongside repurposed drugs such as linezolid in RR-TB or MDR-TB treatment regimens according to WHO guidance, a high proportion of patients experienced sputum culture conversion by 6 months. endTB Observational Study findings are in line with trials and smaller observational cohorts, which have generally reported 6-month conversion outcomes ranging from 70% to 90% (10, 11, 13, 19, 37). This is notable because the endTB cohort included patient groups that are often excluded from trials (i.e., those with HIV and low CD4, XDR-TB, previous treatment for MDR-TB, uncontrolled DM, or coinfection with HIV and hepatitis B or C) (10, 13). Importantly, relative to

culture conversion analyses that censor patients who die, become lost to follow-up, or lack follow-up cultures (e.g., Kaplan-Meier estimates), our approach was conservative in that we classified these patients as having an unfavorable interim outcome (i.e., no conversion) rather than censoring them.

Historically, patients with XDR-TB have experienced a higher risk of unfavorable treatment outcomes than patients with less resistant TB (2). This was not the case in our study. This is likely because the addition of BDQ and DLM as well as repurposed drugs (i.e., linezolid and clofazimine) allowed for the construction of therapeutic TB regimens for these patients, which had previously been impossible. However, patients living with HIV and those with extensive disease were less likely to experience culture conversion within 6 months. Variable interim treatment success across patient subgroups highlights the importance of stratifying and standardizing estimates when drawing comparisons between cohorts.

The combination of a high smear grade and cavitary disease (a phenotype that predicted poor outcomes in a meta-analysis of randomized clinical trials of shortened rifamycin-containing regimens for drug-susceptible TB) (35) was also associated with poor interim outcomes among patients with MDR-TB receiving longer (18 mo or longer) regimens. Identifying

optimal treatment strategies for this subgroup is an important research priority, especially in light of movement toward all-oral shortened regimens.

In secondary analyses, we found some evidence that the lower frequency of culture conversion experienced by patients living with HIV was more pronounced among those who had high CD4 cell counts. This may be a chance finding and must be interpreted with caution because of small numbers and some missing data for baseline CD4 cell count. On the other hand, among patients living with HIV, TB may present differently across the spectrum of CD4 cell counts; patients with lower CD4 cell counts are more likely to have paucibacillary sputum and less parenchymal involvement, and, therefore, their sputum may convert to culture negative more quickly (38, 39). Although TB in patients with HIV and higher CD4 cell count may present more like that observed in HIV-negative patients (e.g., with higher smear grade and cavitary disease), underlying HIV-related immune deficits might still preclude a comparable treatment response. Furthermore, the development of TB disease in patients with high CD4 cell counts may induce HIV disease progression and death (40). Our findings highlight an urgent need to optimize MDR-TB treatment outcomes among patients living with HIV. One recent study raised the possibility that the ART modifications required for patients receiving BDQ might increase pill burden and decrease adherence (41). New WHO recommendations for once-daily dolutegravir-containing ART (42) will ease the difficulties of modifications previously required for patients living with HIV who are receiving BDQ.

Patients with HCV infection may be at increased risk of unfavorable TB treatment outcomes because of an increased risk of anti-TB drug–induced liver injury (43), limited treatment options resulting from anti-TB drug–induced liver injury, or shared risk factors for HCV and MDR-TB that may also place them at higher risk (i.e., substance abuse). In univariable analyses, HCV was associated with a 45% increase in the risk of nonconversion within 6 months (95% CI, 1–107%). After adjustment for other comorbid conditions, TB drug resistance category, and extensive disease, this indicator of HCV infection was associated with only a small to moderate increase in the probability of

Table 1. Baseline Characteristics of Patients Initiating a BDQ- or DLM-Containing Regimen with a Positive Sputum Culture ($N = 1,109$)

