

Concomitant bedaquiline and delamanid therapy in patients with drug-resistant extra-pulmonary tuberculosis in Mumbai, India

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ABSTRACT

Background: World Health Organization suggests concurrent bedaquiline-delamanid (BDQ-DLM) as part of individualised regimens for eligible patients with pulmonary drug-resistant tuberculosis (DR-TB); however, data for patients with drug-resistant extrapulmonary tuberculosis (EPTB) is extremely limited. This study documents the treatment outcomes and adverse events associated with concurrent BDQ-DLM-based regimens in patients with drug-resistant EPTB at a Médecins Sans Frontières clinic in Mumbai, India.

Methods: Retrospective cohort study based on routinely collected programmatic data. Individualised regimens were based on drug-susceptibility testing and previous drug exposure. Drug-resistant EPTB patients initiated on regimens containing concurrent BDQ and DLM from April 2016 to October 2019 were included. Patients who completed treatment were followed up at 12 months.

Results: Of 17 patients, median age was 23 years (IQR = 21–30 years) and 12/17 (71 %) were female. Pre-extensively drug-resistant tuberculosis and extensively drug-resistant TB was reported in 13/17 (76.4 %) and 2/17 (11.7 %) patients respectively. Microbiological reports were unavailable for two patients with central nervous system TB. Lymph node TB was the commonest form of EPTB in 9/17 (53 %) of patients. Median duration of treatment was 18.9 months. At least one grade three or four severe adverse event (SAE) was reported by 13/17 (76.4 %) patients. Thirteen (76.4 %) patients had favourable outcomes. None of the patients relapsed or died in the one-year period of post-treatment follow-up.

Conclusion: Concurrent BDQ-DLM-based regimens in drug-resistant EPTB were effective and associated with manageable adverse events.

1. Introduction

Tuberculosis (TB) in any site other than pulmonary is considered as extrapulmonary tuberculosis (EPTB). As per the WHO Global TB 2020 report, EPTB constituted 16 % of the 7.5 million reported TB cases globally and 19 % in Southeast Asia [1]. The India TB Report 2023 stated that EPTB accounts for 24 % of the total notified TB cases [2].

There are many challenges in the diagnosis of EPTB [3]. The lack of access to BDQ and DLM resistance testing also makes it challenging to diagnose EPTB caused by drug-resistant organisms.

Drug-resistant EPTB is associated with poor treatment outcomes [4,5]. EPTB was an exclusion criterion in India's first national anti-TB

drug resistance survey [6] and is usually an exclusion criterion in clinical trials evaluating regimens with bedaquiline (BDQ) and delamanid (DLM) [7,8]. Studies reporting treatment outcomes of patients who received concurrent BDQ and DLM either only include pulmonary TB patients [9–12] or report few cases of EPTB with no disaggregated descriptions of resistance patterns of EPTB [13,14]. This contributes to the lack of evidence for EPTB resistance patterns and treatment outcomes with BDQ and DLM.

There is limited evidence regarding the penetration of BDQ and DLM in extrapulmonary tissues and its therapeutic drug monitoring. BDQ has a long half-life and the response to BDQ is dependent on the concentration of the drug in blood plasma [15]. DLM achieves adequate

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concentrations in brain tissue and low concentration in cerebrospinal fluid (CSF) [16].

The latest WHO guidelines mention the safety of concurrent use of BDQ and DLM and conclude without recommendation for efficacy or effectiveness due to limited data [17]. According to the Indian National Tuberculosis Elimination Programme (NTEP), both BDQ and DLM can be used respectively for 24 weeks of treatment. DLM can be added to a BDQ-based regimen if high-dose moxifloxacin cannot be used in the proposed all-oral regimen or two or more drugs can't be used, depending on availability of DLM and if the patient fits the eligibility criteria [18].

Médecins Sans Frontières (MSF) has been providing treatment for patients with drug-resistant tuberculosis (DR-TB) on an ambulatory basis with regimens including concomitant BDQ and DLM in its clinic in Mumbai, India since 2016 [14].

To contribute to the evidence base for treatment options for EPTB, this study aims to describe the treatment outcomes and adverse events of BDQ and DLM based regimens in people with drug-resistant EPTB.

2. Methods

2.1. Study design

This is an observational monocentric retrospective cohort study using routinely collected programmatic data.

