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One Step Forward: Successful End-of-Treatment Outcomes of Patients With Drug-Resistant Tuberculosis Who Received Concomitant Bedaquiline and Delamanid in Mumbai, India

Mrinalini Das,[1] Alpa Dalal,[2] Chinmay Laxmeshwar,[1] Shilpa Ravi,[1] Fatima Mamnoon,[1] Augusto C. Meneguim,[1] Roma Paryani,[1] Taanya Mathur,[1] Pramila Singh,[1] Homa Mansoor,[1] Stobdan Kalon,[1] Farah Naz Hossain,[1] Nathalie Lachenal,[3] Sylvine Coutisson,[3] Gabriella Ferlazzo,[4] and Petros Isaakidis[4]

[1]Médecins Sans Frontières, Mumbai, India, [2]Jupiter Hospital, Thane, Maharashtra, India, [3]Pharmacovigilance Unit, Médecins Sans Frontières, Geneva, Switzerland, and [4]Southern Africa Medical Unit, Médecins Sans Frontières, Cape Town, South Africa

Background. The Médecins Sans Frontières Clinic in Mumbai, India, has been providing concomitant bedaquiline (BDQ) and delamanid (DLM) in treatment regimen for patients with drug-resistant tuberculosis (DR-TB) and limited therapeutic options, referred from other healthcare institutions, since 2016. The study documents the end-of-treatment outcomes, culture-conversion rates, and serious adverse events (SAEs) during treatment.

Methods. This was a retrospective cohort study based on routinely collected program data. In clinic, treatment regimens are designed based on culture drug sensitivity test patterns and previous drug exposures, and are provided for 20–22 months. BDQ and DLM are extended beyond 24 weeks as off-label use. Patients who initiated DR-TB treatment including BDQ and DLM (concomitantly for at least 4 weeks) during February 2016–February 2018 were included.

Results. Of the 70 patients included, the median age was 25 (interquartile range [IQR], 22–32) years and 56% were females. All except 1 were fluoroquinolone resistant. The median duration of exposure to BDQ and DLM was 77 (IQR, 43–96) weeks. Thirty-nine episodes of SAEs were reported among 30 (43%) patients, including 5 instances of QTc prolongation, assessed as possibly related to BDQ and/or DLM. The majority (69%) had culture conversion before 24 weeks of treatment. In 61 (87%), use of BDQ and DLM was extended beyond 24 weeks. Successful end-of-treatment outcomes were reported in 49 (70%) patients.

Conclusions. The successful treatment outcomes of this cohort show that regimens including concomitant BDQ and DLM for longer than 24 weeks are effective and can be safely administered on an ambulatory basis. National TB programs globally should scale up access to life-saving DR-TB regimens with new drugs.

Keywords. all-oral regimen; active TB drug-safety monitoring and management (aDSM); cDST; carbapenem; XDR-TB.

The management of drug-resistant (DR) tuberculosis (TB) is known to be challenging. In 2018, the number of new cases of rifampicin-resistant TB in the world were 500 000 (among which 78% were multidrug-resistant [MDR] TB), and the global treatment success rate for rifampicin-resistant/MDR-TB was 56% [1]. Innovative strategies for treatment are required to tackle the high rates of unfavorable outcomes and treatment-related adverse events in patients with DR-TB (MDR-TB and extensively drug-resistant [XDR] TB) [2].

Bedaquiline (BDQ) and delamanid (DLM) are 2 new drugs recommended for treatment of DR-TB by the World Health Organization (WHO) [3–6]. The effectiveness of these individual drugs in treatment regimens have been proven by clinical trials and also under programmatic conditions [7–10]. The 2019 WHO consolidated guidelines on DR-TB recommend concomitant use of BDQ and DLM for DR-TB treatment as "safe"; however, the effectiveness could not be confirmed due to lack of evidence [11].

Clinical trials evaluating the use of BDQ and DLM are still ongoing [12, 13]; however, the interim outcomes of the DELamanId BEdaquiline for ResistAnt TubErculosis (DELIBERATE) trial (NCT02583048) has shown promising results (no deaths, low occurrence of adverse events) for the concomitant use of BDQ and DLM in DR-TB treatment [13]. A systematic review and few individual studies have presented early findings of safety and effectiveness of treatment regimens

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Correspondence: M. Das, Médecins Sans Frontières, Pitruchaaya Building, Sanghavi Corporate Park, Govandi East, Mumbai Maharashtra 400 088, India (msfocb-delhi-epi@brussels.msf.org).