Characteristic	Results
Demographics	
Age at treatment initiation, yr, median (interquartile range; range)	36 (27–46; 12–82)
Sex, F	365 (33)
Comorbidities	
Diabetes mellitus or glucose intolerance ($n = 1,089$)	181 (17)
Poorly controlled diabetes mellitus (HbA1c >8.0%) ($n = 145$)*	83 (57)
HIV infection	119 (11)
CD4 cell count ($n = 93$), median (interquartile range; range)[†]	194 (58–305; 4–722)
CD4 cell count <200 cells/ml ($n = 93$)[†]	48 (52)
On antiretroviral treatment ($n = 114$)	86 (75)
Months on antiretroviral treatment, median (interquartile range; range) ($n = 84$)	25 (4–76; 0–188)
Hepatitis B virus infection ($n = 1,103$)[‡]	46 (4)
Hepatitis C virus infection ($n = 1,103$)[§]	144 (13)
At least one comorbidity other than those above	115 (10)
TB-related characteristics	
Prior TB treatment with second-line drugs	832 (75)
Bilateral disease ($n = 1,017$)[‖]	726 (71)
Cavitary disease ($n = 999$)[‖]	658 (66)
Smear positive sputum by grade (if positive) ($n = 1,086$)	723 (67)
Scanty	55 (5)
1+	333 (31)
2+	198 (18)
3+	192 (18)
Cavitary disease and smear status ($n = 980$)	
No cavitary disease, smear <3+	292 (30)
Cavitary disease, smear <3+	520 (53)
No cavitary disease, smear 3+	40 (4)
Cavitary disease, smear 3+ (extensive disease)	128 (13)
Resistance profile ($n = 1,094$)	
RR-TB or MDR-TB without any injectable or fluoroquinolone resistance	223 (20)
RR-TB or MDR-TB without any injectable or fluoroquinolone testing	50 (5)
RR-TB or MDR-TB with any injectable resistance[¶]	104 (10)
RR-TB or MDR-TB with any fluoroquinolone resistance**	328 (30)
XDR-TB	389 (36)
Body mass index < 18.5 ($n = 1,099$)	483 (44)
Only WHO indication for BDQ or DLM was TB drug toxicity[††]	149 (13)
Drugs comprising the baseline regimen	
BDQ (without DLM)	696 (63)
DLM (without BDQ)	303 (27)
Both BDQ and DLM	110 (10)
Moxifloxacin or levofloxacin	646 (58)
Amikacin	138 (12)
Capreomycin	274 (25)
Kanamycin	69 (6)
Linezolid	911 (82)
Clofazimine	804 (73)
Imipenem and cilastatin or meropenem and amoxicillin-clavulanate	240 (22)
Prothionamide or ethionamide	463 (42)
Cycloserine	735 (66)
P-aminosalicylic acid	313 (28)
Number of likely effective drugs included in baseline regimen, median (interquartile range; range)[‡‡]	5 (4–5; 0–8)

Definition of abbreviations: BDQ = bedaquiline; CD4 = cluster of differentiation 4; DLM = delamanid; MDR = multidrug resistant; RR = rifampin-resistant; TB = tuberculosis; WHO = World Health Organization; XDR = extensively drug resistant.

Results are *n* (%) unless otherwise noted.

*For the purposes of assessing diabetes mellitus disease control, we considered HbA1c results taken up to 90 days before initiation of the BDQ- or DLM-containing regimen or up to 15 days after, with preference given to before.

[†]Baseline CD4 cell count was determined based on the most recent laboratory value corresponding to the 180 days before initiation of a BDQ- or DLM-containing regimen with endTB. In the absence of a laboratory result, the CD4 cell count recorded on the baseline clinical form was used.

[‡]Hepatitis B virus surface antigen positive.

[§]Hepatitis C virus antibody positive.

[‖]Baseline chest radiograph was taken before initiation of the BDQ- or DLM-containing regimen or up to 15 days after (with preference given to before).

[¶]Four people in this group lacked a fluoroquinolone susceptibility test result.

**One person in this group lacked an injectable susceptibility test result.

[††]A regimen of at least four likely effective drugs could not be constructed due to toxicity (vs. resistance).

[‡‡]A drug was considered likely effective if *1*) all reported testing (phenotypic or genotypic) to that drug confirmed susceptibility or *2*) no resistance to the drug was reported and the patient had not previously received the drug for 1 month or more. Otherwise, the drug was not considered likely effective.