2.2. Study setting

Mumbai is a metropolitan city with a population of around 22 million. The percentage of people living in slums is estimated to be as high as 41.3 % in Greater Mumbai [19]. The odds of developing TB are almost three to five times greater in urban slum areas, compared with national TB incidence rates [20]. In 2019, NTEP guidelines prioritised DR-TB drugs, including BDQ in group A and selective addition of DLM (group C) if a regimen cannot be formed with Group A and B drugs [21].

2.3. Clinical management

MSF has been operating a TB clinic in Govandi, Mumbai, a predominantly slum area, providing ambulatory care for patients with complex drug-resistant TB [22,23].

The clinic offers treatment to patients mostly with pre-XDR and XDR TB on an outpatient basis. Patients with advanced resistance profiles, prolonged exposure to second-line TB drugs and limited drugs to form an effective regimen are treated [14]. Patients are evaluated clinically, microbiologically and radiologically. Individualised regimens, based on drug susceptibility testing (DST) and previous exposure to TB drugs, are provided for a duration of 18–22 months. The multidisciplinary treatment and monitoring have been explained in prior publications [23].

All adverse event episodes were clinically managed in accordance with the Expand New Drug markets for End TB (endTB) trial guidelines for clinical and programmatic patient management with new TB drugs [24]. The endTB trial aims to find shorter, less toxic, and more effective treatments for multidrug-resistant TB [7]. Severe adverse events (SAEs) were reported to MSF Pharmacovigilance (PV) unit based in Geneva, Switzerland. Patients were followed for a period of one-year post-treatment.

2.4. Study population

All drug-resistant EPTB patients either confirmed microbiologically (culture and DST) or diagnosed based on radiology/histopathology/cytology findings consistent with TB and a history of failure to improve on second-line TB drugs and initiated on a regimen with concurrent BDQ and DLM from April 2016 to October 2019 at the MSF clinic, Mumbai were included in the study.

2.5. Operational definitions

All SAEs were reported according to the criteria defined under the protocol of the endTB trial [25]. Accordingly, severity is graded based on the standardized MSF severity grading scale, which was developed using the Division of Microbiology and Infectious Diseases adult toxicity tables (November 2007) and the Common Terminology Criteria for Adverse Events v. 4.03 [7,25].

The standard treatment outcomes cured, treatment completed, treatment failure, died and lost to follow-up (LTFU) were used according to WHO definitions and reporting framework for tuberculosis [26]. Treatment completion and cured was considered as a favourable outcome. Treatment failure, died and LTFU were considered unfavourable outcomes.

In this study, treatment completion was determined by improvements observed in either radiological or clinical parameters at the end of treatment compared to the baseline assessment. Baseline was defined as time of initiation of BDQ and DLM, even if there was an ongoing background regimen.

2.6. Data management and analysis

All data was collected from patient medical records and the DR-TB electronic database, all of which were maintained at the MSF clinic for routine programmatic data monitoring.

Clinical and demographic characteristics were assessed using frequencies and proportions for categorical variables and medians and interquartile ranges (IQR) for continuous variables. Treatment outcomes and outcomes at 12 months post treatment completion were described for all patients included in the cohort using frequencies and proportions.

2.7. Ethical considerations

The study received ethics approval from the Institutional Ethics Committee of Jupiter Hospital, Thane, Maharashtra. This study also fulfilled the exemption criteria set by the Médecins Sans Frontières Ethics Review Board (ERB) for a posteriori analysis of routinely collected clinical data and thus did not require MSF ERB review. Prior to initiating treatment, all patients provided written consent to use BDQ and DLM, with full disclosure of the potential side effects of the drugs.

3. Results

3.1. Patient characteristics

During the study period, 185 DR-TB patients were initiated on regimens containing concurrent BDQ and DLM, out of which 17 (9.1 %) patients had drug resistant EPTB.

The study cohort comprised 12 (70.5 %) female patients with a median age of 23 years (IQR: 21–30 years) (Table 1). Out of 17 patients, 12(70.5 %) had received TB treatment in the past and the remaining 5 (29 %) were new patients. The cohort did not have any people living with HIV (PLHIV) and none of the patients reported any comorbidities. The median BMI in the cohort at the initiation of treatment was 21.5 (IQR: 18.3–24.7).