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for DR-TB including BDQ and DLM [14–17]. However, studies reporting end-of-treatment (EOT) outcomes including adverse events are still limited. In addition, patients are usually offered a DR-TB regimen including BDQ and DLM for 24 weeks, however, in some circumstances the removal of BDQ and DLM may lead to a suboptimal regimen. Though the safety of using BDQ beyond 24 weeks has been highlighted in the 2019 WHO consolidated DR-TB guidelines, the use of BDQ or DLM beyond 24 weeks has been recommended as "off-label" use [6, 11, 18]. This highlights the need of additional evidence around safety and effectiveness of concomitant BDQ and DLM for >24 weeks [19].

Médecins Sans Frontières (MSF) has been providing treatment for patients with DR-TB (pre–XDR-TB and XDR-TB) on ambulatory basis with regimens including concomitant BDQ and DLM on compassionate grounds, in its independent clinic in Mumbai, India since 2016. To add to the body of evidence around safety and effectiveness of DR-TB treatment including BDQ and DLM, this study aimed to describe the final treatment outcomes, culture conversion status, and serious adverse events (SAEs) (including QTcF >500 ms) during DR-TB treatment including BDQ and DLM. The study also analyzed treatment outcomes and SAEs in the subgroup of patients who received BDQ and DLM for >24 weeks. We believe the study results will provide evidence for policy and practice recommendations regarding treatment regimens including concomitant BDQ and DLM beyond 24 weeks for patients with DR-TB.

METHODS

Study Design

This was a retrospective cohort study using routinely collected clinical data.

Study Setting

Mumbai is one of the most populous cities in India with a population of 18.4 million [20]. A total of 10 621 patients with MDR-TB were diagnosed in Maharashtra in 2019. Mumbai contributes 22% of TB cases reported in the state of Maharashtra [21, 22]. Mumbai is known to have a high proportion of MDR-TB with fluoroquinolone resistance and advanced TB resistance profiles [23, 24]. Access to BDQ and DLM in India was initially restricted to patients with limited treatment options. In 2019, the Indian National TB Elimination Programme updated its guidelines in line with WHO recommendations, to include BDQ among group A drugs, to be used for all patients with DR-TB, and DLM to group C, recommended when an effective regimen cannot be designed with only drugs from groups A and B [22, 25]. The concomitant administration of BDQ and DLM in DR-TB treatment regimens is carried out in selected healthcare institutions on compassionate grounds for patients among whom a 4-drug effective treatment regimen cannot be prepared with group A and B drugs [16, 25, 26].

The MSF independent clinic in Mumbai has been providing free-of-charge treatment and care to patients with DR-TB since 2007 [27]. The clinic offers treatment to patients with complex TB resistance profiles, who are referred from private or public institutions. These patients may have had multiple episodes of TB treatment from multiple healthcare providers in the past [28]. Thus, at the time of enrollment in the MSF Clinic, patients already have complex TB disease with advanced TB drug resistance. The majority of them are exposed to the second- and third-line TB drugs and have only 1 or 2 effective drugs from groups A and B. Therefore, the patients are left with no treatment options in standard TB treatment packages [29]. Patients are evaluated using GeneXpert, first- and second-line line probe assays, and culture-based drug susceptibility testing (DST). If these evaluations were carried out 3 months prior to referral, then they are accepted for treatment preparation. Chest radiographs (CXRs) are done if requested by the pulmonologist. Treatment regimens are individualized based on DST pattern and previous exposure to TB drugs. The treatment is provided for 20–22 months. Clinical and psychosocial support is provided by a multidisciplinary team to enable patients to complete their treatment successfully.

Individualized regimens including concomitant BDQ and DLM in treatment for patients with DR-TB have been provided by MSF for patients with limited treatment options since February 2016. All cases are reviewed by a DR-TB technical expert committee (a group of clinicians including pulmonologists and infectious diseases specialists) before treatment initiation. The extended use of BDQ and DLM beyond 24 weeks is based on the WHO guidelines for off-label use of BDQ and DLM for DR-TB treatment [6] and other international guidelines [30]. The criteria for extended use of new TB drugs beyond 24 weeks are (1) lack of 4 effective TB drugs (without new TB drugs) to form an effective regimen; (2) lack of culture conversion at the end of month 3; (3) nonimprovement of clinical condition of the patient (eg, persistent symptoms, no weight gain, CXR abnormalities), as assessed by the doctors' committee.