Table 2. Frequency of Sputum Culture Conversion among High-Risk Subpopulations Receiving an MDR-TB Regimen Containing BDQ and/or DLM and Risk Factors for Nonconversion (N = 1,109)

Patients	n/N	Proportion Converted within 6 mo	Univariable Risk Ratio for Nonconversion [Ratio (95% Confidence Interval)]	P Value
All patients	939/1,109	0.85	—	—
HIV infection				
Negative	857/990	0.87	Reference	
Positive	82/119	0.69	1.75 (1.16–2.65)	0.007
Hepatitis C infection				
Negative	826/959	0.86	Reference	
Positive	112/144	0.78	1.45 (1.01–2.07)	0.04
Diabetes mellitus or glucose intolerance*				
No	764/908	0.84	Reference	
Yes	161/181	0.89	0.80 (0.52–1.23)	0.31
Baseline resistance*				0.17[†]
MDR without additional resistance	185/223	0.83	Reference	
MDR without injectable and fluoroquinolone testing	42/50	0.84	0.90 (0.46–1.77)	0.76
Pre-XDR with injectable resistance	87/104	0.84	0.89 (0.53–1.51)	0.67
Pre-XDR with fluoroquinolone resistance	291/328	0.89	0.67 (0.44–1.04)	0.07
XDR	324/389	0.83	1.14 (0.76–1.69)	0.53
Cavitary disease and smear status*				<0.0001[†]
No cavitary disease, smear <3+	265/292	0.91	Reference	
Cavitary disease, smear <3+	456/520	0.88	1.23 (0.79–1.91)	0.35
No cavitary disease, smear 3+	30/40	0.75	2.72 (1.49–4.95)	0.001
Cavitary disease, smear 3+ (extensive disease)	91/128	0.71	2.94 (1.84–4.68)	<0.0001

Definition of abbreviations: BDQ = bedaquiline; DLM = delamanid; MDR = multidrug resistant; TB = tuberculosis; XDR = extensively drug resistant.
*Univariable model included a missing indicator variable.
[†]Type III test.