In the study cohort of 17 patients, 15 patients had a microbiological report available while the remaining two patients had central nervous system (CNS) tuberculomas for which a microbiological report was unavailable; they were confirmed based on clinical evaluation, radiological reports, histopathological reports and failure to improve on prior second-line TB drug regimens. All patients with microbiological confirmation had resistance to fluoroquinolones; out of the 15 patients, 2(13 %) had XDR TB, and 13(87 %) had pre-XDR. Linezolid sensitivity testing was available at baseline for ten patients, out of whom two (20 %) had resistance to linezolid.

The most common anatomical site of DR-TB involvement was lymph

Table 1

Demographic and clinical characteristics of extrapulmonary DR-TB patients who were treated with a combination of bedaquiline and delamanid in MSF Mumbai clinic from April 2016 to October 2019.

Characteristics	N (%)
Median age (IQR)	23 (12–30)
Sex	
Female	12 (70.5)
Male	5 (29.4)
Exposure to second line TB drugs	
Yes	14 (82.4)
No	3 (17.6)
Resistance pattern	
Pre-XDR	13 (76.5)
XDR	2 (11.8)
Not available	2 (11.8)

node (9/17;53 %), followed by CNS (3/17; 18 %), spine and paravertebral abscess (2/17; 12 %) and pleural effusion (1/17;6%) (Fig. 1). Two patients (12 %) had disseminated TB, with one patient having involvement of spine, gluteal, and proximal thigh abscesses, and the other having pleural effusion with multiple cold abscesses. Of the three patients with CNS TB, two patients had tuberculomas and one had microbiologically confirmed TB meningitis.

The median time of exposure to second-line drugs before initiation of a combination of BDQ and DLM regimen was 12 weeks (IQR = 4–98).

3.2. Treatment regimen and duration

The patients were treated with a regimen containing concurrent BDQ and DLM with an optimized background regimen (OBR) of second-line drugs. The most common drugs in the OBR were linezolid and clofazimine (n = 15;88 %), followed by cycloserine (n = 10; 58.8 %), high-dose moxifloxacin (n = 9;52.9 %) and imipenem (n = 8;47 %) (Fig. 2). The patients received BDQ and DLM for the entire duration of treatment. The median number of companion drugs in the regimen, in addition to BDQ and DLM, was 4 (IQR 4–6). The median duration of treatment was 18.9 months (IQR = 14 to 22 months). For the two CNS patients without DST, the regimens were designed based on prior drug exposure history and

drugs with good CNS penetration according to the data available.

3.3. Severe adverse events

In the cohort, 13 patients (76 %) reported at least one grade 3 or 4 SAE. The total number of episodes of grade 3 and 4 SAEs reported was 23, with a median of 1 episode per patient (IQR = 1–2). Three patients needed hospitalisation due to complications not likely to be related to BDQ and DLM. Out of 6 episodes of hospitalization, 4 episodes were due to seizures related to tuberculoma, 1 due to port-site infection and 1 due to poor general status and clinical deterioration. Therefore, the SAE with the most episodes was hospitalization, grade 4 (Table 2). The second most frequent SAE was peripheral neuropathy, which may be attributable to linezolid and/or cycloserine. None of the patients had corrected QT using Fridericia (Qtcf) > 500 msec at baseline. During treatment, 3 episodes of grade 4 QtcF prolongation were reported, in one patient, who was managed with intermittent temporary discontinuation of moxifloxacin and clofazimine.

None of the SAEs required permanent discontinuation of either BDQ or DLM.

3.4. End-of-treatment outcome

All patients were evaluated clinically and radiologically. Thirteen (76 %) patients have completed the treatment and among the remaining four, two (11.7 %) died, one (5.8 %) had treatment failure and one (5.8 %) was LTFU. Among the patients who died, one had CNS TB with clinical deterioration and static radiological picture at six months of treatment. The second patient had pleural effusion, and multiple comorbidities and died potentially due to aspiration pneumonia or sepsis. The cause of death in both cases is likely unrelated to BDQ and DLM. One patient who failed the treatment had disseminated XDR TB with linezolid resistance and was on immunosuppressive drugs due to a renal transplant. The patient had a new TB lesion on magnetic resonance imaging at 18 months of treatment. Although the drug doses were adjusted to prevent drug interactions, immunosuppressive therapy due to renal transplant and baseline linezolid resistance may have contributed to the failure on treatment. None of the patients relapsed in the period of one year of post-treatment follow-up.