Monitoring consists of regular clinical follow-up, sputum culture, blood analysis including liver and renal function, and other recommended tests. When the treatment is initiated, the clinical and laboratory follow-up (including electrocardiographic [ECG] monitoring for assessing cardiotoxicity) is carried out every 2 weeks for the first 3 months. After 3 months or once the patient is comfortable with the treatment, whichever is later, monthly routine clinical and laboratory (hematological, culture, biochemistry, ECG) follow-ups are carried out. The QTcFs are calculated by the treating physician using the Fridericia formula.

Patients are given a phone number to contact in case of emergencies (active 24/7) and advised to visit the clinic any day if they experience any adverse event. All adverse event episodes are clinically managed in a stepwise manner: first managed

symptomatically; later, if required, lowering the dose; followed by intermittent stopping of the likely associated drug. SAEs (following international guidelines [30]) are recorded by the clinical team. The grading of SAEs is based on symptoms reported by patients and follow-up questions asked by the treating physician [31]. The SAEs were graded by the treating physician, on the same day, in consultation with the clinical team, and reported to the MSF pharmacovigilance unit based in Geneva, Switzerland. The pharmacovigilance team reviews the categorization of SAEs, reverts to the clinical team for any clarification, and follows SAE to assign their outcomes.

Study Population

All patients who initiated DR-TB treatment including concomitant BDQ and DLM (for at least 4 weeks during treatment) in the MSF Clinic during February 2016–February 2018 were included in the study. All patients had EOT outcome by November 2019.

The exclusion criteria were (1) DR-TB patients who received either BDQ or DLM but not both; or (2) DR-TB patients who received concomitant BDQ and DLM for <4 weeks during treatment for any reason (including death and loss to follow-up).

Operational Definitions

1. DR-TB resistance profiles: Standard definitions of pre–XDR TB and XDR-TB were used [30].
2. SAEs: Any untoward medical occurrence, regardless of its cause (including TB-related events), leading to the patient's death, life-threatening experience, hospitalization or prolongation of hospitalization, significant disability/incapacity, congenital anomaly, or any other situation requiring a significant intervention (qualified as "medically important") [30]. In our study, SAEs notably included grade 3/4 adverse events and any other life-threatening event [31].
3. Cardiotoxicity (prolonged QTc): (1) Grade 3, prolonged QTc including average QTcF ≥501 ms without signs/symptoms of serious arrhythmia; (2) grade 4, prolonged QTc including average QTcF ≥501 ms and 1 of the following: torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia [30].
4. Treatment outcomes: Standard definitions for treatment outcomes (cured, completed, failed, died, lost to follow-up) were used [25].

Data Management and Analysis

The demographic and clinical characteristics at baseline (age, sex, human immunodeficiency virus [HIV] status, body mass index [BMI], TB site, culture status, TB resistance profile via DST results, previous episodes of TB); treatment details (regimen, TB drug doses, duration of treatment, individual exposure to BDQ, DLM, and combined exposure to BDQ and DLM); culture status and QTcF reports for every month; SAEs during treatment; and EOT outcome were collected. The selected data from patient files and MSF TB program databases (electronic medical records: Bahmni [32]) were exported into and analyzed using Stata software version 15 (StataCorp, College Station, Texas). Categorical variables among the demographic and clinical characteristics were described using proportions, and continuous variables were described using median (interquartile range [IQR]). Numbers and proportions were used to summarize the analytic output (treatment outcomes, episodes of SAEs). Kaplan-Meier curves were used to describe the culture progression over time.

Ethical Considerations

Ethics approval was obtained from the ethics review board of Jupiter Hospital, Mumbai, India (dated 23 August 2019). The study met the criteria for a posteriori analysis of routinely collected clinical data and did not require MSF Ethics Review Board full review. It was conducted with permission of the Medical Director, Operational Centre Brussels, MSF.