nonconversion, and the CIs around this estimate were wide, falling below 1. Many endTB country sites tested for antibodies to HCV rather than antigen or viral load and therefore could not distinguish between chronic and cleared infections. Because infection is spontaneously cleared in approximately 30% of individuals infected with HCV, it is likely that some participants who were HCV antibody positive did not have chronic infection (44). If chronic, but not past, transient HCV infection decreases the probability of conversion within 6 months, this misclassification could have attenuated our effect estimates for HCV (i.e., a true positive association between active HCV infection and absence of conversion would be underestimated or null). Future research should examine whether patients with HCV viremia are at a higher risk for unfavorable outcomes and how treatment with direct-acting antivirals may mitigate any increased risk.
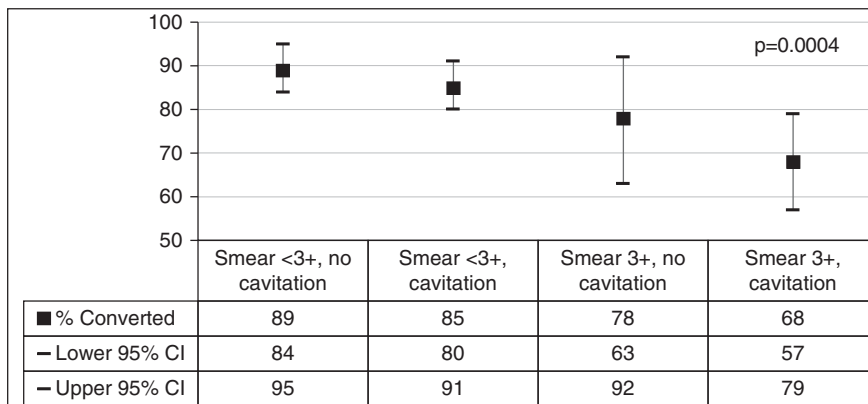
Although patients with TB and DM are more likely to experience adverse treatment outcomes, including death, relapse, and absence of early sputum culture conversion, relative to patients with TB but no DM (25), we did not observe an association between DM or GI and culture conversion within 6 months. Recent evidence suggests that glycemic control may reduce the risk of adverse outcomes among patients with TB and DM (25). If patients in our study went on to experience glycemic control, this could explain the absence of an association between baseline DM or GI and culture conversion. A limitation to our classification of DM or GI was that because DM testing occurred programmatically, patients may have been referred for confirmatory testing, and these results were not always available for research purposes. Therefore, in some instances we were unable to distinguish between a diagnosis of DM and an episode of GI.
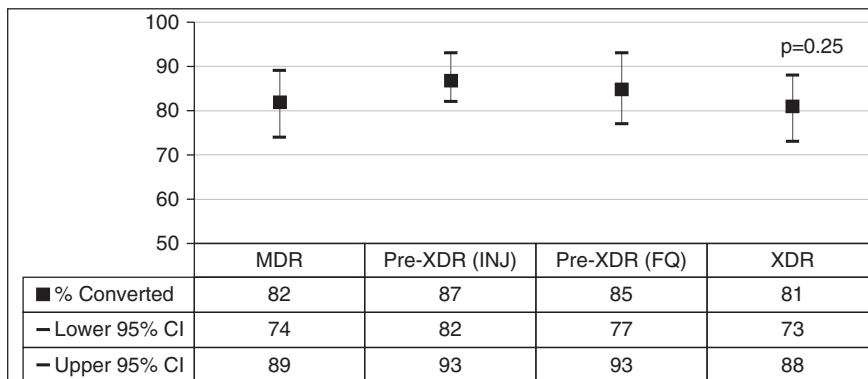
In addition to illustrating that overall good interim outcomes were sustained in several high-risk subgroups, these analyses highlight another unique feature of this study, as follows: TB programs had the option of using BDQ or DLM in patients included in this observational cohort. The choice was made according to local policy and WHO indications in effect at the time of the study, which were different for the two drugs (only BDQ was recommended for patients in whom a regimen of at least four likely effective drugs could not be constructed because of toxicity or resistance generally; DLM use was suggested for patients with high risk for an unfavorable treatment outcome; and either [or both] could be used for patients with resistance to fluoroquinolones and/or injectable agents) (22, 23). Consequently, the results presented herein are the comprehensive, programmatic result achieved through the sum of clinicians' interpretations of this guidance across 16 countries; the comparison of results of regimens containing one or the other of these drugs is not, therefore, appropriate. Instead, we aim to inform programs about the range of results that could be expected if both drugs were used according to the WHO guidance in place between 2015 and 2017, when the endTB Observational Study cohort was enrolled.

A   Extent of disease

	Smear <3+, no cavitation	Smear <3+, cavitation	Smear 3+, no cavitation	Smear 3+, cavitation
■ % Converted	89	85	78	68
— Lower 95% CI	84	80	63	57
— Upper 95% CI	95	91	92	79

p=0.0004

B   Resistance pattern

	MDR	Pre-XDR (INJ)	Pre-XDR (FQ)	XDR
■ % Converted	82	87	85	81
— Lower 95% CI	74	82	77	73
— Upper 95% CI	89	93	93	88