4. Discussion

This study revealed that concurrent use of BDQ and DLM in drug-resistant EPTB patients with advanced resistance profiles and limited

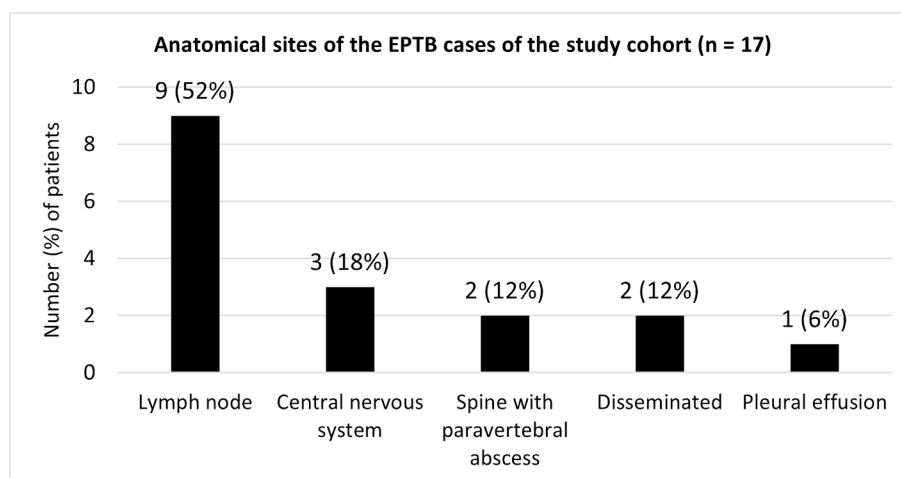


Fig. 1. Anatomical site of DR-TB involvement in patients in initiated on concurrent bedaquiline and delamanid regimen at MSF clinic, Mumbai India from April 2016 to October 2019.

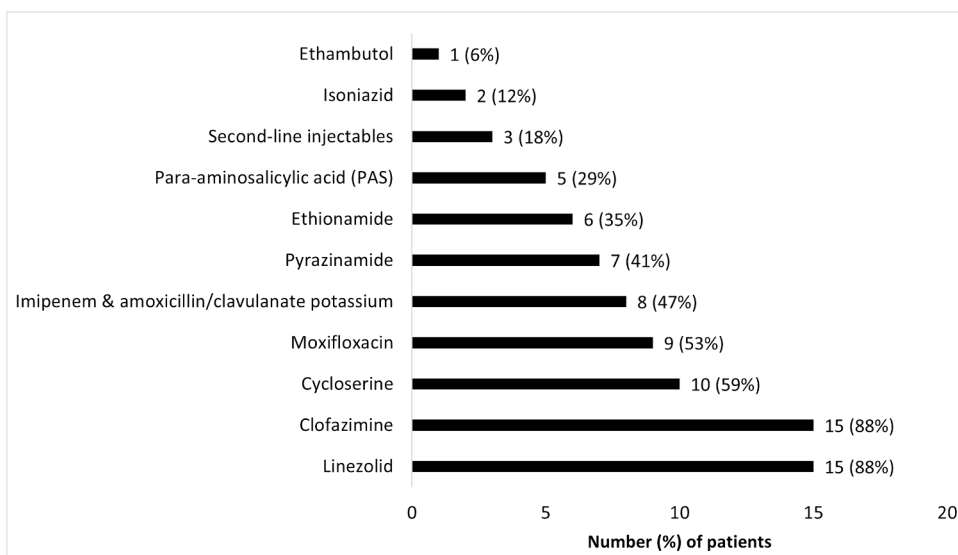


Fig. 2. Optimised background regimen used in regimen containing combination of bedaquiline and delamanid at MSF clinic, Mumbai India from April 2016 to October 2019.

Table 2

Description of severe adverse events among drug resistant EPTB patients who were treated with a combination of bedaquiline and delamanid in MSF Mumbai clinic from April 2016 to October 2019.

Grade of SAE	Category	Number of episodes/patients	Possibly attributable to BDQ and/or DLM	Possibly attributable to other drugs/disease
Grade 3 (n = 10)	Peripheral neuropathy	4/4	No	Cycloserine, Linezolid
	Hepatitis	3/3	Yes	All TB drugs
	Vomiting	1/1	Yes	All TB drugs
	Pellagroid dermatitis	1/1	No	Ethionamide
	Optic neuritis	1/1	No	Linezolid
Grade 4 (n = 13)	Hospitalisation	6/3 a. 4 episodes of seizures b. 1 episode of clinical deterioration c. 1 episode of port infection	No	All TB drugs
	QTC Prolongation	3/1	Yes	Clofazimine, Moxifloxacin
	Psychosis	2/2	No	Cycloserine
	Anemia	1/1	No	Linezolid
	Hepatitis	1/1	Yes	All TB drugs

treatment options for the entire duration is effective and can be safely managed in an outpatient setting.