RESULTS

Patient Characteristics

A total of 70 patients with DR-TB were included. The median age was 25 (IQR, 22–32) years and 39 (56%) were females (Table 1). The demographic and clinical characteristics of the cohort are described in Table 1. One patient was HIV coinfected. The median BMI was 17.2 (IQR, 15.2–19.6) kg/m^2. Most patients were resistant to fluoroquinolone (pre–XDR TB, n = 27; XDR-TB, n = 42). All had a history of previous episode of TB, and 64 (91%) had previously received 1 or more episodes of DR-TB treatment (12 = only DR-TB treatment; 52 = both drug-susceptible TB and DR-TB treatment). The median duration of previous TB treatments (all episodes combined) for patients (n = 19) was 84 (IQR, 40–116) weeks. All of the patients had resistance to rifampicin and isoniazid (Figure 1). More than 90% of patients had additional resistance to ethambutol, streptomycin, and ofloxacin. Resistance to clofazimine was reported in 5% (3/66) of patients in the cohort.

Treatment Regimen and Duration

All patients received concomitant administration of BDQ and DLM with backbone regimen, accompanied by different combination of clofazimine, linezolid, amoxicillin-clavulanate, and imipenem. In addition to BDQ and DLM, the majority of the patients received clofazimine and linezolid (94% and 76%, respectively) in their treatment regimens. About 59% of patients received imipenem and amoxicillin-clavulanate during DR-TB treatment. The most common 4 drugs in treatment regimens (in 71% of patients) were BDQ, DLM, clofazimine, and linezolid administered along with other TB drugs (amoxicillin-clavulanate and imipenem, moxifloxacin, etc). The doses of these drugs were as follows: (1) BDQ for weeks 1–2: 400 mg

day dose, and week 3 onward: 200 mg day dose (100 mg twice a day) 3 times per week; (2) DLM 200 mg/day; (3) clofazimine 100 mg/day; (4) linezolid 600 mg/day. The median duration of treatment was 77 (IQR, 43–96) weeks (Table 1). The median exposure to individual BDQ, individual DLM, and concomitant use of BDQ and DLM was 77 (IQR, 42–88) weeks, 92 (IQR, 70–97) weeks, and 76 (IQR, 42–87) weeks, respectively.

Serious Adverse Events

Thirty-nine episodes of SAEs were reported in 30 of 70 (43%) patients (Table 2). The number of episodes of grade 3 and 4 SAEs was 11 and 28, respectively. Among these 39 episodes of SAEs, 12 (31%, in 11 patients) were possibly related to TB drugs. Nine episodes (in 9 patients; 1 episode in each patient; including 5 instances of QTc prolongation) were assessed as possibly related to BDQ and/or DLM. The ECG monitoring (median QTcF measurements) for each month from baseline to month 12 is presented in Table 3 and Figure 2. None of the patients had a baseline QTcF >500 ms. There were 2 instances of QTcF >500 ms in the first month of treatment (1 had QTcF = 509 ms and the other had QTcF = 571 ms). However, no episodes of QTcF >500 ms were reported in the subsequent 11 months of treatment.

Table 1. Demographicand Clinical Characteristics of Patients With Drug-Resistant Tuberculosis Who Received Treatment Including Concomitant Bedaquiline and Delamanid in the Médecins Sans Frontières Clinic, Mumbai, India, February 2016–November 2019

Characteristic	No.	(%)
Total	70	(100)
Age group, y		
13–17	2	(3)
18–24	29	(41)
25–34	25	(36)
35–44	6	(9)
≥45	8	(11)
Sex		
Male	31	(44)
Female	39	(56)
HIV status		
Positive	1	(1)
Negative	69	(99)
Baseline BMI, kg/m^2, median (IQR)	17.2	(15.2–19.6)
TB site		
Pulmonary	61	(87)
Extrapulmonary	9	(13)
Culture at baseline		
Positive	32	(46)
Negative	38	(54)
TB resistance profile		
Pre–XDR TB[a]	28	(40)
XDR-TB	42	(60)
Previous episode of TB		
Only DS-TB treatment(s)	6	(9)
Only DR-TB treatment(s)	12	(17)
DS-TB and DR-TB treatment(s)	52	(74)
Previous TB treatment duration (all episodes combined), wk, median (IQR) (n = 19)	84	(40–116)
Treatment duration, wk, median (IQR)		
DR-TB treatment duration	77	(43–96)
Individual BDQ exposure	77	(42–88)
Individual DLM exposure	92	(70–97)
DLM and BDQ exposure	76	(42–87)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BDQ, bedaquiline; BMI, body mass index; DLM, delamanid; DR, drug-resistant; DS, drug-susceptible; HIV, human immunodeficiency virus; IQR, interquartile range; TB, tuberculosis; XDR, extensively drug resistant.