p=0.25

C   Comorbidities

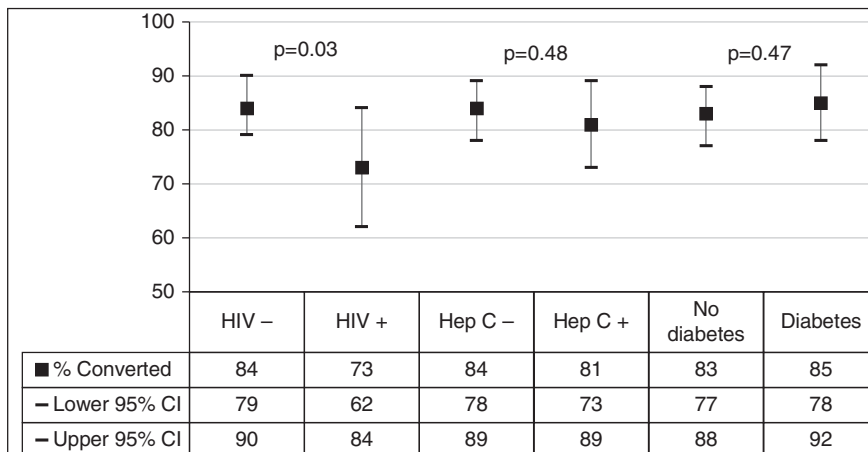|	HIV −	HIV +	Hep C −	Hep C +	No diabetes	Diabetes
■ % Converted	84	73	84	81	83	85
— Lower 95% CI	79	62	78	73	77	78
— Upper 95% CI	90	84	89	89	88	92

p=0.03   p=0.48   p=0.47

Figure 2. Marginal predictions of the probability of culture conversion within 6 months, according to baseline (A) extent of disease, (B) resistance pattern, and (C) presence of comorbidity (n = 1,103). Each probability is adjusted for the other covariates shown in this panel and year of enrollment. CI = confidence interval; FQ = fluoroquinolone resistance; Hep C = hepatitis C; INJ = injectable resistance; MDR = multidrug resistant; XDR = extensively drug resistant.

The following limitation of this study is inherent in the use of sputum culture conversion as the endpoint: analysis is necessarily restricted to patients with a positive baseline sputum culture. A large proportion of patients in this and other cohorts do not meet this criterion and, therefore, are excluded from interim analyses, potentially limiting generalizability. There were several reasons for initiating treatment without a positive baseline culture. First, some patients were diagnosed with TB on the basis of molecular tests, such as GeneXpert, rather than culture. Second, in some patients, BDQ or DLM replaced a toxic drug in an ongoing MDR-TB regimen (at least 13% of this cohort). Third, we limited the period in which cultures could be counted as "baseline" to 90 days before the first initiation of BDQ or DLM. Patients were not included in this analytic cohort if their most recent positive culture preceded this window. Last, some patients, including children, are unable to produce the sputum sample needed for culture or simply have culture-negative pulmonary TB disease. An interim indicator of treatment success is equally important for patients who initiate treatment with a positive or negative culture result. Validating an interim outcome that can also be applied to patients who do not initiate treatment with a positive sputum culture is an important area of future research.

A lack of informed consent precluded the inclusion of a minority of eligible patients in the observational study (6%). These exclusions could introduce bias if associated with a risk factor of interest (e.g., HIV infection) and culture conversion. Although we were not able to compare the characteristics of patients who did and did not provide consent, we expect that this potential bias to be limited by the high participation rate. A third limitation relates to our use of the odds ratio as a measure of association when the binomial model failed to converge. The odds ratio will be farther from the null value than the corresponding risk ratio, with discrepancies between the two measures increasing as the effect size and risk of the outcome increase. In our cohort, the outcome of nonconversion occurred at a frequency of 15%; therefore, the odds ratios may be most usefully interpreted as relative risks for the purposes of qualitative, rather than literal, assessments of effects (45). To circumvent this limitation of the odds ratio and to facilitate the interpretation and assessment of effect size, our primary analyses report average marginal probabilities of conversion. Fourth, local laboratory capacity and norms determined whether cultures were grown in liquid or solid

Table 3. Effect Modification of HIV by CD4 Cell Count and Effect Modification of Diabetes Mellitus by Glycemic Control

Effect	Adjusted Odds Ratio* for No Culture Conversion [*Ratio (95% Confidence Interval)*]	*P* Value
Does any effect of HIV depend on CD4 cell count? (*n* = 1,079)*[†][‡]		
No HIV infection (*n* = 987)	Reference	
HIV infection, CD4 ⩾ 200 cells/ml (*n* = 45)	3.24 (1.47–7.13)	0.004
HIV infection, CD4 < 200 cells/ml (*n* = 47)	1.41 (0.58–3.45)	0.45
Does any of effect of diabetes mellitus depend on glycemic control? (*n* = 1,086)*[§][‖]		
No diabetes mellitus (*n* = 905)	Reference	
Diabetes mellitus, controlled (*n* = 62)	1.00 (0.44–2.27)	0.99
Diabetes mellitus, uncontrolled (*n* = 83)	0.75 (0.34–1.6)	0.47