Females constituted the majority (71 %) of our patients in the study, similar to findings reported by other studies in the same geographic region [27–29]. The overrepresentation of females in our study could be linked to the fact that women are more predisposed to developing EPTB, as evidenced by other studies [28,29]. However, since our cohort size is small, the larger representation of women could also be by chance.

The most common site of extra-pulmonary involvement in our study was lymph nodes (52 %), as reported by other studies from Mumbai [27,30].

We report a treatment completion rate of 76.4 %. This rate is comparable with another study that reported a successful end-of-treatment

outcome rate of 70 % in Pre-XDR and XDR TB pulmonary and EPTB patients receiving concurrent BDQ and DLM in the treatment regimen [14]. The rate is also comparable to successful early treatment outcomes reported by other studies where pulmonary DR-TB patients were treated with concurrent BDQ and DLM [9,11,13].

Our study reported a very low rate of LTFU (5.8 %). This may be a result of the patient-centred approach of extensive adherence counselling and treatment literacy by the patient support team at the clinic [22]. Patient support is important in improving treatment adherence and reducing LTFU rates [31].

The deaths among our patients can be attributed to late presentation to the clinic along with the progression of advanced disease.

Our study reports a higher rate of SAEs as compared to studies reporting adverse events in DR-TB patients treated with concurrent BDQ and DLM [14,32]. The hospitalizations are attributable to the clinical presentation and evolution of extrapulmonary disease. BDQ and DLM were not stopped permanently for any patient, demonstrating encouraging results and manageable adverse events.

This study provides a detailed report on the resistance profile and treatment outcome of drug resistant EPTB patients who received concurrent administration of BDQ and DLM for the entire duration of treatment. The study included an account of severe events due to TB drugs, the evolution of EPTB disease and anatomical site involvement, showing the high number of SAEs that drug resistant EPTB patients endure. The study will add to the evidence base for similar drug resistant EPTB patients who need concurrent administration of BDQ and DLM in their treatment regimen.

The limitations of our study are the small cohort size and heterogeneity of the cohort. Additionally, the MSF clinic treats specific complex cases, which contributes to a smaller cohort as compared to the National TB Elimination Plan centres. Multicentre studies in the future would contribute more data for consolidation and analysis of treatment outcomes of EPTB patients with pre-XDR and XDR resistance profiles, treated with BDQ and DLM.

The outcomes were based on an assessment of clinical and radiological responses to treatment. EPTB sites were not sampled for culture conversion or to obtain a negative sample at the end of the treatment, as either most lymph nodes were biopsied for baseline assessments, or the sampling would have been invasive for the other sites. There was no baseline drug sensitivity report available for BDQ and DLM.

To conclude, given the limitations of the study population size, the regimens were effective and associated with manageable adverse events.

Further studies with a larger sample size that includes PLHIV, children and pregnant women would add to the evidence base for the use of BDQ and DLM in EPTB.

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Author contributions

HM, FM and AS conceived and designed the study. HM, FM and AD provided clinical services and PS, MG, AI and MM collaborated in the implementation of clinical activities. HM and AS collected and analysed the study data. HM, AS and MD interpreted the results and drafted the manuscript. All the authors have contributed to the revisions of the manuscript and approved the final manuscript.

CRediT authorship contribution statement

Himani Mongia: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Fatima Mamnoon:** Investigation, Conceptualization. **Arunima Silsarma:** Writing – review & editing, Visualization, Supervision, Software, Project administration, Formal analysis. **Raman Mahajan:** Writing – review & editing. **Alpa Dalal:** Investigation. **Miriam Arago Galindo:** Writing – review & editing, Project administration, Methodology, Investigation. **Aparna Iyer:** Writing – review & editing. **Pramila Singh:** Writing – review & editing, Project administration. **Homa Mansoor:** Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Mrinalini Das:** Methodology, Conceptualization. **Mabel Morales:** . **Hannah Spencer:** Writing – review & editing. **Petros Isaakidis:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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