[a]Rifampicin + isoniazid + fluoroquinolone resistant, n = 27; rifampicin + isoniazid + second-line injectable resistant, n = 1.

Culture Conversion

The majority (22/32 [69%]) patients with positive culture at baseline had culture conversion before 24 weeks. The median time for culture conversion was 9 (IQR, 7–16) weeks. Table 4 and Figure 3 show the Kaplan-Meier curve of time to culture conversion after treatment initiation in patients (n = 32).

End-of-Treatment Outcome

The EOT outcome was successful for 49 of 70 patients (70%) (Table 5). Thirty-eight patients were cured and 11 completed the treatment. Among the rest, 13 (19%) died, 3 (4%) were lost to follow-up, and 5 (7%) failed treatment. Of the 32 patients who were culture positive at baseline, 14 patients had culture conversion by month 2 and 20 by month 4; the majority of them had successful outcomes (64% and 70%, respectively).

Treatment Including BDQ and DLM Beyond 24 Weeks

Sixty-one (87%) patients received DR-TB treatment including concomitant BDQ and DLM for >24 weeks (Table 5). Among the remaining 9 patients, the treatment was stopped before 24 weeks because of death (7/9) or loss to follow-up (2/9). Of 39 SAE episodes, 12 (31%) episodes (in 10 patients) occurred after 24 weeks of treatment (nontabulated).

DISCUSSION

Our study describes one of the largest global cohorts of patients with difficult-to-treat DR-TB who received regimens including BDQ and DLM for >24 weeks. To our knowledge, this is also among the first studies in India to report EOT outcomes in patients treated with extended combined use of BDQ and DLM. Sixty-one (87%) patients received BDQ and DLM for >24 weeks during treatment. Forty-nine (70%) patients had successful treatment outcomes.

Though early findings of concomitant administration of BDQ and DLM have been reported in India, from Delhi [16] and the MSF Clinic in Mumbai [15], we believe our study reporting EOT outcomes and adverse events provides important insights for policy and practice related to concomitant use of BDQ and DLM in DR-TB treatment regimen (for 24 weeks and beyond).