Definition of abbreviation: CD4 = cluster of differentiation 4.
*Models included variables shown in table, year of enrollment, hepatitis C infection, diabetes mellitus or glucose intolerance, tuberculosis drug resistance pattern, and extent of disease. The interaction term for diabetes mellitus or glucose intolerance was not included in the model examining HIV-related interactions, and vice versa.
[†]*P* value for interaction by CD4 cell count was 0.09.
[‡]Twenty-four patients were excluded from this analysis because of missing data on CD4 cell count.
[§]*P* value for interaction by disease control was 0.60.
[‖]Thirty-six patients were excluded from this analysis because of the absence of a baseline HbA1c value to determine glycemic control.

medium, and we did not analyze whether culture type impacted culture conversion.

Spanning 17 countries on five continents, the endTB Observational Study is the largest multicenter cohort of patients with RR-TB or MDR-TB treated with DLM- and BDQ-containing regimens. We observed culture conversion by 6 months in 85% of the study population, which was particularly remarkable given that patients were treated under routine—not trial—conditions and commonly had comorbidities, XDR-TB, and/or prior treatment for MDR-TB. These findings underscore the importance of expanding access to BDQ, DLM, and repurposed drugs, such as linezolid, to patients with RR-TB or MDR-TB throughout the world. The lower frequency of conversion among patients with HIV highlights the continued need to ensure early diagnosis of, and optimized treatment for, both conditions. ∎

References

1. World Health Organization. Global tuberculosis report 2019. Geneva, Switzerland: World Health Organization; 2019 [accessed 2020 Oct 28]. Available from: https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1.
2. World Health Organization. Global tuberculosis report 2018. Geneva, Switzerland: World Health Organization; 2018 [accessed 2020 Oct 28]. Available from: http://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf?ua=1.
3. Isaakidis P, Rangan S, Pradhan A, Ladomirska J, Reid T, Kielmann K. 'I cry every day': experiences of patients co-infected with HIV and multidrug-resistant tuberculosis. *Trop Med Int Health* 2013;18:1128–1133.
4. Modongo C, Sobota RS, Kesenogile B, Ncube R, Sirugo G, Williams SM, et al. Successful MDR-TB treatment regimens including amikacin are associated with high rates of hearing loss. *BMC Infect Dis* 2014;14:542.
5. Arnold A, Cooke GS, Kon OM, Dedicoat M, Lipman M, Loyse A, et al. Adverse effects and choice between the injectable Agents amikacin and capreomycin in multidrug-resistant tuberculosis. *Antimicrob Agents Chemother* 2017;61:e02586-16.
6. Sagwa EL, Ruswa N, Mavhunga F, Rennie T, Leufkens HGM, Mantel-Teeuwisse AK. Comparing amikacin and kanamycin-induced hearing loss in multidrug-resistant tuberculosis treatment under programmatic conditions in a Namibian retrospective cohort. *BMC Pharmacol Toxicol* 2015;16:36.

7. Reuter A, Tisile P, von Delft D, Cox H, Cox V, Ditiu L, et al. The devil we know: is the use of injectable agents for the treatment of MDR-TB justified? *Int J Tuberc Lung Dis* 2017;21:1114–1126.
8. Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med* 2012;366:2151–2160.
9. Pym AS, Diacon AH, Tang S-J, Conradie F, Danilovits M, Chuchottaworn C, et al.; TMC207-C209 Study Group. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. *Eur Respir J* 2016;47:564–574.
10. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al.; TMC207-C208 Study Group. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014;371:723–732.
11. Mbuagbaw L, Guglielmetti L, Hewison C, Bakare N, Bastard M, Caumes E, et al. Outcomes of bedaquiline treatment in patients with multidrug-resistant tuberculosis. *Emerg Infect Dis* 2019;25:936–943.
12. Mok J, Kang H, Koh W-J, Jhun BW, Yim J-J, Kwak N, et al. Final treatment outcomes of delamanid-containing regimens in patients with MDR-/XDR-TB in South Korea. *Eur Respir J* 2019;54:1900811.
13. von Groote-Bidlingmaier F, Patientia R, Sanchez E, Balanag V Jr, Ticona E, Segura P, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. *Lancet Respir Med* 2019;7:249–259.