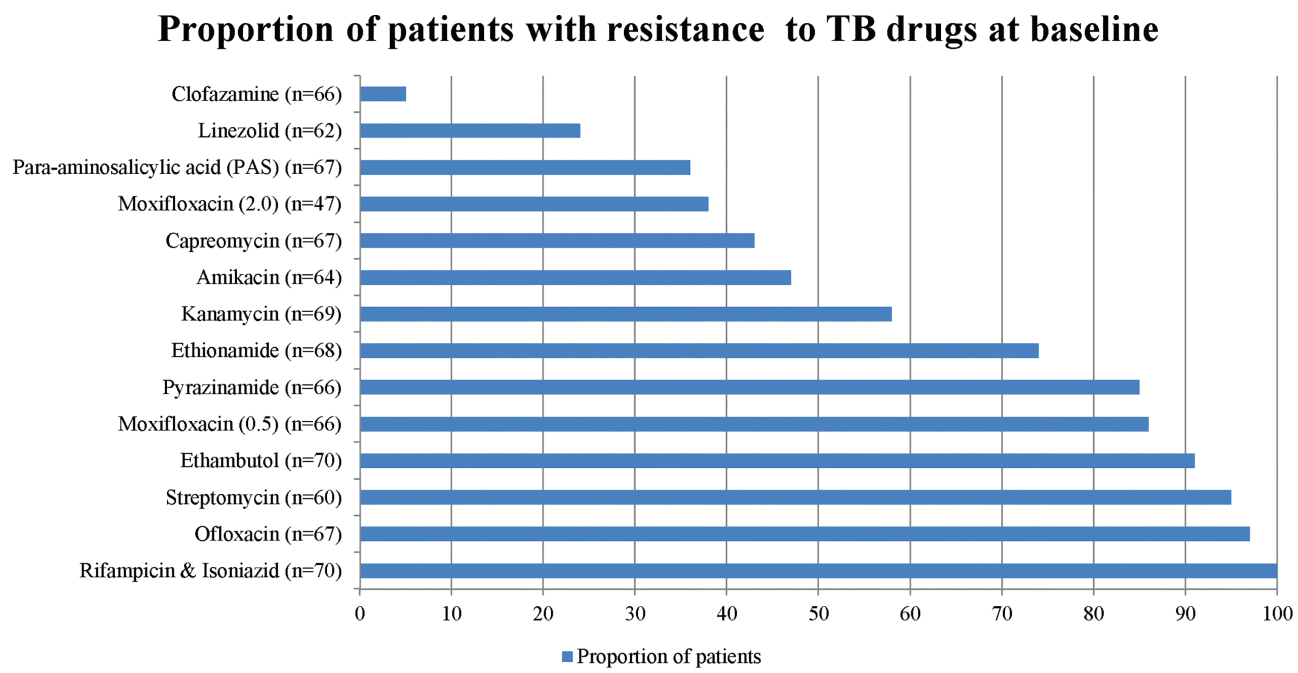

Figure 1. Proportion of patients with resistance to tuberculosis (TB) drugs at baseline among patients with drug-resistant TB who received treatment including concomitant bedaquiline and delamanid from February 2016 to November 2019 in the Médecins Sans Frontières Clinic, Mumbai, India (N = 70).

In our study, most patients received extended use of BDQ and DLM beyond 24 weeks. The reasons for receiving extended BDQ and DLM were patients having prolonged exposure to multiple TB treatments, advanced clinical disease, and complex TB resistance profiles. The clinic enrolled severely ill patients who were left with no treatment options in the standard TB treatment package [29].

The safety and/or effectiveness of extended use of BDQ and DLM (individual or concomitant) beyond 24 weeks have been documented in previous studies [14, 16, 19]. In light of our

Table 2. Serious Adverse Events Among Patients With Drug-Resistant Tuberculosis Who Received Treatment Including Concomitant Bedaquiline and Delamanid in the Médecins Sans Frontières Clinic, Mumbai, India, February 2016– November 2019

SAEs (No. of Episodes)	Categories	No. of Episodes/Patients	Likely Associated With Only BDQ/DLM[a]	Likely Associated With Other TB Drug(s)[a]
Grade 4 (n = 28)	QTc prolongation	3/3	2 BDQ & DLM; 1 DLM	—
	Death due to disease progression	8/8	—	—
	Cardiopulmonary/respiratory complaints	7/6	—	—
	Gastrointestinal complaints	3/3	1 BDQ	1 Ethio
	Sepsis/infection	3/2	—	1 Port-a-cath
	Psychotic disorder	1/1	—	Cs
	Seizures	1/1	—	Cs, Imp
	Hypoxia	1/1	—	—
	Cerebrovascular complaint	1/1	—	—
Grade 3 (n = 11)	QTc prolongation	2/2	2 BDQ & DLM	—
	Gastrointestinal complaints	2/1	2 BDQ & DLM	1 Ethio
	Sepsis/infection	3/3	—	1 Port-a-cath
	Anemia	1/1	—	Imp, Lzd
	Hemoptysis	1/1	—	—
	Increase in lipase/transaminase	2/1	1 BDQ & DLM	—
Total episodes	…	39	…	…

Grading of adverse events is based on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Grade 3: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization possible. Grade 4: Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

Abbreviations: BDQ, bedaquiline; Cs, cycloserine; DLM, delamanid; Ethio, ethionamide; Imp, imipenem; Lzd, linezolid; SAE, serious adverse event; TB, tuberculosis.

[a]Adverse events marked with "—" were not associated with BDQ, DLM, or other TB drug(s) but due to advanced disease condition of the patient.

Table 3. Distribution of Median QTcF Measurements During Treatment in Patients With Drug-Resistant Tuberculosis Who Received Treatment Including Concomitant Bedaquiline and Delamanid in the Médecins Sans Frontières Clinic, Mumbai, India, February 2016– November 2019 (N = 70)

	Month												
	0	1	2	3	4	5	6	7	8	9	10	11	12
	n = 70	n = 68	n = 65	n = 58	n = 57	n = 58	n = 54	n = 51	n = 50	n = 53	n = 48	n = 42	n = 46
QTcF, median (IQR)	420 (400–438)	430 (412–446)	425 (396–446)	429 (407–447)	420 (401–439)	417 (406–435)	412 (398–438)	423 (408–444)	412 (396–440)	407 (398–438)	406 (381–430)	410 (384–443)	407 (386–427)

Abbreviation: IQR, interquartile range.

Figure 2. QTcF measurements during treatment in patients with drug-resistant tuberculosis who received treatment including concomitant bedaquiline and delamanid in the Médecins Sans Frontières Clinic, Mumbai, India, February 2016 -November 2019.

study results and recent evidence [11, 18], national TB programs should consider an all-oral regimen including extended use of BDQ and DLM beyond 24 weeks for patients with complex TB resistance profiles to design an effective 4-drug regimen. Discontinuation of BDQ and DLM after 24 weeks might subject patients to a weaker treatment regimen, leading to poorer treatment outcome [30, 33].

Almost half of the cohort (43% of 70) experienced 1 or more SAEs, but only a minority of these SAE episodes (12 of 39 episodes) were deemed related to any TB drug (11 of 70 patients). Notably, few (13%; 5 episodes of 39) QTc prolongations were reported and assessed as possibly related to BDQ and DLM. Among patients who received BDQ and DLM for >24 weeks, 16% (10/61) experienced any SAE after the first 24 weeks of treatment. Although our study reports a higher proportion of SAE related to BDQ and/or DLM than the report by Borisov et al in 2019 (1% for BDQ and 0.8% for DLM [34]), the proportion of patients with QTc prolongation in our cohort was lower than that reported in a recent systematic review on combined use of BDQ and DLM in DR-TB treatment and interim results of the DELIBERATE clinical trial (16% vs 26% and 26%, respectively) [13, 14]. Thus, the SAE results in our study are encouraging for concomitant administration of BDQ and DLM in patients with DR-TB.

The culture conversion rate at 24 weeks for the study cohort was 69% (22/32 patients with positive baseline culture). The culture conversion rate was lower than rates found in recent studies [16, 35]. However, it must be noted that almost all patients in the cohort were fluoroquinolone resistant including more than half who had XDR-TB. Patients with complex TB resistance profiles are often reported to have poor culture

Table 4. Culture-Positive Probability in Patients With Drug-Resistant Tuberculosis (Culture Positive at Baseline) Who Received Treatment Including Concomitant Bedaquiline and Delamanid in the Médecins Sans Frontières Clinic, Mumbai, India, February 2016–November 2019 (n = 32)

Weeks From Treatment Initiation (Interval)	No. of Patients at Risk, No.	Proportion Remaining Culture Positive, % (95% CI)
0	32	…
4–5	32	0.97 (.80–.99)
8–9	24	0.62 (.43–.76)
12–13	15	0.49 (.30–.65)
16–17	12	0.38 (.21–.54)
21–22	6	0.24 (.10–.42)
26–27	5	0.20 (.07–.37)
32–33	4	0.15 (.04–.32)
46–47	2	0.10 (.02–.26)
58–59	1	0.10 (.02–.26)

The table shows the proportion of patients with positive sputum culture over time among patients with drug-resistant tuberculosis who received treatment including concomitant bedaquiline and delamanid.

Abbreviation: CI, confidence interval.

conversion rates [36]. Among patients who had a positive culture at baseline, the majority of the patients who had culture conversion by month 2 (64%) and month 4 (70%) had successful EOT outcomes. Therefore, culture conversion at months 2 and 4 may be considered a proxy for EOT outcome for patients receiving concomitant BDQ and DLM [37]. Patients who had culture conversion before 6 months continued extended BDQ and DLM, since only 2 of 3 effective drugs were left after 24 weeks for these patients. The culture conversion rates in our study indicate promising results for patients with DR-TB in need of similar treatment regimens including concomitant use of BDQ and DLM.

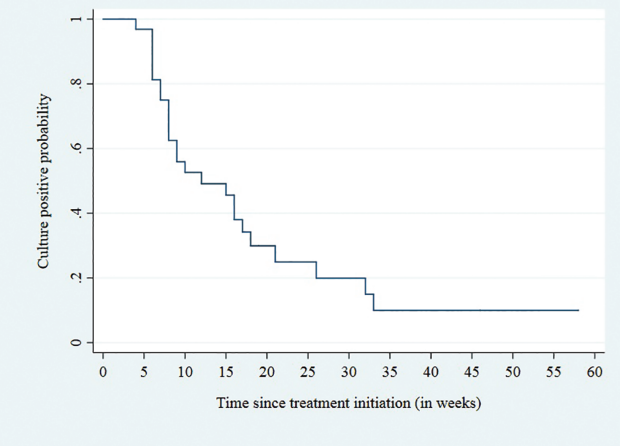

Figure 3. Culture-positive probability in patients with drug-resistant tuberculosis who received treatment including concomitant bedaquiline and delamanid in the Médecins Sans Frontières Clinic, Mumbai, India, February 2016 -November 2019.