14. Schnippel K, Ndjeka N, Maartens G, Meintjes G, Master I, Ismail N, *et al*. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. *Lancet Respir Med* 2018;6:699–706.

15. Borisov SE, Dheda K, Enwerem M, Romero Leyet R, D'Ambrosio L, Centis R, *et al*. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. *Eur Respir J* 2017;49:1700387.

16. 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: 1393–1400.

17. Gupta R, Geiter LJ, Wells CD, Gao M, Cirule A, Xiao H. Delamanid for extensively drug-resistant tuberculosis. *N Engl J Med* 2015;373: 291–292.

18. Wells CD, Gupta R, Hittel N, Geiter LJ. Long-term mortality assessment of multidrug-resistant tuberculosis patients treated with delamanid. *Eur Respir J* 2015;45:1498–1501.

19. Bastard M, Guglielmetti L, Huerga H, Hayrapetyan A, Khachatryan N, Yegiazaryan L, *et al*. Bedaquiline and repurposed drugs for fluoroquinolone-resistant multidrug-resistant tuberculosis: how much better are they? *Am J Respir Crit Care Med* 2018;198: 1228–1231.

20. Seung KJ, Khan P, Franke MF, Ahmed S, Aiylchiev S, Alam M, *et al*. Culture conversion at 6 months in patients receiving delamanid-containing regimens for the treatment of multidrug-resistant tuberculosis. *Clin Infect Dis* 2020;71:415–418.

21. World Health Organization. Consolidated guidelines on drug-resistant tuberculosis treatment. Geneva, Switzerland: World Health Organization; 2019 [accessed 2020 Oct 28]. Available from: https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/.

22. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis interim policy guidance. Geneva, Switzerland: World Health Organization; 2013 [accessed 2020 Oct 28]. Available from: https://apps.who.int/iris/bitstream/handle/10665/84879/9789241505482_eng.pdf;jsessionid=4921D7DAFD36DC11C54EE3A12CDBA830?sequence=1.

23. World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis interim policy guidance. Geneva, Switzerland: World Health Organization; 2014 [accessed 2020 Oct 28]. Available from: https://apps.who.int/iris/bitstream/handle/10665/137334/WHO_HTM_TB_2014.23_eng.pdf?sequence=1.

24. Bastos ML, Lan Z, Menzies D. An updated systematic review and meta-analysis for treatment of multidrug-resistant tuberculosis. *Eur Respir J* 2017;49:1600803.

25. Huangfu P, Ugarte-Gil C, Golub J, Pearson F, Critchley J. The effects of diabetes on tuberculosis treatment outcomes: an updated systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2019;23: 783–796.

26. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. *Int J Tuberc Lung Dis* 2011;15:871–885.

27. Wells CD, Cegielski JP, Nelson LJ, Laserson KF, Holtz TH, Finlay A, *et al*. HIV infection and multidrug-resistant tuberculosis: the perfect storm. *J Infect Dis* 2007;196:S86–S107.

28. Ungo JR, Jones D, Ashkin D, Hollender ES, Bernstein D, Albanese AP, *et al*. Antituberculosis drug–induced hepatotoxicity: the role of hepatitis C virus and the human immunodeficiency virus. *Am J Respir Crit Care Med* 1998;157:1871–1876.

29. Chang T-E, Huang Y-S, Chang C-H, Perng C-L, Huang Y-H, Hou M-C. The susceptibility of anti-tuberculosis drug-induced liver injury and chronic hepatitis C infection: a systematic review and meta-analysis. *J Chin Med Assoc* 2018;81:111–118.

30. Lomtadze N, Kupreishvili L, Salakaia A, Vashakidze S, Sharvadze L, Kempker RR, *et al*. Hepatitis C virus co-infection increases the risk of anti-tuberculosis drug-induced hepatotoxicity among patients with pulmonary tuberculosis. *PLoS One* 2013;8:e83892.

31. Khan U, Huerga H, Khan AJ, Mitnick CD, Hewison C, Varaine F, *et al*. The endTB observational study protocol: treatment of MDR-TB with bedaquiline or delamanid containing regimens. *BMC Infect Dis* 2019;19:733.

32. endTB Consortium. endTB clinical and programmatic guide for patient management with new TB drugs. Version 4.0; January 2018 [accessed 2020 Oct 28]. Available from: https://samumsf.org/sites/default/files/2018-06/EndTB%20Guide%20for%20New%20TB%20Drugs%20Version%204.0.pdf.

33. Kurbatova EV, Cegielski JP, Lienhardt C, Akksilp R, Bayona J, Becerra MC, *et al*. Sputum culture conversion as a prognostic marker for end-of-treatment outcome in patients with multidrug-resistant tuberculosis: a secondary analysis of data from two observational cohort studies. *Lancet Respir Med* 2015;3:201–209.

34. Holtz TH, Sternberg M, Kammerer S, Laserson KF, Riekstina V, Zarovska E, *et al*. Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to treatment outcome. *Ann Intern Med* 2006;144:650–659.

35. Imperial MZ, Nahid P, Phillips PPJ, Davies GR, Fielding K, Hanna D, *et al*. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. *Nat Med* 2018;24:1708–1715.

36. Muller CJ, MacLehose RF. Estimating predicted probabilities from logistic regression: different methods correspond to different target populations. *Int J Epidemiol* 2014;43:962–970.

37. Kim CT, Kim TO, Shin HJ, Ko YC, Hun Choe Y, Kim HR, *et al*. Bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis: a multicentre cohort study in Korea. *Eur Respir J* 2018;51:1702467.

38. Chamie G, Luetkemeyer A, Walusimbi-Nanteza M, Okwera A, Whalen CC, Mugerwa RD, *et al*. Significant variation in presentation of pulmonary tuberculosis across a high resolution of CD4 strata. *Int J Tuberc Lung Dis* 2010;14:1295–1302.

39. Hanrahan CF, Theron G, Bassett J, Dheda K, Scott L, Stevens W, *et al*. Xpert MTB/RIF as a measure of sputum bacillary burden: variation by HIV status and immunosuppression. *Am J Respir Crit Care Med* 2014;189:1426–1434.

40. Collins KR, Quiñones-Mateu ME, Toossi Z, Arts EJ. Impact of tuberculosis on HIV-1 replication, diversity, and disease progression. *AIDS Rev* 2002;4:165–176.

41. O'Donnell MR, Padayatchi N, Daftary A, Orrell C, Dooley KE, Rivet Amico K, *et al*. Antiretroviral switching and bedaquiline treatment of drug-resistant tuberculosis HIV co-infection. *Lancet HIV* 2019;6:e201–e204.

42. World Health Organization. Update of Recommendations on first-and second-line antiretroviral regimens. Geneva, Switzerland: World Health Organization; 2019. [accessed 2020 Oct 28]. Available from: https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf?ua=1.

43. Kim WS, Lee SS, Lee CM, Kim HJ, Ha CY, Kim HJ, *et al*. Hepatitis C and not Hepatitis B virus is a risk factor for anti-tuberculosis drug induced liver injury. *BMC Infect Dis* 2016;16:50.

44. World Health Organization. Hepatitis C key facts. Geneva, Switzerland: World Health Organization; 2019 [accessed 2020 Oct 28]. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c.

45. Davies HTO, Crombie IK, Tavakoli M. When can odds ratios mislead? *BMJ* 1998;316:989–991.