The majority of patients (seven in every ten or 70%) had successful EOT outcome, among whom three-fourths were cured. The study results are encouraging considering that these patients were extremely difficult to treat and poor treatment outcomes have been reported among patients with pre–XDR-TB or XDR-TB in other settings [14, 35, 36, 38]. About 19% of our study cohort died, which can be attributed to complex TB resistance profiles, late arrival, and advanced clinical condition of the patients in the MSF Clinic. We believe that early use of concomitant BDQ and DLM under programmatic conditions for eligible patients would improve treatment outcome for patients [16, 19]. Inclusion of BDQ and DLM in routine TB programs will minimize the risk of treatment failure and prevent transmission of highly resistant TB disease in the community.

Our study has following strengths: It provides a detailed report on treatment outcome and adverse events for patients with DR-TB who received concomitant administration of BDQ and DLM beyond 24 weeks. The study included patients from Mumbai, which is a known DR-TB hotspot with evidence of complex TB resistance profiles. Thus, the results will help in contributing toward evidence for similar DR-TB patients in need of combined administration of BDQ and DLM in their treatment regimen.

The study has following limitations. We document a resource-intensive TB program with individualized care offered to patients that would need additional resource allocation for national TB programs to replicate. However, we believe individualized care is necessary for patients with advanced TB resistance profiles, especially in identified DR-TB hotspots. The study has a small sample size; however, this is one of the largest cohorts of patients who received concomitant BDQ and DLM for >24 weeks during DR-TB treatment in routine program settings. We also believe the findings cannot be generalized to the population in the city, as the clinic provides treatment to patients referred from other healthcare institutions. Most of these patients already had advanced TB disease and complex TB resistance profiles. Only 1 patient was living with HIV, and the results may not correspond to DR-TB patients in high-HIV-prevalence settings. As the study was based on review of clinical and laboratory data, we may have had instances of missing data.

In conclusion, the successful treatment outcomes achieved in this cohort of patients with very complex resistance profiles show that regimens including concomitant use of BDQ and DLM are effective and that extended use beyond 24 weeks is safe and well tolerated. More studies including DR-TB patients receiving BDQ and DLM (including patients coinfected with HIV) will help in adding evidence around use of new TB drugs. We strongly recommend that national TB programs consider inclusion of combined use of BDQ and DLM in all oral treatment regimens beyond 24 weeks for DR-TB patients with complex TB resistance profiles.

Table 5. End-of-Treatment Outcomes of Patients With Drug-Resistant Tuberculosis Who Received Treatment Including Concomitant Bedaquiline and Delamanid in the Médecins Sans Frontières Clinic, Mumbai, India, February 2016–November 2019 (N = 70)

	Patients Who Received BDQ and DLM (Concomitant) for Any Duration		Patients Who Received BDQ and DLM (Concomitant) for ≤24 wk		Patients Who Received BDQ and DLM (Concomitant) for >24 wk	
EOT Outcome	No.	(%)	No.	(%)	No.	(%)
Total	70	(100)	9	(100)	61	(100)
Cured	38	(54)	…	…	38	(62)
Treatment completed	11	(16)	…	…	11	(18)
Died	13	(19)	7	(78)	6	(10)
LTFU	3	(4)	2	(22)	1	(1)
Failed	5	(7)	…	…	5	(8)

Abbreviations: BDQ, bedaquiline; DLM, delamanid; EOT, end of treatment; LTFU, lost to follow-up.

Notes

Author contributions. M. D., A. D., C. L., G. F., and P. I. conceived and designed the study. F. M., R. P., T. M., H. M., and A. C. M. provided clinical services and P. S., S. R., N. L., S. C., S. K., and F. N. H. collaborated in the implementation of clinical activities. M. D., S. R., and A. C. M. collected and analyzed the study data. M. D., C. L., A. D., G. F., and P. I. interpreted the results and drafted the manuscript. All of the authors contributed to revisions of the manuscript and approved the final manuscript.

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